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GERIATRIC DISORDERS (JA CHEONG, SECTION EDITOR)

Management of Late-Life Depression in the Context of Cognitive Impairment: a Review of the Recent Literature

Kathleen S. Bingham [1,2] · Alastair J. Flint [1,2] · Benoit H. Mulsant [1,3]

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Abstract

Purpose of Review Evidence regarding the treatment of late-life depression is not necessarily generalizable to persons with a neurocognitive disorder and comorbid depression. Thus, this article reviews recent evidence that pertains to the treatment of depression in older adults with neurocognitive disorders, and synthesizes and critically analyzes this literature to identify methodological issues and gaps for the purpose of future research.

Recent Findings Controlled trials and meta-analyses examining depression treatment in neurocognitive disorders, published between 2015 and 2019 ($N = 16$ reports), can be divided into those addressing pharmacotherapy, psychological and behavioral therapy, and somatic therapy. The evidence generally does not support benefit of antidepressant medication over placebo in treating depressive disorders in dementia. No pharmacological studies since 2015 have examined antidepressant medication in participants with mild cognitive impairment (MCI). Problem adaptation therapy demonstrates efficacy for depression in MCI and mild dementia. Other psychological and behavioral interventions for depressive symptoms in dementia demonstrate mixed findings. The only somatic treatment trials published since 2015 have assessed bright light therapy, with positive findings but methodological limitations.

Summary Psychological, behavioral, and somatic treatments represent promising treatment options for depression in neurocognitive disorders, but further studies are needed, particularly in participants with depressive disorders rather than subclinical depressive symptoms. Little is known about the treatment of depression in patients with MCI, and rigorous identification of MCI in late-life depression treatment trials will help to advance knowledge in this area. Addressing methodological issues, particularly the diagnosis and measurement of clinically significant depression in dementia, will help to move the field forward.

Keywords Neurocognitive disorders · Dementia · Mild cognitive impairment · Depression · Pharmacotherapy · Psychological therapy · Somatic therapy

Introduction

A neurocognitive disorder diagnosis requires both subjective and objective evidence of cognitive impairment, with the absence or presence of functional impairment differentiating between mild and major neurocognitive disorder (i.e., mild cognitive impairment [MCI] and dementia) [1]. Most patients with late-life depression have some cognitive impairment [2, 3] and many randomized controlled clinical trials have addressed the treatment of late-life depression [4]. However, the evidence in patients with a primary presentation of depression and secondary evidence of mild impairment on neuropsychological testing is not necessarily generalizable to patients with a neurocognitive disorder and depressive symptoms or even a comorbid depressive disorder. A synthesis and critical evaluation of the recent literature specific to treatment of depression with comorbid neurocognitive disorders would assist in clarifying these issues. Therefore, the aims of this paper are to (i) identify and characterize the existing evidence addressing management of depression in the setting of

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✉ Kathleen S. Bingham
kathleen.bingham@uhn.ca

[1] University of Toronto, Department of Psychiatry, Toronto, ON, Canada

[2] University Health Network, Toronto, ON, Canada

[3] Centre for Addiction and Mental Health, Toronto, ON, Canada

neurocognitive disorders and (ii) critically analyze the recent literature to identify methodological issues and gaps for the purposes of future research endeavors.

Methods

Design

This paper was designed as a narrative review with a qualitative synthesis. The synthesis focuses on recent controlled clinical trials or meta-analyses in order to discuss evidence that is most applicable to clinical practice and future research, though we discuss some older studies and observational data as well in order to place the findings in context.

Inclusion Criteria

We included controlled treatment studies or meta-analyses published since 2015 that investigate the pharmacological, psychological, behavioral, or somatic treatment of depressive disorders (defined based on Diagnostic and Statistical Manual of Mental Disorders [DSM] diagnosis or measured via validated rating scales) as a primary or secondary aim in patients with major or mild neurocognitive disorders (dementia or MCI). We included studies if they defined neurocognitive disorders using generally accepted criteria (e.g., DSM, NINCDS-ADRDA), or, in the case of MCI, if they included evidence of subjective and objective cognitive impairment.

Search Strategy

Two databases (Medline [OVID] and Cochrane) and the ClinicalTrials.gov website were searched from 2015 to present. Medline terms were as follows: (*depressive disorder/ or depressive disorder, major/ [MeSH]) AND (*Alzheimer Disease/ [MeSH] OR neurocognitive disorders/ [MESH] or dementia/ [MESH] OR dementia.mp OR major neurocognitive disorder.mp OR mild cognitive impairment.mp) AND (therapeutics/ or drug therapy/ or electric stimulation therapy/ or phototherapy/ or rehabilitation/ [MESH]) OR exp psychotherapy/ [MeSH] OR psychotherapy.mp OR treatment.mp OR management.mp OR electroconvulsive therapy.mp).

Reference lists from landmark studies and reviews were hand-searched to identify potential additional relevant articles.

Data Extraction and Synthesis

Articles were selected for full text review if the title and abstract indicated a focus on treatment of depression in patients with neurocognitive disorders. Articles were then selected for this manuscript based on the inclusion criteria listed above.

Studies were categorized according to treatment type: pharmacological, psychological/behavioral, or somatic. For these purposes, psychological treatments were defined as being structured interventions based on psychological theory (e.g., cognitive behavioral therapy, interpersonal therapy) and behavioral treatments were those that involve concrete activities such as exercise or music therapy that do not require an underlying psychological framework [5••]. In this review, we elected to combine psychological and behavioral treatments in one category since they often overlap, particularly when modified for persons with neurocognitive disorders. Somatic treatments were defined as non-pharmacological interventions that were based on a biological framework (e.g., neurostimulation, light therapy).

Results

Summary of Study Designs and Participants

The results of the literature search are summarized in Fig. 1. In total, 16 articles regarding treatment of depression in patients with neurocognitive disorders were identified, including both primary studies ($N = 8$) and meta-analyses ($N = 8$). Five studies were pharmacotherapy trials, nine involved psychological or behavioral interventions, and two addressed somatic treatments (see Table 1).

Table 1 summarizes the 16 articles identified by the search. Eleven studies focused on participants with a diagnosis of dementia, two included participants with either dementia or MCI/objective neuropsychological impairment, two included MCI only, and one included non-demented participants with objective cognitive impairment who were not formally classified as MCI. Study findings are discussed in more detail below.

Summary of Study Findings

Pharmacotherapy

Reflecting several decades of research in this area, two meta-analyses have been conducted in the past 4 years with a primary aim of examining the efficacy of antidepressants in treating depression in dementia [7••, 13•]. The most recent, a Cochrane review by Dudas et al., included participants with any dementia diagnosis made by accepted criteria and a comorbid depressive disorder [7••]. The average age for all participants was 75 years, and the majority were outpatients with mild to moderate dementia. The authors specifically excluded participants with depressive symptoms that were subthreshold for a depressive disorder. This meta-analysis found high-quality evidence that there is little to no difference between antidepressant and placebo groups in depressive symptoms over 6 to 13 weeks (standardized mean difference [SMD] −

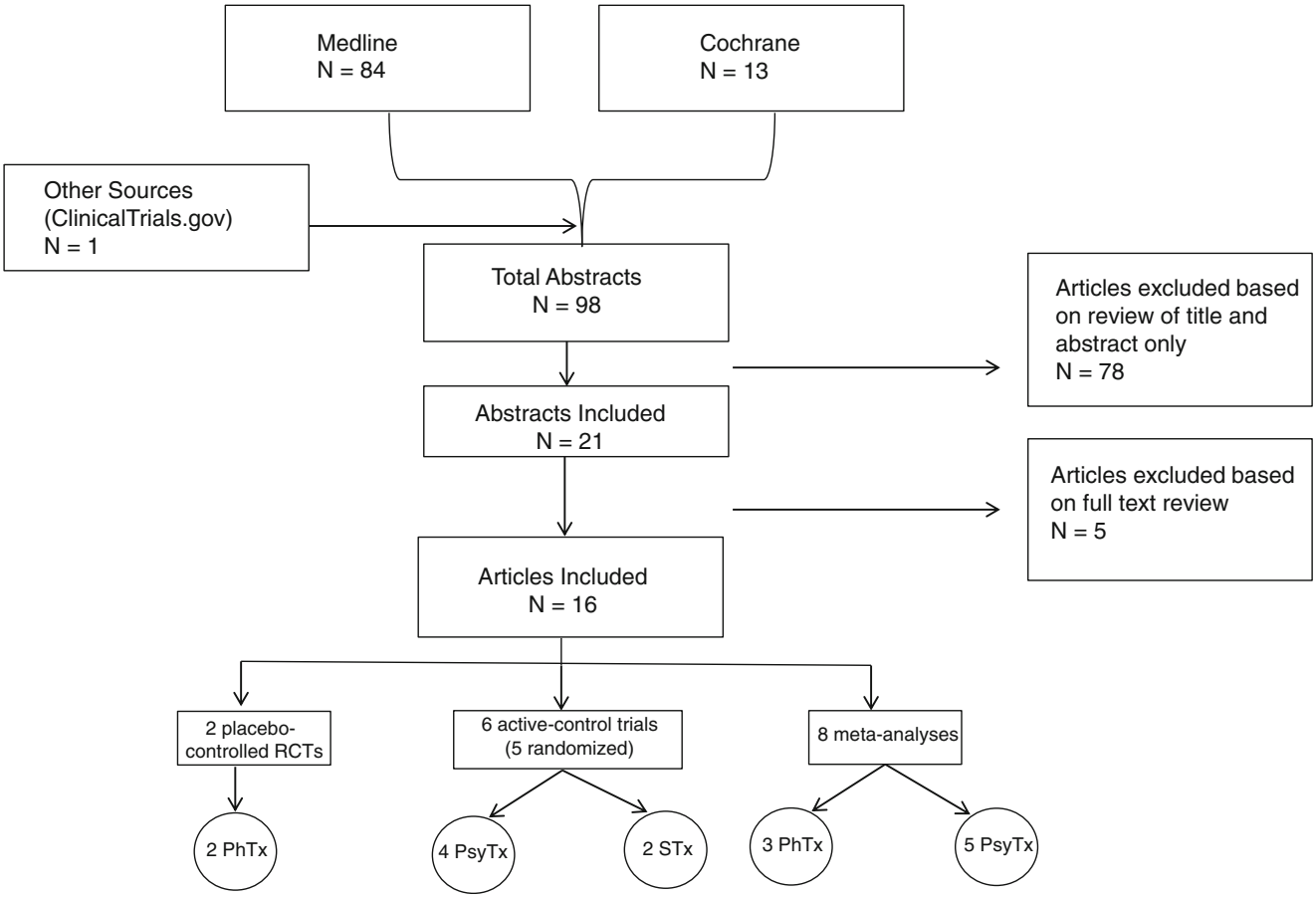

Fig. 1 Search flowchart and study design categorization results. Abbreviations: PhTx = pharmacotherapy; PsyTx = psychological and behavioral treatments; STx = somatic treatment

0.10, 95% confidence interval [CI] − 0.26 to 0.06; 614 participants; 8 studies) with low heterogeneity ($I^2 = 7\%$). However, moderate quality evidence suggested that the remission rate was likely higher in patients treated with antidepressants compared to placebo (antidepressant: 40%, placebo: 21.7%; OR 2.57, 95% CI 1.44 to 4.59; 4 studies). On the other hand, participants taking antidepressants were more likely to drop out of the study or to experience adverse effects than those taking placebo. On the whole, the authors suggested that, while future research may focus on depression remission rates specifically in patients with dementia treated with antidepressants, high-quality evidence available at this point suggests that antidepressants are not associated with improvement in depression symptom scores over and above placebo.

The second meta-analysis, by Orgeta et al., focused specifically on participants with Alzheimer's dementia [13•]. They required depression diagnostic criteria for inclusion similar to the Dudas et al. criteria. In fact, five of the six randomized controlled trials (RCT) identified by Orgeta et al. were included in the Dudas et al. meta-analysis. In both meta-analyses, antidepressants used in primary studies were sertraline, fluoxetine, mirtazapine, imipramine, and clomipramine. Additional medications in primary studies in the Dudas et al. meta-analysis were venlafaxine, escitalopram, maprotiline, and moclobemide. Despite some methodological differences, these two meta-analyses yielded similar conclusions: Orgeta et al. also found that reduction in depression on symptom scores over 6 to 13 weeks did not significantly differ between antidepressants and placebo (SMD of − 0.13; 95% CI − 0.49 to 0.24; five studies, 311 participants). Like Dudas et al., they noted that there was a larger effect when looking at short-term depression outcomes dichotomously (OR 1.95, 95% CI 0.97 to 3.92). However, Orgeta et al. did not rate any of their evidence above moderate quality (partially due to the small number of trials included) and noted substantial heterogeneity ($I^2 = 50\%$ for depression symptom scores; $I^2 = 61\%$ for treatment response). Neither meta-analysis was able to investigate the impact of depression type nor severity on treatment outcomes.

Only one primary study investigating the efficacy of a conventional antidepressant in treating depression in dementia has been reported since 2015. In a double-blind, placebo-controlled RCT, An et al. examined the efficacy of escitalopram in treating depression (defined using the NIMH criteria for depression in Alzheimer's disease [21•]) in 84 participants [12]. In this study, there was no significant difference in the reduction of depression scores between escitalopram

Table 1 Description of trials and treatment meta-analysis regarding treatment of late-life depression in neurocognitive disorders published from 2015 to time of review

Study (author, year)	Design/intervention	Treatment type	Participants	Depression definition	Findings
Gates et al. 2019 [6]	Systematic review and meta-analysis of RCTs evaluating the effect of computerized cognitive training on maintaining or improving cognition or preventing dementia in persons with MCI	Psych.	Participants with a diagnosis of MCI, or otherwise at high risk of cognitive decline	Various depression rating scales	4 RCTs ($N = 179$ participants) evaluated depression as a secondary outcome. No difference between cognitive training and controls in depressive symptoms. Evidence rated as very low quality
Dudas et al. 2018 [7••]	Systematic review and meta-analysis of the efficacy and safety of antidepressant medication for patients with clinically-defined comorbid dementia and depression	Pharm.	Subjects with comorbid diagnoses of dementia and depressive disorders made using "accepted criteria" participating in DB, PBO-controlled RCTs	Various, primarily DSM criteria for depressive disorders	10 RCTs ($N = 1592$ subjects) met inclusion criteria. No significant difference in depression scores between antidepressant and PBO groups after 6–13 weeks (high quality evidence). Likely no difference between antidepressant and PBO after 6–9 months (moderate quality evidence). Remission rates may have been higher in antidepressant vs. PBO groups after 12 weeks (moderate quality evidence). Antidepressants seemed to be associated with higher rates of study drop-out and adverse effects than PBO
Erdal et al. 2018 [8]	13-week DB PBO-controlled RCT investigating a stepwise protocol for treating pain using acetaminophen or buprenorphine	Pharm.	162 LTC residents age ≥ 60 with DSM-defined dementia	Clinically significant depression (CSDD ≥ 8 for 4 weeks' duration)	The estimated treatment effect was 2.64 (0.55–4.72, $p = 0.013$), indicating that buprenorphine or acetaminophen had no effect on depressive symptoms while PBO appeared to improve symptoms. Buprenorphine was associated with psychiatric adverse effects, possibly explaining these findings
Konis et al. 2018 [9]	Non-randomized controlled clustered pilot study examining the effect of sufficient indoor daylight exposure on depressive and other neuropsychiatric symptoms	Somatic	77 LTC residents with AD and related dementias	CSDD	Depressive symptoms in the daylight intervention group improved significantly compared to the control group
van der Steen et al. 2018 [10]	Systematic review and meta-analysis of RCTs of the effects of music-based therapeutic interventions for persons with dementia	Psych.	Participants with dementia diagnoses made using accepted criteria	Various depression rating scales	11 RCTs ($N = 503$ participants) included that investigated depression as a secondary outcome. Music-based interventions probably reduced depressive symptoms at the end of treatment (moderate quality evidence). No evidence for long-term reduction in symptoms (low quality evidence)

Table 1 (continued)

Study (author, year)	Design/intervention	Treatment type	Participants	Depression definition	Findings
Woods et al. 2018 [11]	Systematic review and meta-analysis of RCTs of the effects of reminiscence therapy on persons with dementia and their caregivers	Psych.	Participants with dementia diagnoses made using accepted criteria	Various depression rating scales	10 RCTs ($N = 973$ participants) evaluated depression as an outcome. No difference in depression symptoms between reminiscence therapy and controls generally (high quality evidence). Possible small difference in depression symptoms based on four studies that used individual reminiscence therapy (moderate quality evidence)
An et al. 2017 [12]	12-week DB PBO-controlled RCT investigating efficacy and tolerability of escitalopram	Pharm.	84 persons (42 per treatment group) > 50 with AD	NIMH provisional diagnostic criteria	No difference between escitalopram and placebo groups in depressive symptoms or cognition at study endpoint
Orgeta et al. 2017 [13•]	Systematic review and meta-analysis of the efficacy of antidepressants for depression in AD	Pharm.	Subjects with AD and clinically significant depressive symptoms	DSM criteria, "disease-specific criteria" (i.e., NIMH criteria), or a validated scale for depression in older people	Six RCTs ($N = 297$ patients treated with antidepressants and 223 with PBO) were used in the primary analysis. There was no statistically significant difference in efficacy between antidepressant drugs and placebo in response to treatment or change in depression scores. Quality of evidence deemed to be moderate (methodological limitations, small number of trials)
Burckhardt et al. 2016 [14]	Systematic review and meta-analysis of RCTs evaluating efficacy and safety of omega-3 polyunsaturated fatty acid (PUFA) for dementia treatment	Pharm.	Participants with various types of dementia diagnoses made using accepted criteria	MADRS	One RCT [22] ($N = 174$ participants with AD) evaluated difference in depression scores between treatment and placebo groups; found no difference between PUFAs and placebo
Gustavson et al., 2016 [15]	Secondary analysis of single-blind RCT comparing the efficacy of Problem Solving Therapy (PST) vs. Supportive Therapy in reducing suicidal ideation	Psych.	221 non-demented persons age ≥ 60 with MDD and cognitive impairment (based on neuropsychological testing)	DSM-IV defined MDD	PST was associated with significantly greater reduction in suicidality than Supportive Therapy
Larouche et al. 2016 (abstract) [16]	8-week single-blind RCT examining the efficacy of a mindfulness-based intervention (MBI) in memory, depression and quality of life	Psych.	22 older adults with MCI	GDS	MBI intervention associated with non-statistically significant larger decrease in depressive symptoms from baseline to endpoint vs. active control group
Olsen et al. 2016 [17]	Cluster RCT with 12-week trial evaluating animal-assisted activities vs. TAU	Psych.	10 LTC dementia units with 51 participants who had a dementia diagnosis	Norwegian version of the CSDD	No significant difference in change in depression scores between animal therapy and control group from baseline to study

Table 1 (continued)

Study (author, year)	Design/intervention	Treatment type	Participants	Depression definition	Findings
					endpoint, but statistically greater decrease in scores from baseline to 3-month follow up in animal therapy group
Onega et al. 2016 [18]	DB RCT evaluating the efficacy of 8-weeks of bright light therapy in treating depressive symptoms	Somatic	71 LTC residents with dementia	Evaluated using three observer-rated measures: Depressive Symptom Assessment in Older Adults (DSAOA), Dementia Mood Assessment Scale-17 Item (DMAS-17), CSDD	Bright light exposure was associated with significant improvement in depressive symptoms on all measures compared to low intensity light control
Forbes et al. 2015 [19]	Systematic review and meta-analysis evaluating evidence for exercise-based programs on a number of outcomes in dementia	Psych.	Persons diagnosed with dementia using selected criteria	Various depression rating scales	Evidence from five RCTs ($N = 341$ participants) suggested that there is no clear effect of exercise on depressive symptoms. Evidence rated as moderate quality with low heterogeneity
Kiosses et al. 2015 [20•]	RCT investigating the efficacy of 12-weeks of Problem Adaptation Therapy (PATH) versus supportive therapy	Psych.	74 community dwelling persons age ≥ 65 with DSM-defined dementia or neuropsychological impairment measured with validated cognitive batteries, plus at least one IADL impairment	DSM-IV defined MDD with a MADRS score of 17 or higher	PATH was significantly more efficacious than supportive therapy in reducing depression and disability and was associated with significantly higher rates of MDD remission
Orgeta et al. 2015 [5••]	Systematic review and meta-analysis of RCTs evaluating effectiveness of psychological treatments for depression or anxiety in persons with dementia or MCI	Psych.	Older adults diagnosed with dementia or MCI using accepted diagnostic criteria	Various depression rating scales	Evidence from six RCTs ($N = 439$ participants) suggested that psychological treatments are significantly more effective than control conditions in reducing depression in dementia. Evidence of moderate quality with uncertain risk of bias

AD Alzheimer's dementia, *CSDD* Cornell Scale for Depression in Dementia, *DB* double blind, *DSM* Diagnostic and Statistical Manual of Mental Disorders, *IADL* instrumental activity of daily living, *GDS* Geriatric Depression Scale, *LTC* long-term care, *MADRS* Montgomery-Asberg Depression Rating Scale, *PBO* placebo, *Pharm.* Pharmacotherapy, *Psych.* psychological/behavioral, *RCT* randomized controlled trial *TAU* treatment as usual

and placebo over 12 weeks. An exploratory analysis suggested that participants with "definite major depression" (operationalized as a Cornell Depression in Dementia Scale (CSDD) score > 17) may derive greater benefit from antidepressant medication.

Two other recent studies, one primary RCT and one meta-analysis investigated novel antidepressant medications or medication strategies. Erdal et al. investigated the efficacy of a pain management algorithm in reducing depressive symptoms in long-term care residents with comorbid dementia and depression [8]. They found that patients in the active treatment group actually experienced worsening depressive symptoms, which they speculated may be due to adverse effects of buprenorphine. Burckhardt et al. performed a Cochrane meta-analysis investigating various effects of polyunsaturated omega-3 fatty acids (PUFAs) in participants with Alzheimer's disease [14]. They did not find any difference in depression scores between PUFAs and placebo in the one RCT they identified [22], which they rated as high quality. The authors noted, however, that patients in this study were not selected for the presence of depression, and depression symptom scores were low at baseline.

Psychological and Behavioral Interventions

Nine publications in the past 4 years have examined psychological or behavioral treatments in neurocognitive disorders. Three reports [15, 20•, 23] described the results of two RCTs of problem-solving therapy (PST), a psychological intervention that engages participants in goal setting and behavioral strategies to address challenges, with evidence for use in older adults with depression and executive dysfunction [24]. Most recently, a secondary analysis reported that PST was significantly more efficacious than supportive therapy in reducing suicidality in a large group of older adults with MDD and significant executive dysfunction [15]. The other RCT, by Kiosses et al., demonstrated that a version of PST (problem adaptation therapy; PATH) delivered to older adults with MCI or mild dementia and comorbid MDD in their homes, was significantly more efficacious than supportive therapy in reducing depression [20•]. In addition, a secondary analysis of data from this study found that PATH was efficacious in the subgroup of participants with dementia [23].

Two smaller studies examined other psychological and behavioral treatment strategies [16, 17]. The first, reported as an abstract, found that a mindfulness-based intervention was more efficacious in reducing depressive symptoms in a small group of older adults with MCI compared to a control group [16]. The second study involved a cluster-RCT in the long-term care setting and evaluated the effectiveness of animal-assisted activities in reducing depressive symptoms in residents with dementia compared to a treatment as usual control group [17]. There was no significant difference in change in depression scores between the active and control groups between baseline and study endpoint, though the authors noted that participants in the active group had a significantly greater improvement in depressive symptoms between baseline and a 3-month follow-up. Neither study selected participants based on the presence of depression.

Several meta-analyses examining psychological interventions for neurocognitive disorders have been published in the past 4 years. The most relevant one by Orgeta et al. reported on the results of six RCTs examining psychological interventions targeting depression and anxiety in MCI and dementia [5••]. The authors found evidence that psychological interventions improved depressive symptoms significantly in persons with dementia compared to treatment as usual with low heterogeneity (SMD = − 0.22; 95% CI − 0.41 to − 0.03; I^2 = 21%). Psychotherapies used in the six RCTs were cognitive-behavioral therapy, supportive therapy, and multi-modal interventions. Evidence was classified as being of moderate quality. Orgeta et al. did not identify any studies involving patients with MCI. Further, they were only able to evaluate evidence reporting the efficacy of treatments compared to usual care, not active or attentional controls. Finally, studies were not selected to include persons with comorbid depressive disorders; depression was defined using symptom scores.

Four additional Cochrane reviews in the last 4 years have examined a variety of other psychological and behavioral treatment strategies for neuropsychiatric symptoms in neurocognitive disorders more generally, with depression included as a co-primary or secondary outcome. Treatments evaluated included exercise [19], cognitive training in MCI [6], music therapy in dementia [10], and reminiscence therapy in dementia [11]. Only music therapy showed some evidence (of moderate quality) in reducing depressive symptoms. However, none of these four meta-analyses were intended to examine treatment of clinically defined depression.

Somatic Treatments

The only two somatic treatment studies that have been reported in the last 4 years involved light therapy. Konis et al. reported the results of a non-randomized intervention where long-term care residents with dementia were exposed to periods of daylight and socialization for a specified time each day, compared to those who were exposed to a similar behavioral intervention without daylight in other facilities [9]. The authors reported significant improvement in depressive symptoms in the group exposed to daylight over the 12-week period. However, the raters were not blinded. Given the absence of randomization or blinding, these results should be considered preliminary. An earlier study by Onega et al. provided more robust evidence [18]. This study was an 8-week double-blind RCT in long-term care residents unselected for a diagnosis of depression. It compared the change in depressive

symptoms in those randomized to low light control or bright light therapy, delivered as 10,000 lx of light for 30 min twice a day, five times a week. Raters were blinded to treatment condition. There was a statistically significant interaction between bright light condition and time, with participants in the bright light condition experiencing significant improvement in depressive symptoms over time and participants in the low light condition experiencing no improvement.

Discussion

Antidepressant Pharmacotherapy in Neurocognitive Disorders

Overall, the preponderance of evidence suggests that conventional antidepressant medications have limited benefit over and above placebo in patients with Alzheimer's and related dementia, with several caveats. First, there may be some benefit of antidepressants over placebo when defining treatment outcome as response or remission (as opposed to a reduction in depressive symptoms). Second, evidence regarding the differential impact of depression severity on treatment response is very limited. Although patients with dementia and severe comorbid MDD would theoretically be more likely to benefit from antidepressant treatment than those with subclinical depression, it is also possible that antidepressant medications are less effective in the setting of dementia neuropathology. Further RCTs examining the efficacy of antidepressants in participants with dementia unselected for depression severity are unlikely to add value to the literature (and are arguably no longer ethical given the established lack of benefits and the potential adverse effects). However, future trials could assess the efficacy of antidepressants in patients with MCI or dementia and severe depression. There is also insufficient evidence to determine whether antidepressant treatment has differential effects across the spectrum of dementia severity. For instance, antidepressants may have increased efficacy relative to placebo in mild dementia, when there is theoretically less neurodegeneration and when a depression diagnosis might be clearer. Further, the vast majority of studies have been conducted in persons with Alzheimer's or other unspecified dementia. Very little evidence exists regarding the efficacy and tolerability of antidepressant medications in other types of dementia, such as frontotemporal dementia, or dementia with Lewy bodies. Finally, in several of the primary antidepressant trials cited in the Dudas et al. and Orgeta et al meta-analyses, both antidepressant and placebo groups improved over time, and baseline depression scores were in the mild to moderate range [25–27]. These findings suggest that non-specific factors, such as increased staff attention and behavioral activation, may be playing an important role in participants' improvement in both active and placebo groups. Mulsant et al. noted the benefit of increased study visits in participants receiving placebo treatment in RCTs of late-life depression generally [4]. Overall, this evidence highlights the potential importance of non-pharmacological factors in treatment of depression in dementia. Psychological and behavioral treatments are discussed in more detail below.

None of the studies identified in the past 4 years examined antidepressant pharmacotherapy explicitly in patients with MCI. The largest literature addressing the relationship between late-life depression treatment and cognitive impairment comes from studies of patients with vascular depression; defined as late-life depression with associated cognitive impairment (primarily executive dysfunction) in the context of cerebrovascular risk factors or white matter disease [28]. These patients have been shown to respond more poorly to antidepressants [29]. Although pharmacotherapy studies involving patients with vascular depression have not typically diagnosed MCI using clinical criteria, many of these patients would likely meet DSM-5 criteria for MCI. In fact, treatment studies focused on late-life depression certainly include participants with comorbid MCI given the high rates of cognitive impairment in this disorder [30, 31]. Researchers investigating late-life depression treatment should consider evaluating patients for MCI. Also, MCI is a heterogeneous construct with multiple etiologies that likely have differential influences on depression treatment outcomes. Studies of antidepressants in patients with late-life depression and MCI will need to identify the etiology of MCI, in order to generate clearer and more usable data.

Psychological and Behavioral Treatments for Depression in Neurocognitive Disorders

Given the lack of benefit of antidepressants compared to placebo in dementia, identifying alternative treatments is an unmet need. PATH/PST represents a promising intervention for patients with neurocognitive disorders and major depression, as demonstrated by Kiosses et al. [20•, 23] and Gustavson et al. [15]. This treatment modality deserves further study and replication, as well as investigation in patients with well-defined MCI. A multi-site RCT examining the efficacy of PATH modified for participants with MCI to include both emotional regulation and cognitive strategies is currently underway (https://clinicaltrials.gov/ct2/show/NCT03043573).

Other studies in this area did not select participants with depressive disorders, examining instead depressive symptoms. However, many participants in the primary studies included in the meta-analyses by Orgeta et al. had low depression symptom scores. Thus, one cannot generalize their results to patients with comorbid neurocognitive and depressive disorders. Nonetheless, subclinical depressive symptoms represent a clinically important issue in patients with neurocognitive disorders that deserves to be studied. Also, participants in these studies were mostly community-

dwelling, with mild dementia. This circumstance is not surprising given the cognitive skills required to participate in structured therapies. However, while the evidence cited by Orgeta et al. is promising, the overall standardized mean difference, while statistically significant, was small (− 0.22 [95% CI − 0.41 to − 0.03]) and largely driven by one positive pilot study in which depression change was a secondary outcome measure [32]. Thus, behavioral interventions for depressive symptoms in dementia would benefit from further study. Future studies should select participants with clinically significant depressive disorders, in whom most of these interventions have not been studied.

Somatic Treatments for Depression in Neurocognitive Disorders

The study examining daylight exposure by Konis et al. [9] is preliminary and cannot be used to make conclusions. However, the study by Onega et al. [18] examining bright light therapy in long-term care residents with dementia, had a reasonably large sample size, an appropriate control condition, and participants and raters were blinded to treatment conditions. This study's findings support the potential of bright light therapy in reducing depressive symptoms in patients with dementia. Although participants were not selected for depression, they had fairly high CSDD scores, with pre-intervention mean scores in the active treatment group consistent with probable MDD (mean [SD] = 13 [4]). However, the CSDD baseline mean score in the control group was substantially lower (9.6 [4.8]). Therefore, while bright light therapy is a potentially promising intervention, it requires further study, again ideally stratifying subjects based on the severity of depressive symptoms or the presence of a diagnosed depressive disorder.

We did not identify any RCTs published in the last 4 years that examined neurostimulation, i.e., electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), or transcranial direct current stimulation (tDCS), for depression in neurocognitive disorders. Observational data suggest that ECT is well-tolerated and effective in patients with MCI and dementia [33, 34], but these ECT studies are limited by their lack of randomization, short follow-up periods, or rudimentary cognitive assessment. Recent data suggest that cognition improves in many older patients with depression and associated cognitive impairment treated with ECT [35] or rTMS [36–38]. However, we are not aware of any published studies investigating ECT or rTMS treatment in participants with depression and well-defined comorbid MCI or dementia. Given the limitations of pharmacotherapy in this patient group, neurostimulation therapies offer a potential alternative. A double-blind, sham-controlled RCT is currently underway investigating the efficacy of deep rTMS targeted to the left dorsolateral prefrontal cortex for patients with Alzheimer's dementia and comorbid MDD (https://clinicaltrials.gov/ct2/show/NCT03665831).

Additional Methodological Issues: the Need for Evidence-Based Measurement Tools

One issue cuts through most of the studies cited in this review: measurement of depression in patients with neurocognitive disorders. We lack consensus regarding the optimal definition of depression in dementia, and evidence regarding how to best measure clinically important change in depression over time in this population is limited. As noted by Nunnally in his seminal textbook on psychometric theory, "science… can progress no faster than the measurement of its key variables" [39].

In 2001, the National Institute of Mental Health (NIMH) convened an expert panel to develop diagnostic criteria specific to depression in Alzheimer's, in order to promote recognition of this phenotype as distinct from other depressive disorders [21•]. The panel recognized depression in the context of Alzheimer's dementia as typically being less severe and persistent than classic MDD. They also noted the presence of additional specific symptoms, including social isolation, withdrawal, and irritability. The NIMH diagnostic criteria (NIMH-dAD) are based on DSM criteria, but require three of 11 symptoms for a diagnosis of depression. Raters are instructed to discount symptoms that are likely due to Alzheimer's dementia. Several of the primary studies included in the pharmacotherapy meta-analyses cited above used the NIMH-dAD criteria [12, 40, 41]. NIMH-dAD has evidence for criterion and construct validity in a group of patients with Alzheimer's dementia and was found to correctly identify all patients classified as having MDD by expert raters using the DSM [42]. However, it also identified substantially more patients as being clinically depressed than did the DSM [42]. Thus, it is necessary to establish the clinical importance of picking up these additional potential cases.

When measuring antidepressant treatment response in dementia, early RCTs used depression rating scales validated in older adults with depression: the Hamilton Depression Rating Scale [43], the Montgomery-Asberg Depression Rating Scale [44], or the Geriatric Depression Scale [45]. Studies published after 2010 have primarily used the CSDD, a scale developed and validated specifically to screen for and measure the severity of depression in patients with dementia, taking into account both patient and caregiver report [46–48]. However, no evidence exists regarding the CSDD's responsiveness to change associated with treatment, or its minimal clinically important difference (i.e., thresholds of meaning). This is a critical limitation, as without the ability to capture important change in response to treatment, clinical trials are futile.

Conclusion

In conclusion, existing antidepressant pharmacotherapy shows little evidence of benefit in treating depression in dementia over and above placebo. Alternative treatment strategies are needed. Psychological, behavioral, and somatic treatments represent promising options, but further studies are required, particularly in participants with diagnosed depressive disorders. Little is known about the treatment of depression in patients with well-defined MCI, and rigorous identification of MCI in late-life depression treatment trials will help to advance knowledge in this area. Finally, research regarding the construct validity of depression in neurocognitive disorders as well as its responsiveness to treatment and minimal clinically important difference in depressive symptoms is needed to bring clarity to the literature. Ultimately a better understanding of the neurobiological mechanisms underlying the cognitive and affective symptoms of late-life depression and their relationship with neurocognitive disorders will assist in developing novel treatments.

Compliance with Ethical Standards

Conflict of Interest Kathleen S. Bingham has no disclosures.

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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.

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