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A Review of the Effectiveness of Antidepressant Medications for Depressed Nursing Home Residents

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Abstract

Background—Antidepressant medications are the most common psychopharmacologic therapy used to treat depressed nursing home (NH) residents. Despite a significant increase in the rate of antidepressant prescribing over the past several decades, little is known about the effectiveness of these agents in the NH population.

Objective—To conduct a systematic review of the literature to examine and compare the effectiveness of antidepressant medications for treating major depressive symptoms in elderly NH residents.

Methods—The following databases were searched with searches completed prior to January 2011 and no language restriction: MEDLINE, Embase, PsycINFO, CINHALL, CENTRAL, LILACS, ClinicalTrials.gov, International Standard Randomized Controlled Trial Number Register, and the WHO International Clinical Trial Registry Platform. Additional studies were identified from citations in evidence-based guidelines and reviews as well as book chapters on geriatric depression and pharmacotherapy from several clinical references. Studies were included if they described a clinical trial that assessed the effectiveness of any currently-marketed

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Supplementary Data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jamda.2011.08.009.

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antidepressant for adults aged 65 years or older, who resided in the NH, and were diagnosed by DSM criteria and/or standardized validated screening instruments with Major Depressive Disorder, minor depression, dysthymic disorder, or Depression in Alzheimer's disease.

Results—A total of eleven studies, including four randomized and seven non-randomized open-label trials, met all inclusion and exclusion criteria. It was not feasible to conduct a meta-analysis because the studies were heterogeneous in terms of study design, operational definitions of depression, participant characteristics, pharmacologic interventions, and outcome measures. Of the four randomized trials, two had a control group and did not demonstrate a statistically-significant benefit for antidepressant pharmacotherapy over placebo. While six of the seven non-randomized studies identified a response to an antidepressant, their results must be interpreted with caution as they lacked a comparison group.

Conclusions—The limited amount of evidence from randomized and non-randomized open-label trials suggests that depressed NH residents have a modest response to antidepressant medications. Further research using rigorous study designs are needed to examine the effectiveness and safety of antidepressants in depressed NH residents, and to determine the various facility, provider, and patient factors associated with response to treatment.

Keywords

Antidepressants; nursing homes; depression; effectiveness

Depression is the most prevalent psychiatric mood disorder affecting older nursing home (NH) residents,¹ with the prevalence of Major Depression Disorder (MDD) ranging from 6% to 26% and the prevalence of depressive symptoms ranging from 11% to 50%.^{2,3} Depression has been associated with a number of negative health outcomes for older NH residents including weight loss, dehydration, decline in activities of daily living, and mortality.⁴ Pharmacologic therapy using antidepressants is a much more common method for treating depressed NH residents than other potentially effective treatments such as psychotherapy.⁵ For example, a study involving 921 NHs found that 74% of depressed residents were treated with antidepressants, while only 2.5% received some form of psychotherapy.⁶

Antidepressant effectiveness in older, community-dwelling, patients was summarized in four recent systematic reviews.⁷⁻¹⁰ These reviews found no difference in the effectiveness of older tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors, bupropion, or trazodone for treating depression. The reviews did find that the drugs had different adverse event profiles. Specifically, tricyclic antidepressants were found to be more strongly associated with discontinuation due to side effects than SSRIs.⁸ Moreover, subjects taking trazodone were more likely to experience adverse cognitive effects than those taking bupropion, mirtazapine, or SSRIs.⁷ However, the generalizability of these findings to the nursing home setting might be limited due to significant differences between the institutionalized and noninstitutionalized elderly.

NH residents are typically older, have more medical comorbidity, are prescribed more medications, and have more functional and cognitive impairment than their community-dwelling counterparts. Nearly half of the NH population suffers from Alzheimer's disease (AD) or a related dementia,¹¹ a dramatically higher prevalence than in the general population of persons over the age of 65 where the rate is approximately one of every eight persons.¹² The unique characteristics of NH residents and their clinical environment suggest that a comprehensive inventory and assessment of the current literature would assist clinicians in making more informed pharmacotherapy decisions. The objective of this study was to conduct a systematic review of the literature to examine and compare the

effectiveness of antidepressant medications for abating depression symptoms in elderly NH residents.

Methods

Inclusion Criteria

We searched for all published studies and registered clinical trials that (1) involved NH residents 65 years of age diagnosed by DSM criteria and/or standardized validated screening instruments with MDD, minor depression, dysthymic disorder, or depression in AD¹³; (2) used a randomized or open-label design to study the effectiveness of an FDA-approved antidepressant; and (3) reported outcomes in terms of changes in depression diagnosis (eg, number of residents who transitioned from MDD to non-MDD) or changes in depressive symptoms assessed by validated psychometric depression scales including the Hamilton Depression Rating Scale (Ham-D),¹⁴ Cornell Scale for Depression in Dementia (CSDD),¹⁵ Geriatric Depression Scale (GDS),¹⁶ Montgomery-Asberg Depression Rating Scale,¹⁷ and the Clinical Global Impressions Rating Scale.¹⁸

Data Sources and Search Strategy

The search was conducted with the help of a research librarian (A.S.) and combined terms such as “antidepressant,” “elderly,” “aged,” “nursing home,” “long term care,” “facility,” and “resident” with the individual names of currently marketed antidepressants and their therapeutic classes. An example of a search strategy for the MEDLINE database is included in Supplemental Appendix II. The following databases were searched with searches completed prior to January 2011 and no language restriction: MEDLINE, Embase, PsycINFO, CINAHL, CENTRAL, LILACS, ClinicalTrials.gov, International Standard Randomized Controlled Trial Number Register, and the WHO International Clinical Trial Registry Platform. Additional studies were identified from citations in evidence-based guidelines and reviews as well as book chapters from several clinical references on geriatric depression and pharmacotherapy.¹⁹⁻²⁶

Literature Screening

Using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations as a guide,²⁷ one of the investigators (R.D.B.) screened all titles and abstracts found using the searches described above while a trained research assistant conducted a duplicate screening of a random 20% sample. The full text article described by each title and abstract that was accepted in the first round of screening was then screened by 2 of the study co-investigators (R.D.B. and S.M.H.) for compliance with inclusion criteria. A third co-investigator (J.T.H.) resolved any disagreement between the 2 screeners that could not be resolved by discussion. Also, investigators attempted to contact the primary author of any study that was not clear about clinical setting or subject inclusion criteria. Each study that made it through both rounds of screening was assessed for bias ensuring adequacy of blinding, randomization, concealment, the extent of loss to follow-up, and adherence to the intention-to-treat (ITT) principle²⁸ by a pair of investigators (R.D.B. and J.K.).

Results

A total of 3,175 titles and abstracts were screened to identify 93 full-text articles of which only 11 met this review’s inclusion criteria (see Supplemental Table S1). Table 1 summarizes the study design, facility characteristics, study subjects, intervention, and results of the 11 included studies. Seventy of the 82 excluded studies were review articles or involved persons who were not diagnosed with depression or persons who were receiving

care in the ambulatory or hospital/geriatric inpatient psychiatry settings. An additional 12 primary studies were excluded and further details can be found online as Supplemental Table S2.

Randomized Controlled Trials

A 10-week randomized-controlled trial (RCT) of sertraline and venlafaxine was conducted by Oslin et al in 13 NH facilities.²⁹ Qualifying residents were diagnosed by *DSM-IV* criteria as having major depression, dysthymia, or minor depression; had experienced symptoms for longer than one month; and were judged likely to stay in the NH for longer than 18 weeks. All participants were given placebo for one week under single-blind conditions and then randomized to double-blind treatment of either sertraline or venlafaxine. Sertraline was started at 25 mg/day and increased, as tolerated, to a maximum of 100 mg/day by week six. Venlafaxine was started at 18.75 mg/day and increased, as tolerated, to a maximum of 150 mg/day by week six. The outcome of interest was the relative change in depressive symptoms between the groups as measured by the 21-item Ham-D, the CSDD, and GDS. Fifty-two NH residents were enrolled in the study (44% female, mean age 83 years); of these 25 were assigned to the sertraline arm and 27 to the venlafaxine arm. Thirty-three subjects completed the study and an ITT analysis showed no statistically significant difference between sertraline and venlafaxine according to Ham-D and GDS scores. However, the ITT analysis did find a significant improvement favoring sertraline using the CSDD ($P = 0.008$).

Burrows et al³⁰ conducted an eight-week double-blind RCT to investigate the effectiveness of paroxetine for treating minor depression in NH residents. Residents were evaluated for depressive symptoms using two psychometric tools (Ham-D and Cornell Scale for Depression³¹) and open-ended questions that allowed for a *DSM-IV* diagnosis. Persons with advanced dementia ($MMSE < 10$) and behavioral problems were excluded. Twenty-four NH residents, aged 80 years and older, were enrolled in the study (75% female, mean age 88, mean $MMSE$ 23.8). Participants were randomized to an eight-week course of placebo or paroxetine starting at 10 mg/day and titrated to a maximum of 30 mg/day. Twenty residents completed the study and an ITT analysis found that paroxetine had no statistically significant benefit over placebo for depression based on the proportion of participants who had a >25% reduction in depressive symptoms rated according to either the Ham-D or the CSDD rating scales (the latter modified for use in persons without dementia).

An 8-week double-blind RCT was conducted by Magai et al³² to assess if sertraline had any benefit over placebo for treating depression in NH residents with AD. NH residents satisfying the NINCDS/ADRDA (National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association) criteria for probable or possible AD were identified among residents of five US NHs. Residents were evaluated for minor or major depression using the CSDD¹⁵ and the Gestalt Scale (GS).³³ Thirty-one participants (100% female, mean age 89) were randomly assigned to receive placebo or sertraline starting at 25 mg/day and increased bi-weekly to a maximum of 100 mg/day at week five. Twenty-seven participants completed the study with 16% meeting the criteria for major depression and the remaining 84% meeting the criteria for minor depression. An ITT analysis observed that sertraline had no statistically significant benefit over placebo for depression based on participant scores on the CSDD and GS as well as systematic observation of facial behaviors indicative of emotional response.

Streim et al³⁴ conducted a 10-week double-blind RCT of regular and low-dose nortriptyline involving residents from 8 NH facilities diagnosed by *DSM-IV* criteria with major depression, dysthymia, or minor depression; had experienced symptoms for longer than one month; and were judged likely to stay in the NH for longer than 18 weeks. Sixty-nine

participants (33% female, mean age 80) received placebo for one week and then were randomized to receive doses of nortriptyline up to either 80 mg/day (designated “regular dose”) or 13 mg/day (designated “low dose”) for 10 weeks. The primary outcome measured was the proportion of those treated who exhibited a 33% decrease in the Ham-D or the GDS. Change in depressive symptoms as measured by the nurse-rated CG-I scale was also examined. An ITT analysis observed no statistically significant difference in the proportion of participants in the low-or high-dose groups who experienced a >33% decrease in the Ham-D score (36% and 38% respectively).

Summary of the Included RCTs

In summary, of the four included randomized trials (Table 1), two compared the effectiveness of treatment with an SSRI to placebo,^{30,32} one compared the effectiveness of an SSRI to a serotonin-norepinephrine reuptake inhibitors,²⁹ and one compared the effectiveness of the tricyclic antidepressants nortriptyline at two different dose regimens.³⁴ Two of the RCTs included participants with a wide range of cognitive impairment,^{29,34} one RCT excluded residents with advanced dementia,³⁰ while another included only those residents who satisfied the NINCDS/ADRDA criteria for probable or possible AD.³² Also, two RCTs mention industry sponsorship^{30,32} while the other two do not.^{29,34} It was not feasible to conduct a meta-analysis with the four randomized studies that met inclusion criteria because they were heterogeneous in terms of study design, participant characteristics, pharmacologic interventions, and chosen outcome measures.

Summary of the Included Open-label Studies

Due to space limitations, a full description of the seven open label trials can be found in Supplemental Appendix Si. Briefly, 5 open-label studies examined the effectiveness of an SSRI,³⁷⁻⁴¹ while two examined the effectiveness of mirtazapine.^{35,36} One open-label study included only NH residents diagnosed with Parkinson’s disease,⁴¹ two excluded residents with more than moderate cognitive impairment according to MMSE screening,^{35,36} and four studies made no mention of exclusions based on cognitive ability.³⁷⁻⁴⁰ Three open-label studies mention industry sponsorship^{35,36,38} while 4 do not.^{37,39-41} The majority of the open-label studies (four of seven) had a treatment response rate of 3 50%.^{35,36,38,39}

Discussion

To the best of our knowledge, this is the first systematic review to examine and compare the effectiveness of antidepressant medications for abating depressive symptoms in elderly NH residents. Our study also expands on a previously published book chapter by Bharucha and Borson by including two additional open-label studies.^{36,41} However, one randomized⁴² and one open-label study⁴³ cited in the chapter was excluded for failing to meet this review’s inclusion criteria. While we were unable to perform a meta-analysis of all of the studies included in this review (for reasons described earlier), several conclusions can be drawn that might benefit NH clinicians when deciding to prescribe antidepressant medications.

First, we found that there is indeterminate evidence from RCTs that antidepressant medications are superior to placebo at treating depressed elderly in the NH setting. One possible explanation for this is that the placebo response rate of the two placebo-controlled RCTs was high: 45% in the study by Burrows et al,³⁰ and nearly 50% in the study conducted by Magai et al.³² Burrows et al suggest that the study protocol, which involved frequent interaction with participants in the form of interviews and attention to daily stress, might have been one factor that independently promoted improvement in some participants from both groups. An alternate factor suggested by the authors of both studies was that study inclusion criteria might have limited the number of participants who had depression

requiring pharmacologic intervention. Both factors have been noted as possible explanations for the apparent lack of benefit over placebo found in several other antidepressant effectiveness studies conducted outside of the NH.^{44,45} We think it also relevant that, while nearly half of all NH residents have some level of cognitive impairment, the biology, phenomenology, and assessment of depression in dementia are not fully elucidated. Studying the effect of antidepressants on other neurobehavioral symptoms common in demented elderly, such as apathy, anxiety, agitation, and psychosis, might further clarify who in the NH setting would benefit from antidepressant treatment.

Our second finding is that there is indeterminate evidence from RCTs and open-label studies that cognitively impaired depressed older NH residents respond to antidepressants. This finding is especially relevant given that there may be insufficient evidence on the efficacy of antidepressants for treating patients with comorbid depression and dementia in non-NH settings.⁴⁶⁻⁴⁸ Only one included study, a placebo-controlled RCT,³² was specifically designed to examine if depressed older NH residents with cognitive impairment respond to antidepressants. While no statistically significant benefit over placebo was found with sertraline after eight weeks of treatment, the authors note that there was a trend toward an improved emotional response based on facial expressions. The limitations of this study were mentioned above in the discussion of the placebo-controlled RCTs included in this review. An additional limitation of this study is that the exclusion criteria might have led to a group of participants that are not representative of typical NH residents with AD. Excluded persons included those with a history of cancer (within 5 years), stroke, a prescription for antidepressant or antipsychotic medication, or medical problems that could interfere with participation. Unfortunately, the study reported no analysis of the differences between the included and excluded groups.

Our third finding is that the majority of the open-label trials designed to assess the effectiveness of antidepressants in older NH adults showed an improvement in depressive symptoms of 50%. However, a major concern is that it is impossible to know what the response rates would have been *without* treatment since each open-label trial lacked a comparator group. Another issue is that the potential for information bias is present in all 7 open-label studies since awareness of treatment by both subjects and investigators can artificially inflate subject response and overestimate treatment effectiveness.

A fourth finding is that the small sample sizes and different definitions and scales used to define and determine treatment response in the included RCTs might have limited their power to detect differences in the response rate between comparison groups. For example, the study by Burrows et al³⁰ only included 24 subjects whereas the study by Magai et al³² only included 31 subjects. Regarding treatment response definitions, one RCT³⁰ defined response as a 25% improvement in depressive symptoms, while the other used a 50% improvement as the cut-off point for response.³² We also note that very few of the current “first-line” antidepressant medications used to treat depressed NH residents appear to have been studied specifically in NH residents. Consensus guidelines from as early as 2001 recommend the use of an SSRI or venlafaxine as a “first-line” pharmacotherapy for depressed NH residents.⁴⁹ While several studies in this review, including three RCTs, examined the effectiveness of an SSRI, none examined citalopram, the SSRI that is currently the most commonly prescribed to NH residents,⁵⁰ nor other first-line agents such as escitalopram, bupropion, and desvenlafaxine.

It is valuable to consider the potential limitations of this review. One potential limitation is that some elements of the review’s inclusion criteria were subjective. For example, we excluded one study involving nortriptyline because participants came from both NH and congregate housing environments (rather than just NHs) and outcomes were not stratified by

participant source.⁴² A second potential limitation is that our search strategy might have missed some studies published in languages other than English, studies with negative findings, and studies available in unpublished technical reports, white papers, or other “grey literature” sources. It is important to note however, that we used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations as a guide to designing and executing this review.²⁷ Finally, it is possible that the conclusions drawn and discussed above are unintentionally misleading. To be as objective as possible we used a standardized approach to address potential strengths and weaknesses of included studies.⁵¹

Conclusion

The limited amount of evidence from randomized and non-randomized clinical trials suggests that depressed NH residents have a modest response to antidepressant medications. Further research using rigorous study designs are needed to examine the effectiveness of antidepressants in depressed NH residents and to determine the various facility, provider, and resident factors associated with response to treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Randomized Controlled and Open-Label Trials of Antidepressant Treatment of Depressed Nursing Home Residents^a

Citation	Design	Setting	Subjects	Intervention	Results
Oslin, 2003 ²⁹	A 10-week multi-site active-controlled RCT	13 public, for-profit, or non-profit NHs	52 NH residents with a diagnosis of MDD, dysthymia, or minor depression (DSM-IV) and duration of symptoms longer than one month.	Placebo run-in; sertraline up to 100 mg/day or venlafaxine up to 150 mg/day	63% completed; an ITT analysis showed no SS difference in Ham-D or GDS response but a SS improvement favoring sertraline as per CSDD
Burrows, 2002 ³⁰	An eight week, single-site placebo-controlled RCT	725 bed multi-level LTC facility	24 NH residents age 80 and older with non-major depression (DSM-IV).	Paroxetine 10-30 mg/day	83% completed; paroxetine had no SS benefit over placebo as per Ham-D or CSDD
Magai, 2000 ³²	An eight week, multi-site placebo-controlled RCT	Five US NHs	31 NH residents with depression and probable or possible Alzheimer's Disease as per NINCDS/ADRDA criteria	Sertraline 25-100 mg/day	87% completed. Sertraline had no SS benefit over placebo as per CSDD or GS
Streim, 2000 ³⁴	A ten-week multi-site RCT	Eight US NHs	69 NH residents with a diagnosis of MDD, dysthymia, or minor depression (DSM-IV)	Placebo run-in; nortriptyline up to 80 mg/day vs nortriptyline up to 13mg/day	59% completed. No SS differences in response to treatment between the two groups as per Ham-D or GDS
Roose, 2003 ³⁵	A twelve-week open-label non-randomized trial	30 US NHs	127 NH residents 70 years of age or older with depression and no to moderate cognitive impairment	Mirtazapine 15-45 mg/day	66% completed. 54% responded to mirtazapine as per CGI-I.
Nelson, 2006 ³⁶	A twelve-week open-label non-randomized trial	23 US NHs	50 NH residents 85 years of age or older with depression and no to moderate cognitive impairment	Mirtazapine 15-45 mg/day	72% completed. 55% responded to mirtazapine as per CGI-I.
Oslin, 2000 ³⁷	A ten-week multi-site open-label trial	Eight US NHs	28 NH residents with a diagnosis of MDD, dysthymia, or minor depression (DSM-IV)	Placebo run-in; sertraline 25-100 mg/day	54% completed. 18.2% of cognitively intact participants responded as per Ham-D; no benefit found for cognitively impaired as per Ham-D
Rosen, 2000 ³⁸	A six-week single-site open-label trial	A single NH in Western Pennsylvania	12 NH residents 72 years of age or older with a DSM-IV diagnosis of minor depression	Sertraline 50-100 mg/day	100% completed. 66% responded to treatment with sertraline as per Ham-D
Trappler, 1996 ⁴⁰	A twelve-week single-site open-label non-randomized trial	271-bed LTC facility for Sephardic Jews	29 NH residents 75 years of age or older having a DSM-IV diagnosis of MDD	Fluoxetine 10-30 mg/day	90% completed. 50% responded to treatment with fluoxetine as per Ham-D; 81% no longer presented with MDD based on a psychiatric evaluation.
Trappler, 1998A ⁴¹	A twelve-week single-site open-label trial	271-bed LTC facility for Sephardic Jews	52 NH residents 80 years of age or older having a DSM-IV diagnosis of MDD	Fluoxetine 10 mg/day, sertraline 50 mg/day, or paroxetine 10 mg/day	Starting dose increased as needed; 96% completed. 42% participants responded to treatment as per Ham-D. No SS difference in response between SSRIs as per Ham-D.
Trappler, 1998B ⁴²	A twelve-week multi-site open-label trial	Two skilled nursing facilities in the US	12 NH residents with a diagnosis of (MDD DSM-IV) and an Axis III diagnosis of Parkinson's	Fluoxetine 10 mg/day, sertraline 50 mg/day, or paroxetine 10 mg/day;	Starting dose increased as needed; 100% subjects completed. 25% participants responded to treatment as per Ham-D. No SS difference in response between SSRIs.

^a ADRDA, Alzheimer's Disease and Related Disorders Association; CGI-I, Clinical Global Impression, Improvement; CSDD, Cornell Scale for Depression in Dementia; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders version IV; GDS, Geriatric Depression Scale; GS, Gestalt Scale; Ham-D, Hamilton Rating Scale for Depression; ITT, Intention to Treat;

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LTC, long term care; MDD, major depression disorder; mg, milligrams; NH, nursing home; NINCDS, National Institute of Neurological and Communicative Disorders and Stroke; RCT, randomized-controlled trial; SS, statistically significant