Antipsychotic medication use in treatment of dementia: Is it associated with an increased risk of mortality?  

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Background

- At any time, approximately 80% of patients with dementia residing in long term care settings exhibit neuropsychiatric symptoms.  
- Although first line treatment for these symptoms is non-pharmacological (psychosocial intervention), medications are often utilized instead, with an estimated prevalence of use of antipsychotics of 25-40% for long term care resident with dementia.  
- Some typical antipsychotics and atypical antipsychotics have been shown to provide benefits in treating certain neuropsychiatric symptoms; however, those benefits may be outweighed by the risk of adverse events, including death.  
- The safety of these medications is under careful consideration, and, although there has been a recent decline in use, antipsychotics continue to be used frequently in treating dementia.

Question

- Is the use of antipsychotic medications safe in patients with dementia?  

P = Patients with dementia  
I = Antipsychotic pharmacological therapy  
C= Non-pharmacological or other pharmacological therapy  
O = Risk of mortality

Methods

- A literature search using PubMed was performed limited to papers that were freely available and published in English.  
- Search terms included: antipsychotics, dementia, and mortality  
- Articles selected were assessed for strengths, limitations, and ethical concerns based on the CHS 708-Epidemiology 2 worksheets provided, and the level of evidence was determined

Study Design

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<th>STUDY DESIGN</th>
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<td>Retrospective cohort</td>
<td>This was a retrospective cohort study for patients ≥65 years old with dementia, beginning outpatient treatment with an antipsychotic (risperidone, olanzapine, quetiapine, or haloperidol or valproic acid and its derivatives (as a non-antipsychotic comparator). The total sample included 33,604 patients. Individual drug groups were compared for 180-day mortality rates.</td>
<td>Consistent across analyses was the finding that haloperidol had the highest mortality risk and quetiapine the lowest. Valproic acid and its derivatives generally had mortality risks higher than quetiapine and similar to risperidone. Across all medications other than haloperidol, mortality risk was found to be on average 1.5 times higher in the first 120 days than for the subsequent period; for haloperidol, risk was highest in the first 30 days and then significantly and sharply decreased.</td>
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<td>Retrospective cohort</td>
<td>This was a retrospective cohort study to compare the risk of death associated with atypical and conventional antipsychotics in a large population of nursing home residents with dementia. The study identified new users of ATYPICAL ANTPSYCHOTICS (n=6,524) and CONVENTIONAL ANTPSYCHOTICS (n=1,581) living in 1,581 Medicaid or Medicare certified nursing homes in the US from 1998-2000. The outcome measure was all-cause mortality which was determined during 6 months of follow up.</td>
<td>The rate of death was increased for users of conventional antipsychotics (HR, 1.26; 95% CI, 1.13-1.42). Relative to risperidone (atypical antipsychotic) there was a higher rate of death for haloperidol (HR, 1.31; 95% CI, 1.13-1.55), Phenothiazines (HR, 1.17; 95% CI, 1.00-1.38), Other conventional medications (HR, 1.32; 95% CI, 0.99-1.80). No atypical antipsychotic was associated with a differential risk relative to risperidone.</td>
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<td>Retrospective cohort</td>
<td>This was a retrospective cohort study using the UK General Practice Research Database. The primary objective was to assess the potential risk of cardiac mortality including sudden cardiac death in the antipsychotic exposed population. The secondary objective was to assess the risk of all-cause mortality (including suicide) and of major cardiac events (including AMI, CHD, and life-threatening ventricular arrhythmias in the antipsychotic exposed population. Attempts were made to adjust for additional known risk factors for sudden cardiac death not previously assessed in other studies, smoking status, body mass index, and alcohol status, and to address issues with the definition of sudden cardiac death. 183,392 antipsychotic users (115,401 typical and 67,991 atypical) were identified.</td>
<td>Atypical antipsychotics had lower adjusted relative ratios in various outcomes compared to typical antipsychotics: All-cause mortality - 0.83 (95% CI: 0.80-0.86), Cardiac mortality - 0.88 (95% CI: 0.82-0.97), SCD secondary definition - 0.76 (95% CI: 0.55-1.04).</td>
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Study Results


Meta-analysis Level of evidence: 1

- The goal of this study was to assess the evidence for increased mortality from atypical antipsychotic drug treatment for people with dementia. 3,353 (total 5,110) patients from 15 trials of atypical antipsychotics were identified. Trials included were parallel group, double-blind placebo-controlled with random assignment to an orally administered antipsychotic or placebo; patients had Alzheimer disease, vascular dementia, mixed dementia, or a primary dementia; and numbers of patients randomized, dropouts, and deaths were obtainable.  

Summary

- There is conflicting evidence regarding risk of mortality and antipsychotic use  
- Meta-analysis shows atypical drugs may be associated with an increased risk for death compared with placebo in dementia patients  
- Risk of mortality is lower with atypical compared to typical antipsychotics  
- Haloperidol appears to be associated with the greatest increase in mortality risk  
- The use of conventional agents is not advised for treating behavioral and psychological symptoms of dementia

Recommendations

- Since there is potential for increased risk of mortality and other adverse events with the use of antipsychotics, non-pharmacological interventions should be considered first when available and proven effective  
- When the use of psychotropic medications is necessary, atypical agents should be used rather than typical antipsychotics  
- Relative risk of death may be lower in patients who discontinue antipsychotic therapy, so antipsychotic use should be limited to ≤ 3 mo

Additional References


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