Advances in Pharmacotherapy of Late-Life Depression

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Abstract

Purpose of Summary This paper reviews recent research on late-life depression (LLD) pharmacotherapy, focusing on updated information for monotherapy and augmentation treatments. We then review new research on moderators of clinical response and how to use the information for improved efficacy.

Recent Findings A recent review shows that sertraline, paroxetine, and duloxetine were superior to placebo for the treatment of LLD. There is concern that paroxetine could have adverse outcomes in the geriatric population due to anticholinergic properties; however, studies show no increases in mortality, dementia risk, or cognitive measures. Among newer antidepressants, vortioxetine has demonstrated efficacy in LLD, quetiapine has demonstrated efficacy especially for patients with sleep disturbances, and aripiprazole augmentation for treatment resistance in LLD was found to be safe and effective. Researchers have also been identifying moderators of LLD that can guide treatment. Researchers are learning how to associate moderators, neuroanatomical models, and antidepressant response.

Summary SSRI/SNRIs remain first-line treatment for LLD. Aripiprazole is an effective and safe augmentation for treatment resistance. Studies are identifying actionable moderators that can increase treatment response.

Keywords Late-life depression · Pharmacotherapy · Treatment response moderators

Introduction

Late-life depression has high costs for individuals and society. To the individual, there is increased risk of developing all-cause dementia, especially vascular or Alzheimer’s dementia over 5 years [1, 2] and increased morbidity and mortality from cardiovascular diseases such as hypertension, coronary heart disease, and diabetes [3]. Increased health care costs including increased emergency visits, office visits, increased drug use, higher risk for alcohol and substance use, and increased length of inpatient stay are impacts on society [4, 5]. Therefore, it is important that late-life depression (LLD) be addressed and adequately treated.

There are several pathways for the treatment of LLD, including pharmacotherapy, psychotherapy, somatic modalities such as ECT, and exercise. However, exercise can be difficult for a subset of geriatric patients due to physical limitations. Psychotherapy is effective, but often limited by lack of health insurance coverage and availability of therapists [6, 7, 8]. Not all patients accept ECT as an option. Thus, pharmacotherapy has become the mainstay of LLD treatment. A recent meta-analysis looking at seven trials (n = 2283) found that older patients with a long illness duration and moderate to severe depression appear to benefit from antidepressants as compared with placebo [9]. Unfortunately, in the geriatric population with LLD, suboptimal antidepressant use and inadequate dosing is common [10, 11].

Given the costs to patient health and society and the evidence for the under treatment of depression in older adults, the latest knowledge about effective and safe treatment regimens and dosages to treat LLD in the geriatric population is needed. In this article, the most recent research on the pharmacotherapy of LLD is reviewed. First, an update on monotherapy and augmentation treatment strategies in LLD is presented, with a special emphasis on the findings of clinical trials conducted in the past 10 years. Then, research conducted in the past 5 years that has focused on understanding moderators of clinical response in LLD and how to use the information for improved efficacy is reviewed (Tables 1, 2, and 3).
<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Type of study</th>
<th>Length (weeks)</th>
<th>Age (years)</th>
<th>Sample size</th>
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<th>Outcome</th>
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<tr>
<td>Bali et al. [12]</td>
<td>2017</td>
<td>Propensity score (PS)-matched</td>
<td>2010-2017</td>
<td>≥65</td>
<td>N=4620</td>
<td>Paroxetine versus other SSRIs</td>
<td>No difference; incidence of mortality was 269 (2.9%) for paroxetine and 288 (3.1%) for other SSRIs</td>
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<td></td>
<td></td>
<td>retrospective cohort study</td>
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<td></td>
<td>for paroxetine and 288 (3.1%) for other SSRIs</td>
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<tr>
<td>Bali et al. [13]</td>
<td>2015</td>
<td>Propensity score (PS)-matched</td>
<td>2010-2017</td>
<td>≥65</td>
<td>N=1898</td>
<td>Paroxetine versus other SSRIs</td>
<td>No difference; incidence of dementia was 7.5% for paroxetine and 8.6% for other SSRIs</td>
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<td>retrospective cohort study</td>
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<tr>
<td>Bali et al. [14]</td>
<td>2016</td>
<td>Propensity score (PS)-matched</td>
<td>2010-2017</td>
<td>≥65</td>
<td>N=63 for</td>
<td>Paroxetine versus other SSRIs</td>
<td>No difference; MDS Cognition Scale measure 2.30 for paroxetine and 2.61 for users of other SSRIs</td>
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<td></td>
<td></td>
<td>retrospective cohort study</td>
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<td>paroxetine and 2.61 for users of other SSRIs</td>
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<tr>
<td>Bose et al. [15]</td>
<td>2008</td>
<td>Double-blind randomized controlled trial</td>
<td>12</td>
<td>Average age 68</td>
<td>N=267</td>
<td>Escitalopram 10–20 mg versus placebo</td>
<td>No significant difference for escitalopram over placebo in MADRS total score (p = 0.29)</td>
</tr>
<tr>
<td>Chen et al. [16]</td>
<td>2011</td>
<td>Randomized controlled trial</td>
<td>8</td>
<td>Average age 68.9</td>
<td>N=55</td>
<td>Escitalopram 10 mg versus placebo</td>
<td>Significant difference in efficacy at week 4 (p &lt; 0.05) and at week 8 (p &lt; 0.01) for the escitalopram group versus placebo group</td>
</tr>
<tr>
<td>Hall et al. [17]</td>
<td>2015</td>
<td>Multi-site randomized controlled trial, open label</td>
<td>12</td>
<td>≥60</td>
<td>N=459 (47 black, 412 white)</td>
<td>Venlafaxine ≤300 mg versus placebo</td>
<td>No difference between races: 41% of white participants and 40% of black participants reached remission</td>
</tr>
<tr>
<td>Kornstein et al. [18]</td>
<td>2010</td>
<td>Pooled analysis of nine double-blind randomized controlled trials</td>
<td>8</td>
<td>≥65</td>
<td>N=134</td>
<td>Desvenlafaxine 50–400 mg versus placebo</td>
<td>Significant difference in desvenlafaxine ≥65 subgroup over placebo (p = 0.02)</td>
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<tr>
<td>Kornstein et al. [19]</td>
<td>2015</td>
<td>Pooled analysis of two double-blind randomized controlled trials</td>
<td>8-10</td>
<td>Females, ages 40–70, post-menopausal status</td>
<td>N=547</td>
<td>Desvenlafaxine 100–200 mg versus placebo and desvenlafaxine 50 mg versus placebo</td>
<td>In both trials, desvenlafaxine groups had greater remission than placebo (p&lt;0.001) and greater decrease in menopausal symptoms than placebo (p&lt;0.009)</td>
</tr>
<tr>
<td>Raeken et al. [20]</td>
<td>2007</td>
<td>Double-blind randomized placebo-controlled trial</td>
<td>8</td>
<td>Average age 72</td>
<td>N=311</td>
<td>Duloxetine 60 mg versus placebo</td>
<td>Significant difference in duloxetine group over placebo (p &lt; 0.001)</td>
</tr>
<tr>
<td>Robinson et al. [21]</td>
<td>2014</td>
<td>Multi-site double-blind randomized placebo-controlled trial</td>
<td>24</td>
<td>Average age 73</td>
<td>N=370</td>
<td>Duloxetine 60–120 mg versus placebo</td>
<td>Significant difference in from baseline in Maier subscale and GDS in duloxetine versus placebo at weeks 4, 8, 16, and 20 but not at week 12</td>
</tr>
<tr>
<td>Kerner et al. [22]</td>
<td>2014</td>
<td>Open-label randomized controlled trial</td>
<td>12</td>
<td>Average age 70.7</td>
<td>N=30</td>
<td>Duloxetine 20–120 mg versus placebo</td>
<td>Significant reduction in dysphoria symptoms in duloxetine versus placebo</td>
</tr>
<tr>
<td>Hewett et al. [23]</td>
<td>2010</td>
<td>Multi-site double-blind randomized controlled trail</td>
<td>10</td>
<td>Average age 71</td>
<td>N=418</td>
<td>Bupropion XR 150–300 mg</td>
<td>No difference in remission at week 10 (p = 0.167) but difference in secondary endpoints (motivation, energy, life satisfaction, concernment)</td>
</tr>
<tr>
<td>Cofet al. [24]</td>
<td>2014</td>
<td>Multi-site double-blind randomized placebo-controlled trial</td>
<td>8</td>
<td>Ages 18–70 9% ≥60</td>
<td>N=518</td>
<td>Vilazodone 40 mg versus placebo</td>
<td>Significant difference in remission for the vilazodone group (p &lt; 0.00001)</td>
</tr>
<tr>
<td>Katsia et al. [25]</td>
<td>2012</td>
<td>Double-blind randomized controlled trial</td>
<td>8</td>
<td>Average age 70.6 years</td>
<td>N=452</td>
<td>Vortioxetine 5 mg versus duloxetine 60 mg versus placebo</td>
<td>Significant difference in remission for the vortioxetine group compared to placebo (p = 0.0011)</td>
</tr>
<tr>
<td>Kabney et al. [26]</td>
<td>2015</td>
<td>Open-label trial</td>
<td>6</td>
<td>Age ≥60</td>
<td>N=20</td>
<td>Agomelatine 25–50 mg versus placebo</td>
<td>Significant reduction in depressive and anxiety symptoms</td>
</tr>
<tr>
<td>Hein et al. [27]</td>
<td>2013</td>
<td>Multi-site placebo-controlled trial</td>
<td>8</td>
<td>Average age 71.8</td>
<td>N=222</td>
<td>Agomelatine 25–50 mg versus placebo</td>
<td>No difference in remission (p = 0.179) but significant difference in treatment response (p = 0.004)</td>
</tr>
<tr>
<td>Katila et al. [28]</td>
<td>2013</td>
<td>Multi-site double-blind randomized placebo-controlled trial</td>
<td>11</td>
<td>Average age 71.3</td>
<td>N=338</td>
<td>Quetiapine XR 50–300 mg versus placebo</td>
<td>Significant difference in depression, anxiety, and sleep for the quetiapine group (p &lt; 0.001)</td>
</tr>
</tbody>
</table>
### Table 2  Meta-analyses of antidepressant effectiveness in the past 10 years for patients 65 and older

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Type of study</th>
<th>Length (weeks)</th>
<th>Age (years)</th>
<th>Sample size</th>
<th>Drug</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seitz et al. [29]</td>
<td>2010</td>
<td>Review of seven randomized controlled trials with meta-analysis</td>
<td>4-16</td>
<td>Average age 71.7</td>
<td>N = 647 for citalopram, N = 641 for other antidepressants</td>
<td>Citalopram versus other antidepressants</td>
<td>There was no difference in effectiveness of citalopram over other antidepressants</td>
</tr>
<tr>
<td>Thorlund et al. [30]</td>
<td>2015</td>
<td>Review of 15 randomized controlled trials with meta-analysis</td>
<td>6-12</td>
<td>Average age 71.4</td>
<td>N = 4588</td>
<td>Citalopram, escitalopram, paroxetine, duloxetine, venlafaxine, fluoxetine, and sertraline versus placebo</td>
<td>Sertraline (RR 1.28), paroxetine (RR 1.48), and duloxetine (RR 1.62) were superior to placebo</td>
</tr>
</tbody>
</table>

### Table 3  Studies of adjunctive antidepressant treatments in the past 10 years for patients 65 and older

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Type of study</th>
<th>Length (weeks)</th>
<th>Age (years)</th>
<th>Sample size</th>
<th>Drug</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenze et al. [31]</td>
<td>2015</td>
<td>Multi-site double-blind randomized placebo-controlled trial</td>
<td>12</td>
<td>Average age 66</td>
<td>N = 468</td>
<td>Venlafaxine ER (150–300 mg) plus aripiprazole (2–15 mg) versus continuation venlafaxine plus placebo</td>
<td>Aripiprazole group had higher remission rate than placebo (44 vs 29%; p = 0.03)</td>
</tr>
<tr>
<td>Lavretsky et al. [32]</td>
<td>2016</td>
<td>Single-site randomized placebo-controlled RCT</td>
<td>16</td>
<td>Average age 69.7</td>
<td>N = 143</td>
<td>Citalopram (20–60 mg) plus methylphenidate (5–40 mg) versus citalopram plus placebo and methylphenidate plus placebo</td>
<td>Citalopram plus methylphenidate group showed the highest improvement in depression severity</td>
</tr>
<tr>
<td>Omranifard et al. [33]</td>
<td>2014</td>
<td>Single-site double-blind randomized placebo-controlled trial</td>
<td>8</td>
<td>≥ 60</td>
<td>N = 57</td>
<td>Memantine 20 mg plus citalopram 20 mg versus citalopram plus placebo</td>
<td>There was no significant difference in depression response</td>
</tr>
<tr>
<td>Almeida et al. [34]</td>
<td>2016</td>
<td>Double-blind randomized placebo-controlled trial</td>
<td>52</td>
<td>≥ 50</td>
<td>N = 153</td>
<td>Citalopram 20–40 mg plus vitamin B12 0.5 mg, folic acid 2 mg, and vitamin B6 25 mg versus citalopram plus placebo</td>
<td>There was a lower risk of relapse in citalopram plus supplement group at the end of the study</td>
</tr>
</tbody>
</table>
Antidepressant Monotherapy in LLD

Citalopram The 2001 US Expert Consensus Guidelines recommended selective serotonin reuptake inhibitors (SSRIs) as the “first-line” treatment for geriatric depression. SSRIs were noted to have less side effects, less medication interactions, and higher tolerability than other antidepressant classes. Of all the SSRIs available at that time, citalopram and sertraline received the highest ratings [35]. Interestingly, there has not been a more recent LLD expert guideline panel convened since that time.

Despite citalopram receiving the highest rating for effectiveness, there is no evidence that it is more effective than other antidepressants. A 2010 systematic review and meta-analysis of seven studies comparing citalopram to other antidepressants (including four studies with tricyclics and three studies with non-tricyclic comparators) concluded that there were no significant differences in efficacy, withdrawal due to all cause, or withdrawal due to adverse effects between citalopram and other antidepressants [29].

In addition, safety concerns have subsequently been raised about the use of higher doses of citalopram in the elderly, prompting calls for caution. In 2012, the FDA revised dosing recommendations for citalopram in patients ≥60 years of age to not exceed 20 mg daily [36]. Post-release evidence found that higher doses can lead to Torsade de Points, ventricular tachycardia, or sudden death. Therefore, citalopram is not recommended in patients with congenital long QT syndrome and should not be used at any dose in patients with a QT interval consistently above 500.

Because of these reasons, the prioritization of citalopram in first-line treatment for LLD is undergoing reassessment. In 2015, a systematic review and meta-analysis of 15 randomized controlled trials demonstrated that several SSRIs and selective norepinephrine reuptake inhibitors (SNRIs) performed as well or even better than citalopram for treatment of LLD and have higher tolerability. The study reported calculated relative risk results based on effectiveness and tolerability outcomes for double-blind, placebo-controlled LLD trials using citalopram, escitalopram, paroxetine, duloxetine, venlafaxine, fluoxetine, and sertraline compared to placebo. For partial treatment response, only three interventions [sertraline (RR 1.28), paroxetine (RR1.48), and duloxetine (RR1.62)] were statistically significantly superior to placebo (RR 1.20). Citalopram (RR1.07) and fluoxetine (RR1.08) had the lowest RR estimates [30–3].

Paroxetine There is concern that paroxetine, due to its anticholinergic properties, could have more adverse outcomes in the geriatric population, specifically mortality and cognitive decline. However, a recent retrospective cohort study of 4620 nursing home patients specifically compared paroxetine to other SSRIs for efficacy and tolerability. The authors found that the incidence of mortality was 269 (2.9%) for paroxetine and 288 (3.1%) for all other SSRIs in the matched cohort [12]. The same authors using a similar population, methods, and study design in two separate additional studies also found no difference in dementia risk or cognitive measures for paroxetine compared with other SSRIs [13•, 14•].

Escitalopram Two new randomized controlled trials on the effectiveness of escitalopram for LLD have been published in the last decade. A double-blind randomized trial of 12 weeks duration with escitalopram 10–20 mg or placebo in 267 patients ages 60 years or older showed no significant difference between escitalopram and placebo in Montgomery-Åsberg Depression Rating Scale (MADRS) score (p = 0.29) [15].

Chen et al. [16] conducted a smaller randomized trial of 55 patients with LLD treated with escitalopram 10 mg or placebo for 8 weeks. Patients in the escitalopram group showed a response rate of 74.1%, with significant differences in efficacy noted at week 4 (p < 0.05) and at week 8 (p < 0.01) [16].

Venlafaxine Hall and associates [17] conducted a post hoc analysis of the initial open-label 12-week venlafaxine treatment phase of the IRL-GRey trial on 459 LLD subjects to evaluate a possible difference in remission rates between black and white participants. Forty-seven black (10%) and 412 white (90%) adults ages ≥60 treated with venlafaxine had similar final doses of venlafaxine and similar rates of attrition and remission. With venlafaxine and supportive care, 19 of 47 black participants (40%) and 170 of 412 white participants (41%) attained remission. Of note, black adults in the study had more baseline medical co-morbidities, decreased health-related quality of life, and poorer cognitive function than the white adults.

Desvenlafaxine There are no published placebo-controlled RCT of desvenlafaxine specifically in geriatric patients; however, Kornstein et al. [18] published a pooled analysis of nine studies evaluating the efficacy of desvenlafaxine for the treatment of major depressive disorder by sex and age. Participants received desvenlafaxine 50, 100, 200, or 400 mg for 8 weeks. Sub-analysis found that 134 participants were ≥65 years of age. Response to treatment with desvenlafaxine was noted to be significant compared to placebo in the ≥65 subgroup (p = 0.02). The remission rate was also significantly better in the treatment group for the ≥65 subgroup of women (p = 0.02) but not in any age subgroup of men.

A later pooled analysis of two double-blind placebo-controlled trials by the same author assessed whether desvenlafaxine is effective in perimenopausal and/or postmenopausal women with major depression. The analysis found that 546 postmenopausal women ages 40–70 who received desvenlafaxine 100 to 200 mg versus placebo or
desvenlafaxine 50 mg versus placebo experienced significantly reduced HAM-D17 scores \( (p < 0.001) \), Sheehan Disability Scale (SDS) and Menopause Rating Scale (MRS) scores \( (p < 0.009) \) in the desvenlafaxine treated groups compared to placebo [19].

**Duloxetine** Duloxetine has shown mixed findings in the geriatric population. Raskin et al. (2007) conducted a randomized 8-week double-blind, placebo-controlled study of duloxetine 60 mg for recurrent major depression in older adult patients (median age 72 years). Duloxetine demonstrated a decrease in depressive symptoms, improvement in cognition, and improvement in some pain measures compared with placebo. This improvement was noted as early as the first week and continued through the end of treatment \( (p \leq 0.001) \). In addition, there was a greater advantage of duloxetine over placebo in patients with more severe depression (HAM-D score \( \geq 24 \) [20].

Another randomized controlled trial in depressed patients 65 years or greater did not find that either the 60 or 120 mg dose of duloxetine was significantly better than placebo at 12 weeks. However, this study was somewhat difficult to interpret because, although the primary outcome scale was not positive at week 12, that same scale did show that duloxetine separated from placebo at weeks 4, 8, 16, and 20 weeks. Further, the secondary outcomes, the Geriatric Depression Scale and CGI, also demonstrated similar patterns. Duloxetine had a significant beneficial effect on pain at all weeks of the study [21••].

Duloxetine has also been studied recently in late-life dysthymic disorder. A 12-week open-label trial in patients \( \geq 60 \) years old (mean age 70.7) with dysthymic disorder found that duloxetine (mean dose 51 mg) correlated with a significant decline in HAM-D \( (p < .03) \) and in Treatment Emergent Symptoms Scale \( (p < .001) \). Doses above 60 mg were associated with higher improvements. The authors also found that common somatic symptoms improved with duloxetine treatment [22••].

**Bupropion** There are few randomized controlled trials assessing the effectiveness of bupropion in LLD; however, it is frequently used to treat geriatric depression since it has limited cardiovascular, gastrointestinal, and sexual adverse effects. A small study in 2001 showed efficacy [37]. However, a more recent 10-week placebo-controlled trial looking at the efficacy and tolerability of extended-release bupropion (150–300 mg once daily) in depressed patients \( \geq 65 \) years did not show efficacy for the primary endpoint (remission) at week 10 \( (p = 0.167) \) but did show significant change from baseline in MADRS total score \( (p < 0.001) \) with improvements in subscale measures of sadness \( (p = 0.018) \) and lassitude \( (p = 0.003) \). There were also significant differences in the bupropion group on secondary endpoints including motivation and energy, life satisfaction, and contentment [23].

**Vortioxetine** Vortioxetine is a 5HT3a, 5-HT1d, and 5-HT7 receptor antagonist, 5H-T1B partial agonist, 5-HT1A agonist, and inhibitor of the serotonin transport system approved by the FDA in 2013 for major depression. There is an 8-week double-blind trial in patients with a mean age of 70.6 who were randomized to vortioxetine 5 mg, duloxetine 60 mg, or placebo. Vortioxetine showed significantly \( (p = 0.0011) \) greater improvement on the primary efficacy endpoint compared with placebo at week 8. Duloxetine also showed superiority to placebo at week 8 [25].

**Agomelatine** Agomelatine is a melatonergic agonist approved in Europe in 2009 for the treatment of depression, but it is not available in the USA. A small study of 20 inpatients ages 60 years and over with mild to moderate depression showed response with agomelatine at doses 25–50 mg during a 42-day period [26].

Another 8-week multi-site placebo-controlled trial of agomelatine 25–50 mg in 222 geriatric patients ages \( \geq 65 \) years with moderate to severe major depression showed improved treatment response over placebo for agomelatine \( (p = 0.004) \), but remission did not reach statistical significance \( (p = 0.179) \) [27].

**Tricyclic Antidepressants** Tricyclic antidepressants (TCAs) are primarily reserved for use in the more treatment-resistant patients in the geriatric population. They are not considered first or second line and should be used with caution in patients with cardiac conduction abnormalities and arrhythmias and in Alzheimer’s patients, as they can cause increased confusion due to anticholinergic properties. A 2012 large meta-analysis of 51 geriatric antidepressant studies hypothesized that TCAs would be more effective in psychiatric inpatients and patients more severely depressed. However, the analysis showed that in 27 RCTs looking at efficacy among antidepressant groups, no significant difference could be demonstrated between TCAs and SSRIs [38].

**Quetiapine** Quetiapine monotherapy has evidence of efficacy in geriatric depression especially for patients with sleep disturbances. A 9-week double-blind, placebo-controlled study of 338 patients ages \( \geq 66 \) years with major depression randomized patients to quetiapine XR with flexible-dosing at 50–300 mg or placebo. The quetiapine XR group had significantly reduced MADRS \( (p < 0.001) \) and Pittsburgh Sleep Quality Index \( (p < 0.001) \) scores versus placebo [28••].
**Augmentation Strategies in LLD**

Treatment-resistant depression is a challenge to treat in the geriatric population. First-line pharmacologic treatments are unsuccessful in over 50% of adults over age 65 with major depressive disorder [39]. Clinically, antipsychotics are often used as stand-alone second-line agents if antidepressants fail; however, guidelines recommend that they be used only as adjunctive treatment [40]. In a recent survey of clinicians, 76.3% indicated the desire for a large randomized study on augmentation and switching strategies for treatment-resistant LLD to help guide treatment [41]. In addition, studies guiding characteristics of patients who would benefit from specific augmentation strategies providing a more personalized approach are needed [42].

**Aripiprazole** The most prominent augmentation study in the last decade is the 2015 IRL-GRey trial, a multi-site randomized, double-blind, placebo-controlled trial testing the efficacy and safety of aripiprazole augmentation for adults ≥60 years with treatment-resistant depression. Results indicated that aripiprazole augmentation was effective. The trial involved a pre-trial treatment with venlafaxine ER 150–300 mg daily. Of 468 participants, 181 (38.7%) did not achieve remission and were randomized to 12 weeks of double-blind augmentation with aripiprazole (started at 2 mg and titrated to a target dose of 10 mg, but which could be increased up to 15 mg if needed) or placebo. More participants in the aripiprazole group achieved remission than the placebo group (p = 0.03). The most common side effects of aripiprazole were akathisia, reported by 26% of the aripiprazole group compared to 12% of the placebo group and Parkinsonism reported in 17% of the aripiprazole group versus 2% on placebo [31-3].

**Stimulants** Past studies show that stimulants alone have little effectiveness over placebo for the treatment of geriatric depression. However, recent studies show promise for methylphenidate as an adjunctive medication. A randomized double-blind placebo-controlled 16-week trial examining the effectiveness of citalopram (20-60 mg) plus methylphenidate (5–40 mg), citalopram plus placebo, and methylphenidate plus placebo for treatment of geriatric depression in 143 older adults found significant improvement in depression severity and cognitive performance in all three groups. The citalopram plus methylphenidate group showed the highest improvement in depression severity and faster treatment response (p = 0.03). Treatment of depression was shown to be overall beneficial for cognition; however, cognitive improvement did not differ among the groups [32-3].

**Memantine** Given memantine’s activity as an NMDA receptor antagonist similar to ketamine and the usefulness of memantine in the geriatric population with Alzheimer’s disease, a recent trial examined the use of memantine as an adjunctive agent to citalopram in the treatment of LLD. The double-blind placebo-controlled trial included two groups: memantine 20 mg daily plus citalopram 20 mg and citalopram plus placebo and compared depression severity at 4 and 8 weeks. At 8 weeks, there was no significant difference in response of depression or quality of life between the memantine and placebo group (p = 0.216) [33-3]. Similarly, another 12-week study of older adults with depression and apathy after a disabling medical event found memantine monotherapy to be ineffective at treating depression or improving functional outcomes [43].

**B Vitamins** There have been recent trials investigating the use of supplements as adjunctive agents to treat geriatric depression. B vitamins have been of particular interest due to their effect on lowering high plasma homocysteine levels associated with depression. A 52-week double-blind placebo-controlled trial examined citalopram 20–40 mg plus vitamin B12 0.5 mg, folate acid 2 mg, and vitamin B6 25 mg in 153 adults aged ≥50. Study authors did not find significance between the citalopram plus supplement versus citalopram plus placebo groups in depression response at 12, 26, or 52 weeks. However, at the end of the study, there was a lower risk of relapse among those who had achieved remission of symptoms at week 12 in the citalopram plus supplement group [34]. The results of this study suggest that B vitamins may be a safe and inexpensive strategy to assist with depression treatment in middle-aged and older adults.

**Moderators of Treatment Response in LLD**

As noted above, there are many good treatment options available for LLD, but unfortunately, more than half of older adults do not adequately respond to the initial therapies [44]. In fact, a 2008 meta-analysis of placebo-controlled trials of second-generation antidepressants in LLD found that, though antidepressants were more effective than placebo, the advantage was modest (NNT = 11) [45].

In the past 5 years, there has been increased research focus on identifying potential moderators of depression response in order to better match patients with treatments. Research has asked which factors predict either a better or poorer outcome to antidepressant treatment in general. Early studies evaluating predictors of outcome have been mixed. Some studies were unable to identify any predictors [46, 47, 48] although this may have been due in part to the limited variables evaluated. In general, over the past two decades, a gathering consensus of studies have suggested that the following are poor predictors of treatment response in LLD: advanced age, greater medical burden, greater severity of depressive symptoms at baseline,
Executive dysfunction (EF) has been increasingly investigated as a potential moderator/predictor of treatment response. The idea is predicated on the assumption that cognitive deficits (often noted in LLD) are indirect indicators of neurobiological functioning. Structural and functional neuroimaging studies have documented common pathways for mood regulation and EF areas of the brain (primarily the frontostriatal areas). As noted above, EF dysfunction and abnormalities in neural systems related to EF have been associated as poor predictors of remission rates in LLD [50, 51]. Recent studies have built on these data by trying to identify specific EF processes that may both help identify differing neuroanatomical substrates/types of depression as well as the likelihood of response to treatment.

For example, a recent study by Morimoto et al. (2012) evaluated how subjects with LLD used strategies for word memorization and its relationship to treatment response [52]. They found that a subject’s ability to adjust their initial strategy of clustering words in a list for memorization predicted remission rates (even if the same number of words were recalled by both groups). These findings support the idea that measuring EF at baseline may be useful in predicting antidepressant response.

Identifying which EF is involved in LLD may help determine not only the neuroanatomy of LLD but also how antidepressants work. Alexopoulos and colleagues (2015) noted that EF may be divided into two distinct groups: ones concerned with cognitive control (CC) (such as response inhibition, planning, problem solving, and working memory) and ones concerned with reward-related decision making (RRDM) (such as valuation, reward learning, and decision-making) [53•]. These two functions appear to function on different neuroanatomical pathways though with some key overlaps.

Alexopoulos et al. observed that several tests demonstrating impairment in CC function (such as the semantic processing strategy noted in the Morimoto study, but especially the Stroop Color/Word Test, Tower of London, Dementia Rating Scale-Initiation/Perseveration Domain (DRS-IP)) have been associated with poor outcomes in LLD treated with antidepressants. They further noted that functional neuroanatomical changes (such as white matter hyperintensities, microstructural white matter changes, low volume of the anterior cingulate, hypoactivation/reduced resting functional connectivity of the CC network) are associated with CC dysfunction.

On the other hand, while dysfunction in the RRDM tasks has also been associated with LLD, the neuroanatomical areas involved appear to be primarily related to the ventromedial prefrontal cortex. Dombrovski et al. (2012) have suggested that impairment in the RRDM is associated with critical clinical symptoms (including functional impairment and suicidality), but it is unknown if abnormal tasks related to the RRDM functions (such as the Iowa Gambling Test (IGT)) are linked to LLD antidepressant treatment outcomes [54].

Alexopoulos et al. conducted a study of 53 subjects with LLD treated with escitalopram 20 mg for 12 weeks [53•]. Hierarchical cluster analysis of depressed subjects identified three groups with differing cognitive functioning: an impaired CC cluster (abnormal Stroop, Tower, DRS-IP), an impaired RRDM cluster (RR) (abnormal IGT), and an unimpaired EF cluster (UEF). As expected, the UEF cluster patients with depression had significantly greater improvement of symptoms compared with the impaired CC cluster. However, the impaired RR cluster depressed patients also had similar improvement in treatment response to the EUF cluster, and much
better treatment response than the CC cluster. In their discussion, the authors postulated that CC dysfunction may be a distinct syndrome of LLD. Further, they noted that using simple-to-administer cognitive tests may be helpful in identifying depressed older patients at risk for poor outcomes to SSRIs.

This suggestion is also supported by an analysis of data from the IRL-GRey study (noted earlier in the article) evaluating aripiprazole augmentation treatment in LLD patients who failed to remit with venlafaxine monotherapy [43]. The authors noted that aripiprazole augmentation was associated with an NNT of 6.6. However, when they did a subset analysis of outcomes in those patients who did not demonstrate abnormalities before treatment on the Trail Making Test (a measure of set-shift impairment and one of the CC functions noted above), aripiprazole augmentation remission was associated with an NNT of 4.0 [55•]. Of note, the authors hypothesized that the improvement in depression predicted by the set-shifting task may be related to aripiprazoles’ action on the D1 and D2 receptors in the prefrontal cortex. Another study evaluating characteristics of subjects that did not remit with aripiprazole augmentation discovered that participants with higher pain, higher work/activity impairment, and libido symptoms experienced a smaller aripiprazole treatment effect and appeared to benefit more from continuation venlafaxine plus placebo [56]. These studies on the IR-Gray trial support the idea of multiple subtypes of depressive disorders and the possibility that antidepressant treatment can be more tailored for improved efficacy providing a personalized approach.

Unfortunately, the use of neuropsychological testing in LLD patients may not be available or feasible in many clinical settings. Interestingly, a study by Manning and colleagues (2015) evaluated treatment response of 100 subjects with LLD to escitalopram [57]. They found that even subjective complaints of EF by patients (as noted on the Frontal Systems Behavior Scale (FrSBe)) predicted a slower speed of response to the antidepressant and could help serve as a marker for EF treatment response moderators.

Obviously, there is still much work to be done in this area before we can begin to implement moderators in antidepressant selection. First, we are still in the process of identifying what moderators should be identified. For example, not all studies have noted the association between cognition and depression improvement. Victoria et al. (2017) reported a secondary analysis of the STOP-PD study, which evaluated the treatment response of LLD patients with psychosis to a combination of olanzapine and sertraline or placebo [58]. They noted that, as seen in the studies above, improvement in depressive symptoms was significantly associated with improvement in global cognitive function, but this finding was present only in the “Young Old,” not the “Older” participants. This suggests that we are still learning how to associate moderators, neuroanatomical models, and antidepressant response.

The second is that the moderators we identify must be “actionable.” Joel and colleagues (2014) conducted a study to identify how to use clinically meaningful parameters to predict response/remission [59•]. Their group (Andreescu et al. [60]) had previously reported on a LLD clinical trial with paroxetine in which three factors (early symptom improvement (change in HAM-D-17 total score from baseline to week 4), lower baseline anxiety, and an older age of onset) could be used to predict antidepressant response at week 12. They used a similar analysis to evaluate predictors of treatment remission in a large open-label study of LLD with venlafaxine.

Joel et al. found that subjects whose MADRS scores decreased by > 27% in the first 2 weeks and had only moderately severe initial depressive symptoms (MADRS score of < 27) had the best chance for remission (89%). In addition to these “good” predictive factors, they also identified several factors that were “poor” predictors of treatment response, including higher severity of depressive symptoms at baseline, smaller symptom improvement during the first 2 weeks of treatment, male sex, duration of current episode of > 2 years, and multiple adequate past depression treatments.

Based on these data, they recommended that if a patient has poor treatment response by week 2 (MADRS not decreased by at least 27%) and a profile suggesting higher likelihood of treatment resistance (poor predictors of treatment response), then the clinician should consider other treatment strategies (such as switching or augmentation). However, if the LLD patient has a profile indicating higher chance of remission over time, then “staying the course” would be an appropriate plan.

Conclusion

As noted in this brief update, there are still many active research questions being investigated in order to better understand treatment and treatment response in LLD. Traditionally, treatment of the elderly has been a significant unmet need, often due to the complexities with which many LLD patients present. The geriatric population is vulnerable with medical co-morbidities and unique social situations that can lead to under-treatment and increased costs. However, there is increasing awareness that the unique factors in LLD may also provide significant keys toward understanding depression and treatment response. The awareness of the need to include elderly patients in clinical trials and treatment studies is increasing. Still, more research is needed, especially in evaluating how the geriatric population responds to common accepted treatment guidelines and how best to augment treatment-resistant cases. In addition, more studies are needed on new therapies that show promise in the general adult population.
such as vilazodone [24], levomilnacipran [61], brexpiprazole [62], and ketamine [63].

Compliance with Ethical Standards

Conflict of Interest  Kim G. Johnson declares no conflict of interest. John L. Beyer has received grants from Allergan, Forest, Janssen, Takeda, and Sunovion.

Human and Animal Rights and Informed Consent  This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
• Of major importance


12. • Bali V, Chatterjee S, Johnson ML, Chen H, Carnahan RM, Aparasu RR. Risk of mortality in elderly nursing home patients with depression using paroxetine. Pharmacotherapy. 2017;37(3):287–96. This study shows there is no increased risk of mortality with use of paroxetine in nursing home patients.

13. • Bali V, Chatterjee S, Carnahan RM, Chen H, Johnson ML, Aparasu RR. Risk of dementia among elderly nursing home patients using paroxetine and other selective serotonin reuptake inhibitors. Psychiatr Serv. 2015;66(12):1333–40. This study shows there is no increased risk of dementia with use of paroxetine in nursing home patients.

14. • Bali V, Chatterjee S, Johnson ML, Chen H, Carnahan RM, Aparasu RR. Risk of cognitive decline associated with paroxetine use in elderly nursing home patients with depression. Am J Alzheimers Dis Other Dement. 2016;31(8):678–86. This study shows there is no increased risk of cognitive decline with use of paroxetine in nursing home patients.


21. • Robinson M, Oakes TM, Raskin J, Liu P, Shoemaker S, Nelson JC. Acute and long-term treatment of late-life major depressive disorder: duloxetine versus placebo. Am J Geriatr Psychiatry. 2014;22(1):34–45. This study shows no increased efficacy for treatment of depression of duloxetine over placebo for the primary endpoint at 12 weeks but it did separate from placebo at weeks 4, 8, 16 and 20 weeks. There was also a significant beneficial effect on pain at all weeks of the study.


37. Steffens DC, Doraiswamy PM, McQuoid DR. Bupropion SR in the naturalistic treatment of elderly patients with major depression. Int J Geriatr Psychiatry. 2001;16(9):862


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