Use of Antipsychotics for the Treatment of Behavioral Symptoms of Dementia

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Abstract

Antipsychotic medications are widely used in the management of behavioral and psychological symptoms of dementia. While nonpharmacological interventions should be the first-line treatment for behavioral symptoms of dementia, these are often unfeasible and/or ineffective. Conventional and atypical antipsychotic agents appear to have modest to moderate clinical efficacy in the treatment of these symptoms, though it is unclear which individual agents are most effective. No conclusive evidence exists that any available alternative medications are safer and more effective than antipsychotics. A number of studies have shown an increased risk of mortality associated with antipsychotics in patients with behavioral symptoms of dementia, though the observed risk increase may be partially confounded by illness severity and/or preexisting health determinants. The mechanisms of increased mortality risk are not fully established, but are likely to involve cardiovascular events. It is probable, though not certain, that conventional antipsychotics are associated with a greater number of poor outcomes than atypical antipsychotics. In certain patients with refractory behavioral symptoms, antipsychotics are a viable treatment option. Key considerations for antipsychotic prescribing for this population are published in regulatory guidelines, and include minimization of dosage and duration of treatment, continuous reevaluation of symptoms, and involvement of caregivers.

Keywords

antipsychotics, behavioral symptoms, dementia, nursing homes
dangerous behavior requires attention and resources that are not always available. The use of antipsychotic medications in nursing homes is extensive. The 2004 National Nursing Home survey found that 26% of nursing home residents received an antipsychotic; 40% of these were off-label.6

The prescribing of antipsychotic medications to nursing home patients with dementia is a controversial and polarizing issue. Reports in the lay press often allege that antipsychotic use in nursing homes constitutes elder abuse and unethical use of “chemical restraints.”7–9 This has complicated critical, evidence-based assessments of whether antipsychotics are a viable option for the treatment of behavioral symptoms of dementia. The purpose of this review is to evaluate the circumstances under which antipsychotics could be useful in this population, and to pose clinical considerations to ensure their appropriate use. Based on a search of the PubMed database, the review will draw from a representative (although not necessarily completely comprehensive) sampling of literature that addresses the efficacy, safety, and therapeutic role of antipsychotics in dementia.

Controversy Surrounding Antipsychotics for Behavioral and Psychological Symptoms of Dementia

The allegation that antipsychotic prescribing for dementia patients is categorically unnecessary, dangerous, and even unethical is sometimes expressed by the lay press, plaintiff’s attorneys, patient advocacy groups, medicolegal experts, and health care professionals.10–18 These claims may be driven in part by valid though anecdotal reports of dementia patients who experienced poor outcomes attributable to antipsychotic drug use. Proponents of this view generally raise issues relating to staffing of care facilities, “chemical restraints,” inappropriate Medicare billing, pharmaceutical promotion for off-label prescribing, and mortality risk associated with antipsychotics (Table 1).

In response to these issues, government agencies, patient advocacy groups, and professional societies in the United States and elsewhere in the world have developed approaches to modifying and reducing the extent of antipsychotic prescription in nursing homes.19–26 The problem of understaffing of nursing homes is an unfortunate reality, and inappropriate prescribing and/or promotion of antipsychotics likely does occur. There is no clear evidence as to the past or present incidence of these infractions. Regarding the FDA Black Box Warning, this in general is an objective statement of observed risk that does not reflect the potential benefits of a drug, nor does it mean that an individual patient should or should not receive the drug.18 For example, SSRI antidepressants carry a Black Box Warning regarding suicidal ideation in children and adolescents, yet these drugs are among the most widely prescribed—often with considerable therapeutic benefit—for these populations. Some expert and government groups have, with a correct interpretation of the Black Box Warning in mind, taken a position on the appropriateness of antipsychotics for dementia. A 2011 report from the American Society of Consultant Pharmacists concluded that an antipsychotic may be appropriate in some dementia patients, provided the medication is appropriately indicated (where an off-label prescription is not equivalent to an inappropriate indication), a specific and documented goal of treatment exists, the patient is closely monitored, and the medication is used as sparingly as possible.25 In addition, guidelines released by the Centers for Medicare and Medicaid Services in 2013 stated that an antipsychotic may be appropriate only when used to treat specific symptoms related to a documented, diagnosed medical condition.26

Alternatives to Antipsychotics for Behavioral Symptoms of Dementia

Both pharmacological and nonpharmacological alternatives to antipsychotic use have been studied, with nonpharmacological interventions universally considered first-line treatment.27–32 A 2014 panel formulated

Table 1. Points Commonly Discussed by Opponents of Antipsychotic Medication Use in Patients With Behavioral and Psychological Symptoms of Dementia

<table>
<thead>
<tr>
<th>Point</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Nursing homes are inadequately staffed and do not have the capacity to manage difficult behaviors nonpharmacologically. Thus, antipsychotics are tantamount to “chemical restraints” used primarily for the convenience of the nursing home staff, not for the well-being of the patient. When such “restraints” are used, informed consent is often withheld from families before an antipsychotic is prescribed.</td>
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<tr>
<td>2.</td>
<td>Legal action has been initiated against individual nursing homes accused of billing Medicare for unnecessary medications or prescribing for unapproved indications.13–15 One government report found that 51% of Medicare claims for atypical antipsychotics in 2007 were “erroneous.”17 Pharmaceutical manufacturers have also been fined for “aggressively” marketing antipsychotics to nursing homes for non-FDA-approved indications.13–15 Events of this type are used to support the view that a profit motive partially underlies the prescribing of antipsychotics in dementia.</td>
</tr>
<tr>
<td>3.</td>
<td>The FDA has issued a Black Box Warning regarding an increased risk of mortality in elderly dementia patients prescribed an antipsychotic.18 Opponents of antipsychotic prescribing interpret these warnings as evidence that the majority of prescribing of these medications in this context is dangerous and contraindicated.</td>
</tr>
</tbody>
</table>
a “Dice” approach to behavioral symptoms of dementia (“Describe, Investigate, Create, Evaluate”), which stresses that a provider must investigate and rule out an environmental cause of any problem behavior before considering any medication. Caregiver education is also a critical component of nonpharmacological management, given the possibility that controllable factors (e.g., temperature, pain, or specific fears) underlie the agitation seen in a certain percentage of patients with behavioral disorders. One study reported that prophylactic pain management in dementia patients produced a therapeutic effect similar to that seen with antipsychotics, though this approach included the use of analgesics. Personalized social interaction, psychosocial treatment, simulated presence therapy, and reminiscence therapy also produce a modest clinical benefit, as do sensory and music therapies. When behavioral symptoms take the form of “sundowning,” melatonin therapy has been associated with at best modest symptom improvement; light therapy has also been investigated in these patients. Most of these interventions are difficult to study because in randomized, controlled trials, researchers and observers cannot easily be blinded.

It is likely that non-drug therapies alleviate agitation on a short-term basis in some fraction of dementia patients. However, these interventions require considerable human resources that are not necessarily available in many nursing homes, and they are less likely to be effective in acute or emergent situations in which a patient poses a danger to him/herself or others.

Drug therapies that are potentially safer and more effective than antipsychotics have been evaluated. Citalopram, an SSRI antidepressant, produces a statistically significant reduction in patient agitation, and also leads to reduced anxiety on the part of caregivers. However, the efficacy of citalopram was compared only to placebo, as opposed to a comparator antipsychotic; in addition, this study reported adverse cognitive and cardiac effects associated with citalopram. Finally, citalopram, due to its mechanism of action, is unlikely to be effective as an agent treatment for patients with acute intermittent agitation, as opposed to persistent agitation. Galantamine, an acetylcholinesterase inhibitor, was shown slightly inferior to risperidone, an antipsychotic, in a randomized, controlled trial. The combination of dextromethorphan and quinidine had clinically significant efficacy in at least 1 study, although it has not been directly compared to antipsychotics. A number of other new and existing compounds, including carbamazepine, cannabinoids, mibampator, and prazosin, are currently under investigation, though no conclusive evidence about their benefits is yet available. Thus, antipsychotics remain a widely used option for the treatment of behavioral symptoms of dementia in part because no other class of medications has a risk-benefit ratio established as being more favorable.

### Efficacy of Antipsychotics for Behavioral Symptoms of Dementia

Antipsychotics are not FDA-approved for this purpose, and published evidence has not conclusively validated their efficacy. A large meta-analysis (n > 100,000) evaluating the efficacy of 4 atypical antipsychotics in North American nursing homes yielded inconsistent conclusions. A smaller meta-analysis (n = 1683) found, in general, no statistically or clinically significant behavioral symptom improvement in patients receiving antipsychotics compared to placebo. A 2-year longitudinal study of nursing home residents with dementia found that antipsychotics were not associated with improvement in cognition or activities of daily living. In a multicenter placebo-controlled trial, risperidone, olanzapine, and quetiapine could not be distinguished from placebo in terms of efficacy in elderly dementia patients with psychosis, aggression, or agitation. At least 1 further study has raised the question of whether antipsychotics are superior to SSRIs for the treatment of behavioral symptoms of dementia.

However, other evidence indicates that antipsychotics have at least modest efficacy. Two meta-analyses of randomized, placebo-controlled trials involving atypical antipsychotics (aripiprazole, olanzapine, quetiapine, risperidone; n = 5050 and 2511) found consistent, statistically significant symptom improvement in patients receiving antipsychotic compared to placebo. Two further literature reviews concluded that aripiprazole and risperidone significantly improve both psychiatric symptoms and cognition after 3 months of treatment, with olanzapine associated with significant improvement in 1 of the reviews. In all, antipsychotics appear to be at least comparable to placebo and possibly meaningfully efficacious in the treatment of behavioral symptoms of dementia.

Two important issues are not fully resolved. First, are conventional or atypical antipsychotics more effective? One study has demonstrated significantly greater efficacy for olanzapine and risperidone compared with promazine, but similar studies of this type are scarce. Second, within each class, which agent(s) are most effective? Recent literature has not resolved this question, with the relative efficacy of 4 atypical antipsychotics dependent on which rating scale was used to assess symptoms. Without these guidelines, clinicians who prescribe antipsychotics at present often base their therapeutic approach on their own clinical experience and/or institutional habit.
Adverse Events and Excess Mortality Associated With Antipsychotics

In April 2005, the FDA first issued a warning regarding an increased risk of sudden death in elderly dementia patients prescribed atypical antipsychotics. Although the FDA bulletin stated that it was based upon “seventeen placebo controlled trials performed with olanzapine, aripiprazole, risperidone or quetiapine in elderly dementia patients with behavioral disorders,” the results of these trials were not made available to the public. In 2008, the agency attached a Black Box Warning applicable to all atypical antipsychotics, citing an increased risk of death in elderly dementia patients. It is not clear whether the Black Box Warnings brought about a subsequent decrease in antipsychotic use for behavioral symptoms of dementia. In the same year, regulators also issued a new advisory that postulated a similar risk of excess mortality in dementia patients for both conventional and atypical antipsychotics. In neither document were data from randomized, placebo-controlled trials released. The FDA alert regarding conventional antipsychotics cited 2 retrospective cohort studies as evidence that these drugs increase the risk of death compared to no treatment. However, the briefing itself commented, “The methodological limitations in these two studies preclude any conclusion that conventional antipsychotics have a greater risk of death with use than atypical antipsychotics.”

Does the published evidence (not including the elusive “seventeen placebo controlled trials”) support the FDA’s ruling on atypical and/or conventional antipsychotics? The FDA’s comment on “methodological limitations” introduces an important caveat. Confounding by the severity of the underlying illness may seriously compromise the validity of conclusions from case-control studies evaluating the relative risk of mortality among dementia patients. For antipsychotic versus no-treatment or other-treatment comparisons, the core methodologic limitation is that patients prescribed an antipsychotic tend to have worse dementia and so have an increased mortality risk for this reason alone. For trials comparing conventional versus atypical antipsychotics, clinicians might favor prescribing one class over another depending on the nature and severity of the underlying disease. This methodologic limitation can in principle be overcome through prospective, randomized, placebo-controlled trials to determine the relative mortality risks.

In a review of randomized, placebo-controlled trials of atypical antipsychotics in elderly dementia patients, the relative risk of death in the treatment group relative to controls was found to be 1.52. The number of deaths was 46 out of 2071 patients in the placebo group (2.2%), and 120 out of 3336 in the antipsychotic group (3.6%). In an earlier study, the relative risk was 1.54, with 41 deaths out of 1851 patients (2.2%) and 118 out of 3353 patients (3.5%) in the placebo and antipsychotic groups, respectively. However, a third large review found the relative risk to be 1.06, which was not statistically significant, although the same study reported significantly more frequent adverse events in the active treatment group. An earlier, smaller meta-analysis (n = 1721) also found no increased mortality risk in dementia patients treated with risperidone versus placebo. In these analyses, there was considerable overlap and redundancy in the trials that were considered. In general, the weight of published placebo-controlled trials on this question is somewhat limited. The available evidence suggests that atypical antipsychotics when used in dementia patients carry a risk of mortality that is no less—and possibly greater—than that of placebo. There is no clear evidence that establishes which specific atypical antipsychotic is associated with the greatest risk. A large review of studies comparing individual agents found evidence insufficient to suggest whether any particular agent is safest or most hazardous.

Studies comparing the safety risk associated with atypical antipsychotics versus typical antipsychotics have not been fully conclusive. At least 1 review of retrospective studies comparing conventional antipsychotics to placebo concluded that conventional and atypical antipsychotics carry a similar mortality risk. An analysis of 17 placebo-controlled trials (n = 2387) concluded that conventional antipsychotics do not increase the risk of death compared to placebo in elderly patients. A review of major cardiac adverse events associated with antipsychotic agents found no clinically significant difference between conventional and atypical agents. In 1 study, autopsy data also suggested that haloperidol is not associated with sudden death in dementia patients. However, 1 retrospective study found a greater relative risk associated with conventional antipsychotics, as did 3 reviews of observational studies. One of these found that hip fracture, stroke, myocardial infarction, and ventricular arrhythmia are among the factors that explain the mortality difference between conventional and atypical agents. A further review, which adjusted its relative risk calculations to account for confounding by terminal illness, also found conventional agents to carry a greater relative risk of mortality than atypical agents. It appears, therefore, that conventional agents have at best a safety profile similar to atypical agents, but most likely carry a significantly increased relative mortality risk.

If an excess mortality hazard exists with conventional or atypical antipsychotics, one potential mechanism of drug-related deaths is a cardiovascular
event. Many conventional antipsychotics have significant affinity for the hERG potassium channel (hERG potassium channel); this can lead to prolongation of the QTc interval and potentially to torsades de pointes, a precursor of ventricular tachycardia. Thioridazine, pimozide, and sertindole are considered to have relatively high risk in this context. Atypical antipsychotics tend to have lower but nonzero hERG affinity; risperidone prolongs QTc without affecting QTc dispersion, which would be necessary to induce ventricular arrhythmia. A large review of QTc prolongation and torsades de pointes associated with atypical antipsychotics concluded that atypical antipsychotics do cause varying degrees of QTc prolongation, although not necessarily associated with torsades de pointes. The rarity of serious arrhythmias precluded a conclusion about the relative risks associated with individual drugs. As with the risk of all-cause mortality associated with antipsychotics, the risk of sudden cardiac death associated with antipsychotics cannot be adequately assessed through retrospective case-control studies. The available evidence based on placebo-controlled trials suggests that, if antipsychotics increase sudden cardiac deaths in dementia patients, the mechanism may well involve QTc prolongation. Acute myocardial infarction is another proposed mechanism of antipsychotic-associated sudden cardiac death. Dopamine type 3 (D3) receptor blockade has been suggested to initiate a thrombogenic cascade and therefore could mediate an increased risk of myocardial infarction. Venous thromboembolism has also been suggested as a mechanism of antipsychotic-associated mortality, although the literature on this question is almost exclusively limited to retrospective case-control studies. A longitudinal study found that the risk of thromboembolism may be mediated by the onset of hyperprolactinemia, a known adverse effect of atypical antipsychotics, although the incidence of this event in elderly dementia patients is not known. Finally, sedating antipsychotics may increase the risk of aspiration pneumonia as a cause of death; 1 study showed a higher relative risk of pneumonia associated with atypical agents versus conventional agents, although this finding has not been replicated. Overall, further investigation is needed to establish the mechanism by which antipsychotics may increase the risk of cardiac death, and what the individual patient risk factors might be.

**Clinical Considerations**

Nonpharmacological management should be the initial approach to patients with behavioral and psychological symptoms of dementia. The Centers for Medicare and Medicaid Services have produced a set of dementia care principles that should be followed in the nursing home care of any patient with serious agitation (Table 2). These emphasize the need for personalized care and adequate staffing in nursing homes, such that any new or worsening symptoms may be thoroughly investigated and individually managed. "Sundowning" poses an especially great challenge, since patients who become agitated at night often have a more minimal night staff to care for them; widespread improvement may be needed in the adequacy of nursing home night staffing. In reality, as these guidelines acknowledge, a number of dementia patients will decline to the point at which nonpharmacologic options would be ineffective or incompletely effective—regardless of the adequacy and skill of the nursing home staff—and caregivers will need to consider other approaches. At least 2 additional care algorithms have been devised that may advise clinicians as to when pharmacological interventions should be considered. From a government perspective, the Department of Health and Human Services has issued recommendations to ensure adequate surveillance of Medicare antipsychotic claims, with the goal that all antipsychotic prescriptions be necessary and appropriately indicated (Table 3).

When faced with situations that may require pharmacologic treatment, clinicians can take steps to assure that therapy is ethical, and proceeds with the minimum possible risk. Involvement of family and/or caregivers is essential. Patients with behavioral symptoms may not be able to give informed consent for drug treatment. Consultation from an independent psychiatrist or neurologist may be required for a determination of a patient’s capacity to give informed consent. If a clinician judges that a patient without capacity would benefit most from an antipsychotic, the institution’s administrative representative and/or legal counsel should be consulted to identify the appropriate surrogate to provide consent. In many cases this may be a close family member or other individual able to act as the patient’s advocate or surrogate.

The clinician should then meet with the patient’s family/caregivers and present a series of facts objectively (Table 4). A summary of the meeting, and the specific topics that were discussed, are entered into the patient’s medical record. After receiving this information, the patient’s family/caregivers must weigh a variety of ethical considerations. Other pharmacological options should then be discussed, along with the available evidence regarding their efficacy. The clinician should also offer a realistic prognosis for the patient, including the possible need for more austere nondrug interventions.

If antipsychotic treatment is initiated, the clinician should begin therapy at the lowest effective dose and for
Table 2. Dementia Care Principles

<table>
<thead>
<tr>
<th>Principle</th>
<th>Details</th>
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<tbody>
<tr>
<td>Person-Centered Care</td>
<td>CMS requires nursing homes to provide a supportive environment that promotes comfort and recognizes individual needs and preferences.</td>
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<tr>
<td>Quality and Quantity of Staff</td>
<td>The nursing home must provide staff, both in terms of quantity (direct care as well as supervisory staff) and quality to meet the needs of the residents as determined by resident assessments and individual plans of care.</td>
</tr>
<tr>
<td>Thorough Evaluation of New or Worsening Behaviors</td>
<td>Residents who exhibit new or worsening behavioral symptoms should have an evaluation by the interdisciplinary team, including the physician, in order to identify and address treatable medical, physical, emotional, psychiatric, psychological, functional, social, and environmental factors that may be contributing to behaviors.</td>
</tr>
<tr>
<td>Individualized Approaches to Care</td>
<td>Current guidelines from the United States, United Kingdom, Canada and other countries recommend use of individualized approaches as a first line intervention (except in documented emergency situations or if clinically contraindicated) for behavioral symptoms. Utilizing a consistent process that focuses on a resident’s individual needs and tries to understand behavior as a form of communication may help to reduce behavioral expressions of distress in some residents.</td>
</tr>
<tr>
<td>Critical Thinking Related to Antipsychotic Drug Use</td>
<td>In certain cases, residents may benefit from the use of medications. The resident should only be given medication if clinically indicated and as necessary to treat a specific condition and target symptoms as diagnosed and documented in the record. Residents who use antipsychotic drugs must receive gradual dose reductions and behavioral interventions, unless clinically contraindicated, in an effort to discontinue these drugs.</td>
</tr>
<tr>
<td>Interviews With Prescribers</td>
<td>Surveyors are instructed to evaluate the process of care. Surveyors interview the attending physician or other primary care provider, behavioral health specialist, pharmacist and other team members to better understand the reasons for using a psychopharmacological agent or any other interventions for a specific resident.</td>
</tr>
<tr>
<td>Engagement of Resident and/or Representative in Decision-Making</td>
<td>In order to ensure judicious use of psychopharmacological medications, residents (to the extent possible) and/or family or resident representatives must be involved in the discussion of potential approaches to address behavioral symptoms. These discussions with the resident and/or family or representative should be documented in the medical record.</td>
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Table 3. Recommendations to Ensure Adequate Surveillance of Medicare Antipsychotic Medication Reimbursement Claims16

1. Facilitate access to information necessary to ensure accurate coverage and reimbursement determinations.
2. Assess whether survey and certification processes offer adequate safeguards against unnecessary antipsychotic drug use in nursing homes.
3. Explore alternative methods beyond survey and certification processes to promote compliance with federal standards regarding unnecessary drug use in nursing homes.
4. Take appropriate action regarding the claims associated with erroneous payments.

the shortest duration possible. International prescribing guidelines have been proposed whereby the maximum appropriate duration for antipsychotic use in dementia patients is 12 weeks.10 Table 5 shows stipulations by the Centers for Medicare and Medicaid Services regarding the maximum recommended daily dose of various antipsychotic agents. Any patient receiving an antipsychotic should be monitored as closely and assessed as frequently as possible. Family/caregivers should, if possible, be given frequent updates as to the patient’s status as therapy is initiated. The goal of treatment should be to ease the patient’s distress without producing excessive sedation or incurring undue risk of adverse events. Clinical judgment and experience are needed to select and titrate the dosage of the most appropriate antipsychotic medication.
The patient’s symptoms can no longer be nonpharmacologically managed in a way that preserves the patient’s dignity and/or ensures a reasonable environment for other patients. (Note that if the patient poses an immediate physical danger to the self or others, this is a critical consideration. In this scenario, a caregiver’s consent may not be necessary before starting antipsychotic therapy.)

2. Potentially reversible and treatable causes of the patient’s symptoms have been evaluated and ruled out.

3. There are no approved drug treatments for the patient’s observed symptoms, but based on available evidence and the clinician’s experience, antipsychotics are more likely than not to ease symptoms to a greater degree than placebo. Therefore, the clinician recommends starting antipsychotic therapy at this time.

4. There is considerable, but not overwhelming, evidence that antipsychotics are associated with an increased risk of sudden death in dementia patients. It is not clear which individual drugs carry a greater or lesser mortality risk. (It may be useful for clinicians to provide their own experience with this clinical situation.)

5. The FDA has issued a Black Box Warning regarding the above risk. However, this does not mean that the patient is likely to die once he or she begins antipsychotic therapy, or that prescribing is not permitted. The absolute risk with any drug is small. A Black Box Warning is a cautionary statement regarding the risks associated with a drug, not a statement as to whether the potential benefits may outweigh the potential risks.

### Conclusion

Conventional and atypical antipsychotics may have modest efficacy in the management of patients with behavioral and psychological symptoms of dementia. However, a risk of excess mortality has been consistently observed in dementia patients treated with antipsychotics. The mechanism of mortality may be cardiovascular in nature, involving either arrhythmia susceptibility from QTc prolongation or increased thrombogenesis. Conventional antipsychotics are likely to carry a greater risk of mortality than atypical antipsychotics, in addition to the known risk of extrapyramidal side effects (involuntary movement disorders) associated with these drugs. It is unclear whether particular conventional or atypical agents are either safer or more hazardous than others.

Guidelines exist about how new or worsening behavioral symptoms should be managed in a nursing home setting; nonpharmacological interventions should always be tried before a new medication is prescribed. However, drug therapy may be necessary in many such patients, especially if they pose a danger to themselves or danger/significant disruption to others.

In the absence of other FDA-approved treatments, antipsychotics remain an option for clinicians, although the treatment of behavioral symptoms with these medications entails considerable precautions. Consultation with caregivers/family and alignment at each step of the treatment process are essential.

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### Declaration of Conflicting Interests
The authors have no conflicts of interest to declare.

### References


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**Table 5. Daily Dose Limits for Antipsychotic Medications Used to Treat Residents With Behavioral Symptoms of Dementia**

<table>
<thead>
<tr>
<th>Antipsychotic Name</th>
<th>Maximum Total Daily Dosage (mg)</th>
</tr>
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<tbody>
<tr>
<td>Chlorpromazine (FG)</td>
<td>75</td>
</tr>
<tr>
<td>Fluphenazine (FG)</td>
<td>4</td>
</tr>
<tr>
<td>Haloperidol (FG)</td>
<td>2</td>
</tr>
<tr>
<td>Loxapine (FG)</td>
<td>10</td>
</tr>
<tr>
<td>Molindone (FG)</td>
<td>10</td>
</tr>
<tr>
<td>Perphenazine (FG)</td>
<td>8</td>
</tr>
<tr>
<td>Thoridazine (FG)</td>
<td>75</td>
</tr>
<tr>
<td>Thiothixene (FG)</td>
<td>7</td>
</tr>
<tr>
<td>Trifluoperazine (FG)</td>
<td>8</td>
</tr>
<tr>
<td>Aripiprazole (SG)</td>
<td>10</td>
</tr>
<tr>
<td>Clozapine (SG)</td>
<td>50</td>
</tr>
<tr>
<td>Olanzapine (SG)</td>
<td>5</td>
</tr>
<tr>
<td>Quetiapine (SG)</td>
<td>150</td>
</tr>
<tr>
<td>Risperidone (SG)</td>
<td>2</td>
</tr>
<tr>
<td>Ziprasidone (SG)</td>
<td>(Not adequately studied)</td>
</tr>
</tbody>
</table>

Reproduced from the Centers for Medicare and Medicaid Services (CMS) Guidelines.®

FG, first-generation agent; SG, second-generation agent.

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**Table 4. Topics Proposed for Discussions Between the Treating Physician and the Patient’s Family or Caregivers**

1. The patient’s symptoms can no longer be nonpharmacologically managed in a way that preserves the patient’s dignity and/or ensures a reasonable environment for other patients. (Note that if the patient poses an immediate physical danger to the self or others, this is a critical consideration. In this scenario, a caregiver’s consent may not be necessary before starting antipsychotic therapy.)

2. Potentially reversible and treatable causes of the patient’s symptoms have been evaluated and ruled out.

3. There are no approved drug treatments for the patient’s observed symptoms, but based on available evidence and the clinician’s experience, antipsychotics are more likely than not to ease symptoms to a greater degree than placebo. Therefore, the clinician recommends starting antipsychotic therapy at this time.

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