REVIEW OF CLINICAL GUIDELINES ON USE OF ANTIPSYCHOTIC DRUGS IN THE TREATMENT OF BEHAVIORAL SYMPTOMS IN ALZHEIMER’S DISEASE AND THEIR IMPACT ON PATIENT OUTCOMES

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2Evidera & 3Lundbeck LLC

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Key Events That Have Shaped the Environment of Neuropsychiatric Symptoms Management

1986
Nursing Home Reform Act (a.k.a. OBRA ‘87)
- Implemented the Minimum Data Set requirement
- Unnecessary physical restraint use warranted citation from state inspectors
- Physical restraint use dropped substantially. Including bedrails.

1986
FDA Black Box Warnings
- Continued utilization of psychiatric drugs for behavioral issues

2009 / 2010 / 2013
- Billions of $$ in fines for marketing of atypical antipsychotics for off-label uses in nursing homes

2011
- 14% of elderly nursing home residents are prescribed atypical antipsychotics
- 83% of use was for off-label conditions; 88% were used for the condition specified in the FDA boxed warning.
- 51% of use considered “erroneous” (mostly because use was off-label), amounting to $116 M.
- 22% of these drugs were not administered in accordance with the Centers for Medicare & Medicaid Services (CMS) standards regarding unnecessary drug use in nursing homes.

2015
Two quality measures related to antipsychotic agents added to CMS Nursing Home Compare
Objective

• Study objectives were:
  • To review the literature evaluating professional clinical guidelines on antipsychotic drug usage for Neuropsychiatric symptoms (NPS) in Alzheimer’s disease and
  • To evaluate the impact of clinical guidelines on patient outcomes
Methods

- Two literature review searches conducted in MEDLINE and Embase over 2006-2016 focused on:
  - Professional clinical guidelines of antipsychotic use in AD treatment
  - Publications reporting on the impact of published guidelines related to antipsychotic use on patient clinical and humanistic outcomes

- Adult patients with AD and agitation; agitation symptoms identified per the 2015 International Psychogeriatric Association (IPA) working group definition\(^1\)

<table>
<thead>
<tr>
<th>Excessive Motor Activity</th>
<th>Verbal Aggression</th>
<th>Physical Aggression</th>
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<tbody>
<tr>
<td>pacing</td>
<td>yelling</td>
<td>biting</td>
</tr>
<tr>
<td>pointing</td>
<td>Screaming</td>
<td>pacing</td>
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<tr>
<td>Restless</td>
<td>Shouting</td>
<td>rocking</td>
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<tr>
<td>rocking</td>
<td>using profanity</td>
<td>gesturing</td>
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<td>fidget</td>
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- Outcomes: Search 1 {Clinical practice treatment guidelines in AD Off-label usage of APs for behavioral symptoms (e.g., agitation) in AD} Search 2 {agitation burden, clinical outcomes, humanistic burden; quality of life, patient-reported outcomes, and utilities}

- Abstracts screened by three reviewers; studies meeting predetermined inclusion criteria were summarized

16 Guidelines reviewed spanning across US, Canada, and EU

**Recommendation Type**

**General**
- Drug Use Minimization
- NP intervention first line
- Underlying Cause Rule-Out
- Alternative Treatment*
- NP Intervention continued

**Antipsychotic Treatment**
- Initiate to Target Specific Symptoms
- Agitation/Other NPS target
- Agitation-Related Behavioral Symptoms**
- Limit to Severe Symptoms
- Limit to Moderate/Severe Symptoms

**Best Practices Defined for AP Administration**
- Dose Monitoring
- Full withdrawal
- Dose Reduction
- Practice of Minimal Dosing
- Target Specific Behavioral Symptoms

**Percent including**
- Drug Use Minimization: 88%
- Initiate to Target Specific Symptoms: 94%
- Dose Monitoring: 44%

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**AP= Antipsychotic; NP= Non-pharmacologic; NPS= Neuropsychiatric Symptoms**

- acetylcholinesterase (AChEI), or, if not tolerant, memantine, benzodiazepines, cholinergics, selective serotonin reuptake inhibitors (SSRIs), and/or beta-adrenergic antagonist drugs for the treatment of behavioral disturbances in persons with AD; zoplicone, an anti-depressant and adjunct to AP’s, for treatment of night-time agitation.

**psychomotor agitation, agitation with anxiety, night-time agitation, wandering, verbal agitation, physical aggression and combativeness**
No studies were identified that directly assessed the impact of AP guidelines on patient outcomes.

5% (11/209) of potential studies met abstraction criteria with variable designs including: Guideline-based interventions, Staff Education, Qualitative study, Retrospective review of reasons for AP use, Expert opinion survey.

**Populations**
- Nursing home/long-term care or staff
- Psychiatrists
- Community Dwelling Veterans

**Interventions**
- Guidelines Based Interventions
- NP Intervention
- Pain Intervention

**Outcomes**
- Behavioral Symptoms
- AP Use/Use Patterns
- Agitation

**Measures**
- Neuropsychiatric Inventory
- Cohen-Mansfield Agitation Inventory

**Findings**
- Reduction in AP Use/Dosage
- Decreased Agitation Levels

AP = Antipsychotic; NP = Non-pharmacologic
Conclusions

- Overall, clinical guidelines discussed alternative clinical approaches as a first-line intervention including ruling out underlying causes and initiating and attempting non-pharmacological interventions such as behavioral interventions.

- The most recently published guideline (Reus 2016 American Psychiatric Association) recommended a comprehensive, person-centered non-pharmacological approach prior to initiating the use of AP.

- Agitation and other NPS explicitly noted as potentially appropriate symptoms for treatment with an antipsychotic.

- Assessments of the impact of guidelines have focused solely on prescription patterns but have not addressed issues of patient outcomes.

- Limited data exists evaluating the impact of safety warnings of antipsychotic treatment on patient outcomes.

- Formal research should be conducted to determine impact of guidelines on patient/caregiver satisfaction and broader patient outcomes like activities of daily living and mortality/morbidity.
Guidelines Reviewed


2. American Association for Geriatric Psychiatry Statement on the Use of Antipsychotic Medications for the Treatment of Agitation and Psychosis in Persons with Dementia; Marc E. Agronin, M.D., Susan K. Schultz, M.D., Gary W. Small, M.D. and the Board of Directors of the American Association for Geriatric Psychiatry (2016).


Studies Reviewed


Thank You!
Back-up
Clinical Guidelines Targeted Literature Review: Data Sources, Search Limits, and Inclusion Criteria

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<th>Guidelines Review</th>
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<td><strong>Literature Databases</strong></td>
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<td>• MEDLINE (via PubMed)</td>
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<td><strong>Guideline Reports</strong></td>
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<td>• Centers for Medicare &amp; Medicaid Services Guideline Report</td>
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<td>• American Health Care Association</td>
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<td>• Alzheimer’s Association</td>
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<td>• Other Professional Organization Websites</td>
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<td><strong>PICOS Inclusion Criteria</strong></td>
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<td><strong>Population</strong></td>
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<td><strong>Intervention/ Comparator</strong></td>
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<td><strong>Study Design</strong></td>
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Abbreviations: AD = Alzheimer’s disease; PRO = Patient-reported outcome; QOL = Quality of life; RCT = Randomized controlled trial; US = United States
**Impact on Patient Outcomes Targeted Review: Data Sources, Search Limits, and Inclusion Criteria**

<table>
<thead>
<tr>
<th>Patient Outcome Review</th>
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</table>
| **Literature Databases** | • MEDLINE (via PubMed)  
• Excerpta Medica Database (Embase) |
| **Limits** |  |
| **Language** | English language |
| **Time Period** | Past 10 years (since 2006-2016) |
| **Geography** | No limits |
| **PICOS Inclusion Criteria** |  |
| **Population** | Adult patients with AD with agitation |
| **Intervention/Comparator** | Clinical guidelines specific to use of antipsychotic use in AD patients |
| **Outcomes** | • Agitation burden  
• Clinical and economic outcomes (costs, comorbidity, and resource use)  
• Humanistic burden; QoL/PROs/utilities |
| **Study Design** | RCTs, observational cohort studies, epidemiologic studies |

**Abbreviations:** AD = Alzheimer’s disease; PRO = Patient-reported outcome; QOL = Quality of life; RCT = Randomized controlled trial; US = United States