Controversies in Management of Psychosis In Alzheimer’s Disease

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Disclosure

- Speaker Bureaus
  - Pfizer
  - Forest
  - Norvartis

- Grant Support
  - Pan American Health Organization/WHO
  - NIA
  - HRSA
How Common is Psychosis in Alzheimer’s Disease?

- Review of 55 studies
  - 41% of those with Alzheimer’s Disease have psychosis
  - 36% Delusions
  - 18% Hallucinations
  - 13% Co-occurring delusions and hallucinations
  - 18.7% Visual hallucinations > 9.2% auditory hallucinations

Use of Antipsychotics in Dementia by Nursing Homes

- Based on 2004 National Nursing Home Survey
  - 6103 USA nursing home residents over 64 with dementia
- 32.9% received antipsychotics
  - Most were atypical agents 31.6% vs. 1.8%
- Factors associated with use
  - Males > Females
  - More beds in the facility
  - Increased dependence in decision making ability
  - Indicators of depression
  - Indicators of behavioral disturbance
  - Comorbid psychiatric diagnosis of Schizorphenia, Bipolar mania, Anxiety

Kamble et al. Drugs Aging 26:483-492, 2009
FDA Approved Meds

• There are no FDA psychopharmacological agents approved for use in managing any behavioral problem in Alzheimer’s disease
  • Antipsychotics are not FDA approved for treatment of psychosis or agitation in dementia

• The only FDA approved drugs in Alzheimer’s disease are to manage cognitive decline
  • Donepezil (Aricept)
  • Galantamine (Razadyne)
  • Rivistigmine (Exelon)
  • Tacrine (Cognex)
  • Memantine (Namenda)
FDA Approved Use of Antipsychotics

• Some people with Dementia will have been using antipsychotics prior to dementia for legitimate FDA indications

• These disorder may not necessarily disappear with the onset of Alzheimer’s Disease
  • Schizophrenia
  • Bipolar disorder
  • Major depression
    • As an augmentation (aripiprazole only)
    • Major depression with psychosis
      • Not an indication, but not controversial
Differential Diagnosis of Psychosis

- Psychosis in Alzheimer’s Disease
- Non-affective psychosis including schizophrenia
- Bipolar disorder
- Major depression
- Anxiety disorder
- Alcohol misuse disorder
- Delirium
- Sun downing – circadian rhythm disorders
- Catastrophic reaction
- Other agitation without psychosis
Controversy 1: Do They Work?
CATIE-AD Methods

- The Clinical Antipsychotic Trials of Intervention Effectiveness – Alzheimer’s Disease (CATIE-AD)

- Objectives: Examine atypical antipsychotics to treat psychosis, agitation, and aggression in Alzheimer’s disease

- 421 outpatients with Alzheimer’s disease psychosis, agitation and aggression in 42 sites

- NIMH sponsored study

- Placebo control trial with random assignment
  - Olanzapine, quetiapine, or risperdone
  - Followed for 36 weeks

- Outcome was Clinical Global Impression of Change
  - Examined at 12 weeks

- All caregivers were given counseling first 18 weeks
CATIE-AD Results

- No significant differences among treatments
  - Similar rates of discontinuation for any reason
  - Olanzapine and risperidone were less likely though to be discontinued due to lack of efficacy
  - Lack of discontinuation due to adverse events favored placebo

- No difference in groups in improvement on CGIC score
  - Olanzapine 32% improved
  - Risperdone 39% improved
  - Quetiapine 26% improved
  - Placebo 21% improved
What was the behavioral presentation on entry to the study based on the Neuropsychiatric Inventory (NPI)?

- Delusions 82%
- Hallucinations 49%
- Agitation or aggression 86%
- Depression 61%

MMSE

- Average MMSE 15
- Range 5 - 26

17% required equivalent of nursing home care
CATIE-AD What are the issues?

- What is psychosis in the elderly and how to measure it
  - What is a delusion?
    - Is thinking someone stole your money because you misplaced it the same as believing someone is going to kill you, or that a stranger is in the house?
    - Are visual and auditory hallucinations equivalent?
    - These distinctions were never addressed and perhaps may respond differently to psychopharmacological intervention
  - How are behavioral problems measured
    - CGCI, NPI, BPRS, Cohen-Mansfield
      - Changes in NPI and BPRS not reported in initial report
    - Who reports the behavioral problems and how well do they know the patient
CATIE-AD What are the issues?

• What is the target population
  • This study was done on outpatients but are they the ones who have most of the behavioral issues we treat?
  • What about nursing home patients.

• What impact did the caregiver support have on the placebo group?

• Should we use older antipsychotics
  • This study provides no data
  • Safety issues of Parkinsonism and anticholinergic side effects persists with older medications
Clinical Symptom Responses to Atypical Antipsychotic Medications in Alzheimer’s Disease: Phase 1 Outcomes From the CATIE-AD Effectiveness Trial

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Robert A. Rosenheck, M.D.
John K. Hsiao, M.D.
Jeffrey A. Lieberman, M.D.
Lon S. Schneider, M.D.
CATIE-AD Study Group

Objective: The study measured the effects of atypical antipsychotics on psychiatric and behavioral symptoms in patients with Alzheimer’s disease and psychosis or agitated behavior.

Method: The Clinical Antipsychotic Trials of Intervention Effectiveness—Alzheimer’s Disease (CATIE-AD) Alzheimer’s disease effectiveness study included 421 outpatients with Alzheimer’s disease and psychosis or agitated/aggressive behavior. Patients were assigned randomly to masked, flexible-dose treatment with olanzapine, quetiapine, risperidone, or placebo for up to 36 weeks. Patients could be randomly reassigned to a different medication at the clinician’s discretion, which ended phase 1. Psychiatric and behavioral symptoms, functioning, cognition, care needs, and quality of life were measured at regular intervals.

Results: In relation to placebo, the last observation in phase 1 showed greater improvement with olanzapine or risperidone on the Neuropsychiatric Inventory total score, risperidone on the Clinical Global Impression of Changes, olanzapine and risperidone on the Brief Psychiatric Rating Scale (BPRS) hostile suspiciousness factor, and risperidone on the BPRS psychosis factor. There was worsening with olanzapine on the BPRS withdrawn depression factor. Among patients continuing phase 1 treatment at 12 weeks, there were no significant differences between antipsychotics and placebo on cognition, functioning, care needs, or quality of life, except for worsened functioning with olanzapine compared to placebo.

Conclusion: In this descriptive analysis of outpatients with Alzheimer’s disease in usual care settings, some clinical symptoms improved with atypical antipsychotics. Antipsychotics may be more effective for particular symptoms, such as anger, aggression, and paranoid ideas. They do not appear to improve functioning, care needs, or quality of life.

Maybe There are Clinical Benefits?

- Re-analysis of outcome measures from baseline to last observation
  - BPRS – no difference with placebo
  - CGCI – Risperidone showed greater improvement from baseline to last observation than placebo
  - NPI – Olanzapine or risperidone showed greater improvement from baseline to last observation than placebo
- Specific symptoms on BPRS
  - Risperidone greater improvement on psychosis factor than placebo
  - Olanzapine or risperidone greater improvement on hostile suspiciousness factor than placebo
  - Olanzapine worsening symptoms on withdrawn depression factor than placebo
- ADLS
  - Olanzapine worse functioning than placebo
Atypical antipsychotics for aggression and psychosis in Alzheimer's disease (Review)

Ballard CG, Waite J, Birks J
Cochrane Review 2006

- 16 RTC’s
  - 5 Risperdone
  - 3 Olanzapine
  - 3 Quetiapine
  - 3 Aripipraozole
  - 1 Risperdal and Olanzapine Arms
  - 1 CATIE-AD

- All but one were multi-center

- 3 studies were in non-institutional setting

- Outcome measures
  - CAMI
  - Behave-AD
  - NPI-NH
Cochrane Review 2006

Does treatment reduce psychosis compared with controls?

- Risperidone had a significant beneficial effect upon psychosis
  - High placebo response rates also
  - Doses 1 mg – 2 mg / day were effective
  - Greater effect size than in Cochrane review for typical antipsychotic haloperidol
- Olanzapine
  - Significant benefit of olanzapine at 5 -10 mg
- Other antipsychotics
  - Insufficient data to meaningfully evaluate
# Cochrane Review 2006

## Risperdone vs Placebo

**Outcome:** BEHAVE-AD or NPI PSYCHOSIS (change from baseline at 8-13 weeks) ITT

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Risperdone</th>
<th>Placebo</th>
<th>Std. Mean Difference</th>
<th>Weight</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
</tr>
<tr>
<td>Risperdone 0.5 mg/day</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RG-USA-63/Katz 1</td>
<td>146</td>
<td>-1.6 (3.6)</td>
<td>161</td>
<td>-1.5 (3.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>146</strong></td>
<td><strong>161</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Heterogeneity:** not applicable

Test for overall effect: Z = 0.24 (p = 0.81)

| Risperdone 1.0 mg/day | | | | | | | | |
| Brodatz 2001 1 | 149 | -1.3 (6.5) | 152 | -0.8 (5.7) | 23.7 % | -0.24 [-0.47, -0.02] |
| FID-MC-I/SGI/Doddrich 1 | 190 | -4.2 (5.8) | 91 | -4.7 (5.3) | 19.5 % | 0.09 [0.16, 0.34] |
| RG-USA-232/Colin 1 | 201 | -2.9 (3.91) | 212 | -2.5 (3.91) | 32.6 % | -0.10 [0.30, 0.09] |
| RG-USA-63b/Elitzur 1 | 148 | -1.5 (3.6) | 161 | -1.5 (3.8) | 24.2 % | -0.27 [-0.49, -0.04] |
| **Subtotal (95% CI)** | **688** | **616** | | | | **100.0 %** | **-0.14 [-0.25, -0.03]** |

**Heterogeneity:** Chi² = 5.45, df = 3 (p = 0.14); I² = 45%

Test for overall effect: Z = 4.74 (p = 0.001)

| Risperdone 2.0 mg/day | | | | | | | | |
| RG-USA-63/Katz 2 | 162 | -1.2 (3.8) | 161 | -1.5 (3.8) | 100.0 % | -0.18 [-0.40, 0.03] |
| **Subtotal (95% CI)** | **162** | **161** | | | | **100.0 %** | **-0.18 [-0.40, 0.03]** |

**Heterogeneity:** not applicable

Test for overall effect: Z = 1.63 (p = 0.099)

Test for subgroup differences: Chi² = 1.07, df = 2 (p = 0.59), I² = 0.0%
Cochrane Review 2006

- Side effects
  - Risperidone
    - 4 fold increased risk of serious cerebrovascular adverse events
    - 2 fold increase in extrapyramidal symptoms
    - Increased risk for somnolence, upper respiratory infection, edema, urinary tract infection, and fever
    - High drop out rate
  - Olanzapine
    - Increased risk for somnolence, abnormal gait
    - High drop out rate
Controversy 2: Cost Benifit

Cost-Benefit Analysis of Second-Generation Antipsychotics and Placebo in a Randomized Trial of the Treatment of Psychosis and Aggression in Alzheimer Disease

Robert A. Rosenheck, MD; Douglas L. Leslie, PhD; Jody L. Sindelar, PhD; Edward A. Miller, PhD; Peter N. Tartis, MD; Karen S. Dagerman, MS; Sonia M. Davis, DPh; Barry D. Lohowitz, PhD; Peter Rabins, MD, MPH; John K. Hojio, MD; Jeffrey A. Lieberman, MD; Lon S. Schneider, MD; for the Clinical Antipsychotic Trial of Intervention Effectiveness—Alzheimer’s Disease (CATIE-AD) investigators

**Context:** Second-generation antipsychotics (SGAs) are prescribed for psychosis, aggression, and agitation in Alzheimer disease (AD).

**Objective:** To conduct a cost-benefit analysis of SGAs and placebo (taken to represent a “watchful waiting” treatment strategy) for psychosis and aggression in outpatients with AD.

**Design:** Randomized placebo-controlled trial of alternative SGA initiation strategies.

**Setting:** Forty-two outpatient clinics.

**Participants:** Outpatients with AD and psychosis, aggression, or agitation (N=421).

**Intervention:** Participants were randomly assigned to treatment with olanzapine, quetiapine fumarate, risperidone, or placebo with the option of double-blind rerandomization to another antipsychotic or clozapine hydrobromide or open treatment over 9 months.

**Main Outcome Measures:** Monthly interviews documented health service use and costs. The economic perspective addressed total health care and medication costs. Costs of study drugs were estimated from wholesale prices with adjustment for discounts and rebates. Quality-adjusted life-years (QALYs) were assessed with the Health Utilities Index Mark 3 and were supplemented with measures of functioning, activities of daily living, and quality of life. Primary analyses were conducted using all available data. Secondary analyses excluded observations after the first medication change (ie, phase 1 only). Cost-benefit analysis was conducted using the net health benefits approach in a sensitivity analysis in which QALYs were valued at $50,000 per year and $100,000 per year.

**Results:** Average total health costs, including medications, were significantly lower for placebo than for SGAs, by $50 to $100 per month. There were no differences between treatments in QALYs or other measures of function. Phase 1–only analyses were broadly similar. Net-benefit analysis showed greater net health benefits for placebo as compared with other treatments, with probabilities ranging from 50% to 90%.

**Conclusions:** There were no differences in measures of effectiveness between initiation of active treatments or placebo (which represented watchful waiting) but the placebo group had significantly lower health care costs.

**Trial Registration:** clinicaltrials.gov Identifier: NCT00015548.

Arch Gen Psychiatry. 2007;64(11):1259-1268
Cost Benefit Analysis

- CATIE-AD secondary data analysis
  - Found that the placebo group had overall lower health costs
  - There was no difference in treatment efficacy between placebo and anti-psychotics
Controversy 3: Side Effects and Mortality

Metabolic Changes Associated With Second-Generation Antipsychotic Use in Alzheimer’s Disease Patients: The CATIE-AD Study

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Cheryl Vigen, Ph.D.
Lon S. Schneider, M.D.

Objective: The second-generation antipsychotics are associated with metabolic abnormalities in patients with schizophrenia. Elderly patients with Alzheimer’s disease are frequently treated with these antipsychotics, but limited data are available on their metabolic effects.

Method: The authors assessed 106 male and 235 female Alzheimer’s disease outpatients from the Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer’s Disease (CATIE-AD) for changes in weight, waist circumference, blood pressure, fasting glucose, and lipids in relation to duration of second-generation antipsychotic use (i.e., olanzapine, quetiapine, and risperidone) throughout the 36-week trial, using logistic regression and mixed-effects models.

Results: Women showed significant weight gain (0.14 lb/week of use) while change was nonsignificant in men. Clinically significant weight gain (i.e., ≥7% of body weight) was seen among patients with antipsychotic use ≤12 weeks (odds ratio [OR]=1.56, 95% CI=0.53 to 4.58), between 12 and 24 weeks (OR=2.89, 95% CI=0.97 to 8.64), and ≥24 weeks (OR=3.38, 95% CI=1.24 to 9.23) relative to patients who did not use antipsychotics during the trial. Olanzapine and quetiapine treatments were significantly associated with weight gain (0.12 and 0.14 lb/week, respectively). In addition, olanzapine was significantly associated with decreases in HDL cholesterol (-0.19 mg/dl/week) and increased girth (0.07 inches/week) relative to the placebo group. No treatment effects were noted for changes in blood pressure, glucose, and triglycerides.

Conclusion: Second-generation antipsychotic use was associated with weight gain in women, with olanzapine and quetiapine in particular, and with unfavorable change in HDL cholesterol and girth with olanzapine. The potential consequences of these effects suggest that patients with Alzheimer’s disease treated with second-generation antipsychotics should be monitored closely.
Increased Weight

FIGURE 2. Association of Clinically Significant Weight Gain With Cumulative Duration of Second-Generation Antipsychotic Use Adjusted for Age at Randomization and Gender

<table>
<thead>
<tr>
<th>Duration of Cumulative Second-Generation Antipsychotic Use</th>
<th>Adjusted Odds Ratio of Weight Gain 27%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Use (N=71)</td>
<td>1.00</td>
</tr>
<tr>
<td>1 day–12 weeks (N=131)</td>
<td>1.56 (95% CI: 0.53 to 4.58, p=0.42)</td>
</tr>
<tr>
<td>Between 12–24 weeks (N=75)</td>
<td>2.89 (95% CI: 0.97 to 8.64, p=0.06)</td>
</tr>
<tr>
<td>24 weeks+ (N=141)</td>
<td>3.38 (95% CI: 1.24 to 9.23, p=0.02)</td>
</tr>
</tbody>
</table>

Note: Relative to the prevalence of clinically significant weight gain (i.e., >7% in subjects with no use (7%)), second-generation antipsychotic use was associated with increased risk for clinically significant weight gain in a duration-dependent manner (p=0.03): up to 12 weeks: 10% (odds ratio=1.56, 95% CI: 0.53 to 4.58, p=0.42), between 12 and 24 weeks: 17% (odds ratio=2.89, 95% CI: 0.97 to 8.64, p=0.06), >24 weeks: 20% (odds ratio=3.38, 95% CI: 1.24 to 9.23, p=0.02).
Metabolic Syndrome

- Atypical antipsychotics are associated with the metabolic syndrome in patients with schizophrenia

- In CATIE-AD women showed significant weight gain
  - Greater than 7% of body weight
  - Men no clinically significant weight change
  - Olanzapine and Quietalpine were significantly associated with weight gain

- Olanzapine
  - Increased girth
  - Decrease in HDL cholesterol

- No changes in
  - Glucose
  - Triglycerides
  - Blood pressure

- The full Metabolic syndrome is not necessarily as big of a risk
Dementia Death and Atypical Antipsychotics

Risk of Death With Atypical Antipsychotic Drug Treatment for Dementia
Meta-analysis of Randomized Placebo-Controlled Trials

Lou S. Schneider, MD, MS  
Karen S. Hargraves, MS  
Philip Insel, MS

A majority of elderly patients with dementia develop aggression, delusions, and other neuropsychiatric symptoms during their illness course. Antipsychotic medications are commonly used to treat these behaviors, along with psychosocial and environmental interventions. They have been the mainstay of pharmacological treatment for this purpose during the last several decades despite their clear adverse effects and federal regulations implemented in the early 1990s requiring their widespread and monitoring in nursing homes.

During the last decade, the newer atypical antipsychotic drugs (e.g., risperidone, olanzapine, quetiapine, and ziprasidone, in order of introduction) have largely replaced the older conventional or first-generation antipsychotic drugs (e.g., haloperidol and thioridazine) and have been considered preferred treatments for these behavioral disturbances associated with dementia. Reasons for this preference include emerging clinical trials evidence, perceived relative safety advantages compared with older antidepressants and other medications, the opinions of expert clinicians, and clinical experience.

Conclusions Atypical antipsychotic drugs may be associated with a small increased risk for death compared with placebo. This risk should be considered within the context of medical need for the drug, personal history, and the efficacy and safety of alternatives. Individual patient analyses must take survival and causes of death into account.
Mortality

- Meta-analysis examined 15 randomized placebo controlled trials
  - 9 are unpublished
  - 3 Aripiprazole (Abilify)
  - 5 Olanzapine (Zyprexa)
  - 3 Quetiapine (Seroquel)
  - 5 Risperidone (Risperdal)

- Death was greater in those randomized to atypical antipsychotics, 3.5% vs 2.3%
  - OR = 1.54

- No differences in individual drugs
Mortality by Individual Drugs

- Not statistically significant for any individual drug
- 1% excess risk of death in 8 – 12 week trial
- 4% – 5% increase risk of death in one year of treatment
Dementia Death and Typical Antipsychotics

Risk of Death in Elderly Users of Conventional vs. Atypical Antipsychotic Medications

Philip S. Wang, M.D., Dr.P.H., Sebastian Schneeweiss, M.D., Jerry Avorn, M.D., Michael A. Fischer, M.D., Helen Mogun, M.S., Daniel H. Solomon, M.D., M.P.H., and M. Alan Brookhart, Ph.D.

ABSTRACT

BACKGROUND
Recently, the Food and Drug Administration (FDA) issued an advisory stating that atypical antipsychotic medications increased mortality among elderly patients. However, the advisory did not apply to conventional antipsychotic medications; the risk of death with these older agents is not known.

METHODS
We conducted a retrospective cohort study involving 22,890 patients 65 years of age or older who had drug insurance benefits in Pennsylvania and who began receiving a conventional or atypical antipsychotic medication between 1994 and 2005. Analyses of mortality rates and Cox proportional-hazards models were used to compare the risk of death within 180 days, less than 40 days, 40 to 79 days, and 80 to 180 days after the initiation of therapy with an antipsychotic medication. We controlled for potential confounding variables with the use of traditional multivariate Cox models, propensity-score adjustments, and an instrumental-variable analysis.

RESULTS
Conventional antipsychotic medications were associated with a significantly higher adjusted risk of death than were atypical antipsychotic medications at all time intervals studied (≤180 days: relative risk, 1.37; 95 percent confidence interval, 1.27 to 1.49 < 40 days: relative risk, 1.56; 95 percent confidence interval, 1.37 to 1.78; 40 to 79 days: relative risk, 1.37; 95 percent confidence interval, 1.19 to 1.59) and 80 to 180 days: relative risk, 1.27; 95 percent confidence interval, 1.14 to 1.41) and in all subgroups defined according to the presence or absence of dementia or nursing home residence. The greatest increase in risk occurred soon after therapy was initiated and with higher dosages of conventional antipsychotic medications. Increased risks associated with conventional as compared with atypical antipsychotic medications persisted in confirmatory analyses performed with the use of propensity-score adjustment and instrumental-variable estimation.

CONCLUSIONS
If confirmed, these results suggest that conventional antipsychotic medications are at least as likely as atypical agents to increase the risk of death among elderly persons and that conventional drugs should not be used to replace atypical agents discontinued in response to the FDA warning.
Mortality

- Both atypical and conventional antipsychotics are associated with increased mortality in dementia compared to non-users

- What is the risk 1% at 12 weeks to 4% - 5% over one year
Pharmacological Treatment of Neuropsychiatric Symptoms of Dementia
A Review of the Evidence

Karen M. Sink, MD
Karen P. Holden, MD
Keanne Yaffe, MD

U p to 50% of community-dwelling elderly individuals older than 65 years have dementia, with Alzheimer disease (AD), vascular dementia, and dementia with Lewy bodies accounting for most cases. Although cognitive deficits are the clinical hallmark of dementing illnesses, neuropsychiatric symptoms are common and worsen dementia disease presentation. These include an array of neuropsychiatric symptoms, such as agitation, aggression, delusions, hallucinations, repetitive vocalizations, and wandering, among other symptoms. Neuropsychiatric symptoms have been observed in 40% to 90% of patients with dementia, especially in later stages, and are associated with caregiver stress and depression, as well as reduced caregiver employment and income.1,2

Neuropsychiatric symptoms are also associated with increased hospital lengths of stay and commonly lead to nursing home placement.3,4 Federal expenditures for dementia are expected to triple in the next 10 years and 10% of the cost of caring for patients with AD is attributed directly to the management of neuropsychiatric symptoms.5,6

Context Neuropsychiatric symptoms of dementia are common and associated with poor outcomes for patients and caregivers. Although nonpharmacological interventions should be the first line of treatment, a wide variety of pharmacological agents are used in the management of neuropsychiatric symptoms; therefore, current evidence-based recommendations are needed.

Objective To evaluate the efficacy of pharmacological agents used in the treatment of neuropsychiatric symptoms of dementia.

Evidence Acquisition A systematic review of English-language articles published from 1966 to July 2004 using MEDLINE, the Cochrane Database of Systematic Reviews, and a manual search of bibliographies was conducted. Inclusion criteria were double-blind, placebo-controlled, randomized controlled trials (RCTs) or meta-analyses of any drug therapy for patients with dementia that included neuropsychiatric symptoms. Trials reporting only depressive outcomes were excluded. Data on the inclusion criteria, patients, methods, results, and quality of each study were independently abstracted. Twenty-nine articles met inclusion criteria.

Evidence Synthesis For typical antipsychotics, 2 meta-analyses and 2 RCTs were included. Generally, no difference among specific agents was found. Efficacy was similar at all doses. Adverse effects were common. Six RCTs with typical antipsychotics were included; results showed modest, statistically significant efficacy of olanzapine and risperidone, with minimal adverse effects at lower doses. Typical antipsychotics are associated with an increased risk of stroke. There have been no RCTs designed to directly compare the efficacy of typical and atypical antipsychotics. Due trials of antidepressants were included; results showed no efficacy for treating neuropsychiatric symptoms other than depression, with the exception of 1 study of olanzapine. For atypical antipsychotics, 3 RCTs investigating quetiapine showed no efficacy. Two small RCTs of clozapine had conflicting results. Two meta-analyses and 4 RCTs of clozapine demonstrated efficacy. Two RCTs of iloperidone also had conflicting results for treatment of neuropsychiatric symptoms.

Conclusions Pharmacological therapies are not particularly effective for management of neuropsychiatric symptoms of dementia. Of the agents reviewed, the physical antipsychotic haloperidol and olanzapine currently have the best evidence for efficacy. However, the effects are modest and further complicated by an increased risk of stroke. Additional trials of cholinesterase inhibitors enabling patients with high levels of neuropsychiatric symptoms may be warranted.

CME available online at www.jama.com

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Alternatives to Antipsychotics

- 6 RTCs show modest statistically significant results for risperdone and olanzapine
  - However, associated with increased risk of stroke
- 5 RTCs Antidepressants showed no benefit other than treating depression except one study of citalopram
- 3 RTCs no efficacy for valproate
- 2 RTC conflicting results of carbamezapine
- 2 RTCs conflicting results of memantine
- 6 RTCs showed small statistical benefit for acetylcholinesterase inhibitors
Figure. Recommended Algorithm for Management of Neuropsychiatric Symptoms of Dementia

Patient With Dementia and a Behavior Problem

Evaluate for and Manage Delirium, Pain, Other Medical, and Environmental Causes for the Behavior

Evaluate the Behavior Problem
Specify the Problem Behavior (e.g., "Agitation" is Less Useful Than "Screaming," "Hitting When Bathed")
Identify What Brings It on and What Makes It Go Away
Identify Whom the Behavior is Bothering (The Patient? The Caregiver/Staff? Other Patients?)

Begin Nonpharmacological Management* Directed at Specific Behavior
Educate Caregivers

Behavior Problem Improved?

No

Does the Patient Have Symptoms of Depression or Anxiety?

Yes

Monitor for Recurrence

No

Is the Patient Receiving a Cholinesterase Inhibitor?

Yes

Begin Trial of SSRI

No

Behavior Problem Improved?

Yes

Monitor for Recurrence and Adverse Drug Events

No

Begin Trial of Atypical Antipsychotic Medication†

Behavior Problem Improved?

Yes

Monitor for Extrapyramidal Symptoms and Sedation
Attempt Medication Taper Every 6 mo

No

Begin Trial of SSRI

Behavior Problem Improved?

Yes

Monitor for Recurrence and Adverse Effects

Consider Trial of Carbamazepine
Recommend Referral to a Specialist

SSRI indicates selective serotonin reuptake inhibitor.

*Music therapy, aromatherapy, pet therapy, or other approaches.
†Caution is advised in patients with dementia with Lewy bodies.
Conclusions on Treating Psychosis

- What to do is controversial
  - Antipsychotics have a black box warning for early mortality and cerebrovascular events
  - The CATIE-AD study suggested that there was little benefit in dementia psychosis for antipsychotics versus placebo
  - Many antipsychotics can cause weight gain, metabolic syndrome may be a concern, and drug induced Parkinsonism
Conclusions on Treating Psychosis

- Does the symptom really merit treatment
  - Is the patient distressed by it?
  - Are there non-pharmacological interventions that can be made?
- Who are we treating the staff, caregiver or patient?
  - Is the behavior disruptive to other residents?
- Will the behavior result in loss of placement?
Conclusions on Treating Psychosis

• If the symptoms are mild consider
  • Acetylcholinesterase inhibitor
  • Memantine

• If an antipsychotic needs to used
  • Document informed consent from the patient and/or caregiver
  • Response may occur with small dosages
    • Unless the patient is chronically mentally ill