Management of Agitation in Dementia
2016 Update

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Relevant Disclosures
Current or past

• Grant support (research or CME)

• Payment as consultant or advisor
  – Astra-Zeneca, Glaxo-Smith Kline, Eisai, Novartis, Forest, Supernus, Adlyfe, Takeda, Wyeth, Lundbeck, Merz, Lilly, Pfizer, Genentech, Elan, NFL Players Association, NFL Benefits Office, Avanir, Zinfandel, BMS, Abvie, Janssen, Orion, Otsuka, Servier, Astellas

• Honorarium or travel support
  – Pfizer, Forest, Glaxo-Smith Kline, Health Monitor
Outline

• NPS in Alzheimer disease (AD)
• Focus on agitation
• Treatment considerations
• The pipeline
• Algorithm
Figure 1  The growth in numbers of people with dementia (in millions) in high income countries, and low and middle income countries

35.5 million people have dementia today
The number of living cases doubles every 20 years
115.3 million people with dementia by 2050—NEW CASES

Alzheimer’s Disease International
World Alzheimer’s Report, September 21, 2009
Dementia has higher societal and economic impact than other important chronic diseases. NIH research funding lags far behind.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Annual Care ($bn)</th>
<th>NIH Funding ($bn)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart disease</td>
<td>$102</td>
<td>$3.75</td>
</tr>
<tr>
<td>Cancer</td>
<td>$77</td>
<td>$7.00</td>
</tr>
<tr>
<td>Dementia</td>
<td>$109</td>
<td>$1.68</td>
</tr>
</tbody>
</table>


Facing reality: balancing “cure” with “care”

• Near and medium term outcome: extend the time course of MCI and dementia → higher prevalence

• We must take proper care of 100+ million patients & caregivers worldwide
“There exists currently an effective, systematic care & treatment model for patients with dementia…” (2006)
Potentially modifiable factors

- Medical co-morbidity
- FDA approved meds
- Neuropsychiatric symptoms
- Judicious use of psychototropic medications
- Early activities, especially mental
- Caregiver closeness, coping style
The common view of dementia
The real view of dementia

[Map of the United States with various regions labeled with symptoms related to dementia, such as Irritability, Aggression, Apathy, Change in Function, Anxiety, Hallucinations, Memory, Sleep Problems, Appetite, Pacing, Repetitive Questions, Rejection of Care, Leaving home, Arguing, Rumination/Hoarding, and Wandering.]

JOHNS HOPKINS MEDICINE
Cumulative prevalence of NPS = 98%

Cache County Dementia Progression Study

Five-year period prevalence of NPI symptoms (NPI>0)

Percentage

0 10 20 30 40 50 60 70 80 90 100

Delusions Hallucinations Agitation/Aggression Depression/Dysphoria Apathy/Indifference Elation/Euphoria Anxiety Disinhibition Irritability/Lability Aberrant Motor Behavior NPI total

baseline=408 1.5 years=236 3.0 years=106 4.1 years=61 5.3 years=36

Steinberg et al, Int J Ger Psychiatry 2008
NPS fluctuate after dementia onset
Cache County Dementia Progression Study

Panel A: Cognition

Panel B: Function

Panel C: Behavior (NPS)

Tschanz et al, Am J Geriatr Psychiatry 2012
NPS are “bad” for patients & caregivers

• Greater ADL impairment\(^1\)
• Worse quality of life\(^2\)
• Earlier institutionalization\(^3\)
• Major source of caregiver burden\(^4\)
• $10,000/year additional care costs\(^5\)
• Shorter time to severe dementia\(^6\)
• Accelerated mortality\(^6\)

\(^1\)Lyketsos et al, 1997; \(^2\)Gonzales-Salvador et al, 1999; \(^3\)Steele et al, 1990; \(^4\)Lyketsos et al, 1999; \(^5\)Murman et al, 2002; Peters et al, 2015
NPS and onset of severe dementia

Cache County Dementia Progression Study

Rabins et al, Alzheimer’s & Dementia 2012
Etiologies of NPS

Neurodegeneration associated with Dementia
- Changes in ability of the person with dementia to interact with others and the environment
- Disruption in neurocircuitry

Increased Vulnerability to Stressors

Patient Issues
- Acute medical (e.g., urinary tract infection; pneumonia; dehydration; constipation)
- Unmet needs
  - Pain, sleep problems, fear, boredom, loss of control or purpose

Environmental Issues
- Over or under-stimulation
- Lack of activity & structure
- Mismatch with cognitive level

Caregiver Issues
- Stress/burden
- Depression
- Communication issues with patient
- Mismatch of dementia severity and expectations

Behavioral and Psychological Symptoms of Dementia

Kales, Gitlin, Lyketsos, British Medical Journal 2015
How do we develop Rx targets for NPS? more efficient and less toxic medications

• Based on phenomenology
  – Individual symptoms
  – Using DSM-IV categories
  – Empirically

• By cause
Empirical classification

**Groups of disturbance** (selected examples)

  - Agitation (aggression, restlessness); Psychosis
- Hope at al, IJGP 1997
  - Overactivity: trailing caregiver, wandering; Aggressive behavior; Psychosis: hallucinations, delusions
- Lyketsos et al, IJGP 2001
  - Affective syndrome (depressive or agitated); Psychotic syndrome; Mono-symptomatic
- Aalten et al, IPG 2005
  - Depressive; Psychotic; Overactive-agitated
Target NPS in Dementia

Accepted by regulators
- Agitation
- Psychosis

Proposed to regulators
- Depression
- Apathy
- Sleep disorders
Agitation phenotype

- **Emotional agitation**: distress, upheaval, anger, tension, anxiety, worry, inability to relax
- **Lability**: rapid changes in mood, irritability, unexpected outbursts, overreacting, catastrophizing
- **Psychomotor agitation**: pacing, rocking, gesticulating, pointing fingers, restless
- **Verbal aggression**: yelling, excessively loud voice, screaming, uses profanity, threatens, "in your face"
- **Physical aggression**: grabs, shoves, pushes, resists, hits, kicks, gets in the way
Rx options are disappointing
few with proven efficacy—significant risks

• Non-pharmacologic: very few data
  – Custom Activity Program (CAP) trial at Hopkins

• Pharmacologic: none approved in US
  – FDA approved AD meds (cholinesterase inhibitors; memantine): weak benefit
  – Antipsychotics: widely used, black box warning
  – Anticonvulsants: ineffective risky
  – Benzodiazepines: ineffective, risky
  – Antidepressants: ineffective EXC. CITALOPRAM
Meta-analysis of 23 RCTs supporting family caregivers

- Outcomes: NPS and caregiver well-being
- Significant treatment effect, effect size=0.34
- Variation in dose, intensity and delivery mode
- Key features of successful trials
  - 9-12 sessions; tailoring to patient and caregiver; delivered in the home; multiple components
- No adverse effects for any of the trials

Brodaty et al, Am J Psychiatry 2012
Non-pharmacologic: behavioral, environmental, & caregiver interventions

Numerous expert bodies recommend first-line, but has largely NOT been translated to real-world care

- Lack of provider training
- Lack of reimbursement
- Lack of guidelines
- Perceived lack of efficacy
- Heterogeneity of interventions

Molinari et al, 2010; Cohen-Mansfield et al, 2013
Effectiveness of Atypical Antipsychotic Drugs in Patients with Alzheimer’s Disease


ABSTRACT

BACKGROUND

Second-generation (atypical) antipsychotic drugs are widely used to treat psychosis, aggression, and agitation in patients with Alzheimer’s disease, but their benefits are uncertain and concerns about safety have emerged. We assessed the effectiveness of atypical antipsychotic drugs in patients with Alzheimer’s disease.

METHODS

In this 12-week, double-blind, placebo-controlled trial, 216 outpatients with Alzheimer’s disease and psychosis, aggression, or agitation were randomly assigned to receive olanzapine (mean dose, 15.5 mg per day; quetiapine (mean dose, 26.5 mg per day; risperidone (mean dose, 10 mg per day); or placebo. Doses were adjusted as needed, and patients were followed for up to 36 weeks. The main outcomes were the time from initial treatment to the discontinuation of treatment for any reason and the number of patients with at least minimal improvement on the Clinical Global Impression of Change (CGIC) scale at 12 weeks.

RESULTS

There were no significant differences among treatments with regard to the time to the discontinuation of treatment for any reason: olanzapine (mean, 28.1 weeks); quetiapine (median, 5.3 weeks); risperidone (median, 7.4 weeks); and placebo (median, 5.0 weeks) (P=0.52). The median time to the discontinuation of treatment due to a lack of efficacy for olanzapine (22.1 weeks) and risperidone (36.7 weeks) as compared with quetiapine (9.1 weeks) and placebo (9.9 weeks) (P=0.003). The time to the discontinuation of treatment due to adverse events or intolerance favored placebo. Overall, 28% of patients who received olanzapine, 50% of patients who received quetiapine, 36% of patients who received risperidone, and 5% of patients who received placebo discontinued their assigned treatment owing to intolerance (P<0.001). No significant differences were noted among the groups with regard to improvement on the CGIC scale. Improvement was observed in 32% of patients assigned to olanzapine, 36% of patients assigned to quetiapine, 34% of patients assigned to risperidone, and 19% of patients assigned to placebo (P=0.22).

CONCLUSIONS

Adverse effects offset advantages in the efficacy of atypical antipsychotic drugs for the treatment of psychosis, aggression, or agitation in patients with Alzheimer’s disease. (ClinicalTrials.gov number, NCT00015544.)
Antipsychotics for agitation: small benefit
Antipsychotics carry BLACK BOX warning

Aripiprazole
Benedetti, 2004
Mintzer, 2007
Streim, 2004/Streim, 2008
Subtotal (I-squared = 0.0%, p = 0.554)
Effect Size (SMD) = 0.20

Olanzapine
DeCeyn, 2004
Deberdt, 2004
Schneider, 2006/Seltzer, 2008
Streim, 2009
Subtotal (I-squared = 0.0%, p = 0.454)

Quetiapine
Baiard, 2005
Falescu, 2005
Schneider, 2006/Seltzer, 2008
Tariot, 2006
Subtotal (I-squared = 35.4%, p = 0.185)

Risperidone
Brodsky, 2003/Brodsky, 2005
Deberdt, 2004
DeCeyn, 1999
Katz, 1999
Mintzer, 2006
Schneider, 2006/Seltzer, 2008
Subtotal (I-squared = 43.7%, p = 0.114)

Effect Size (SMD) = 0.20

NOTE: Weights are from random effects analysis

Favors Placebo * Favors Treatment
VA antipsychotic studies

Both conventional and atypical antipsychotics associated with significantly higher 12-month mortality than other psychotropics. Haloperidol is one of the largest “offenders.”

Kales et al, AJP 2007

Kales et al, AJP 2013
# Antidepressants for agitation or NPS (placebo controlled)

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Comparator</th>
<th>Outcome</th>
<th>Follow-Up</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lawlor BA 1994</td>
<td>10 AD with agitation</td>
<td>Trazodone vs. Buspirone vs. PBO</td>
<td>BPRS, DMAS</td>
<td>12 weeks</td>
<td>TRA&gt;PBO</td>
</tr>
<tr>
<td>Auchus AP 1997</td>
<td>15 AD outpatients</td>
<td>Fluoxetine vs. Haloperidol vs. PBO</td>
<td>Agitation</td>
<td>4 weeks</td>
<td>FLU=PBO</td>
</tr>
<tr>
<td>Teri L 2001</td>
<td>149 AD agitation</td>
<td>Haloperidol vs. trazodone, vs. behavior mgmt vs. PBO</td>
<td>ADCS-CGIC</td>
<td>16 weeks</td>
<td>TRA=PBO</td>
</tr>
<tr>
<td>Lanctot K 2002</td>
<td>22 non-depressed AD w/ behavioral disturbance</td>
<td>Sertraline 100mg/d vs. PBO</td>
<td>NPI</td>
<td>4 weeks</td>
<td>SER=PBO</td>
</tr>
<tr>
<td>Pollock BG 2002</td>
<td>85 hospital dementia</td>
<td>Citalopram vs. perphenezine vs. PBO</td>
<td>NBRS</td>
<td>17 days</td>
<td>CIT&gt;PBO</td>
</tr>
<tr>
<td>Finkel SI 2004</td>
<td>24 pAD outpatients</td>
<td>Sertraline (24) vs. PBO (120) after open donepezil</td>
<td>NPI, CGI-I</td>
<td>8 weeks then 12 weeks</td>
<td>SER=PBO</td>
</tr>
</tbody>
</table>
# Divalproex for agitation

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcome Measures</th>
<th>Duration</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tariot P 2001</td>
<td>172 dementia nursing home and secondary mania</td>
<td>Valproate 20-30mg/kg/d</td>
<td>BRMS, CMAI, CGI</td>
<td>6 weeks</td>
<td>DVS=PBO</td>
</tr>
<tr>
<td>Porsteinsson A 2001</td>
<td>56 nursing home dementia &amp; agitation</td>
<td>Valproate individualized vs. PBO</td>
<td>BPRS-agitation</td>
<td>6 weeks</td>
<td>DVS&gt;PBO ?</td>
</tr>
<tr>
<td>Sival RC 2002</td>
<td>42 dementia hospitalized</td>
<td>Valproate</td>
<td>SADS-9 target aggression</td>
<td>3 weeks</td>
<td>DVS=PBO</td>
</tr>
<tr>
<td>Tariot P 2005</td>
<td>153 nursing home pAD with agitation</td>
<td>Valproate target 750/d vs. placebo</td>
<td>BPRS, CMAI</td>
<td>6 weeks</td>
<td>DVS=PBO</td>
</tr>
<tr>
<td>Hermann N 2007</td>
<td>14 AD—MMSE below 10</td>
<td>Valproate</td>
<td>NPI agitation-aggression, CMAI</td>
<td>6 weeks</td>
<td>DVS&lt;PBO</td>
</tr>
</tbody>
</table>
Preliminary study

Comparison of Citalopram, Perphenazine, and Placebo for the Acute Treatment of Psychosis and Behavioral Disturbances in Hospitalized, Demented Patients

Bruce G. Pollock, M.D., Ph.D.
Benoit H. Mulsant, M.D.
Jules Rosen, M.D.
Robert A. Sweet, M.D.
Sati Mazumdar, Ph.D.
Ashok Bharucha, M.D.
Robert Marin, M.D.
N.J. Jacob, M.D.
Kimberly A. Huber, B.A.
Kari B. Kastango, M.S.
Marci L. Chew, B.S.

Objective: Until recently, conventional antipsychotics were the standard pharmacotherapy for psychosis and behavioral disturbances associated with dementia. This double-blind, placebo-controlled study compared the acute efficacy of the selective serotonin reuptake inhibitor citalopram and the neuroleptic perphenazine with placebo for the treatment of psychosis and behavioral disturbances in nondepressed patients with dementia.

Method: Eighty-five hospitalized patients with at least one moderate to severe target symptom (aggression, agitation, hostility, suspiciousness, hallucinations, or delusions) were randomly assigned to receive either citalopram, perphenazine, or placebo under double-blind conditions for up to 17 days.

Results: Patients treated with citalopram or perphenazine showed statistically significant improvement on several Neurobehavioral Rating Scale factor scores. Compared to those receiving placebo, only patients treated with citalopram showed significantly greater improvement in their total Neurobehavioral Rating Scale score as well as in the scores for the agitation/aggression and lability/tension factors. Side effect scores were similar among the three treatment groups.

Conclusions: Citalopram was found to be more efficacious than placebo in the short-term hospital treatment of psychotic symptoms and behavioral disturbances in nondepressed, demented patients.

(Am J Psychiatry 2002; 159:460–465)
Main finding

![Graph showing mean improvement from baseline score for three groups: Citalopram (N=31), Perphenazine (N=33), and Placebo (N=21). The x-axis represents neurobehavioral rating scale factors, and the y-axis represents mean improvement from baseline score. The bars indicate significant differences among the groups for various factors, such as Cognition, Agitation, Retardation, Depression, Apathy, Psychosis, and Lability.]
A Double-Blind Comparison of Citalopram and Risperidone for the Treatment of Psychotic Symptoms Associated with Dementia (n = 103)

Effect of Citalopram on Agitation in Alzheimer Disease
The CitAD Randomized Clinical Trial

Anton P. Porsteinsson, MD; Lea T. Drye, PhD; Bruce G. Pollock, MD, PhD; D. P. Devanand, MD; Constantine Frangakis, PhD; Zahinoor Ismail, MD; Christopher Marano, MD; Curtis L. Meinert, PhD; Jacobo E. Mintzer, MD, MBA; Cynthia A. Munro, PhD; Gregory Pelton, MD; Peter V. Rabins, MD; Paul B. Rosenberg, MD; Lon S. Schneider, MD; David M. Shade, JD; Daniel Weintraub, MD; Jerome Yesavage, MD; Constantine G. Lyketsos, MD, MHS; for the CitAD Research Group

CONCLUSIONS AND RELEVANCE  Among patients with probable Alzheimer disease and agitation who were receiving psychosocial intervention, the addition of citalopram compared with placebo significantly reduced agitation and caregiver distress; however, cognitive and cardiac adverse effects of citalopram may limit its practical application at the dosage of 30 mg per day.

TRIAL REGISTRATION  clinicaltrials.gov Identifier: NCT00898807

Big benefit: 26% placebo 40% citalopram


R01AG031348; PI: Lyketsos
CitAD (N=186): focus on “big effect”
citalopram 40% v. placebo 26%

<table>
<thead>
<tr>
<th>Table 2. Primary and Secondary Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Citalopram</strong></td>
</tr>
<tr>
<td>No. randomized</td>
</tr>
<tr>
<td>No. with any week-9 data</td>
</tr>
<tr>
<td>Primary Agitation Outcomes</td>
</tr>
<tr>
<td>NBRS-A</td>
</tr>
<tr>
<td>No. with ≥1 follow-up measurement</td>
</tr>
<tr>
<td>No. with week-9 data</td>
</tr>
<tr>
<td>Estimated score at 9 weeks, mean (SE)</td>
</tr>
<tr>
<td>Estimated treatment effect, mean (95% CI)</td>
</tr>
<tr>
<td>ADCS-CGIC, No. (%)</td>
</tr>
<tr>
<td>No. with week 9 data</td>
</tr>
<tr>
<td>Marked improvement</td>
</tr>
<tr>
<td>Moderate improvement</td>
</tr>
<tr>
<td>Minimal improvement</td>
</tr>
<tr>
<td>No change</td>
</tr>
<tr>
<td>Minimal worsening</td>
</tr>
<tr>
<td>Moderate worsening</td>
</tr>
<tr>
<td>Marked worsening</td>
</tr>
<tr>
<td>Estimated treatment effect, OR (95% CI)d</td>
</tr>
</tbody>
</table>

Porsteinsson et al, JAMA 2014
Placebo response (28%) by week 3
Citalopram (40%) response 9+ weeks

Weintraub et al, Am J Geriatric Psych 2015
## Benefit to “psychotic” symptoms

### Table 2 Neuropsychiatric Inventory (NPI) domains at week 9

<table>
<thead>
<tr>
<th>Domain</th>
<th>Citalopram</th>
<th>Placebo</th>
<th>OR* (95% CI)</th>
<th>p-value</th>
<th>Participants reporting symptom**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n† (%)</td>
<td>n† (%)</td>
<td></td>
<td></td>
<td>Citalopram Median (IQR)**</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo Median (IQR)** p-value</td>
</tr>
<tr>
<td>Number with week 9 NPI data</td>
<td>86</td>
<td>83</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Individual domains</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delusions</td>
<td>22 (26 %)</td>
<td>35 (42 %)</td>
<td>0.40 (0.18, 0.91)</td>
<td>0.03</td>
<td>4 (2, 8)</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>11 (13 %)</td>
<td>13 (16 %)</td>
<td>1.53 (0.50, 4.71)</td>
<td>0.46</td>
<td>1 (1, 3)</td>
</tr>
<tr>
<td>Agitation/aggression</td>
<td>66 (77 %)</td>
<td>70 (84 %)</td>
<td>0.63 (0.28, 1.41)</td>
<td>0.26</td>
<td>3 (2, 8)</td>
</tr>
<tr>
<td>Depression/dysphoria</td>
<td>24 (28 %)</td>
<td>30 (36 %)</td>
<td>0.69 (0.34, 1.39)</td>
<td>0.30</td>
<td>3 (1, 6)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>36 (42 %)</td>
<td>54 (65 %)</td>
<td>0.43 (0.22, 0.84)</td>
<td>0.01</td>
<td>4 (2.5, 8)</td>
</tr>
<tr>
<td>Elation/euphoria</td>
<td>3 (3 %)</td>
<td>5 (6 %)</td>
<td>0.45 (0.09, 2.21)</td>
<td>0.32</td>
<td>1 (1, 8)</td>
</tr>
<tr>
<td>Apathy/indifference</td>
<td>41 (48 %)</td>
<td>42 (51 %)</td>
<td>0.92 (0.47, 1.80)</td>
<td>0.82</td>
<td>4 (3, 8)</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>27 (31 %)</td>
<td>34 (41 %)</td>
<td>0.71 (0.35, 1.46)</td>
<td>0.35</td>
<td>4 (2, 8)</td>
</tr>
<tr>
<td>Irritability/lability</td>
<td>49 (57 %)</td>
<td>61 (73 %)</td>
<td>0.38 (0.19, 0.76)</td>
<td>0.01</td>
<td>4 (2, 6)</td>
</tr>
<tr>
<td>Aberrant motor behavior</td>
<td>34 (40 %)</td>
<td>47 (57 %)</td>
<td>0.49 (0.24, 0.99)</td>
<td>0.05</td>
<td>4 (3, 8)</td>
</tr>
<tr>
<td>Sleep and nighttime behavior</td>
<td>21 (24 %)</td>
<td>30 (36 %)</td>
<td>0.56 (0.27, 1.16)</td>
<td>0.12</td>
<td>4 (3, 12)</td>
</tr>
<tr>
<td>Appetite and eating disorders</td>
<td>22 (26 %)</td>
<td>18 (22 %)</td>
<td>1.32 (0.62, 2.82)</td>
<td>0.47</td>
<td>4 (4, 8)</td>
</tr>
<tr>
<td><strong>Summary scores</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-mood score</td>
<td>78 (91%)</td>
<td>79 (95%)</td>
<td>1.04 (0.10, 2.00)</td>
<td>0.41</td>
<td>8.5 (5, 17)</td>
</tr>
<tr>
<td>Affective score</td>
<td>72 (84%)</td>
<td>78 (94%)</td>
<td>0.33 (0.11, 1.03)</td>
<td>0.06</td>
<td>7 (4, 14.5)</td>
</tr>
<tr>
<td>Psychotic score</td>
<td>28 (33%)</td>
<td>37 (45%)</td>
<td>0.67 (0.31, 1.44)</td>
<td>0.30</td>
<td>4 (2, 6)</td>
</tr>
</tbody>
</table>

CitAD: adverse events

- Anorexia, diarrhea, fever more common on citalopram (p<0.05)
- MMSE decline of 1pt on citalopram (P<0.05)
- QTc prolongation on citalopram

Table 3. Patients Experiencing Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Citalopram</th>
<th>Placebo</th>
<th>OR (95% CI)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>P Value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. randomized</td>
<td>94</td>
<td>92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. with adverse event data&lt;sup&gt;b&lt;/sup&gt;</td>
<td>90</td>
<td>86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. who died</td>
<td>0</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious adverse events, No.&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged QT interval on ECG, No. (%)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>3 (12.5)</td>
<td>1 (4.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight loss &gt;5% at week 9, No. (%)</td>
<td>1 (1.3)</td>
<td>8 (10.3)</td>
<td>.02</td>
<td></td>
</tr>
<tr>
<td>Hyponatremia, No. (%)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>4 (5)</td>
<td>6 (8)</td>
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<td>Get up and Go timed assessment at week 9, No. (%)</td>
<td>53 (67.9)</td>
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<td>21 (26.9)</td>
<td>19 (26.0)</td>
<td>1.05 (0.51-2.16)</td>
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Porsteinsson et al, JAMA 2014
QTc Prolongation

Each solid line with filled circles shows the baseline and week 3 QTc measurements of an individual participant in the citalopram group. A dashed line with open circles represents a participant in the placebo group. Lines with positive slopes correspond to a participant with increasing QTc and negative slopes correspond to a participant with decreasing QTc.

Drye et al, PLOS ONE 2014
R- and S-citalopram concentrations have differential effects on neuropsychiatric scores and QTc intervals in elders with dementia and agitation

Authors:
T Ho¹, R Bles¹2, BH Mulsant², DP Devanand³, JF Mintzer⁴, AP Porsteinsson⁵, LS Schneider⁶, D Weintraub⁷, J Yesavage⁸, LT Drye⁹, CA Munro¹⁰, DM Shade¹¹, C Lyketsos¹², BG Pollock²* for the CitAD Research Group

J Clinical Pharmacology, in press
Response limited to a subgroup

Heterogeneity of Treatment Response to Citalopram for Patients With Alzheimer’s Disease With Aggression or Agitation: The CitAD Randomized Clinical Trial

Lon S. Schneider, M.D., M.S., Constantine Frangakis, Ph.D., Lisa T. Drye, Ph.D., D.P. Devanand, M.D., Christopher M. Marano, M.D., Jacob Minzer, M.D., M.B.A., Benoit H. Mutant, M.D., M.S., Cynthia A. Munro, Ph.D., Jeffery A. Newell, B.A., Sonia Pawluczyk, M.D., Gregory Pelton, M.D., Bruce G. Pollock, M.D., Ph.D., Anton P. Portsteinsson, M.D., Peter V. Rabins, M.D., Lisa Rein, S.M., Paul B. Rosenberg, M.D., David Shade, J.D., Daniel Weintraub, M.D., Jerome Yesavage, M.D., Constantine G. Lyketsos, M.D., M.H.S., for the CitAD Research Group

Objective: Pharmacological treatments for agitation and aggression in patients with Alzheimer’s disease have shown limited efficacy. The authors assessed the heterogeneity of response to citalopram in the CitAD trial for Agitation in Alzheimer’s Disease (CitAD) study to identify individuals who may be helped or harmed.

Method: In this double-blind parallel-group multicenter trial of 196 patients with Alzheimer’s disease and clinically significant agitation, patients were randomly assigned to receive citalopram or placebo for 8 weeks, with the dosage titrated to 30 mg/day over the first 3 weeks. Five planned potential predictors of treatment outcome were assessed along with six additional predictors. The authors then used a two-stage multivariate method to select the most likely predictors; grouped participants into 10 subgroups by their index scores; and estimated the citalopram treatment effect for each.

Results: Five covariates were likely predictors, and treatment effect was heterogeneous across the subgroups. Patients for whom citalopram was more effective were more likely to be outpatients, have the least cognitive impairment, have moderate agitation, and be within the middle age range (76–82 years). Patients for whom placebo was more effective were more likely to be in long-term care, have more severe cognitive impairment, have more severe agitation, and be treated with lorazepam.

Conclusions: Considering several covariates together allowed the identification of responders. Those with moderate agitation and with lower levels of cognitive impairment were more likely to benefit from citalopram, and those with more severe agitation and greater cognitive impairment were at greater risk for advance responses. Considering the dosages used and the association of citalopram with cardiac QT prolongation, use of this agent to treat agitation may be limited to a subgroup of people with dementia.
Response depends on Affective vs. Executive phenotype

### EDS (dysexecutive)

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### % Response at 9w

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<th>Placebo</th>
<th>Citalopram</th>
<th># of Patients</th>
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<td>overall</td>
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<td>40</td>
<td>186</td>
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<td>red</td>
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Charu et al, under review
What’s next? S-CitAD

test the “Affective Agitation” hypothesis

N=589

PSI = Psychosocial Intervention
S-Cit = Escitalopram

Eligible? Run-in (PSI) Improvement

PSI Only

PSI+S-Cit

PSI+Placebo

No Improvement

Screen Enroll Randomize Visit Visit Visit Visit Phone Phone
Week 3 Week 6 Week 9 Week 12 Week 18 Week 24

3 Weeks 12 Weeks 12 Weeks

R01AG052510; PI: Lyketsos
Novel medications for agitation

- Dextromethorphan (Avanir)
- Prazosin (ADCS)
- Dronabinol (AbbVie)
- Brexpiprazole (Otsuka/Lundbeck)
- Scyllo-inositol (Transition)
- PF-05212377 (SAM-760) (Pfizer)
- ORM-12741 (Orion/Janssen)
Original Investigation

Effect of Dextromethorphan-Quinidine on Agitation in Patients With Alzheimer Disease Dementia
A Randomized Clinical Trial

Jeffrey L. Cummings, MD, ScD; Constantine G. Lyketsos, MD, MHS; Elaine R. Peskind, MD; Aaron P. Porsteinsson, MD; Jacobo E. Mintzer, MD, MBA; Douglas W. Scherr, MD; Jose E. De La Gandara, MD; Marc Agronin, MD; Charles S. Davis, PhD; Uyen Nguyen, BS; Paul Shin, BS; Pierre N. Tartaj, MD; Julo Siffert, MD

IMPORTANT
Agitation is common among patients with Alzheimer disease; safe, effective treatments are lacking.

OBJECTIVE
To assess the efficacy, safety, and tolerability of dextromethorphan hydrobromide-quinidine sulfate for Alzheimer disease-related agitation.

DESIGN, SETTING, AND PARTICIPANTS
Phase 2 randomized, multicenter, double-blind, placebo-controlled trial using a sequential parallel comparison design with 2 consecutive 5-week treatment stages conducted August 2012-August 2014. Patients with probable Alzheimer disease, clinically significant agitation (Clinical Global Impression-Severity agitation score ≥4), and a Mini-Mental State Examination score of 8 to 28 participated at 42 US study sites. Stable dosages of antidepressants, antipsychotics, hypnotics, and antidementia medications were allowed.

INTERVENTIONS
In stage 1, 220 patients were randomized in a 3:4 ratio to receive dextromethorphan-quinidine (n = 93) or placebo (n = 127). In stage 2, patients receiving dextromethorphan-quinidine continued; those receiving placebo were stratified by response and rerandomized in a 1:1 ratio to dextromethorphan-quinidine (n = 59) or placebo (n = 60).

MAIN OUTCOMES AND MEASURES
The primary end point was change from baseline on the Neuropsychiatric Inventory (NPI) Agitation/Aggression domain (scale range, 0 [absence of symptoms] to 12 [symptoms occur daily and with marked severity]).

RESULTS
A total of 194 patients (88.2%) completed the study. With the sequential parallel comparison design, 152 patients received dextromethorphan-quinidine and 127 received placebo during the study. Analysis combining stages 1 (all patients) and 2 (rerandomized placebo nonresponders) showed significantly reduced NPI Agitation/Aggression scores for dextromethorphan-quinidine vs placebo (ordinary least squares statistic, −3.95; P < .001). In stage 1, mean NPI Agitation/Aggression scores were reduced from 2.1 to 1.8 with dextromethorphan-quinidine and from 7.0 to 5.3 with placebo. Between-group treatment differences were significant in stage 1 (least squares mean, −1.5; 95% CI, −2.8 to −0.2; P = .001). In stage 2, NPI Agitation/Aggression scores were reduced from 5.8 to 3.8 with dextromethorphan-quinidine and from 6.7 to 5.8 with placebo. Between-group treatment differences were also significant in stage 2 (least squares mean, −1.6; 95% CI, −2.9 to −0.3; P = .002). Adverse events included falls (8.6% vs 3.9% for placebo), diarrhea (5.9% vs 3.1% for placebo), and urinary tract infection (5.3% vs 3.9% respectively). Serious adverse events occurred in 7.9% with dextromethorphan-quinidine vs 4.7% with placebo. Dextromethorphan-quinidine was not associated with cognitive impairment, sedation, or clinically significant QTc prolongation.

CONCLUSIONS AND RELEVANCE
In this preliminary 10-week phase 2 randomized clinical trial of patients with probable Alzheimer disease, combination dextromethorphan-quinidine demonstrated clinically relevant efficacy for agitation and was generally well tolerated.

TRIAL REGISTRATION
clinicaltrials.gov Identifier: NCT01584440


Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Jeffrey L. Cummings, MD, ScD, Cleveland Clinic Lou Ruvo Center for Brain Health, 888 W Bonneville Ave, Las Vegas, NV 89106 (cummins@ccf.org).
PRAZOSIN FOR THE TREATMENT OF BEHAVIORAL SYMPTOMS IN ALZHEIMER’S DISEASE PATIENTS WITH AGITATION AND AGGRESSION

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1 VA Northwest Network Mental Illness Research, Education, and Clinical Center (MIRECC)
2 Alzheimer’s Disease Research Center and Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle, WA

Abstract

Objectives—Agitation and aggression in Alzheimer’s disease (AD) is a major cause of patient distress, caregiver burden, and institutionalization. Enhanced behavioral responsiveness to central nervous system norepinephrine release may contribute to the pathophysiology of agitation and aggression in AD. Prazosin, a nonsedating generic medication used for hypertension and benign prostatic hypertrophy, antagonizes norepinephrine effects at brain postsynaptic alpha-1 adrenoreceptors. This pilot study examined the efficacy and tolerability of prazosin for behavioral symptoms in patients with agitation and aggression in AD.

Design—Double-blind, placebo controlled, parallel group study.

Setting—A university AD center and a nursing home in Seattle.

Participants—Twenty-two nursing home and community dwelling participants with agitation and aggression and probable or possible AD (mean age 80.6 ± 11.2).

Intervention—Randomization to placebo (n=11) or prazosin (n=11). Medication was initiated at 1mg/day and increased up to 6mg/day using a flexible dosing algorithm.

Measurements—The Brief Psychiatric Rating Scale (BPRS) and Neuropsychiatric Inventory (NPI) at weeks 1, 2, 4, 6, and 8. The Clinical Global Impression of Change (CGIC) at week 8.

Results—Participants taking prazosin (mean dose 5.7 ± 0.9mg/day) had greater improvements than those taking placebo (mean dose 5.6 ± 1.2mg/day) on the NPI (mean change -19 ± 21 versus -2 ± 15, X²=6.32, df=1, p=0.012) and BPRS (mean change -9 ± 9 versus -3 ± 5, X²=4.42, df=1, p=0.036) based on linear mixed effects models, and the CGIC (mean 2.6 ± 1.0 versus 4.5 ± 1.6, Z=2.57, p=0.011 [Mann-Whitney test]). Adverse effects and blood pressure changes were similar between prazosin and placebo groups.

Conclusion—Prazosin was well tolerated and improved behavioral symptoms in patients with agitation and aggression in AD.

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No disclosures to report.

This research was presented in part as a poster at the 11th International Conference on Alzheimer’s Disease and Related Disorders, Chicago, Illinois, July 2008.
Dronabinol for the Treatment of Agitation and Aggressive Behavior in Acutely Hospitalized Severely Demented Patients with Noncognitive Behavioral Symptoms


Objective: Behavioral disturbances occur frequently in demented individuals and greatly increase the burden of their care. The efficacy of pharmacotherapeutic treatment options is modest. This study was conducted to explore the efficacy and safety of dronabinol as an adjunctive treatment for agitation and aggressive behavior in severely demented patients.

Methods: Using a retrospective systematic chart review, we studied 40 inpatients from the McLean Hospital Geriatric Neuropsychiatry Inpatient Unit diagnosed with dementia and treated with dronabinol for behavioral or appetite disturbances. A group of geriatric psychiatrists consulted medical records to rate the patients’ behaviors prior to initiation of dronabinol treatment and following up to seven days of treatment, using the Pittsburgh Agitation Scale, Clinical Global Impression, and Global Assessment of Functioning. Data on percentage of food consumed at each meal, sleep duration, and adverse events were also collected from medical records.

Results: The addition of dronabinol to patients’ treatment regimens was associated with significant decreases in all domains of the Pittsburgh Agitation Scale. There were also significant improvements in Clinical Global Impression scores, sleep duration and percentage of meals consumed during the treatment periods. Twenty-six adverse events were recorded during dronabinol treatment, none of which led to medication discontinuation.

Conclusion: This report represents the largest studied cohort of dementia patients treated with dronabinol to date and confirms earlier reports that dronabinol can serve as an adjunctive treatment for neuropsychiatric symptoms in dementia. Further research, including prospective controlled trials, is needed to clarify dronabinol’s role in treating noncognitive behavioral symptoms of demented individuals. (Am J Geriatr Psychiatry 2014; 22:415–419)

Key Words: Dementia, behavioral disturbances, dronabinol

Behavioral disturbances are highly prevalent among both community-dwelling and institutionalized demented individuals, with reported rates as high as 88%. Among behaviorally disturbed patients, agitated and aggressive behaviors, irritability, and aberrant motor behavior are frequent. For community-dwelling demented individuals, rates of agitation and aggression are estimated to be approximately 35%.

Agitated behavior, defined as “inappropriate verbal, vocal, or motor activity that is not explained by needs or confusion per se” can be characterized as either aggressive or nonaggressive. Aggressive behavioral symptoms, which can occur with or without agitation, include fighting, throwing, grabbing, destroying items, verbal outbursts, cursing, and screaming, whereas nonaggressive symptoms include restlessness, pacing, wandering, repetitive questioning, chatting, inappropriate disrobing, and verbal outbursts. Neuropsychiatric symptoms, including restlessness, anxiety, disinhibition, and unusual motor behavior, have been reported to more strongly predict caregiver burden.
Use The DICE Approach

**Describe**
- Caregiver describes problematic behavior
  - Context (who, what, when and where)
  - Social and physical environment
  - Patient perspective
  - Degree of distress to patient and caregiver

**Investigate**
- Provider investigates possible causes of problem behavior
  - Patient
    - Medication side effects
    - Pain
    - Functional limitations
    - Medical conditions
    - Psychiatric comorbidity
    - Severity of cognitive impairment, executive dysfunction
    - Poor sleep hygiene
    - Sensory changes
    - Fear, sense of loss of control, boredom
  - Caregiver effects/expectations
  - Social and physical environment
  - Cultural factors

**Create**
- Provider, caregiver and team collaborate to create and implement treatment plan
  - Respond to physical problems
  - Strategize behavioral interventions
    - Providing caregiver education and support
    - Enhancing communication with the patient
    - Creating meaningful activities for the patient
    - Simplifying tasks
    - Ensuring the environment is safe
    - Increasing or decreasing stimulation in the environment

**Evaluate**
- Provider evaluates whether “CREATE” interventions have been implemented by caregiver and are safe and effective

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Kales, Gitlin, Lyketsos, JAGS 2014
Combining DICE with pharmacologic interventions
Facing reality: balancing “cure” with “care”

• Near and medium term outcome: extend the time course of MCI and dementia → higher prevalence

• We must take proper care of 100+ million patients & caregivers worldwide
Potentially modifiable factors

• Medical co-morbidity
• FDA approved meds
• Neuropsychiatric symptoms
• Judicious use of psychototropic medications
• Early activities, especially mental
• Caregiver closeness, coping style
Thank you!
Ευχαριστώ!