

# Antipsychotics



**What now? Evidence and clinical wisdom support a 5-step evaluation of psychosis and aggression**

# in dementia

## Beyond ‘black-box’ warnings

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**D**iagnosed 7 years ago with Alzheimer’s disease (AD), Mrs. B, age 82, resides in an assisted living facility whose staff is trained to care for older persons with dementia. Over the past 2 months she has shown an escalating pattern of psychosis and aggression, despite one-to-one attention and verbal reassurance.

At first Mrs. B’s psychosis was restricted to occasional rape accusations during assisted bathing and aggression manifested by banging her hand repetitively on furniture, causing skin tears. In the last week, she has been accusing staff and patients of stealing her belongings and has assaulted a staff member and another resident. When supervisors at the facility advise Mrs. B’s husband that she can no longer stay there, he takes her to a local emergency room, from which she is admitted involuntarily to a geriatric psychiatry inpatient unit.

For many patients and families, the most problematic aspects of dementia are neuropsychiatric symptoms—depression, sleep disturbance, psychosis, and aggression. Psychosis affects approximately 40% of persons with AD, whereas  $\geq 80\%$  of persons with dementia experience agitation at some point in the illness.<sup>1</sup> These symptoms can lead to:

- caregiver morbidity
- poor patient quality of life
- early patient institutionalization.<sup>2</sup>

Although no drug has been FDA-approved for treating dementia’s neuropsychiatric symptoms, psychiatrists often use off-label psychotropics—especially antipsychotics—to ameliorate them. This practice is controversial because of public perception that antipsychotics are used in dementia patients to create “zombies” to lighten healthcare workers’ burden. Nonetheless, because dementia patients with psychosis and severe agitation/aggression can pose risks to themselves and those around them, efforts to treat these symptoms are warranted.

continued



## Antipsychotics in dementia

### Clinical Point

Carefully review the patient's drug list for potentially reversible causes of psychosis and agitation

#### Box

### Atypical antipsychotics' 'black-box' warnings: What are the risks?

The FDA warned prescribers in 2003 of increased risk of "cerebrovascular adverse events including stroke" in dementia patients treated with risperidone vs placebo. Similar cerebrovascular warnings have been issued for olanzapine and aripiprazole. Although the absolute risk difference was generally 1% to 2% between antipsychotic- and placebo-treated patients, the relative risk was approximately 2 times higher with antipsychotics because the prevalence of these events is low in both groups.<sup>3</sup>

Perhaps more daunting, after a meta-analysis of 17 trials using atypical antipsychotics in elderly patients with dementia-related psychosis, the FDA in 2005 issued a black-box warning of increased mortality risk with atypical antipsychotics (relative risk 1.6 to 1.7) vs placebo. The mortality rate in antipsychotic-treated patients was about 4.5%, compared with about 2.6% in the placebo group. Although causes of death varied, most were cardiovascular (heart failure, sudden death) or infectious (pneumonia). This warning was applied to atypical antipsychotics as a class. As with cerebrovascular risks, the absolute mortality risk difference was 1% to 2%.<sup>4</sup>

The FDA's "black-box" warnings about using atypical agents in patients with dementia add another layer of complexity to your treatment decisions (*Box*).<sup>3,4</sup> The public is well served by evidence identifying risks associated with prescription medications, but the FDA data do little to help millions of families answer the question, "And so, what now?"

Recognizing that solid empiric evidence is lacking, we attempt to address this lingering question for clinicians, patients, and caregivers who must deal with these symptoms while science tries to provide a more definitive answer.

### 5-step evaluation

A 5-step initial evaluation of persons with dementia who present with psycho-

sis and/or agitation/aggression includes establishing the frequency, severity, and cause of these symptoms as well as the effectiveness of past treatments and strategies (*Algorithm, page 55*).<sup>5</sup>

Because adverse drug effects are a potentially reversible cause of psychosis and agitation, review the patient's drug list—including "as needed" medications—from records at a facility or from family report. Mrs. B's record from the assisted living facility reveals she was receiving:

- atenolol, 25 mg/d
- aspirin, 81 mg/d
- extended-release oxybutynin, 10 mg at bedtime
- psyllium, one packet daily
- hydrocodone/acetaminophen, 5/500 mg every 4 hours as needed for pain
- lorazepam, 1 mg every 6 hours as needed for agitation
- diphenhydramine, 25 mg at bedtime
- paroxetine, 20 mg/d
- haloperidol, 5 mg at bedtime
- memantine, 10 mg twice a day.

Mrs. B's medication list is revealing for reasons that, unfortunately, are not rare. She is receiving 3 anticholinergic medications—oxybutynin, diphenhydramine, and paroxetine—that may be worsening her mental status and behavior directly through CNS effects, possibly in combination with frequent benzodiazepine use.

Anticholinergics also can lead to behavior changes via peripheral side effects. Constipation and urinary retention may cause discomfort that an aphasic patient "acts out." A patient may be experiencing pain related to these side effects and receiving opioid analgesics, which can worsen constipation and urinary retention. Uncontrolled pain related to musculoskeletal disease or neuropathy may merit treatment that will reduce behavioral disturbances.

Mrs. B also was being catheterized every 8 hours as needed for urinary retention. The invasive and unpleasant nature of urinary catheterization is likely to worsen behavior and increases the risk of one of the most common "asymptomatic" etiologies of behavioral symptoms in dementia—urinary tract infection (UTI).

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**Algorithm****5-step evaluation of dementia patients with psychosis and/or agitation/aggression\*****1. How dangerous is the situation?**

- If the patient or others are at significant risk and the patient does not respond quickly to behavioral strategies (such as verbal redirection/reassurance, stimulus reduction, or change of environment), consider acute pharmacotherapy. For instance, offer the patient an oral antipsychotic (possibly in dissolvable tablets) and then if necessary consider intramuscular olanzapine, aripiprazole, ziprasidone, haloperidol, or lorazepam
- For less acute situations, more thoroughly investigate symptom etiology and obtain informed consent before treatment

**2. Establish a clear diagnosis/etiology for the symptoms**

- Rule out causes of delirium (such as urinary tract infection, subdural hematoma, pneumonia) through appropriate physical examination and diagnostic studies
- Rule out iatrogenic causes, such as recent medication changes
- Rule out physical discomfort from arthritis pain, unrecognized fracture, constipation, or other causes
- Assess for potentially modifiable antecedents to symptom flares, such as seeing a certain person, increased noise, or social isolation
- Explore other common causes of behavioral disturbances, including depression, anxiety, and insomnia

**3. Establish symptom severity and frequency, including:**

- Impact on patient quality of life
- Impact on caregiver quality of life
- Instances in which the safety of the patient or others has been jeopardized
- Clear descriptions of prototypical examples of symptoms

**4. Explore past treatments/caregiver strategies used to address the symptoms and their success and/or problematic outcomes****5. Discuss with the patient/decision-maker what is and is not known about possible risks and benefits of pharmacologic and nonpharmacologic treatments for psychosis and agitation/aggression in dementia**

Source: Reference 5

\* Agitation is defined as "inappropriate verbal, vocal, or motor activity that is not judged by an outside observer to be an obvious outcome of the needs or confusion of the individual"<sup>24</sup>

**Clinical Point**

Anticholinergics can worsen mental status and behavior through CNS effects or side effects that cause discomfort

**CASE CONTINUED****Persistent agitation**

After evaluating Mrs. B, the psychiatrist limits her medications to atenolol, aspirin, psyllium, and memantine, and begins to taper lorazepam and paroxetine. Laboratory, radiologic, and physical examinations reveal UTI, fecal impaction, bladder distension, and mild hyponatremia. She is given a phospho-soda enema and ciprofloxacin, 250 mg/d for 5 days.

Despite one-to-one nursing care, frequent reorientation, and attempts to interest her in art therapy, Mrs. B remains agitated and postures to strike staff members and other patients. She denies pain or discomfort. Fearing that someone might be injured, the nurse pages the on-duty psychiatrist.

The nurse then calls Mr. B, who has durable power of attorney for his wife's healthcare. When the nurse advises Mr. B that the psychiatrist has





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There is no evidence that typical antipsychotics mitigate the risks of stroke or death compared with atypical agents

ordered risperidone, 0.5 mg, he immediately interjects that the psychiatrist at the assisted living facility told him haloperidol should be used for his wife's symptoms because other antipsychotics can cause strokes and death.

### Typical vs atypical antipsychotics

Mrs. B's nurse may have to delay administering risperidone while she puts Mr. B in contact with the psychiatrist. In an emergent situation when well-trained staff have assessed for common reversible causes of agitation and tried reasonable nonpharmacologic means to calm the patient, few people would argue against using medication to preserve the safety of the patient and others. To avoid questions such as this during a crisis, obtain informed consent at admission from the patient or (more likely) the proxy decision-maker for medications you anticipate the patient might receive during hospitalization.

The larger question is whether typical antipsychotics are preferred for dementia-related psychosis and agitation/aggression because the FDA has not issued the same global black-box warning for this class. Astute clinicians realize that a lack of evidence of harm is not evidence of a lack of harm. In fact, since the black-box warnings for atypical antipsychotics in dementia emerged, several studies have examined whether the same risks exist for typical agents.

Evidence regarding risk of stroke and death with the use of typical and atypical antipsychotics in patients with dementia is summarized in *Table 1*.<sup>6-13</sup> Most evidence, including numerous studies in the past year, comes from retrospective database analyses. Prospective head-to-head comparisons of atypical and typical antipsychotics in dementia are scarce, and future prospective comparisons would be unethical.

No evidence suggests that typical antipsychotics mitigate the risks of stroke or

death in dementia compared with atypical agents. Moreover, typical agents are more likely than atypicals to cause movement-related side effects—especially tardive dyskinesia and parkinsonism—in older adults with dementia.<sup>14</sup>

### CASE CONTINUED

#### Moderate relief from risperidone

After the psychiatrist explains the data on atypical vs typical antipsychotics in dementia—and the lack of FDA-approved treatments—Mr. B consents to the use of risperidone. He believes his wife would have wanted to try a medication with a moderate chance of relieving her internal distress and preventing her from harming anyone.

Risperidone provides moderate relief of Mrs. B's aggression and paranoia. The next day Mr. B visits the unit and asks to speak with the psychiatrist. Although he appreciates the staff's caring attitude, he says, "There must be safer or better ways to deal with these symptoms than medications like risperidone. I just don't want the guilt of causing my wife to have a stroke or pass away." He also asks, "How long will she have to take this medication?"

### Evidence for efficacy

In addition to discussing antipsychotics' risk in dementia, we also need to highlight their efficacy and effectiveness. A recent meta-analysis of 15 randomized controlled trials of atypical antipsychotics for agitation and/or psychosis in dementia included studies with risperidone, olanzapine, aripiprazole, and quetiapine.<sup>3</sup> Most study participants were institutionalized, female, and had AD.

Psychosis scores improved in pooled studies of risperidone, whereas global neuropsychiatric disturbance improved with risperidone and aripiprazole. Effects were more notable in:

- persons without psychosis
- those living in nursing homes
- patients with severe cognitive impairment.

Subsequent placebo-controlled trials of risperidone, quetiapine, and aripiprazole—most focusing on patients with AD—reveal that atypical and typical antipsychotics have

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Table 1

## Typical antipsychotics: Safer than atypicals for older patients?

Study	Population	Summarized results
<b>Mortality</b>		
Nasrallah et al <sup>6</sup>	VA patients age ≥65 taking haloperidol or an atypical antipsychotic (n=1,553)	Approximately 4 times higher rate of death in those receiving haloperidol compared with those receiving atypicals
Wang et al <sup>8</sup>	Pennsylvania adults age ≥65 with prescription coverage taking antipsychotics (n=22,890)	Typicals had higher relative risk (RR) of death at all time points over 180 days (RR 1.27 to 1.56), both in persons with and without dementia; higher risk associated with increased typical doses
Gill et al <sup>10</sup>	Canadians age >65 with dementia (n=27,259 matched pairs)	Mortality rate was higher for users of typical vs atypical antipsychotics (RR 1.26 to 1.55)
Kales et al <sup>11</sup>	VA patients age >65 prescribed psychotropics after a dementia diagnosis (n=10,615)	Risk of death similar for atypical and typical antipsychotics
Schneeweiss et al <sup>7</sup>	Cancer-free Canadians age ≥65 taking antipsychotics (n=37,241)	Higher mortality rates for those taking typical antipsychotics than those taking atypicals (RR 1.47); higher mortality associated with higher typical doses
Trifirò et al <sup>9</sup>	Adults age >65 with dementia receiving antipsychotics in Italy (n=2,385)	Equivalent rates of mortality in those taking typical and atypical antipsychotics
<b>Stroke</b>		
Gill et al <sup>12</sup>	Canadians age ≥65 with dementia receiving antipsychotics (n=32,710)	Equivalent rates of ischemic stroke in those taking atypical and typical agents compared with those receiving atypicals
Liperoti et al <sup>13</sup>	Nursing home residents with dementia hospitalized for stroke or TIA and matched controls (n=4,788)	Rates of cerebrovascular adverse events equivalent between users of atypical and typical antipsychotics

VA: Veterans Affairs; TIA: transient ischemic attack

### Clinical Point

Compared with atypical antipsychotics, typical agents are more likely to cause movement-related side effects

modest efficacy in reducing aggression and psychosis.<sup>15-19</sup> However, to some extent the National Institute of Mental Health Clinical Antipsychotic Trial of Intervention Effectiveness Study for Alzheimer’s Disease (CATIE-AD)—the largest nonindustry-funded study conducted to address this question—called this conclusion into question.<sup>20</sup> Risperidone and olanzapine (but not quetiapine) were efficacious in that fewer patients taking them vs placebo dropped out because of lack of efficacy. Antipsychotics were not effective overall, however, because the primary outcome—all-cause discontinuation rate—was similar for all 3 drugs and placebo. This indicates that on average these medications’ side effect burden may offset their efficacy, though individual patients’ responses may vary.

### Alternatives to antipsychotics

Mr. B also raised the issue of treatment alternatives, such as no treatment, other psychotropics (*Table 2, page 58*),<sup>5,21</sup> and non-pharmacologic methods (*Table 3, page 64*).<sup>22</sup>

“No treatment” does not imply a lack of assessment or intervention. Always examine patients for iatrogenic, medical, psychosocial, or other precipitants of behavioral symptoms. No treatment may be viable in mild to moderate cases but is impractical for patients with severe psychosis or agitation. Untreated, these symptoms could compromise safety or leave the patient without housing options.

Although possibly underused because of time constraints, reimbursement issues, or lack of training, nonpharmacologic strategies to treat aggression and psycho-



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Typical and atypical antipsychotics have modest efficacy in reducing aggression

Table 2

## Pharmacologic alternatives to antipsychotics: What the evidence says

Treatment	Evidence/results
<b>Selective serotonin reuptake inhibitors</b>	2 positive studies with citalopram (more effective than placebo for agitation in 1 trial and equivalent to risperidone for psychosis and agitation with greater tolerability in the other); 2 negative trials with sertraline
<b>Other antidepressants</b>	1 study showed trazodone was equivalent to haloperidol for agitation, with greater tolerability; another found trazodone was no different from placebo; other agents have only case reports or open-label trials
<b>Anticonvulsants</b>	3 trials showed divalproex was equivalent to placebo; 2 positive trials for carbamazepine, but tolerability problems in both; other agents tried only in case reports or open-label trials
<b>Benzodiazepines/anxiolytics</b>	3 trials showed oxazepam, alprazolam, diphenhydramine, and buspirone were equivalent to haloperidol in effects on agitation, but none used a placebo control; trials had problematic methodologies and indicated cognitive worsening with some agents (especially diphenhydramine)
<b>Cognitive enhancers</b>	Some evidence of modest benefit in mostly post-hoc data analyses in trials designed to assess cognitive variables and often among participants with overall mild psychiatric symptoms; prospective studies of rivastigmine and donepezil specifically designed to assess neuropsychiatric symptoms have found no difference compared with placebo
<b>Miscellaneous drugs</b>	Failed trial of transdermal estrogen in men; small study showed propranolol (average dose 106 mg/d) more effective than placebo

Source: References 5,21

sis in dementia are appealing alternatives to antipsychotics. Little empiric evidence supports nonpharmacologic strategies, however.<sup>22</sup>

**Treatment decisions** need to consider patients' and caregivers' value systems. Proxy decision-makers should examine treatment decisions in terms of how they believe the patient would view the alternatives. Without a specific advance directive, however, even well-intentioned decision-makers are likely to "contaminate" decisions with their own values and interests.

After discussing with the decision-maker various treatments' risks and benefits, it might be useful to ask, for example, "If Mrs. B could have foreseen her behaviors 10 years ago, what do you think she would have wanted us to do? Some people might have been mortified by the thought of attacking other people, whereas other people would not mind this as much as the fear of being 'overmedicated.' Which end

of the spectrum do you think she would have leaned toward?"

When medical research does not offer clear answers for the "right" next clinical step, clinicians can:

- acknowledge our own limits and those of human knowledge
- engage the caregiver (or, when appropriate, the patient) in shared decision-making, recognizing that some people will appreciate the opportunity for "equal partnership" whereas others will want us to decide based on our best clinical judgment.

### Duration of treatment

Limited evidence leaves psychiatrists largely on our own in regards to how long to continue pharmacotherapy with antipsychotics. Neuropsychiatric symptoms such as psychosis and agitation exhibit variable patterns. Symptoms may wax and wane for unclear reasons.



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Little evidence supports nonpharmacologic treatments of aggression and psychosis in dementia

**Table 3**

## How well do psychosocial/behavioral therapies manage psychosis/agitation in dementia?\*

Treatment	Evidence/results
Caregiver psychoeducation/support	Several positive RCTs (evidence grade A)
Music therapy	6 RCTs, generally positive in the short term (evidence grade B)
Cognitive stimulation therapy	Three-quarters of RCTs showed some benefit (evidence grade B)
Snoezelen therapy (controlled multisensory stimulation)	3 RCTs with positive short-term benefits (evidence grade B)
Behavioral management therapies (by professionals)	Largest RCTs with some benefits (grade B)
Staff training/education	Several positive studies of fair-to-good methodologic quality (evidence grade B)
Reality orientation therapy	Best RCT showed no benefit (evidence grade D)
Teaching caregivers behavioral management techniques	Overall inconsistent results (evidence grade D)
Simulated presence therapy	Only 1 RCT which was negative (evidence grade D)
Validation therapy	1-year RCT with mixed results (evidence grade D)
Reminiscence therapy	A few small studies with mixed methodologies (evidence grade D)
Therapeutic activity programs (such as exercise, puzzle play)	Varied methods and inconsistent results (evidence grade D)
Physical environmental stimulation (such as altered visual stimuli, mirrors, signs)	Generally poor methodology and inconsistent results; best results with obscuring exits to decrease exit-seeking (evidence grade D)

\* Evidence grades from A (strongest) to D (weakest) were assigned in a review by Livingston G, Johnston K, Katona C, et al. Systematic review of psychological approaches to the management of neuropsychiatric symptoms of dementia. *Am J Psychiatry* 2005;162:1996-2021

RCT: randomized controlled trial

Source: Reference 22

**Table 4**

## Atypicals in dementia: Starting and target doses

Drug	Starting dose	Target dose
Aripiprazole	2.5 to 5 mg/d	7.5 to 12.5 mg/d
Olanzapine	2.5 to 5 mg/d	5 to 10 mg/d
Quetiapine	12.5 to 25 mg/d	50 to 200 mg/d
Risperidone	0.25 to 0.5 mg/d	0.5 to 1.5 mg/d

Source: Reference 23

Given the tenuous nature of the risk-benefit profile for atypical antipsychotics in dementia, consider a gradual taper for persons with dementia who remain asymptomatic after 3 to 6 months of atypical antipsychotic treatment. Monitor them closely for symptom recurrence.<sup>5</sup>

Carefully consider the necessary duration of antipsychotic therapy in patients (such as Mrs. B) in whom you can identify possibly reversible precipitants of psychosis and aggression. Patients may have a delayed beneficial response to the correction of precipitating factors such as medical illness, physical discomfort, or medication side effects.

Mrs. B received risperidone, but evidence for efficacy and safety in dementia-related psychosis or agitation does not yet significantly distinguish among the atypical agents (except that data are limited for ziprasidone and clozapine). Usual starting and target doses are provided in *Table 4*.<sup>23</sup>

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## Related Resources

• Jeste DV, Blazer D, Casey D, et al. ACNP White Paper: update on use of antipsychotic drugs in elderly persons with dementia. *Neuropsychopharmacology* 2008;33(5):957-70.

• American Association for Geriatric Psychiatry position statement: principles of care for persons with dementia resulting from Alzheimer disease. [www.aagponline.org/prof/position\\_caredmnlz.asp](http://www.aagponline.org/prof/position_caredmnlz.asp).

### Drug Brand Names

Alprazolam • Xanax	Lorazepam • Ativan
Aripiprazole • Abilify	Memantine • Namenda
Atenolol • Tenormin	Olanzapine • Zyprexa
Bupirone • Buspar	Oxazepam • Serax
Carbamazepine • Tegretol	Oxybutynin • Ditropan
Ciprofloxacin • Ciloxan	Paroxetine • Paxil
Citalopram • Celexa	Propranolol • Inderal
Clozapine • Clozaril	Quetiapine • Seroquel
Diphenhydramine • Benadryl	Risperidone • Risperdal
Divalproex • Depakote	Rivastigmine • Exelon
Donepezil • Aricept	Sertraline • Zoloft
Haloperidol • Haldol	Trazodone • Desyrel
Hydrocodone/acetaminophen • Lortab, Vicodin	Ziprasidone • Geodon

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## Bottom Line

No evidence-based treatment exists for psychosis or agitation/aggression in dementia. Atypical antipsychotics carry a 'black-box' warning for increased risk of death and cerebrovascular events in dementia; typical antipsychotics appear no safer. If you choose atypical antipsychotics, use them judiciously as part of a shared decision with the patient's proxy decision-maker. Consider gradual withdrawal after 3 to 6 months, and monitor for symptom recurrence.

## Clinical Point

Consider initiating a gradual taper in patients who remain asymptomatic after 3 to 6 months of antipsychotic treatment