

# Prescribing Antidepressants in Depressed Nursing Homes Residents with Dementia: Is it Evidence-based?

**Keywords:** Depression; Dementia; Antidepressant; Nursing home

## Abstract

Depression and dementia are common comorbidities among Nursing Home (NH) residents. Antidepressants are widely used in this vulnerable population. However, the evidence for anti-depressant use, including from randomized controlled trials, systematic reviews, and evidence-based clinical practice guidelines, is inconsistent and conflicting. Additionally, antidepressants are associated with multiple adverse effects. Long-term care providers often need to deal with requests from patients' families, nursing staff, and colleagues to prescribe antidepressants, while following recommendations from pharmacists and regulations from the Center for Medicare and Medicaid Service (CMS) and Federal Drug Administration (FDA) not to prescribe or to discontinue antidepressants. It is difficult for long-term care providers to decide whether they should prescribe antidepressants and meet regulations and quality of care standards based on the few Randomized Controlled Trials (RCTs). A large randomized control study to examine the efficacy of antidepressants among depressed NH residents with dementia is urgently needed. We propose a practical step-wise approach to prescribe antidepressants for this vulnerable population.

## Abbreviations

AD: Alzheimer's Disease; CMS: Center for Medicare and Medicaid Service; CSDD: the Cornell Scale for Depression in Dementia; DSM: Diagnostic and Statistical Manual of Mental Disorders; FDA: Federal Drug Administration; NH: Nursing Home; RCT: Randomized Controlled Trial

## Introduction

Long-term care providers often see the following scenario at NH. This is a patient, Ms. Smith, is 85 years old. She is on multiple medications for her hypertension, diabetes mellitus, arthritis, urinary incontinence, constipation, cataract, and insomnia. She often requires assistance from nursing staff for medication administration as well as her activities of daily living such as bathing and toileting. She was diagnosed with advanced dementia several years ago. She is only oriented to person. However, she follows simple command slowly. She looks sad, anxious, and is sometimes tearful. The nursing staff also notices that she has significant apathy and tires easily. At night, she wanders and often needs medication to sleep. Due to her poor appetite, she has lost 10 pounds within the last 6 months. Additionally, Ms. Smith is easily annoyed and agitated. Sometimes she yells, curses, and hits the nursing staff. Based on the above observation and brief assessment for depression, both the nursing staff and I agree that Ms. Smith has depression. The nursing staff suggests prescription of an antidepressant and antipsychotics as well (which would be another topic) for this patient. The patient's family also thinks she is depressed and asks whether I could prescribe an



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antidepressant to improve her depression and quality of life. Because the FDA and CMS have strict regulations on antidepressants [1,2], the pharmacist often asks me to reduce the dose of antidepressants or discontinue antidepressants as a result of regularly scheduled patient medication reviews. This is a challenging situation which I am sure other providers experience as well. The goal of this mini-review is to promote the use of evidence-based practice guidelines in prescribing antidepressants for this vulnerable geriatric population. In this review, we examine the therapeutic evidence for prescribing antidepressants in this population using randomized controlled trials (RCTs), systematic reviews, and evidence-based clinical practice guidelines. The potential adverse effects of antidepressants will be briefly reviewed. Finally, we propose a practical step-wise approach to prescribing antidepressants for depressed NH residents with dementia.

## Evidence of Antidepressants to Treat Depression in Depressed NH Residents with Dementia

Depression and dementia are common and often co-exist in older NH residents [3-8]. For example, a recent study based on 2,564,687 participants in the MDS (Minimum Data Set) among 5,445 U.S. facilities showed that as many as 50% NH residents with dementia had major depression or depressive symptoms [7]. Depression is associated with impaired physical function, poor quality of life, suffering, disability, increased mortality and health care utilization [3,9,10], and increased use of psychotropic drugs such as antidepressants [5,6,8]. One recent study found that the use of antidepressants for depressed NH residents with dementia significantly increased from 69% in 1999 to 81% in 2007 [7]. Perhaps, this widely use of anti-depressants is because general reviews [3,11-20] and guidelines [21-24] recommend that antidepressants are effective to treat depression in NH residents with dementia. However, the evidence of effectiveness of antidepressants in this vulnerable population is inconsistent and conflicting. First, no systematic review focuses on the use of antidepressants to treat depression in depressed NH residents with dementia based on our recent preliminary search of PubMed and Cochrane reviews; Second, four

systematic reviews [9,25-27] on the use of antidepressant were not specific to depressed NH residents with dementia. For example, one systematic review included depressed NH patients with or without dementia [25]. Other three systematic reviews included depressed patients with dementia at NH and non-NH setting [9,26,27]. Two systematic reviews suggested a modest effect of antidepressants on depressed older adults with dementia [9,25]. In contrast, another two systematic reviews based on RCTs using antidepressants as primary intervention and placebo as control came to the opposite conclusion [26,27]. Our recent preliminary literature review suggests that the use of antidepressants to treat depression in depressed older adults with dementia is less effective based on eight RCTs [28-35] listed on Table 1. RCTs are considered the gold standard for therapeutic intervention. Among four previous systematic reviews [9,25-27] and other two reviews [36,37], only one published RCT tested the efficacy of an antidepressant (Sertraline) for depressed NH residents with dementia [34]. This study was a randomized, placebo-controlled, double blind trial designed to test the efficacy of Sertraline in thirty one depressed female NH patients with dementia (intervention group=17, placebo group=14). Mean ages in the intervention and control groups were 88 and 90 years old, respectively. In this trial, the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association (NINCDS/ADRDA) criteria for probable or possible Alzheimer’s disease (AD) were used to diagnose dementia. The subjects in this study had late-stage Alzheimer’s disease. The Cornell Scale for Depression in Dementia (CSDD) was used to assess depression. Only 10% of participants met the criteria for “definite” major depression (CSDD ≥ 10 on a scale 0-38). The Gestalt scale (GS), Facial Behaviors, Cohen-Mansfield Agitation Index (CMAI), Aversive Feeding Behavior Scale (AFBS), Knit-brow face and sad face were used as secondary outcomes. 497 subjects were screened (the recruitment fraction was 6%). 101 of them were eligible (the eligible fraction was 20%). Thirty-one participants were enrolled in this study (the enrollment fraction was

31%). Twenty-seven participants completed the trial (the completion rate was 87%). In this eight week trial, Sertraline was first given at 25 mg/day for two weeks, then at 50 mg/day during the third and fourth week and finally at 100 mg/day for the last four weeks. This study reported randomization method and allocation concealment, used intention-to-treat analysis, and had a low drop rate (13%), which indicates excellent internal validity of the study. The mean CSDD scores in the intervention and placebo groups were 3.53 and 4.43, respectively, on a scale of 0-38 (0=no depression, 38=worst depression). Sertraline did not significantly reduce depression severity. Exclusion criteria in this study included participants who were on antipsychotics or antidepressants, or had a history of cancer within the past 5 year, a history of stroke, or other severe medical problems that could interfere with participation, which indicates poor external validity. Very low recruitment rate (6%) also suggests poor external validity. Despite the limitations of this RCT, it was cited 72 times since it was published in 2000 based on Web of Science [38]. Conducting a large RCT to test effectiveness of antidepressants at NH setting is urgently needed.

Because of insufficient RCTs in the NH setting, it merits to examining results from RCTs that test the efficacy of antidepressants in depressed older patients with dementia in other clinical settings. Eight RCTs including only RCT at NH [28-35], are listed on Table 1. Seven out of eight RCTs were conducted in outpatient clinic settings. Two out of eight RCTs showed a statistically significant effect of reducing depression severity with antidepressants among depressed older patients with dementia. The other six RCTs didn’t show any difference in depression severity between the placebo and antidepressant groups.

In the era of evidence-based medicine, health providers often use evidence-based guidelines to guide their clinical practice. We used PubMed and the National Guideline Clearinghouse to search clinical practice guidelines based on the following two simple criteria:

**Table 1:** RCT in treating depression in demented older patients.

The first author and publication year	Setting	Sample size	Age (years)	Female (%)	Antidepressants	Depression outcome between treatment and placebo arms
2011 Banerjee	Old-age psychiatry services in clinical centers (15% were living in care home)	326	79	68	Sertraline or mirtazapine	No difference
2010 Rosenberg	Memory clinic at 5 academic centers in the US	131	77	54	Sertraline	No difference
2007 de Vasconcelos Cunha	Outpatient clinic (all patient were living at home)	31	78	74	Venlafaxine	No difference
2003 Lyketsos	Outpatient Clinic of University Neuropsychiatry Service (patients were living home or assisted living)	44	78	68	Sertraline	Statistically significant
2001 Petracca	Outpatient Dementia Clinic of Institute of Neurological Research	41	71	59	Fluoxetine	No difference
1989 Reifler	Outpatient clinic (Geriatric and Family Service Clinic and Geriatric Research, Education, and Clinical Center at Veterans Administration). Patients were living at homes or retirement homes	28	72	59	Imipramine	No difference
2000 Magai	Nursing home	31	89	100	Sertraline	No difference
1996 Roth	In- and out-patient setting (78% were inpatients)	726	74	77	Moclobemide	statistically significant

1) the guidelines focused on depressed NH residents with dementia; 2) the guidelines provide at least two components i.e., quality of the evidence (level of evidence) and strength of the recommendation (grade or class). Our literature search didn't find any clinical practice guideline that met our inclusion criteria. Nevertheless, we found two Expert Consensus papers and two guidelines which might help make an extrapolation-based decision. The first Expert Consensus paper [21] focused on management of depressed NH residents with dementia. It included a list of RCTs with levels of evidence for the recommendations. This expert consensus recommended that pharmacological interventions were effective in NH residents with major depression (level I evidence). For residents who met criteria for minor depression, alternative treatments including non-pharmacological interventions, antidepressants, and watchful waiting were recommended (level IV evidence). These recommendations, however, were not graded. In the 2<sup>nd</sup> Canadian Expert Consensus Conference on Dementia, seven RCTs were selected, reviewed, and used as supporting evidence to treat depression in depressed patients with dementia [22]. The use of antidepressants or a mood stabilizer to treat patients who are demented and suffer from disturbing emotional lability or pathological laughing and crying was determined to be a Grade B recommendation with Level 3 evidence [22]. However, this expert consensus was not specific to depressed NH residents with dementia. Two other guidelines on treating depression at NH setting recommended antidepressants, but did not provide the evidence from RCTs, levels of evidence, or grades of their recommendations [23,24]. In 2011, the American Medical Director Association (AMDA) developed a guideline to treat depression with or without dementia in the long-term care setting and was collected in National Guideline Clearinghouse. It stated "the practitioners should discuss the rationale for adding pharmacotherapy to the patient's regimen with team members as well as with the patient and his or her family" [23]. Unfortunately, the evidence from RCTs, grades of recommendation, and levels of evidence were not provided in this guideline [23].

Taken together, the current literature suggests that the evidence of prescribing antidepressants to treat depression in depressed NH residents with dementia is inconsistent and conflicting. Thus, long-term care providers are forced to make prescribing decisions based on only negative RCT and in consistent evidence from seven RCTs at non-NH settings.

### Potential Adverse Effect of Antidepressants

A recent large cohort study of 60,746 patients aged 65 to 100 years old showed that antidepressants were significantly associated with hyponatremia, increasing mortality, attempted suicide or self-harm, myocardial infarction, stroke, upper gastrointestinal bleeding, epilepsy or seizure, road traffic accidents, adverse drug reactions, falls, and fractures [39]. Perioperative use of selective serotonin reuptake inhibitors (SSRIs) was associated with increasing inpatient mortality, bleeds, and 30-day readmission in another recent large cohort study of 530,016 subjects [40]. Antidepressants were also associated with increasing bone absorption and potentially increasing fracture risk in older patients [41]. NH residents often have multi-morbidity [42] and polypharmacy [43,44]. Adding antidepressants in this vulnerable population could significantly increase drug-drug and drug-disease interactions thus further increasing the risk of polypharmacy. Not surprisingly, antidepressants are on the Beers' list of medications that should be prescribed cautiously in geriatric population [45].

### Proposed Practical Approach in Prescribing Antidepressants

Antidepressants are widely prescribed to treat depressed NH residents with dementia [5,6,8] despite lack of the evidence from RCTs, systematic reviews, and evidence-based clinical guidelines. In our opinion, many depressed NH residents with dementia might not need antidepressants. Ideally, patient families, pharmacists, nursing staff, and long-term care providers at NH could work together to decide on antidepressant use and to meet the FDA and CMS regulations [1,2]. All stakeholders need to balance the limited benefits and multiple potential risks associated with antidepressants. Here, we propose a practical step-wise approach to prescribing antidepressants at NH setting for long-term care providers.

First, long-term providers should share with the patients' families, nursing staff, and other colleagues that there is little evidence-based support for antidepressant use. Engaging patients' families, pharmacists, and nursing staff is critical for making good decisions on the use of antidepressants; Second, long-term care providers should look for potential medical causes of the depression and treat them accordingly. An example is to treat uncontrolled chronic pain; Third, long-term care providers should assess the severity of the patient's depression i.e., differentiating between depressive symptoms versus major depression following DSM-IV [46]. Depressive symptoms or minor depression often do not require antidepressants; Fourth, long-term care providers should try non-drug therapies first such as physical activity [47] and a structured multidisciplinary approach [48] before prescribing any antidepressant. The use of pleasant events and activity participation has been studied as alternative approach to improving depression [49,50]. Group activities, one-one visit, religious service, and family visit could have positive affect in depressed NH residents; Fifth, as a last resort, the use of tricyclic antidepressants (TCAs) or SSRIs, or other types of antidepressants, if non-drug therapy approaches fail. Close monitoring for adverse effects should be in place if antidepressants are prescribed. A recent small study showed that discontinuation of antidepressants could result in rebound depressive symptoms [51]. Thus, discontinuation should be done slowly and carefully; Sixth, referral to a psychiatrist may be in order, especially a geriatric psychiatrist. Many geriatric psychiatrists have expanded their practices to the NH setting; lastly, consider tapering the patient off of the antidepressants if pharmacotherapy does not prove beneficial.

We now return to the patient described in the beginning. We decided not to prescribe an antidepressant and, after discussions with her family, suggested that palliative care should be included in her treatment goals. Several non-drug therapies were employed to attempt to alleviate the patient's agitation and depression. For example, the nursing staff would often hold her hand and assist her to participate in simple exercise and musical events in activity room. Regular family visits were encouraged.

### Conclusion

Depression and dementia are common and often co-exist among NH residents. The use of antidepressants is epidemic in this vulnerable population. However, the evidence for the efficacy of antidepressants in depressed NH residents with dementia is inconsistent and conflicting. Antidepressants are associated with multiple adverse effects. We believe that the use of antidepressants should be reduced



in this population. We propose a practical step-wise approach to prescribing antidepressants for this vulnerable population in the absence of good evidence. A large RCT to test the effectiveness of antidepressants in depressed NH residents with dementia is urgently needed.

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