Antipsychotic Use in Dementia

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Overview

This resource page provides the rationale and evidence for the "IA-ADAPT: Improving Antipsychotic Appropriateness in Dementia Patients" pocket guides and other resources as they relate to antipsychotic use. The bulk of this evidence comes from a systematic review of evidence for off-label use of antipsychotics, commissioned by the Agency for Healthcare Research and Quality (AHRQ). As of this writing, the last update was released on September 27th, 2011 [Maglione et al. 2011]. We encourage users to view the summary guides and full report on the AHRQ website for further details. http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=786

Other key sources of evidence for our pocket guides include Centers for Medicare and Medicaid Services (CMS) guidelines addressing use of antipsychotics in nursing homes [Centers for Medicare and Medicaid Services 2011], and other reviews and individual research studies.

This overview will summarize key points regarding antipsychotic use, as well as other commonly studied medication treatment options. The overview will at times discuss "conventional" (or "typical") antipsychotics. Conventional antipsychotics are mostly older agents, and generally pose a higher risk of movement side effects compared to the newer atypical antipsychotics. Atypical antipsychotics are occasionally referred to as "second generation" antipsychotics.

Before Considering an Antipsychotic

Antipsychotics should not be considered a first-line treatment for problem behaviors, or even psychosis, in people with dementia. They should only be considered when non-drug behavioral management strategies have been unsuccessful, and the behavior or target symptoms causes danger or severe distress to the person with dementia or others. This is because antipsychotics pose a serious risk of side effects, including an increased risk of death when compared to placebo [Jeste et al. 2008]. It is also important to thoroughly explore the possible causes of the problem behavior or psychosis, and address these causes before considering an antipsychotic. An exception may be short-term use in acutely dangerous emergency situations, where the antipsychotic may be used first for the immediate safety of the person or others and a full evaluation of the underlying source of the problem can then be conducted after the acute situation has resolved. Addressing possible causes of behaviors may include treating a medical condition; discontinuing medications; and altering the environment, routines, activities, caregiver approaches, or other factors that might be contributing to the problem. For further information on assessment and non-drug management strategies, please see *Algorithm for Treating Behavioral and Psychological Symptoms of Dementia: Assessment and Non-Drug Management*.

Appropriate and Inappropriate Treatment Targets for Antipsychotics

CMS guidelines for long-term care facilities list appropriate and inappropriate treatment targets [Centers for Medicare and Medicaid Services 2011]. To be considered an appropriate treatment target, a symptom must present a danger to the person with dementia or others, or cause the person with dementia to experience one of the following:

- Inconsolable or persistent distress
- A significant decline in function
- Substantial difficulty receiving needed care

Appropriate treatment targets include:

- Aggressive behavior
  - Includes particularly physically aggressive or violent behavior that cannot be managed using non-drug strategies (excluding restraints, since restraints have their own serious risks).
- Hallucinations
  - Most often includes seeing or hearing things that are not real. For example, hearing voices or seeing people who aren't there.
  - Antipsychotics should only be used if the hallucinations are distressing to the patient, or causing danger, a significant decline in function, or substantial difficulty providing needed care.
- Delusions
  - False beliefs that a person has in spite of evidence they aren't true. For example, a person may think his/her spouse is having an affair without any reason for believing it, or think family members are imposters.
  - It's important to recognize that, as dementia progresses, patients cannot discern what is real from what is not real. It generally is not helpful to argue with them about false beliefs, or to remind them of distressing things they've forgotten (e.g., the death of a spouse). This may worsen behaviors and agitation.
  - As with hallucinations, delusions should only be treated with an antipsychotic if they're distressing to the patient, or causing danger, a significant decline in function, or substantial difficulty providing needed care.

Inappropriate treatment targets include:

- Wandering
- Unsociability
- Poor self-care
- Restlessness
- Nervousness
- Fidgeting
- Mild anxiety

- Impaired memory
- Uncooperativeness without aggressive behavior
- Inattention or indifference to surroundings
- Verbal expressions or behaviors that do not represent a danger to the patient or others

Antipsychotics are not recommended for these symptoms because any benefits generally do not justify the risks. For most of these symptoms, antipsychotics would provide no benefit. It is also not considered appropriate to use an antipsychotic to induce sedation for the ease of caregiving, except perhaps in extreme cases where symptoms prevent medically necessary care and pose a risk to the person or others as a result.

Antipsychotic Selection

If an antipsychotic is considered necessary for a person with dementia, effectiveness and side effects should be considered when selecting a specific drug for a specific patient. The patient's comorbidities may help determine which side effects are most important to avoid. This will be discussed further under the side effects section.

Cost may also be a factor. Currently available generic medications with some evidence for efficacy in dementia include haloperidol, olanzapine, and risperidone. Olanzapine was not available in a generic form when our mini-lectures were filmed, so this is not noted in the lecture on antipsychotic selection.

Antipsychotic Efficacy/Effectiveness in Dementia

Atypical Antipsychotics: The AHRQ-funded evidence review addressing the off-label use of atypical antipsychotics summarized the strength of evidence for using atypical antipsychotics to treat agitation or psychosis in dementia. Readers should keep in mind that "agitation" is not an appropriate target symptom for antipsychotics, but rather refers to a cluster of symptoms that may include aggressive behavior or other appropriate treatment targets. The evidence review describes the results of randomized controlled trials of four atypical antipsychotics studied in people with dementia: aripiprazole (Abilify®), olanzapine (Zyprexa®), quetiapine (Seroquel®), and risperidone (Risperdal®). As of the time of this writing, there is no strong randomized controlled trial evidence supporting the efficacy of other atypical antipsychotics for this purpose. Table 1 summarizes the evidence on efficacy of atypical antipsychotics in dementia.

Table 1: Summary of Evidence for Efficacy of Atypical Antipsychotics in Dementia

	Aripiprazole (Abilify®)	Olanzapine (Zyprexa®)	Quetiapine (Seroquel®)	Risperidone (Risperdal®)
Dementia overall	+ +	+	+	+ +
Dementia psychosis	+	+ / -	+ / -	+ +
Dementia agitation	+	+ +	+ / -	+ +

+ + = moderate or high evidence of efficacy

+ = low or very low evidence of efficacy

+/ - = mixed results

As can be seen from Table 1, risperidone has the strongest and most consistent evidence suggesting that it is effective for agitation and psychosis in dementia. Aripiprazole is also rated as having strong evidence overall, based on global ratings of severity, though the evidence is rated low or very low for psychosis and agitation. "Dementia overall" should not be mistaken as an indication that these drugs improve cognition or other aspects of dementia beyond the appropriate treatment targets for antipsychotics. These categories reflect different types of measurement scales used in the studies. Olanzapine is rated as having moderate or high evidence of efficacy for agitation in dementia, but as having mixed results for psychosis. This relates to clinical trial results suggesting that olanzapine may worsen psychosis in some patients.

We do not recommend quetiapine as a first-line antipsychotic in dementia based on available evidence. Of four randomized controlled trials of quetiapine for agitation or psychosis in dementia, none have found that quetiapine is more effective than placebo on the main analysis of the primary outcome measure. A secondary analysis of one study suggested that 200 mg/day might be more effective than placebo, but this exceeds the CMS allowable maximum dose for chronic treatment in long-term care facilities (150 mg/day). Overall, the evidence in dementia studies, which mostly included people with Alzheimer's disease, suggests that it has minimal or no effectiveness. It is sedating, however, which may lead to the false appearance of efficacy due to somnolence.

Some studies also suggested that quetiapine worsens cognition in dementia [Ballard et al. 2005, Schneider et al. 2006]. This is not surprising since its active metabolite, norquetiapine, has anticholinergic properties [Seroquel XR® Package Insert 2011]. Anticholinergic medications are known to worsen cognition in dementia, and may be a risk factor for psychosis [Cancelli et al. 2009]. However, all the atypical antipsychotics summarized here showed some capacity to impair cognition and cause confusion in people with dementia, whether or not they are anticholinergic. Olanzapine appears to pose the greatest risk of this side effect [Schneider et al. 2006]. It is also highly anticholinergic, whereas risperidone and aripiprazole have negligible anticholinergic effects [Chew et al. 2008].

Conventional Antipsychotics: Unfortunately, conventional antipsychotics as a class have not been the subject of such a recent and thorough review on use in dementia as the atypical antipsychotics. In general, they also have not been studied in as large of clinical trials in dementia as the atypical antipsychotics, since they have been off-patent for many years. However, the Cochrane Collaboration has published systematic reviews on specific conventional antipsychotics in dementia, haloperidol and thioridazine [Lonergan et al. 2002, Kirchner et al. 2001].

The review on haloperidol suggested that it is effective for treatment of aggression in dementia at doses of 1.2-3.5 mg/day. It concluded that no strong evidence has been found of any significant general improvement of manifestations of agitation other than aggression [Lonergan et al. 2002]. It is notable that haloperidol has a higher risk of movement side effects (e.g., parkinsonism) than the atypical antipsychotics. In clinical trials in dementia, dropouts due to movement side effects were twice as common with haloperidol compared to placebo. Dropouts due to sedation were also twice as common with haloperidol [Lonergan et al. 2002]. Some patients may tolerate the drug, however, particularly at lower doses.

The review on thioridazine stated that there is "no evidence to support the use of thioridazine for dementia." It also notes that it is quite sedating, and has marked anticholinergic properties which may worsen cognition in people with dementia. The review generally recommends against using thioridazine in dementia [Kirchner et al. 2001].

In contrast to these reviews, older meta-analyses had difficulty identifying significant differences among conventional antipsychotics that have been studied for neuropsychiatric symptoms in dementia, despite finding some evidence for efficacy overall. A systematic review published in 2005, which reviewed these meta-analyses and other data, concluded that there is no clear evidence that conventional antipsychotics are effective for treating neuropsychiatric symptoms when defined broadly. This review affirmed the finding of the Cochrane review that haloperidol may have efficacy for reducing aggression [Sink et al. 2005]. It is notable that many low-potency antipsychotics (e.g., chlorpromazine) have potent anticholinergic properties, and can also cause substantial orthostatic hypotension.

Antipsychotic Side Effects Comparison

Antipsychotics are often referred to as 'conventional' or 'atypical' with atypical antipsychotics generally causing fewer extrapyramidal movement side effects compared to conventional antipsychotics. However, the broad categories of atypical versus conventional actually contain very diverse drugs within them. Haloperidol is the only conventional antipsychotic that is discussed in our pocket guides, because it is the only one for which efficacy in dementia is supported by a strong systematic review. Haloperidol does have a higher risk of extrapyramidal movement side effects compared to the atypical antipsychotics. This is reflected in Table 2, which can be found in our pocket guides. The most common extrapyramidal movement side effects include:

- Parkinsonism
    - Symptoms resembling Parkinson's disease, including tremor, tight muscles, cogwheel rigidity, shortened and unsteady gait, swallowing difficulties, and others. This is generally thought to be the most common extrapyramidal movement side effect in older people.
- Akathisia
    - Feeling of internal restlessness that leads to an irresistible urge to move or pace. Difficulty sitting still. This may look like agitation to an observer. This side effect is less frequent in older adults and restlessness more commonly occurs as a consequence of the dementia itself.
- Dystonia
    - Abrupt tensing or contraction of a muscle group that will not relax. Often this occurs in the muscles of the neck or trunk. The person is stuck in a position and can't move the muscles. This requires rapid treatment with anticholinergic drugs for resolution. Occasionally if an acute dystonic reaction does not resolve with anticholinergic medication (e.g., benztropine) , then a benzodiazepine may be necessary for resolution. An acute reaction may require parenteral treatment to achieve the necessary rapid response.
- Tardive dyskinesia
    - Side effect of longer-term use, often characterized by twitching of muscles in the face or trunk. This may be irreversible.

In addition to movement side effects, it is important to consider the risk of mortality with various drugs. All antipsychotics appear to increase mortality in people with dementia. The absolute risk has been estimated as 3.5% in people receiving antipsychotics compared to 2.3% with placebo. The relative risk is about 1.6-1.7. The number needed to harm is 83, meaning that for every 83 people approximately one additional death will occur in antipsychotic-treated patients. The number needed to treat has been estimated to range from 5-14 depending on the drug, meaning that 5-14 people have to be treated in order for one to respond to the antipsychotic. This means that for every 9-25 people helped by an antipsychotic, one death is associated with the antipsychotic treatment [Jeste et al. 2008].

Randomized controlled trials provide insufficient evidence to compare antipsychotics on the risk of mortality. All antipsychotics seem to increase risk of death [Jeste et al. 2008]. However, a growing body of evidence from observational studies examining both community-based and long-term care cohorts suggests that the risk may be higher with conventional antipsychotics. A large study of Medicaid beneficiaries residing in nursing homes using data from 45 states on over 80,000 patients found that about 30% of patients receiving conventional antipsychotics died within 180 days of initiation, compared to about 20% of those receiving atypical antipsychotics. The investigators used multiple contemporary approaches to adjust for patient characteristics and consistently found an elevated risk with conventional antipsychotics. These studies raise concern that conventional antipsychotics such as haloperidol may pose a higher risk of mortality compared to atypical antipsychotics [Huybrechts et al. 2011].

In addition to the increased risk of mortality, antipsychotics appear to increase the risk of stroke in people with dementia. In 2006, a pooled analysis of randomized controlled trials of atypical antipsychotics found that cerebrovascular events occurred in 1.9% of those receiving atypical antipsychotics compared to 0.9% receiving placebo [Schneider et al. 2006b]. The rate was not elevated with quetiapine, though the available data was insufficient to rule out risk. Observational studies have found comparable risk among people receiving conventional or atypical antipsychotics [Jeste et al. 2008].

Table 2 compares the antipsychotics on the risk of a number of other important side effects. We chose to use boxes and colors to compare risk of each side effect among antipsychotics instead of using specific numbers to illustrate side effect risk. This is because different sources provide different information, and it is difficult to decide which specific number to use as a rate. The evidence used to create this table comes from the AHRQ systematic review on off-label use of antipsychotics [Maglione et al. 2011], the CATIE-AD trial that compared antipsychotics in dementia [Schneider et al. 2006], two Cochrane systematic reviews [Lonergan et al. 2002, Ballard et al. 2006], and a review of the cardiovascular risks of atypical antipsychotics [Drici and Priori 2007]. The number of boxes reflecting risk should be interpreted as a qualitative and subjective summary of the various adverse event rates found from different sources, and not a reflection of absolute rates.

The table can be used to select a medication based on patient comorbidities. For example, olanzapine is probably a poor choice for a person with obesity, diabetes, or hyperlipidemia, since it may induce metabolic side effects on its own as well as exacerbate preexisting conditions. In a person who is sensitive to extrapyramidal movement side effects, haloperidol usually isn't the best choice. Quetiapine causes the most sedation, but has a very low risk of movement side effects. It might be an option for people at high risk of movement side effects, except that the vast majority of evidence suggests that it is ineffective.

Urinary symptoms related to antipsychotics were identified as a safety signal in the AHRQ systematic review [Maglione et al. 2011]. The comparison of drugs in this regard was difficult. The highest rate of urinary symptoms was reported in people receiving aripiprazole compared to what was reported with other drugs. Thus, it was assigned an extra box suggesting higher risk. However, the rate was also higher in the placebo groups in studies of aripiprazole, to the extent that the odds ratio for urinary symptoms with aripiprazole versus placebo was non-significant (OR 1.37, 95% CI 0.92-2.09). Thus, the higher rate may have actually reflected better reporting of urinary symptoms in these studies or differences in patient populations treated. The odds ratio for urinary symptoms was actually numerically highest with olanzapine despite a much lower reported rate of urinary symptoms (OR 9.51, 95% CI 1.47-401.07), next highest for quetiapine (OR 2.37, 95% CI 1.16-5.15), and next highest for risperidone (1.55, 95% CI 1.13-2.13). The numbers needed to harm were 16 for quetiapine, 21 for risperidone, and 36 for olanzapine. Ultimately, it is difficult to fully differentiate the risk of this side effect with these drugs given the variability in the rates among placebo groups in these trials.

Table 2: Antipsychotic Side Effects Comparison

Drug *Brand Name* (daily dose range)	Aripiprazole *Abilify* (2-10 mg)	Haloperidol *Haldol* (0.25-2 mg)	Olanzapine *Zyprexa* (2.5-7.5 mg)	Quetiapine *Seroquel* (12.5-150 mg)	Risperidone *Risperdal* (0.25-2 mg)
Movement Side Effects[1]	■■	■■■	■■	■	■■
Central Nervous System					
Sedation	■■	■■	■■■	■■■■	■■
Confusion, delirium, cognitive worsening	■	0	■■	■	■
Worsening psychotic symptoms	0	0	■	0	0
Cardiovascular/Metabolic					
Orthostatic hypotension	■?	■■	■	■?	■?
Edema	■?	0	■	0	■■
Weight gain/glucose ↑	0	■?	■■■	■	■■
Triglyceride ↑	0	0	■■■■	■■■	0
Urinary incontinence, UTI	■■■	■■	■■	■■	■■

■= more boxes indicates greater risk. Colors are darker with increasing risk.
■? = evidence poor in dementia, but evidence in other conditions indicates some risk
0 = no clear evidence that the drug causes this side effect in a clinically important way, or very rarely
[1] Movement side effects = parkinsonism, akathisia (restlessness), dystonia, tardive dyskinesia

Antipsychotic Dosing and Dosage Forms

Doses: CMS provides specific recommendations for antipsychotic doses that are acceptable for chronic use in long-term care facilities. These provide reasonable guidance for the dosage ranges that might be considered acceptable in patients with dementia. Occasionally, higher doses are used for acute treatment. Generally, starting with a very low dose is recommended to reduce the chance of side effects, and to ensure that the lowest necessary dose is used. The dose ranges considered acceptable by CMS for use in long-term care facilities are listed in Table 3.

Timing: Antipsychotics are usually given once daily at night prior to bedtime. This may help reduce sedation-related adverse effects. In patients with sundowning, or behaviors and psychotic symptoms that arise late in the day, they are sometimes given in the evening prior to the usual time of onset of symptoms. It is important to monitor for sedation-related adverse effects, especially when the drug is given some hours before bedtime.

Dosage Forms: Table 3 also describes various dosage forms that are available other than standard tablets. It should be noted that rapidly disintegrating tablets are absorbed at the same rate as standard tablets, according to pharmacokinetic studies of these drugs [Currier and Medori 2006]. They may offer advantages for patients with difficulty swallowing. Regular-release tablets may also be crushed and mixed with food such as applesauce in patients with swallowing difficulty.

Short-acting intramuscular injection preparations of antipsychotics can be used for emergency situations, but are generally not used if the patient will take oral medication. The table does not discuss the availability of long-acting injectable formulations. Haloperidol, olanzapine, and risperidone are available as long-acting injections, but would rarely if ever be recommended for someone with dementia.

We also recommend against the use of topical antipsychotic preparations that are sometimes compounded by pharmacies. We are unaware of any evidence to guide proper dosing, and it is unclear whether they are absorbed consistently or at all. As an example, a recent study of a topical gel containing haloperidol, lorazepam, and diphenhydramine found that no haloperidol or lorazepam was detectable in the blood stream up to 4 hours after application. Diphenhydramine absorption was minimal and erratic [Smith et al. 2011]. Uncertainties about absorption raise concerns about effectiveness, patient safety, and prescriber liability if an adverse event was to occur. While some patients may improve when given topical antipsychotic formulations, one has to ask whether it is because they are being given attention and touch when the formulation is applied, or whether it's really because of the antipsychotic contained in the topical formulation.

Table 3: Antipsychotic Dosing and Dosage Forms

	Starting Dose (mg/day)	Maximum Dose for Maintenance* (mg/day)	Special Dosage Forms**
Aripiprazole	2-5	10	ODT, L , IM
Haloperidol	0.25	2	L , IM
Olanzapine	2.5-5	7.5	ODT, L , IM
Quetiapine	12.5-25	150	XR
Risperidone	0.25-0.5	2	ODT, L

*per CMS regulations for long-term care facilities. Doses for acute treatment sometimes exceed maintenance doses [CMS 2011].
**ODT = orally dissolving tablet, L = liquid, IM = short-acting intramuscular, XR = extended release.

Guidance for Special Populations: frontotemporal dementia, Parkinson's disease, Lewy body dementia, renal impairment, hepatic impairment

Frontotemporal Dementia (FTD)

FTD differs from other dementias in its pathophysiology and response to treatment. The frontal and temporal lobes of the brain that are primarily damaged are responsible for maintaining social appropriateness of behaviors, among other things. This damage can lead to socially inappropriate behavior, changes in personality, a lack of empathy for others, poor financial judgment, impulsiveness, and apathy. Language deficits are common, particularly problems with expression, naming difficulties, and difficulty remembering the meaning of words. Early in the disease memory is usually intact, though it worsens later. This is in contrast to Alzheimer's disease, in which social appropriateness is usually

maintained in the early stages of disease but memory problems are a major feature. Other symptoms of FTD can include overeating, including unusual compulsive dietary patterns. Parkinsonism can occur in certain types of FTD. Early symptoms of FTD are commonly misdiagnosed as primary psychiatric disorders [McKhann et al. 2001]. Though it makes up a relatively small proportion of dementias overall, FTD is about as common as Alzheimer's disease in people 45-64 years of age, occurring at a rate of about 15 per 100,000 people. Alzheimer's and other dementias are predominant among older age groups [Cardarelli et al. 2010].

Medications for Behavioral Symptoms in FTD

Clinical trials of various medications have been conducted for FTD, though medications have not been studied to the extent that they have in other more common types of dementia. Unfortunately, the results of most clinical trials have not been very promising to-date. Therefore, prescribing in clinical practice often comes down to trial and error, or N of 1 trials [Huey et al. 2006]. Small trials have been conducted suggesting possible benefits from certain medications, however, which provide some guidance when sorting through treatment options.

Antidepressants: Antidepressants that affect serotonin have been studied for behavioral symptoms in FTD, based in part on observations of damage to the serotonin system in FTD. Despite these observations, a number of studies were not able to show reductions in cerebrospinal fluid serotonin metabolites in FTD, though some studies found non-significant trends in that direction [Huey et al. 2006]. At least three small controlled studies of antidepressants have been conducted [Deakin et al. 2003, Moretti et al. 2002, Lebert et al. 2004].

Paroxetine (Paxil®) was studied at a dose of 40 mg/day in a 6-week randomized placebo-controlled trial for FTD patients. In contrast to open label studies suggesting a benefit of SSRIs on behavior, this study showed no benefit of paroxetine for behavioral symptoms. The trends in rating scales actually suggested that paroxetine might have worsened behavioral symptoms. Cognition was worsened significantly in the paroxetine group compared to placebo, possibly reflecting the anticholinergic properties of this drug [Huey et al. 2006, Deakin et al. 2003].

Paroxetine was studied at a dose of 20 mg/day in another 14-month randomized trial, compared to piracetam. The study included 8 patients per group. No differences were seen in cognition, with both groups worsening from baseline. However, neuropsychiatric symptoms improved in the paroxetine group, and were significantly less than with piracetam. Transitory nausea occurred in 3 of 8 patients who received paroxetine and resolved within 10 days. No other adverse effects were noted, other than worsening of agitation and aggressiveness in half of the piracetam-treated patients. It is difficult to determine whether both paroxetine and piracetam worsened cognition during this study, or if this was a result of disease progression and not the drug. Thus, this study is slightly more supportive of paroxetine use in FTD, particularly at this lower dose, but leaves unanswered questions about its safety [Moretti et al. 2002].

Trazodone, an antidepressant with mixed and unique pharmacology, was studied in 26 FTD patients in a double-blind placebo-controlled crossover study at doses up to 300 mg/day. In contrast to others, this study showed a significant decrease in neuropsychiatric symptoms with the drug, and no changes in cognition. Despite some efficacy, about half of patients had a treatment-emergent adverse event. These included fatigue, dizziness, hypotension, and cold extremities. It is difficult to discern whether the benefits observed in this study were due to anything other than sedation. However, this study suggests trazodone may be a reasonable option to help manage behaviors in FTD given the limitations of evidence on other treatments [Huey et al. 2006, Lebert et al. 2004].

Cholinesterase Inhibitors: Evidence on cholinesterase inhibitor use in FTD suggests little if any benefit, and potential harm in some subjects. The lack of benefit is consistent with observations that the cholinergic neural system remains relatively intact in FTD [Huey et al. 2006].

Only one randomized controlled trial of a cholinesterase inhibitor in FTD has been published to date. Galantamine (Razadyne®) was studied in a group of 36 FTD patients with either predominant behavioral manifestations or primary progressive aphasia. In this study, all patients received galantamine for 18 weeks. They were then randomized to either continued galantamine or placebo for 8 more weeks. No differences were identified in behavior or language for the group as a whole, suggesting that galantamine is not of benefit for behavioral symptoms. A subgroup of patients with primary progressive aphasia showed better global severity scores, but this was not statistically significant after adjusting for multiple comparisons. They also showed stable language scores in contrast to a decline in the placebo group. Overall, this study does not support the use of galantamine in FTD [Kertesz et al. 2007].

While not a randomized or placebo-controlled study, another open label trial examined donepezil (Aricept®) in 12 subjects for 6 months, using 12 FTD patients who did not receive donepezil as controls. The donepezil group had worse FTD Inventory scores after 6 months of treatment, despite similar scores between groups at baseline, suggesting a harmful effect of the drug. No changes in cognition or other measures were seen. Caregivers of 4 patients who received donepezil reported increased disinhibited or compulsive acts, which led to discontinuation of the drug. These problems returned to baseline levels after 4 weeks off of the drug. When these 4 patients were not included in the analysis, no differences between groups was seen. Overall, this study does not support the use of donepezil, and suggests that some patients may be vulnerable to behavioral worsening when they receive donepezil [Mendez et al. 2007].

Antipsychotics or Stimulants: Dopamine deficits have been found in FTD. This has led some to believe that stimulants may be helpful since they increase dopamine neurotransmission and improve executive function in some conditions (e.g., attention deficit hyperactivity disorder). A small amount of evidence supports this theory. Antipsychotics, in contrast, generally block dopamine, so they could conceivably worsen this condition. They are often used clinically to manage FTD behaviors despite a general lack of evidence to support their use. It is notable that some patients with FTD appear to be extra sensitive to extrapyramidal movement side effects of antipsychotics, possibly due to these dopamine deficits [Huey et al. 2006].

No randomized placebo-controlled studies of antipsychotics or stimulants in FTD were identified, though one cross-over study comparing a stimulant to an antipsychotic has been conducted [Huey et al. 2008]. Dextroamphetamine 20 mg/day and quetiapine 150 mg/day were compared in 8 patients with the behavioral variant of FTD in a double-blind cross-over trial, in which the order of drug was randomized. Each drug was given for 3 weeks, with a 1-week washout period between treatments. The study showed improvement in neuropsychiatric symptoms with dextroamphetamine compared to baseline, though there were no significant differences between quetiapine and baseline or quetiapine and dextroamphetamine. Though this study is small and thus preliminary, it suggests there could be some benefit to the use of stimulants. The long-term effect of these treatments in FTD remains unknown [Huey et al. 2008].

Parkinson's Disease and Lewy Body Dementia

Parkinson's disease dementia (PDD) and Lewy body dementia (LBD) share many similarities. Some have argued that the distinction is arbitrary since they are ultimately slightly different manifestations of the same underlying pathologic processes, possibly distinguished by the areas of the brain that are impacted first or to the greatest extent. Both commonly involve cognitive deficits, psychiatric manifestations, and movement disorders. PDD is diagnosed if motor symptoms occurred greater than 12 months prior to the onset of dementia. LBD is diagnosed if dementia symptoms occur before the onset of motor symptoms or within 12 months of the onset of motor symptoms [McKeith 2007].

LBD is characterized by visual hallucinations, fluctuations in attention and cognition, and parkinsonism. While one might expect hallucinations to respond to antipsychotics, these drugs are often harmful to patients with LBD. They can worsen attention and cognition, and lead to life-threatening neuroleptic malignant syndrome (NMS). NMS usually presents with rigidity and fever and autonomic fluctuations, among other symptoms. People with PDD are also more vulnerable to neuroleptic malignant syndrome. In general, people with PDD and LBD may have substantially slowed motor activity and slow cognition, but comparatively their memory may be more intact than other patients with dementia. For this reason, behavioral approaches that permit more time to complete tasks and conduct ADLs may be helpful in avoiding agitation and the need for antipsychotics.

People with PDD or LBD are also extremely sensitive to the extrapyramidal movement side effects of antipsychotics. Many treatments for the movement manifestations of these disorders work by increasing dopamine or stimulating dopamine receptors (e.g., dopamine agonists). Antipsychotics block dopamine, counteracting the effects of dopamine agonists, and thus worsen movement symptoms in people who already have a movement disorder at baseline. Thus, if antipsychotics are used it is best to choose one with a very low risk of movement side effects and use a very low dose. It is unclear that these drugs are effective in PDD and LBD, and even those with the lowest risk of movement side effects can cause severe reactions in these patients. The evidence is discussed further in the subsequent sections on specific drug classes.

Prior to considering an antipsychotic, it is important to consider that Parkinson's disease treatments such as dopamine agonists frequently worsen psychosis. It is often advisable to decrease the dose of antiparkinsonian medications to see if the psychotic symptoms resolve or become manageable prior to considering an antipsychotic [Weintraub and Hurtig 2007].

Medications for psychosis and related symptoms in PDD and LBD

The number of well-controlled studies of medications to treat neuropsychiatric symptoms in PDD and LBD is limited. However, those studies that have been conducted provide useful information. Medications that have been studied include cholinesterase inhibitors, memantine, and atypical antipsychotics. Evidence suggests that cholinesterase inhibitors, specifically rivastigmine, might lessen hallucinations and improve attention in some patients. Memantine appears to benefit global disease severity, but its effect on neuropsychiatric symptoms is unclear. Antipsychotics pose significant risks, and the few studies that have been conducted do not support their use in PDD and LBD.

Cholinesterase Inhibitors: Cholinesterase inhibitors have been studied to treat neuropsychiatric symptoms in PDD and LBD. Several small randomized placebo-controlled trials of donepezil in PDD showed no benefit on psychiatric symptoms. However, these studies included only people with minimal psychiatric symptoms at baseline [Weintraub and Hurtig 2007]. One large placebo-controlled 24-week study of rivastigmine in 541 patients with PDD was more positive. The rivastigmine group was less likely to report hallucinations as an adverse event [Emre et al. 2004, Weintraub and Hurtig 2007]. A follow-up analysis suggested that rivastigmine provided the greatest benefit for patients with hallucinations at baseline [Burn et al. 2006, Weintraub and Hurtig 2007]. This evidence complements case reports and observations of clinicians suggesting that cholinesterase inhibitors may reduce psychosis in PDD [Weintraub and Hurtig 2007]. Side effects of rivastigmine included nausea, vomiting, tremor, anorexia and dizziness. Movement symptoms overall did not differ between groups [Emre et al. 2004, Weintraub and Hurtig 2007].

Another randomized controlled 24-week trial compared donepezil to placebo in 550 patients with PDD [Dubois et al. 2009, Ballard et al. 2011]. The donepezil group performed better than the placebo group on one cognitive test but not another. The overall clinician-rated severity scores favored donepezil, but measures of activities of daily living and neuropsychiatric symptoms showed no difference from placebo. The benefit of donepezil is unclear from these data. It is notable that syncope and carotid sinus hypersensitivity leading to falls has been observed with donepezil [McLaren et al. 2003]. This may be a particular concern in PDD and LBD, since autonomic dysfunction is common. It is unclear whether cholinesterase inhibitors differ in their likelihood of inducing autonomic dysfunction [Ballard et al. 2011]. One randomized placebo-controlled trial evaluated rivastigmine in 120 patients with LBD [McKeith et al. 2000]. A composite neuropsychiatric symptom scale showed greater improvements with rivastigmine compared to placebo, though subscale scores for psychotic symptoms were not reported. Hallucinations at baseline did predict improvements in attention with rivastigmine treatment, however [McKeith et al. 2004]. Side effects included nausea, vomiting, anorexia, and somnolence. No difference in movement symptoms between groups was observed [McKeith et al. 2000, Weintraub and Hurtig 2007].

Overall the strongest data support the use of cholinesterase inhibitors in PDD or LBD, particularly those patients with hallucinations. The best evidence is for rivastigmine. The most common side effects are gastrointestinal, but cardiovascular effects leading to falls are also a concern.

Memantine: Memantine appears to have some benefit in PDD and LBD, and is well-tolerated. However, it is unclear whether it provides benefit for neuropsychiatric symptoms.

Memantine has been studied in 3 randomized placebo-controlled trials in people with PDD or LBD, ranging in size from 25 to 195 participants [Ballard et al. 2011]. All 3 studies allowed people with either a PDD or LBD diagnosis to participate. The smallest study showed that memantine was well-tolerated, and there was a trend towards better global outcomes with memantine [Leroi et al. 2009]. The 2 larger trials, both 24 weeks in duration, showed global improvements with memantine. In one, the memantine group showed improvement in neuropsychiatric symptoms but not cognition. In the other, the memantine group showed improvement in cognition but not neuropsychiatric symptoms. The studies also differed in whether people with PDD or LBD improved to a greater extent [Ballard et al. 2011]. Given the similarities in the pathophysiology and symptoms of these disorders, any observed difference in people classified as one or the other may be irrelevant. A secondary analysis of one study suggested that sleep improved in the memantine group, which has been suggested as a possible explanation for the global improvement observed with the drug [Ballard et al. 2011].

Overall, these studies suggest that memantine may benefit people with PDD or LBD, but they are inconclusive regarding any benefit for neuropsychiatric symptoms. Side effect rates were similar with memantine and placebo in all studies, suggesting that it is well-tolerated [Ballard et al. 2011].

Antipsychotics: The risks of antipsychotics in people with PDD or LBD cannot be overemphasized. Exacerbation of movement symptoms is a likely result of antipsychotic use, and in the worst cases severe reactions such as neuroleptic malignant syndrome (NMS) may be deadly. Cognitive problems may also result from antipsychotic use.

Quetiapine and clozapine have the lowest risk of extrapyramidal movement side effects. This is very likely because they rapidly dissociate from dopamine receptors [Seeman and Tallerico 1999]. They have thus been recommended as the antipsychotics of choice for psychosis in Parkinson's disease, and are sometimes used at very low doses to treat psychosis in this disorder [Weintraub and Hurtig 2007]. However, only one placebo-controlled study in PDD has evaluated an antipsychotic in PDD or LBD. Low-dose quetiapine was tested in patients with PDD, LBD, or Alzheimer's disease with parkinsonism and no benefit was seen [Kurlan et al. 2007, Weintraub and Hurtig 2007]. Other studies in people with Parkinson's disease and psychosis related to dopaminergic drugs have supported the efficacy of low-dose clozapine, but its impact when dementia is present is unclear [Weintraub and Hurtig 2007]. In addition, even clozapine has caused NMS in some patients with PDD or LBD [Ballard et al. 2011]. Clozapine is highly anticholinergic, and quetiapine has a highly anticholinergic active metabolite [Seroquel XR prescribing information, Young et al. 1998]. Thus, there may be a risk of cognitive

worsening in PDD and LBD since anticholinergics can impair cognition [Cancelli et al. 2009]. Use of clozapine is also complicated by the need for frequent blood draws to monitor for drops in white blood cell counts.

Overall, evidence suggests that antipsychotics should usually be avoided in PDD and LBD because of their substantial risks and questionable efficacy. Lowering the dose of dopamine agonists or other movement symptom treatments is recommended as a first option to treat psychosis. If an antipsychotic is deemed necessary for an extreme case, very low dose quetiapine or clozapine are probably better options than other antipsychotics because of the lower risk of movement side effects with these drugs. However, extreme caution and careful monitoring for adverse effects is needed.

Renal Impairment

Product labeling recommends caution and slow titration if risperidone is given to people with renal impairment. This is largely because it has an active metabolite that is eliminated by the kidneys (9-OH-risperidone, also marketed as paliperidone or Invega®). Product labels of other antipsychotics described in the pocket guides do not recommend dose changes in renal impairment.

In dementia, antipsychotics should be started at low doses and titrated slowly regardless of whether renal function is impaired. However, it is important to recognize that it will take longer to reach maximum steady state levels of risperidone and its active metabolite when renal function is impaired.

Hepatic Impairment

Product labeling recommends caution, slow titration, and possibly lower doses of olanzapine, quetiapine, and risperidone when used in people with hepatic impairment. All five antipsychotics highlighted in our tools are metabolized by the liver, so it is wise to use caution with all of them and generally titrate doses more slowly in people with severe liver problems.

Monitoring for Antipsychotic Response

The most important tip for monitoring for response is to be as specific and objective as possible when documenting problem behaviors or psychotic symptoms. A number of behavioral monitoring tools are available for this purpose. "Agitation" is not a good description of a behavior, for example, while "hitting," "kicking," or "biting" is more specific. The circumstances surrounding behaviors are also important to describe in documentation, since these may provide clues on what is triggering the behavior. With objective documentation, it's possible to create charts to describe changes in behaviors over time. If behaviors lessened in severity and frequency after starting an antipsychotic, the drug may have been effective.

It is also important to keep in mind that behaviors change over time with or without drug treatment. If behaviors have been manageable for a while, it is very reasonable to reduce the dose or discontinue the antipsychotic to see if it's actually necessary. While nursing home guidelines require documentation of dose reductions or reasons for not reducing the dose every six months, some experts recommend using

time-limited trials of antipsychotics and reducing the dose or discontinuing after only one or two months of treatment to determine if the drug is necessary. Studies of antipsychotic discontinuation in dementia have shown that many people do not get worse when the antipsychotic is removed, and some actually get better [Thapa et al. 1994, Ballard et al. 2008, Ballard et al. 2011]. Long-term follow-up of one antipsychotic discontinuation trial showed a higher risk of death in people who continued their antipsychotic (mostly risperidone and haloperidol) compared to those randomized to placebo [Ballard et al. 2008, Ballard et al. 2011]. In addition, there were no differences in symptoms between groups after randomization to antipsychotic discontinuation, suggesting that most were not benefiting from continued antipsychotic use. However, there was some suggestion that those with higher levels of neuropsychiatric symptoms at baseline may have benefited from continued treatment [Ballard et al. 2008].

Monitoring for Antipsychotic Adverse Effects

Antipsychotics can cause a multitude of adverse effects. Some of the most catastrophic adverse effects of antipsychotics include falls leading to fracture, stroke, arrhythmias, neuroleptic malignant syndrome, and death. Other adverse effects include extrapyramidal movement side effects, sedation, confusion or worsened cognition, worsening psychotic symptoms, orthostatic hypotension, edema, weight gain, hyperglycemia or diabetes, triglyceride increases, and urinary problems such as urinary tract infection, incontinence, or urinary retention.

Monitoring for many of these adverse effects should occur through carefully observing the patient. Any significant change in health status or new symptom should prompt a more thorough evaluation.

Adverse effects such as orthostatic hypotension, other changes in blood pressure, weight gain, and changes in blood sugar or lipids can be monitored objectively. The recommendations on the pocket guides for glucose and lipid monitoring are based on an expert consensus panel's recommendations for people receiving atypical antipsychotics [American Diabetes Association et al. 2004]. They were not developed specifically for people with dementia who receive these drugs, so providers should use their judgment on whether exceptions should be made. Often people with dementia suffer from weight loss, so weight gain is not always an undesirable effect [Smith and Greenwood 2008]. Hunger induced by some antipsychotics could conceivably result in agitation in some patients, however [Balt et al. 2011]. Other objective monitoring recommendations are based on the time of onset of the adverse effect, as-needed assessments, and standard assessment schedules for nursing home residents.

Some adverse effects can be evaluated using rating scales. For example, the Abnormal Involuntary Movement Scale is the most commonly used scale to assess tardive dyskinesia, a late onset movement side effect that can be permanent. It should be administered at baseline and every six months in people receiving antipsychotics, and also if any new abnormal movements are noted.

Antipsychotics can prolong the QTc interval in a dose-dependent manner, which may contribute to arrhythmias and sudden death. While a baseline electrocardiogram (ECG) is often recommended for people receiving antipsychotics, it is not always done since it is impractical for some settings and

patients. Providers should especially consider monitoring ECGs in people with known cardiovascular disease, a history or family history of syncope, electrolyte disturbances, or who are receiving other drugs that prolong the QT interval [Gupta et al. 2007, Vieweg et al. 2009]. A list of drugs that prolong the QT interval can be found at http://www.azcert.org/medical-pros/drug-lists/bycategory.cfm.

Recommendations for monitoring for antipsychotic side effects can be found in Tables 4 and 5, excerpted from the pocket guides. Note that the Table 4 is meant for clinicians. Table 5 is meant for direct care providers with less training on health conditions and medication side effects. It provides more details of specific observations that should prompt them to contact a clinician or prescriber to further evaluate a sign or symptom.

Table 4: Monitoring for Antipsychotic Side Effects: Clinician Table

Other possible adverse effects include: falls, constipation, urinary tract infection, urinary incontinence or retention, stroke, arrhythmias, and neuroleptic malignant syndrome.

Side Effect	Monitoring
Movement Side Effects	Observation for tremor, gait changes, difficulty swallowing, signs of parkinsonism, restlessness (akathisia), unusual movements (tardive dyskinesia).
	Abnormal Involuntary Movement Scale (AIMS) at baseline, every 6 months, or if movement side effects are suspected.
Central Nervous System	
Sedation	Observation, sedation scale if needed.
Confusion, delirium, or other cognitive worsening	Observation for mental status or behavior changes.
	Delirium screening tool, e.g., CAM (Confusion Assessment Method) if delirium is suspected.
Psychotic symptoms	Observation for worsening symptoms.
Cardiovascular / Metabolic	
Orthostatic hypotension	Observation for signs of dizziness or falls.
	Orthostatic blood pressure (if feasible). Monthly, or if signs of dizziness occur. More frequent on initiation or after dose increase.
Edema	Observation for swelling of extremities.
Weight gain	Monthly weight. Consider weekly for 1 month if overweight. Watch for increased appetite.
Hyperglycemia / Diabetes	Blood glucose at baseline, 3 & 6 months, then q6 months. Also PRN symptoms or mental status change. Monitor symptoms: increased thirst, urination, hunger, weakness.
Triglyceride ↑	Fasting blood lipid panel at baseline, 3 & 6 months, then q6 months. Especially if patient has cardiovascular risk factors: e.g., obesity, diabetes, hyperlipidemia.

Table 5: Monitoring for Antipsychotic Side Effects: Direct Care Provider Table

Side Effect	Report to RN or prescriber if these problems occur
Movement Side Effects	Tremors, tight muscles, changes in walking or falls, abnormal movements like face or eye twitching, drooling.
Central Nervous System	
Sedation	Sleepiness, slow to respond, hard to wake up.
Confusion, delirium, or other cognitive worsening	Worsening mental status compared to normal. Seems more confused; sedated or agitated; worsened communication abilities; problems paying attention; slower movements or speech. These may be a sign of a serious medical illness or a drug side effect.
Worsening psychotic symptoms (delusions or hallucinations)	Hallucinations: seeing, hearing, smelling, tasting, or feeling things that aren't there. Delusions: false fixed beliefs that a person holds in spite of evidence they aren't true. Antipsychotics usually lessen these symptoms, but sometimes make them worse.
Cardiovascular / Metabolic	
Rapid drop in blood pressure on standing	Signs of dizziness or falls. Check an orthostatic blood pressure by checking the blood pressure when lying down and then again shortly after standing. Drugs sometimes cause an unwanted drop in blood pressure.
Swelling	Swelling is most common in the legs and ankles, but can occur in other places.
Weight gain	Big increases in appetite. Hungry even after eating. Unwanted increases in weight.
High blood sugar	Confusion, increased thirst, frequent urination, unusual tiredness, blurred vision. Blood sugar can be checked to see if this might be the cause of these symptoms.
Urinary Symptoms	Changes in frequency—increased, or decreased with urinary retention. Worsened incontinence. Pain on urination. May be infection or drug-related problem.
Constipation	Fewer bowel movements. Hard stools. Poor appetite. Gut pain or distention.

Other Options for Drug Therapy to Manage Problem Behaviors or Psychosis

Many drug therapies have been studied for the treatment of problem behaviors and psychosis in dementia. Few have been shown to be effective when studied in randomized controlled trials, the study design that provides the strongest evidence. This section summarizes evidence for several treatment options that have been historically used in clinical practice. It is notable that most are not recommended given currently available data, while evidence is mixed on others such as antidepressants. A pain control algorithm even in the absence of an identified source of pain was also effective in a recent trial. This evidence applies mostly to Alzheimer's disease, and in some cases to mixed or vascular dementia. Evidence on treatment of frontotemporal dementia, Parkinson's disease dementia, and Lewy body dementia is discussed under the Guidance for Special Populations section on page 9 of this review.

Pain Control

Uncontrolled pain can contribute to behavioral and psychiatric symptoms in people with dementia [Tosato et al. 2011]. People with dementia can have difficulty communicating about their pain, so agitation may sometimes reflect uncontrolled pain. A recent cluster randomized trial using a stepwise pain medication protocol and staff training to improve management of pain found that this reduced agitation in nursing home residents with dementia. It is important to note that these patients were not selected because they were known to be in pain, but rather because they had shown symptoms of agitation for at least a week. The treatment steps and percent of the intervention group receiving them included: step 1—acetaminophen (68%), step 2—oral morphine (2%), step 3—buprenorphine transdermal patch (23%), and step 4—pregabalin (7%). This intervention was effective in reducing agitation in the 8-week trial. Agitation worsened in the 4 weeks after the intervention was discontinued, providing further support that the intervention was effective. Activities of daily living measures and cognition were similar between groups [Husebo et al. 2011].

While factors such as staff training need to be considered when interpreting these results, they support the effectiveness of pain management for reducing agitation. The majority of patients in the intervention group received only acetaminophen, a relatively safe medication at appropriate doses. Therefore, acetaminophen may be considered a first-line treatment for agitation without a known cause. Other pain medications should also be considered if the patient shows signs and symptoms consistent with poorly controlled pain.

Anticonvulsants

Valproate (Depakote®) and carbamazepine (Tegretol®) have been studied to treat agitated behaviors in dementia in randomized controlled trials. Valproate has consistently been found to be ineffective [Lonergan and Luxenberg 2009]. In the most recent and largest study to date, it was found to be ineffective and harmful [Tariot et al. 2011]. The group receiving valproate showed a more rapid cognitive decline than those receiving placebo. The hippocampus, an area of the brain related to memory, also reduced in volume to a greater extent in the valproate group compared to placebo [Fleisher et al. 2011]. Thus, it is possible that valproate accelerates brain damage in dementia. Other noteworthy side effects of valproate include movement disorders (e.g., tremor and gait disturbances),

sedation, diarrhea, and weakness [Tariot et al. 2011]. Given the available evidence, we recommend against the use of valproate.

The little evidence regarding the effectiveness of carbamazepine for agitation or aggression in dementia has been mixed [Sink et al. 2005, Konovalov et al. 2008]. Many clinicians do not use it because of side effects. Drug interactions are also problematic. Early side effects of carbamazepine include ataxia, cognitive impairment, sedation, and nausea. Many of these side effects decrease after time on the drug, but tolerability remains a concern, especially since studies in older people with dementia have not characterized long-term safety and tolerability. In addition, carbamazepine is a strong inducer of cytochrome P450 enzymes 2C19 and 3A4, which are important to the metabolism of many drugs. Use of carbamazepine requires careful attention to these drug interactions and their effect on other drug therapies received by the patient. It is difficult to recommend carbamazepine as a first-line medication given the limited evidence and concerns about adverse effects, though it might be a reasonable option to try for some patients with close monitoring for adverse effects and drug interactions.

Antidepressants

Antidepressants have been studied for both agitation and depression in people with dementia. The bulk of the evidence suggests that they are not very effective, if at all, for treating depression in people with dementia [Bains et al. 2002]. Limited and inconsistent evidence suggests certain antidepressants may reduce agitation and psychosis in people with dementia [Seitz et al. 2011].

Depression: Recent randomized controlled trials have evaluated sertraline (Zoloft®), a selective serotonin reuptake inhibitor (SSRI), for depression in dementia. The largest found no benefit [Rosenberg et al. 2010]. Some believe that an earlier trial showed small positive effects because the inclusion criteria were stricter and captured more severe depression. A key difference was that the earlier trial required a one-week placebo run-in period to confirm that depression was persistent (i.e., both groups get placebo and people who respond are excluded thereafter so that only more persistent depression is included) [Lyketsos et al. 2003]. Mood often fluctuates in dementia, so a person may look depressed at one time point but shift to a better mood with time and positive interactions. Another proposed explanation was that caregivers were provided training and support in the more recent trial in which sertraline was no more effective than placebo. Both the sertraline and placebo groups showed improvement, suggesting that caregiver training and support may be more important than the medication in improving depressive symptoms for people with dementia [Lyketsos 2010]. Despite the mixed evidence, it may be reasonable to consider an SSRI for more severe and persistent cases of depression in people with dementia. However, the possibility needs to be considered that the presence of dementia limits the effectiveness of these treatments, even though they are often effective in people without dementia and may be modestly effective even in the context of dementia.

More common side effects of SSRIs include headache and gastrointestinal disturbances such as diarrhea or nausea. Hyponatremia (low sodium levels) due to syndrome of inappropriate antidiuretic hormone secretion is another side effect to be aware of in older people. This can lead to confusion or delirium,

irritability, fatigue, headache, gastrointestinal symptoms, and other symptoms. SSRIs may also increase the risk of falls, bleeding (e.g., GI bleeds), parkinsonism, and akathisia (restlessness), among other less common side effects [Murphy et al. 2008, Spigset 1999, Jacob and Spinler 2006].

Agitation and Psychosis: Some randomized controlled trials suggest certain antidepressants may produce slight reductions in agitation and psychotic symptoms compared to placebo, but the evidence is mixed and most studies were relatively small. Therefore additional research is recommended by the authors of a systematic review on the topic [Seitz et al. 2011].

SSRIs: Studies of sertraline (Zoloft®) and citalopram (Celexa®), another SSRI, showed slight reductions in agitation and psychotic symptoms with these drugs compared to placebo. Combined analysis of all studies of SSRIs versus placebo also showed some benefit, though this finding was mostly due to one large study. Not all studies showed advantages of SSRIs over placebo. Citalopram had similar efficacy to risperidone, an atypical antipsychotic, in one study, with fewer adverse events. Three studies that compared SSRIs to conventional antipsychotics (haloperidol—2 studies, perphenazine—1 study) did not show statistically significant differences between the SSRIs and antipsychotics, even when the studies were combined and analyzed in a meta-analysis. It is likely that the small sample sizes in these studies may have kept them from identifying differences in safety and efficacy. Overall, there is some evidence that citalopram or sertraline might reduce agitation or psychosis in some patients. Given the side effects of antipsychotics, it would not be unreasonable to consider citalopram or sertraline as a treatment option despite the mixed evidence [Seitz et al. 2011].

Trazodone: Trazodone has also been studied in people with dementia and agitation or psychosis in randomized controlled trials. It is sometimes used for its sedative properties, which some think may be helpful in calming an agitated person. Occasionally prescribers use small doses (e.g., 25 mg) multiple times a day for the sedative effects. As far as evidence, one study compared trazodone to placebo and found no differences in efficacy or tolerability. Two studies compared trazodone to haloperidol, and also found no statistically significant differences in efficacy or tolerability. It is notable that all of these studies were small, which limits their ability to identify differences between treatments. Overall, the evidence on trazodone for treatment of agitation or psychosis is inconclusive, so it is difficult to make a strong recommendation for or against its use. Possible side effects to consider include orthostatic hypotension, falls, and over-sedation, among others [Seitz et al. 2011].

Benzodiazepines

Benzodiazepines are generally not recommended for use in dementia. Case reports and other evidence suggest their use can worsen confusion and increase risk of falls. Cases of paradoxically increased agitation have also been observed in dementia, which may be due to disinhibition related to intoxication by these drugs. Generally, benzodiazepines worsen cognition and should be avoided. Expert consensus recommendations reinforce this position. The occasional use of benzodiazepines for acute anxiety may be acceptable, but they should not be used long-term [Sink et al. 2005]. In particular, long-acting benzodiazepines such as clonazepam and diazepam have a greater likelihood of inducing adverse events

such as falls in the elderly than short-acting benzodiazepines. The duration of action is essentially equivalent to the duration of risk with benzodiazepines, and long-acting benzodiazepines may accumulate over time and cause excessive sedation.

Cholinesterase Inhibitors

Most studies of cholinesterase inhibitors for dementia have not been designed to address their effects on neuropsychiatric symptoms, such as problem behaviors and psychosis. Small benefits have been seen in some trials and a meta-analysis comparing the effect of these drugs and placebo on neuropsychiatric symptoms. The differences were small and not likely to be clinically significant. In addition, studies that have examined these drugs specifically for patients with neuropsychiatric symptoms have shown no benefit. Therefore, these drugs are not recommended specifically to treat problem behaviors or psychosis in dementia [Sink et al. 2005]. Lewy body dementia or Parkinson's disease dementia are exceptions, since cholinesterase inhibitors appear to reduce fluctuations in consciousness and hallucinations in some patients [Ballard et al. 2011, Ballard et al. 2009].

Memantine

Similar to cholinesterase inhibitors, most studies of memantine did not use the drug specifically to target problem behaviors or psychosis. Two studies in people with moderate to severe Alzheimer's disease that examined neuropsychiatric symptoms as secondary outcomes had differing results. One found no difference between memantine and placebo. The other showed a slight worsening of symptoms in the placebo group and no significant change in the memantine group, but this difference was small and of questionable clinical significance. Thus, there does not appear to be an important benefit of memantine on these symptoms. Based on these data, the decision to use or not use memantine should probably not be driven by the presence of problem behaviors or psychosis [Sink et al. 2005].

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