Introduction

In the United States (US), approximately 7.9 million people live with dementia. Of these individuals, 3.95 million carry a diagnosis of at least 1 dementia type, including Alzheimer’s disease dementia, vascular dementia, dementia with Lewy bodies, Parkinson’s disease dementia, or frontotemporal dementia. However, postmortem pathology data from 2 large databases indicated that more than half of individuals with dementia had mixed neuropathologies.

According to a longitudinal US population-based survey, the prevalence of dementia increases with age, ranging from 2% among people aged 65 years to 69 years to 33% among those aged 90 years or older. As the US population ages, the number of people with dementia is expected to grow. For example, the number of individuals aged 65 years or older with Alzheimer’s disease has been projected to nearly triple between 2010 and 2050, growing from 4.7 million individuals to 13.8 million.

Many patients with dementia experience hallucinations and delusions

Neuropsychiatric, behavioral, and/or psychological symptoms, which include hallucinations and delusions, are common among people with dementia, and their onset can occur at various times over the course of the disease. Approximately 2.4 million people with dementia in the US experience hallucinations and delusions. Hallucinations and delusions in this population often present as symptoms of dementia-related psychosis.

Unmet Medical Need

Some studies have found that in patients with Alzheimer’s disease dementia, delusions and—to a lesser degree—hallucinations may be associated with aggression. Importantly, the presence of hallucinations and/or delusions in patients with dementia may increase their risk of institutionalization. No antipsychotic medications are currently approved for the treatment of dementia-related psychosis, and all antipsychotics carry a Boxed Warning indicating that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Available antipsychotics are also associated with adverse events, including extrapyramidal symptoms (EPS), sedation, and confusion or mental-status change. The prevalence and burden of dementia-related hallucinations and delusions, combined with the aging US population and increasing number of people with dementia, underscores the critical need to develop safe and effective treatments for dementia-related psychosis.

Treatment considerations for older adults experiencing symptoms of psychosis associated with dementia

In a position statement, the Alzheimer’s Association outlines considerations for making treatment decisions for individuals experiencing behavioral and psychotic symptoms of dementia, including hallucinations and delusions. The considerations for determining the use of antipsychotic therapy in this population are: Identify and
Older individuals with dementia often have specific vulnerabilities that healthcare professionals should consider when devising a treatment regimen, including the presence of multiple comorbidities and polypharmacy. The potential risks associated with various medications in older adults are addressed in the 2019 update of the American Geriatric Society (AGS) Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults With Dementia or Cognitive Impairment. The AGS Beers Criteria provide a list of potentially inappropriate drugs—including anticholinergics; benzodiazepines; nonbenzodiazepine, benzodiazepine receptor agonist hypnotics; and antipsychotics—that are best avoided by older individuals.

**Antipsychotics and increased risk of mortality for elderly patients with dementia-related psychosis**

Available antipsychotics are used off-label to treat hallucinations, delusions, aggression, and agitation in patients with dementia. As noted previously, no antipsychotic medications are currently approved for the treatment of dementia-related psychosis, and all antipsychotics carry a Boxed Warning indicating that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. The US Food and Drug Administration (FDA) conducted an analysis of 17 placebo-controlled trials that demonstrated an approximate 1.6- to 1.7-fold increase in mortality with the use of atypical antipsychotics by elderly patients with dementia-related psychosis compared to placebo-treated patients. The majority of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature.

**Adverse events associated with antipsychotic use in patients with dementia**

Following the FDA analysis, an independent, individual study–based meta-analysis of 15 placebo-controlled atypical antipsychotics clinical trials was conducted by Schneider et al to assess the evidence for efficacy and adverse events associated with the use of atypical antipsychotics in patients with dementia and hallucinations, delusions, aggression, or agitation. Trials were included in the study if they met 3 criteria: 1) The study was parallel group, double-blinded, placebo-controlled with random assignment to an orally administered atypical antipsychotic or placebo; 2) the patients enrolled had Alzheimer’s disease, vascular dementia, mixed dementia, or a primary dementia; and 3) the patients were randomized and at least 1 outcome measure or adverse event was obtainable. These criteria resulted in the inclusion of 3353 patients randomized to drug and 1757 randomized to placebo. This analysis revealed that the use of atypical antipsychotics in patients with dementia was significantly associated with adverse events, including somnolence (P=0.00001), EPS (P=0.0005), abnormal gait (P=0.0002), edema (P=0.008), urinary tract infections (P=0.04), and cerebrovascular adverse events (P=0.009) (Table). Lastly, this analysis of the odds ratio associated with deaths (odds ratio, 1.54; P=0.02) was consistent with the FDA analysis.

**Table. Adverse events associated with atypical antipsychotic use in patients with dementia: a meta-analysis of 15 placebo-controlled clinical trials.**

<table>
<thead>
<tr>
<th>Adverse event (AE)</th>
<th>Odds ratio</th>
<th># of studies reporting AE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>2.84†</td>
<td>13</td>
</tr>
<tr>
<td>Injury/accidental injury</td>
<td>0.93</td>
<td>11</td>
</tr>
<tr>
<td>Extrapyramidal effects</td>
<td>1.51†</td>
<td>11</td>
</tr>
<tr>
<td>Abnormal gait</td>
<td>3.42†</td>
<td>4</td>
</tr>
<tr>
<td>Edema</td>
<td>1.99†</td>
<td>8</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>1.28†</td>
<td>11</td>
</tr>
<tr>
<td>Cerebrovascular adverse events</td>
<td>2.13†</td>
<td>‡</td>
</tr>
</tbody>
</table>

*Trials may not have reported AEs if they presented in less than 5% or 10% of the study population
†Indicates statistically significant increase in odds ratio compared to placebo (P<0.05).
‡Data from additional sources outside of the 15 placebo-controlled published trials analyzed by Schneider et al.31

Because atypical antipsychotics are used to treat psychosis, aggression, and agitation in patients with Alzheimer’s disease, a large, naturalistic study—the Clinical Antipsychotic Trials of Intervention Effectiveness—Alzheimer’s Disease (CATIE-AD)—was conducted to evaluate their effectiveness and safety in this...
Patient population. The double-blind, placebo-controlled study was conducted between 2001 and 2004 at 45 US sites and consisted of 2 phases. In Phase 1, 421 outpatients (mean age, 77.9 years) were randomly assigned double-blind to 1 of 3 atypical antipsychotics or placebo in a 2:2:2:3 ratio. The dose of the antipsychotics could be adjusted as clinically indicated by the study physicians. Treatment could be discontinued after the first 2 weeks if the response was inadequate, while patients with an adequate response could be treated for up to 36 weeks.

Patients whose initial treatment was discontinued (n=253) could be enrolled in Phase 2 of the study. These patients were randomly assigned under double-blind conditions to receive 1 of the antipsychotic drugs to which they were not initially assigned or to receive a selective serotonin reuptake inhibitor. The primary outcome measure was time until discontinuation of treatment for any reason. The main secondary outcome was the attainment of minimal or greater improvement in the Clinical Global Impression of Change scale at Week 12 while the patients continued to receive the Phase 1 drug.

Phase 1 of the study found no significant overall differences among treatment groups in time to discontinuation for any reason. It also reported no significant differences in response rate at 12 weeks. The overall rate of discontinuation for any reason at 12 weeks was 63%. Further, discontinuation of treatment due to intolerability of the study drug, adverse events, or death ranged from 16% to 24%, depending on the atypical antipsychotic, and was 5% with placebo (P=0.009 for Kaplan-Meier estimate of time to discontinuation, overall comparison). There were no significant differences among the groups with regard to the proportion of patients who had at least 1 serious adverse event and the proportion who had any adverse event.

In Phase 1, the rate of individual adverse events was also examined. The following adverse events were reported more commonly with atypical antipsychotics than placebo, and the differences among the treatment groups were statistically significant: sedation, cognitive disturbance, psychotic symptoms, and confusion or mental-status change.

Potential link between movement disorder and atypical antipsychotics in older adults with dementia

In the same study (CATIE-AD, Phase 1), patients with Alzheimer’s disease dementia who received atypical antipsychotics also experienced higher rates of EPS or parkinsonism (2%-12%, depending on the atypical antipsychotic) than patients treated with placebo (1%) (P<0.001). Furthermore, the neurologic effects of atypical antipsychotics on patients with dementia were assessed via 3 scales. Consistent with the higher adverse event rates of EPS or parkinsonism, the proportion of patients who scored at least 1 on the Simpson-Angus Scale, indicating at least mild EPS, was higher for patients treated with 2 of 3 atypical antipsychotics than those prescribed placebo (Figure 2). No significant differences were seen among the treatment groups on the 2 other neurologic measures—the Abnormal Involuntary Movement Scale (global severity score ≥2) or the Barnes Akathisia Rating Scale (global score ≥3).

Figure 2. Neurologic effects of atypical antipsychotics in CATIE-AD: proportion of patients with Simpson-Angus Scale mean score ≥1. *Scale of 0-4 (1=mild EPS; 4=severe EPS). Percentages are based on the number of patients who did not meet the criteria at baseline and who underwent ≥1 postbaseline measurement in Phase 1. †P=0.02 vs placebo. ‡P=0.06 vs placebo.

Association between antipsychotic use and metabolic changes

The CATIE-AD study also measured the patients’ weight and other metabolic parameters throughout the 36-week observation period. A prospective analysis of the data by Zheng et al revealed that the duration of antipsychotic use (range, 0-46 weeks; median, 12.1 weeks) was significantly associated with weight gain after adjusting for age (P=0.02). The researchers found a significant interaction between the duration of antipsychotic use and gender (P=0.008), with females showing a significant weight gain of 0.14 pounds per week (P=0.006) versus a weight change in males of -0.02 pounds per week (P=0.64). One of the 3 antipsychotics studied was also significantly associated with increased waist circumference (P=0.004) and decreased high-density lipoprotein cholesterol levels (P=0.004). No change in blood pressure, glucose, or triglycerides was noted in association with antipsychotic use in this study population.

A separate post hoc analysis of 7 antipsychotic clinical trials assessed the risk associated with the development of treatment-emergent diabetes in 1398 patients aged 65 years or older with Alzheimer’s disease dementia, vascular dementia, or mixed/vascular dementia. The study found no significant differences in the rates of treatment-emergent diabetes between patients treated with an atypical antipsychotic versus placebo or an active comparator.

Effects of pharmacologic treatment on cognitive function and risk of dementia diagnosis

Atypical antipsychotic use and cognitive function in patients with dementia

By design, the CATIE-AD study included measures at baseline and during follow-up to assess the effects of time and treatment on cognitive function. Vigen et al analyzed these outcomes among
357 patients (mean age, 77.6 years) for whom baseline measures and at least 1 follow-up assessment during the 36-week observation period were available. These measures included the Mini-Mental State Examination (MMSE); the cognitive factor on the Brief Psychiatric Rating Scale (BPRS); Alzheimer’s Disease Assessment Scale (ADAS) subscales of cognition (ADAS-Cog), concentration/distractibility, number cancellation, and executive function (mazes); tests of category instances; finger-tapping tests (preferred and nonpreferred hands); Trail Making Test Part A; and working memory deficit. The researchers also calculated a cognitive summary score by averaging the normalized z scores for each of the component measures (ADAS-Cog, ADAS subscales, category instances tests, finger-tapping tests, Trail Making Test Part A, and working memory deficit) and then normalizing these averaged scores. Significant worsening of cognitive function from baseline was reported for the following measures: MMSE (P=0.004), BPRS cognitive factor (P=0.05), tests of category instances (P=0.01), and cognitive summary score (P=0.004). A significant difference from baseline was not observed for the following measures: ADAS cognition, concentration/distractibility, number cancellation, and execution function; finger-tapping tests; Trail Making Test Part A; and working memory deficit.

Anticholinergic drug exposure and cognitive performance in older adults
Anticholinergic activity in general may also be associated with reduced cognitive function in older adults. One study of 26 individuals (mean age, 83.6 years) with moderate to severe dementia analyzed clinical trial baseline data and found that higher levels of serum anticholinergic activity were associated with poorer cognitive performance, as demonstrated by lower MMSE scores (P=0.049).

A separate analysis of data from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) and the Indiana Memory and Aging Study longitudinal studies also noted a significant association between anticholinergic medication use and clinical progression to mild cognitive impairment and/or Alzheimer’s disease among older adults who were cognitively normal at baseline. In the ADNI cohort, the association of anticholinergic use and longitudinal clinical decline (mean [SD] follow-up period, 32.1 [24.7] months; range, 6 months to 108 months) was examined using a Cox regression model. ADNI participants (mean age, 73.3 years) were either taking anticholinergic medication (n=52) or not taking at least 1 medication with medium or high anticholinergic activity (n=350). The cumulative survival without mild cognitive impairment and/or Alzheimer’s disease diagnosis was significantly lower for people with anticholinergic drug use (hazard ratio, 2.47; P=0.01) in the ADNI cohort.

Anticholinergic drug exposure and risk for dementia
In an observational, nested case-control study, Coupland et al examined whether exposure to anticholinergic drugs was associated with a greater likelihood of a dementia diagnosis. The study included 58,769 patients aged 55 years or older (mean age, 82.4 years) with a diagnosis of dementia and 225,574 matched controls. Of the patients in the dementia group, 36,666 cases had a specific dementia diagnosis recorded. Of these patients, 60.1% had a diagnosis of Alzheimer’s disease (including mixed), 36.3% had vascular dementia, and 3.6% had other types of dementia. Exposure to drugs with strong anticholinergic properties was summarized to obtain total standardized daily doses (TSDDs) for each patient. The highest adjusted increased odds, for more than 1905 TSDDs 1 year to 11 years before the index date, was 49% compared with nonuse of anticholinergics. For the same use category, this increase was 46% 3 years to 13 years before the index date and 44% 5 years to 20 years before the index date. In the same study, the adjusted odds ratios for dementia were especially high for anticholinergic antipsychotics (Figure 3), particularly in the period of 1 year to 11 years before the index date.

Figure 3. Adjusted odds ratio for dementia, by years of exposure to anticholinergic antipsychotics (cumulative use >1095 TSDDs) before dementia diagnosis.*

Conclusions
Dementia-related hallucinations and delusions represent a prevalent and burdensome healthcare challenge for which there are no FDA-approved treatments. Pharmacologic treatment of older patients with dementia can be complicated by comorbidities, polypharmacy, and vulnerability of the aged population to specific adverse events. Specifically, all antipsychotics carry a Boxed Warning about the increased risk of death in elderly patients with dementia. Furthermore, the treatment of dementia-related psychosis with antipsychotic agents may be associated with several adverse events, including EPS, metabolic changes, and cognitive challenges. As the US population ages and the number of people with dementia is expected to grow, the development of safe, effective treatments for dementia-related psychosis in older adults represents an urgent unmet medical need.
References:

27. Leonard R, Tintetti ME, Allore HG, Drickamer MA. Potentially modifiable resident characteristics that are associated with physical or verbal aggression among nursing home residents with dementia. *Arch Intern Med*. 2006;166(12):1295-1300.