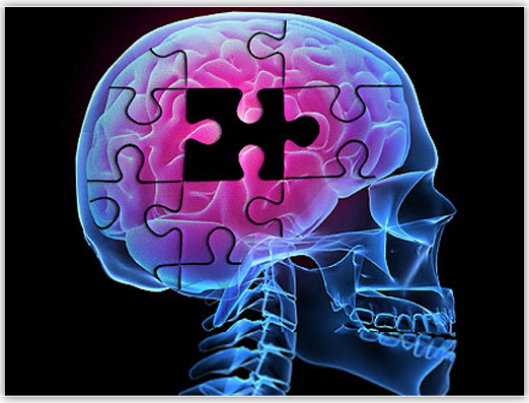
Atypical Antipsychotic Use For Agitation In Alzheimer's Disease: When to Call AAA for Curbside Assistance



Roxana Lang, Pharm.D.
PGY-1 Pharmacy Resident
VA Texas Valley Coastal Bend Health Care System
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Learning Objectives:

- Identify Alzheimer's Disease progression and occurrence of common neuropsychiatric symptoms
- Determine non-pharmacologic therapy options to target behavior disturbances
- Assess appropriateness of medications in late stage Alzheimer's Disease
- Apply literature findings to targeting agitation in Alzheimer's Disease

Patient case: FJ

- 67 y.o. male with 2 year history of dementia
- Presents to clinic with caregiver who reports the following symptoms: forgetfulness, difficulty sleeping, and withdrawal from family events
- Current medications:

Atorvastatin 40mg daily
Trazodone 25mg qHS as needed for sleep
Donepezil 10mg daily

I. Background of Alzheimer's Disease[1,3]

Table 1: Causes of Dementia[1]			
Alzheimer's Disease (60-80%)	Vascular	Lewy Body	Huntington's disease
Parkinson's disease dementia	HIV disease	head trauma or not otherwise specified dementia	

- 5.3 million adults in US with AD[2]
  - 63% are women over age of 65

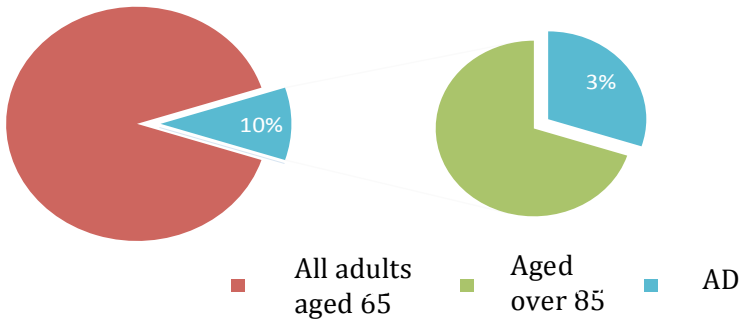

Figure 1: Prevalence of AD

- Progressive and incurable illness
- AD patients present with cognitive difficulties that may manifest as memory loss, anomia, aphasia, agnosia, and apraxia.
- The pathophysiology and causes are not completely understood. Through brain imaging or postmortem examination, neurofibrillary tangles and amyloid plaques are typically found
- The accumulation of plaques and tangles disrupt neurotransmitters and nerves in the hippocampus, amygdala, and cerebral cortex
- Plaques and tangles lead to the nerve degeneration and cortical atrophy. As AD progresses in severity and worsening of cognitive function, motor and sensory function also decline

- DSM-5 Criteria: Major and Mild Neurocognitive disorder
  - Cognitive decline in multiple areas including executive function, learning/memory, language, perceptual-motor, or social cognition.
  - Cognitive decline noticed by family member or patient has concerns
  - Does not occur under context of delirium or other psychiatric disorder

II. Signs and Symptoms of AD[1,4-7]

- Loss of memory evolves from short term to long term
- Clinicians use the Mini Mental Status Exam (MMSE) as a measure of cognitive function
- MMSE is an eleven-item tool that reviews orientation to time and place, attention, naming, repetition, and other measures of cognition.
- A person with AD has an average decline of 2-4 points per year in MMSE
- Late stage is characterized by inability to ambulate, swallowing difficulties, diminished communication, bowel/bladder incontinence and complete dependence for care
- Dyspnea, pain, pressure ulcers, aspiration and agitation/neuropsychiatric symptoms are present in late state AD

Table 2: Behavioral and Psychological Symptoms[6]			
Apathy	Depression	Delusions	Sleep disturbances
Agitation	Disinhibition	Hallucinations	Hypersexuality
Anxiety	Euphoria	Irritability	Psychomotor disturbance

- Behavioral and psychological symptoms are present in 60-90% of all AD patients
    - Agitation, aggression, hallucinations, and depression are most likely to lead to nursing home placement

Table 3: Expected behaviors based on stage of AD[4,7]		
Early AD (MMSE 20-25)	**Moderate AD (MMSE 10-19)**	**Advanced AD (MMSE <9)**
Mood changes	Hallucinations	Hallucinations
Irritability	Delusions/Paranoia	Delusions/Paranoia
Agitation	Wandering	Wandering
Depression	Irritability	Aggression
Insomnia	Agitation	Weight loss
Loss of initiative	Loss of impulse control	Groaning, grunting
	Sundowning	Increased sleeping

- Clinical course
    - Pre-diagnosis: depression, apathy, social withdrawal for years prior to diagnosis
    - Progression: gradual onset and slowly progressive cognitive decline
        - Initial memory loss then functional decline interferes with daily activities
        - Frequency and intensity of agitation and aggression worsen
    - End stage: episodes of agitation and aggression may diminish in the last few months of life

III. Agitation[4,6,7]

- Not always presented with aggression however may progress in severity and become more dangerous to patient and caregiver
- Present in 60-90% of AD patients
- Varied severity of agitation that may present at any stage as cognitive function worsens
- Later stages of AD may be cause for nursing home placement
- May present as:
    - Physically aggressive- pushing biting kicking
    - NON aggressive movement- pacing, wandering, undressing
    - Verbally aggressive- screaming or yelling
    - Verbally NON aggressive- repeatedly calling out

- Possible causes of agitation
    - Pain
    - Infection
    - Delirium
    - Other chronic medical problems
    - Medications: benzodiazepines, antihistamines, anticholinergics

Table 4: Common rating scales used to measure behavior[9-12]		
Scale Name	**Score**	**Purpose**
Neuropsychiatric Inventory (NPI)	Total score range from 10-144 from 12 domains	Indicate frequency and severity of behavioral problems across 12 domains
Burden Interview	Range 0-88	22 item tool: physical health, finances, and interactions with patient
Alzheimer's Disease Cooperative Study Clinical Global Impression of Change (ADCS-CGIC)	Range 1-7	Determine progression by clinician in 15 domains
Functional Assessment Staging Tool (FAST)	Range from 1-7	Indicate impact on activities of daily living

IV. Advanced Decision Making[5,6,8,13-17]:

- Establish proxies and advance directives
    - Discuss disease stages and trajectory
    - Expected complications

- Base future care on
    - Patient centered goals
        - Aggressive intervention
        - Conservative treatment
        - Maximizing comfort
        - Hospitalization
        - Hospice enrollment

    - Caregiver involvement
        - Increased caregiver stress and burden
        - Reduced caregiver employment and income
        - Increased hospital lengths of stay
        - Early nursing home placement
        - Increased costs of care

- Non-pharmacologic management of agitation/aggression behaviors
    - **Social intervention**
        - Intervene early and recognize the patient's behavior
        - Stay calm when interacting with the patient
        - Avoid arguing or trying to reason with the patient
        - Approach the patient from the front with slow movements and sit or stand with the patient at eye level
        - Redirect and refocus attention to something pleasant
        - Consider moving the patient to a quieter room or activity

- **Music therapy-** Meta analyses showed improvement in agitation in mostly short term studies
- **Activities** – reduced agitation of all levels, no difference shown between different type of activity
- **Light therapy** –study analysis has showed an increase in agitation and irritability when exposed to light stimuli however change reflected in scales is not clinically significant.
- **Aromatherapy** or massage therapy- no benefit shown in multiple studies

V. Pharmacologic Agents used for Agitation:[4,6,12,17-20]

- Antidepressants
- Antipsychotics
- Benzodiazepines
- Cognitive enhancers
- Mood stabilizers

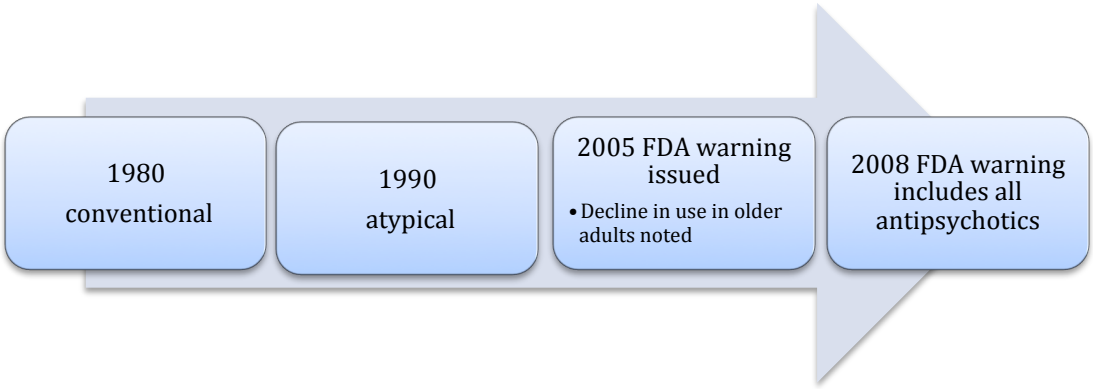

Figure 2: Antipsychotic Timeline

April 2005: Elderly patients with dementia-related psychosis treated with atypical antipsychotics are at an increased risk of death compared to placebo

June 2008: Warning expanded to include all antipsychotics

- Antipsychotics are associated with:
  - Worsening of cognitive function
    - Decreases in MMSE and cognitive summary scores and increase in Alzheimer's Disease Assessment Scale (ADAS) score indicate cognitive decline
  - An increased risk of falling
    - No difference between typical and atypical antipsychotics in terms of fall risk, longer term use (>90 days versus <30 days) of either class associated with increased risk
  - Higher risk of stroke due to high binding affinity for M1 and alpha 2 adrenergic receptors
    - M1: Thioridazine > clozapine > olanzapine > chlorpromazine > quetiapine
    - α2: Risperidone > quetiapine > clozapine > olanzapine > perphenazine > haloperidol > chlorpromazine > thioridazine

Patient Case: FJ Follow-up appointment

- FJ presents to clinic with his wife 6 months later
- Wife reports FJ has begun to get more grumpy after dinner and around bedtime
- She reports he was recently prescribed alprazolam for this and it helps

- Benzodiazepines are used for management of NPS including agitation, aggression, anxiety and irritability
    - Efficacy has not been shown based on limitations of studies and lack of large RCTs.
    - Several trials have shown worsened cognitive decline, increased risk of adverse events associated with worsening cognition as well as increased fall risk
    - Recent studies have shown a relationship between diagnosis of dementia or cognitive disorder later in life with individuals who had a history of long term benzodiazepine use

- Atypical options:
    - Modest efficacy seen with risperidone, olanzapine and aripiprazole in reducing overall aggression and overall agitation in majority of 37 randomized controlled trials

Table 5: Level of Evidence for Use per AHRQ 2011 Update[21]

	Aripiprazole	**Olanzapine**	**Quetiapine**	**Risperidone**
Agitation	Very low/low	Moderate/high	Mixed	Moderate/high
Psychosis	Very low/low	Mixed	Mixed	Moderate/high
Overall	Moderate/high	Very low/low	Very low/low	Moderate/high
Dose	**5-15 mg**	**2.5-10mg**	**25-75mg**	**1mg**

VI. Literature review

<table>
<tr><td colspan="3">Effectiveness of Atypical antipsychotic drugs in patients with AD (CATIE-AD)</td></tr>
<tr><td colspan="3">Schneider LS, Tariot PN, Dagerman KS, et al. Effectiveness of Atypical Antipsychotic drugs in patients with AD. N Engl J Med. 2006 12;355(15):1525-38.</td></tr>
<tr><td>Purpose</td><td colspan="2">Evaluate efficacy of antipsychotics with AD patients experiencing NPS</td></tr>
<tr><td>Design</td><td colspan="2">42 site, double-blind, placebo-controlled trial</td></tr>
<tr><td>Population</td><td colspan="2">Patients average age of 77.9 years AD diagnosis with delusions, hallucination, aggression, or agitation that disrupts function but are still able to ambulate.</td></tr>
<tr><td></td><td>Inclusion:
Required to have a caregiver with regular contact and could participate in activities.
MMSE score 5-25</td><td>Exclusion:
Diagnosis of schizophrenia, delirium or other type of dementia
Require psychiatric admission or suicidal
Received previous treatment with two of the three atypical antipsychotics</td></tr>
<tr><td>Outcomes</td><td colspan="2">1) Time from initial treatment to discontinuation: overall, lack of efficacy, and adverse events
2) Number of patients with at least minimal improvement on the Clinical Global Impression of Change (CGIC) scale at 12 weeks</td></tr>
<tr><td>Methods</td><td colspan="2">421 outpatients with psychosis, aggression or agitation randomly assigned to receive olanzapine (mean dose=5.5 mg/day), quetiapine (mean dose=56.5 mg/day), risperidone (mean dose=1 mg/day) or placebo followed for up to 36 weeks</td></tr>
<tr><td>Results</td><td colspan="2">
<table>
<tr><td colspan="5">Time to discontinuation</td></tr>
<tr><td>Group</td><td>any reason (weeks)</td><td>HR (95% CI)</td><td>Lack of efficacy (weeks)</td><td>HR</td></tr>
<tr><td>olanzapine</td><td>8.1</td><td>0.83(0.62-1.11) p=0.21</td><td>22.1</td><td>0.51 (p<0.001)</td></tr>
<tr><td>quetiapine</td><td>5.3</td><td>1.01(0.75 – 1.36) p=0.95</td><td>9.1</td><td>0.81 (p= 0.24)</td></tr>
<tr><td>risperidone</td><td>7.4</td><td>0.88(0.64- 1.20) p=0.41</td><td>26.7</td><td>0.61 (p = 0.01)</td></tr>
<tr><td>placebo</td><td>8.0</td><td></td><td>9.0</td><td></td></tr>
</table>

24% of patients who received olanzapine discontinued
16% of patients who received quetiapine discontinued
18% of patients who received risperidone discontinued and
5% of patients who received placebo discontinued due to intolerability (P=0.009)
and 39% 53% 44% and 70% (P=0.002) discontinued from lack of efficacy for NPS</td></tr>
<tr><td>Authors conclusion</td><td colspan="2">• Risperidone and olanzapine showed beneficial effects on NPI total score (longer time to discontinuation)
• Antipsychotic medications may be more effective for particular symptoms, such as anger, aggression, and paranoid ideas
• Functional abilities, care needs, or quality of life do not appear to improve with antipsychotic treatment
• Subgroup analysis of the CATIE-AD study showed better response to atypical antipsychotics in patients without psychosis</td></tr>
<tr><td>Critique</td><td colspan="2">No washout period prior to starting trial
Inequality among treatment groups in baseline medications</td></tr>
<tr><td>Take home</td><td colspan="2">Large drop out rate due to intolerability and lack of efficacy.
Clinically significant reduction in NPI was seen for agitation and aggression but not for other functions related to daily activities, use of CGIC to interpret the impact of agent.
Antipsychotics have high intolerability from side effects but possibly have efficacy if able to tolerate side effects.</td></tr>
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<tr><td colspan="3">Effect of second generation antipsychotics on Caregiver Burden in Alzheimer disease</td></tr>
<tr><td colspan="3">Mohamed S, Rosenheck R, Lyketsos CG et al. Effect of second-generation antipsychotics on caregiver burden in Alzheimer's disease. J Clin Psychiatry. 2012;73(1):121-8. doi: 10.4088/JCP.10m06574. Epub 2011 Sep 6.</td></tr>
<tr><td>Purpose</td><td colspan="2">Assess clinical implication of antipsychotic efficacy in agitation</td></tr>
<tr><td>Design</td><td colspan="2">Post hoc data analysis of CATIE-AD data</td></tr>
<tr><td>Population</td><td colspan="2">CATIE-AD data with one post baseline outcome, caregivers of AD with moderate-severe AD with aggression, or agitation that disrupts function Required to have a caregiver with regular contact and could participate in activities.</td></tr>
<tr><td></td><td>Inclusion: same as CATIE-AD above</td><td>Exclusion: same as CATIE-AD above</td></tr>
<tr><td>Outcomes</td><td colspan="2">1) Burden outcome on patient caregivers based on data of CATIE-AD trial</td></tr>
<tr><td>Methods</td><td colspan="2">Utilized data obtained from CATIE-AD phase 1 was examined with intention to treat analysis and applied to scales to measure for caregiver burden, depression, and distress as well as patients level of needed care and quality of life.</td></tr>
<tr><td>Results</td><td colspan="2">Second generation antipsychotic group scored lower on Burden Interview and NPI-caregiver distress scale compared to placebo group. No difference on scales assessing depression or quality of life.
<table>
<tr><td colspan="4">Intention to treat</td></tr>
<tr><td>Scale/tool</td><td>Agent group</td><td>Placebo group</td><td>p value</td></tr>
<tr><td>Burden Interview</td><td>30</td><td>33</td><td>0.009</td></tr>
<tr><td>NPI</td><td>9</td><td>10.6</td><td>0.02</td></tr>
<tr><td>Beck Depression Inventory</td><td>7.8</td><td>8.1</td><td>0.24</td></tr>
</table>
<table>
<tr><td colspan="4">Phase 1 only</td></tr>
<tr><td>Scale/tool</td><td>Agent group</td><td>Placebo group</td><td>p value</td></tr>
<tr><td>Burden Interview</td><td>27.5</td><td>31.6</td><td>0.02</td></tr>
<tr><td>NPI</td><td>7.6</td><td>9.7</td><td>0.04</td></tr>
<tr><td>Beck Depression Inventory</td><td>7.0</td><td>7.1</td><td>0.88</td></tr>
</table></td></tr>
<tr><td>Authors conclusion</td><td colspan="2">• Use of antipsychotics have an impact on lowering NPI score and reduced burden for caregivers by decreasing agitation, hostility and psychosis
• Depression associated with caregiver burden was not improved statistically</td></tr>
<tr><td>Critique</td><td colspan="2">Study data was used from a previous trial and not specifically designed for caregiver burden.</td></tr>
<tr><td>Take home</td><td colspan="2">Statistically significant reduction in NPI for agitation and aggression is not always clinically applicable to all aspects of caregiver burden such as depression, quality of life.
The impact of agitation and other behavioral symptoms on caregiver is also used when making decisions for treatment.</td></tr>
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<table>
<tr><th colspan="3">Relapse Risk after Discontinuation of Risperidone in Alzheimer's Disease[22,24,26]</th></tr>
<tr><td colspan="3">Devanand DP Mintzer, J, Schultz SK. Et al Relapse risk after discontinuation of Risperidone in Alzheimer's Disease. N Engl J Med 2012; 367(16) 1497-1507</td></tr>
<tr><td>Purpose</td><td colspan="2">Determine long-term risk of relapsing following the discontinuation of antipsychotic agent. US federal regulations urge nursing homes to discontinue after antipsychotic medications 3-6 months of treatment (OBRA)</td></tr>
<tr><td>Design</td><td colspan="2">Open label initial treatment followed by randomized double blind placebo control</td></tr>
<tr><td>Population</td><td colspan="2">AD patients with psychosis or agitation. Outpatient or nursing home setting.
Average age 79, 60% were female and an average of 71% were classified as white.
11 patients had a wash-out of antipsychotic medication before phase A</td></tr>
<tr><td></td><td>Inclusion:
Aged 50-95 years
Intellectual impairment present for six months
Able to mobilize independently
Washout of psychotropic medications one week prior to trial entry</td><td>Exclusion:
Non-AD psychiatric disorder
Substance abuse or dependence within the last year
Dementia due to head trauma or other
History of seizure disorder
Use of MAOI or inability to wash out prior to trial
Depot antipsychotic use within 2 weeks of trial</td></tr>
<tr><td>Outcomes</td><td colspan="2">1) Time to relapse of psychosis or agitation
2) Rate of adverse events</td></tr>
<tr><td>Methods</td><td colspan="2">Phase A: all participants were given open label risperidone (average daily dose 0.97mg) for 16 weeks and 61% (N=110) showed a response to risperidone and were continued to Phase B.
Phase B was randomized into three groups: risperidone, risperidone and placebo for 16 weeks and then those that showed a response were continued to risperidone, placebo, and placebo respectively for another 16 weeks.</td></tr>
<tr><td>Results</td><td colspan="2">
<table>
<tr><th>Time Frame</th><th colspan="2">Relapse rate</th><th>p value</th></tr>
<tr><td></td><td>Placebo group</td><td>Treatment group</td><td></td></tr>
<tr><td>0-16 weeks</td><td>Group 3 (60%)</td><td>Group 1 and 2 (33%)</td><td>p = 0.004</td></tr>
<tr><td>17-32 weeks</td><td>Group 2 (48%)</td><td>Group 1 (15%)</td><td>p = 0.02</td></tr>
</table>
</td></tr>
<tr><td>Authors conclusion</td><td colspan="2">• AD patients with psychosis or agitation who respond to risperidone within four months of treatment have a higher relapse risk in the following four months after tapering risperidone.
• Risk of psychosis or agitation relapse should be evaluated with risk of adverse events</td></tr>
<tr><td>Critique</td><td colspan="2">Sample size was small and unable to determine factors associated with relapse and unable to distinguish adverse events between groups
Baseline characteristics of population included moderate NPI scores for agitation entering study (Group 2 had a higher percent of NPI agitation scores >4 at baseline).
Confidence interval for weeks 17-32 was wide (CI 1.08-21.98) and less likely to occur again if replicated.
Lorazepam was utilized (max dose 1mg daily) if needed and was not equally used among groups once randomized. Group 2 included a lower number of participants using anxiolytics at baseline</td></tr>
<tr><td>Take home</td><td colspan="2">Within this small study a large number of participants dropped from the study or relapsed based on moderate to severe symptoms.
From phase A 38% discontinued and from phase B Group 1, 68% of participants discontinued treatment compared to CATIE-AD where 77% discontinuation was observed for risperidone.
Nursing homes have implemented protocols to discontinue agents however must also evaluate severity when deciding on if and when to decrease use of agent.
Discontinue agent sooner if not responding and consider delaying attempts to discontinue if symptoms are severe.</td></tr>
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<table>
<tr><td colspan="3">Antipsychotics, other psychotropic and the risk of death in patients with dementia: number needed to harm</td></tr>
<tr><td colspan="3">Maust DT, Kim Hm, Seyfried LS et al. Antipsychotics, other psychotropics, and the risk of death in patients with dementia: number needed to harm. JAMA Psychiatry. 2015 May;72(5):438-45. doi: 10.1001/jamapsychiatry.2014.3018.</td></tr>
<tr><td>Purpose</td><td colspan="2">Determine the incidence of adverse events associated with antipsychotics</td></tr>
<tr><td>Design</td><td colspan="2">Retrospective case control study</td></tr>
<tr><td>Population</td><td colspan="2">Patients at VA Ann Arbor HCS (n=90,786; 45393 pairs) October 1998 through September 2009</td></tr>
<tr><td></td><td>Inclusion:
Over 65 years old
Established diagnosis of dementia from an inpatient or outpatient visit</td><td>Exclusion:
Recent (<6 months) exposure to antipsychotic, antidepressant or anticonvulsant
Patients with diagnosis of seizure disorder taking valproate</td></tr>
<tr><td>Outcomes</td><td colspan="2">1) Absolute change in mortality risk and NNH over 180 days of follow-up in medication users compared with non-medication users matched on several risk factors.
2) Dose-adjusted absolute change in mortality risk.</td></tr>
<tr><td>Methods</td><td colspan="2">For each medication-using patient, potential matching nonuser patients were first identified matching on the calendar year of the initial dementia diagnosis. Then matched with patient characteristics including age (±2.5 years), race, delirium diagnosis within the preceding 12 months, psychiatric hospitalization within the preceding 12 months, and 3-category Charlson Comorbidity Index score.
Treatment group (pairs):
• Haloperidol (1921)
• Olanzapine (1908), Risperidone (6338), Quetiapine (4621)
• Valproic acid (901)
• Antidepressant (29704)</td></tr>
<tr><td>Results</td><td colspan="2"><table>
<tr><th></th><th>Treatment group death (%)</th><th>Control group death (%)</th><th>Absolute risk difference (95% CI)</th><th>NNH</th></tr>
<tr><td>Risperidone</td><td>883 (13.9)</td><td>538 (8.5)</td><td>3.7% (2.2%-5.3%) p < .01</td><td>27</td></tr>
<tr><td>Olanzapine</td><td>265 (13.9)</td><td>187 (9.8)</td><td>2.5% (0.3%-4.7%) p = .02</td><td>40</td></tr>
<tr><td>Quetiapine</td><td>545 (11.8)</td><td>378 (8.2)</td><td>2.0% (0.7%-3.3%); p < .01</td><td>50</td></tr>
</table></td></tr>
<tr><td>Authors conclusion</td><td colspan="2">• Mortality associated with antipsychotic use might be a greater risk than previously assumed based on longer trial duration
• NNH for quetiapine (50) has lowest risk but not as effective in agitation compared to olanzapine (NNH 40) haloperidol had highest mortality risk
• Dose related increase in mortality was also evident for high dose group over low dose group used haloperidol equivalent dosing (low <1.5mg, med 1.5-3mg, and high >3mg)
• Dose-adjusted mortality risk was increased with both risperidone and olanzapine with greater mortality in the high-dose subgroup relative to the low-dose group</td></tr>
<tr><td>Critique</td><td colspan="2">Majority of patients in quetiapine and risperidone arms were in the low dose group and relatively few in high dose equivalent.</td></tr>
<tr><td>Take home</td><td colspan="2">Risks of mortality may not be as high as indicated in this study though shown to be higher over longer periods of time than previously indicated when the black box warning was placed on these agents.
High risk of mortality is dose related however, it is still is associated with antipsychotic use at the low doses used in AD and low doses should be used with caution.</td></tr>
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VII. Alternative trials

- Other agents beyond antipsychotics are being sought out to evaluate impact on agitation without the potential adverse events
  - Dextromethorphan-quinidine
  - Citalopram
  - Buspirone
  - Memantine
  - Gabapentin
  - Depakote
  - Lithium

- On the horizon Currently recruiting for:
  - Dextromethorphan – larger trial
  - ORM-12741 (alpha 2c) ~ completion in 02/17
  - Brexpiprazole
  - Aripiprazole

Patient case: return to FJ
Two years later FJ presents to clinic

- FJ is non-communicative
- Wife reports:

Increased irritability and aggression when she helps bathes him
Unable to contain anxiety at doctor appointments
Admitted and discharged six months ago with a prescription for olanzapine 5mg at bedtime
Last 6 months has been easier to bathe him and not an issue at doctor appointments

All attempts at non-pharmacological therapy have failed

- Continue to implement behavior management
- Assess for harm to patient or caregiver
- Continue olanzapine 5mg qHS? or an alternative agent?

VIII. Conclusion

- Elimination of causative factors and psychosocial intervention are treatments of choice
- Drug therapy can be recommended but adverse events limit utility of these agents, risk of adverse events associated with aggressive treatment must be assessed on an individual basis
- Consider initiating only when severe enough to cause harm or marked caregiver distress and discontinuing non severe cases
- New study alternatives for treating NPS including agitation/aggression are needed and dextromethorphan-quinidine is a start

IX. Recommendation

- Establish advanced care directives
- Rule out other causes of agitation
- Non-pharmacological therapy is the first option
- Assess severity of aggression and burden on caregiver
- Antipsychotics should *only* be used with careful consideration to treat severe agitation when alternatives have not shown to improve of symptoms

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Appendix

Table A: Neurocognitive Diagnostic Criteria [3,29]	
DSM-5	Major or minor neurocognitive disorder Must specify which as dementia type/cognitive disorder Must specify if with or without behavior disturbances 1. Major neurocognitive disorder -*Significant* cognitive decline from prior level in multiple areas: executive function, learning/memory, language, perceptual-motor, or social cognition -*Substantial* impairment in cognitive performance on clinic assessments -Cognitive deficits interfere with activities of daily living 2. Minor neurocognitive disorder -*Modest* cognitive decline from prior level in one or multiple areas: executive function, learning/memory, language, perceptual-motor, or social cognition -*Modest* impairment in cognitive performance on clinic assessments -Cognitive deficits do not interfere with activities of daily living AD 1. Meet criteria for neurocognitive disorder as listed above 2. Gradual progression of impairment in multiple cognitive domains 3. Cognitive disturbance not best explained by other neurodegenerative disease, substance use, other mental, neurological or systemic disorder 4. Probable or possible AD based on: a. Major neurocognitive disorder- probable: i. Evidence of genetic mutation from genetic testing or family history ii. Clear evidence of decline in memory/learning and one other cognitive domain, progressive and gradual decline in cognition without extended plateaus, and no evidence of mixed etiology b. Minor neurocognitive disorder- i. Probable if evidence of genetic mutation from genetic testing or family history ii. Possible without evidence but all of the following: 1. Clear evidence of decline in memory/learning, progressive and gradual decline in cognition without extended plateaus, and no evidence of mixed etiology
DSM-IV	1. Multiple cognitive impairments manifested by: memory impairment and a cognitive disturbance (aphasia, apraxia, agnoisa, executive functioning) 2. Cognitive deficit- significant decline that impacts social or occupational functioning 3. Gradual onset 4. Cognitive deficits not due to: other CNS conditions, systemic condition, or substance induced 5. Not accounted for by another Axis 1 disorder

- Major Neurocognitive disorder
  - Memory- unable to rely on short lists for daily activities or itemized lists for shopping. Requires frequent reminders to reorient to task. Repeats sentences in conversation
  - Language- may not recall names of family or friends. Decreased speech or difficulty with expressive language
  - Attention- difficulty with multiple stimuli and easily distracted. Difficulty retaining new information

- Executive function- can only focus on one task at a time, abandons more complex tasks. Requires help from others to make decisions or plan daily activities
- Sensory/motor function- difficulty with previously simple activities. Difficulty with navigation. More confusion seen with lower light or at night
- Social function- unacceptable behaviors related to society or lack of insight (choice of conversation topics or dress). Disregard of safety for oneself

Table B: Medication classes and agents in late stage dementia[6]

Appropriate	Possibly appropriate	Discontinue
• Antiemetic • Antidiarrheal • Analgesics • Eye drops • Diuretics • Expectorants	• Hypoglycemic agents • Gout therapy • Digoxin • Antihypertensive	• Lipid lowering agents • Antiplatelets • Antiestrogens/antiandrogens • Hormone antagonists • Bisphosphonates • Benzodiazepines

Table C: Common Rating Scales used for Cognitive and Behavioral Symptoms in AD Literature[1,9-12,30,31]

Rating Scale	Score range	Purpose
Mini Mental Status Exam (MMSE)	Scores range from 0-30 o 20-24: Mild dementia o 13-20: Moderate dementia o < 12: Severe dementia	Measure to indicate cognitive ability and can be related to level of function.
Saint Louis University Mental Status (SLUMS)	Scores range from 0-30 <20 indicates possible dementia	Used to indicate cognitive ability based on deficits
Neuropsychiatric Inventory (NPI)	12 domains Additive scores range from 0-144	Indicate severity and frequency of behavioral problems from initial onset over one month.
Functional Assessment Staging Tool (FAST)	Scores range from 1-7	Indicate impact on activities of daily living
Behavioral Pathology in AD (BEHAVE-AD)	Scores range from 0-78	Assess severity of behavioral symptoms
Alzheimer's Disease Cooperative Study Clinical Global Impression of Change (ADCS-CGIC)	Scores range from 1-7 o 1 shows improvement o 7 shows decline	To assess difference from baseline across 15 areas
Cohen-Mansfield Agitation inventory (CMAI)	Scores range 14-70	Symptoms specific for rating elderly behaviors
Pain assessment in Advanced Dementia (PAIN –AD)	Scores range from 0-10	Difficult to assess pain in AD, useful in determining cause of agitation
Burden Interview	Scores range from 0-88	22 item scale to assess burden of caregivers in areas including physical health, well-being, finances, and interaction with patient. Higher score is related to greater burden
Brief Psychiatric Rating Scale (BPRS)	Each item scored 1-7 for not present to severe	18 or 24 item measures psychiatric and behavioral symptoms.
Activities of Daily living (ADLS-ADL)	Scores from 0-78	Measures observed actions or behaviors over last 4weeks administered by clinician
Beck Depression Inventory	Scores from 0 -63	21 self reported questions

Table D: Background Literature Review[9-11,13-17]

Type of intervention Study name	Design: N and duration	Inclusion sample	Results	Conclusion
Music therapy Lin et al (2011)	N= 100 Music therapy twice weekly for 6 weeks	Residents with an average age 82 from three nursing facilities for elderly patients with dementia in Taiwan between August 2008 and January 2009 75% were prescribed an antipsychotic	C-CMAI scores at midpoint, 12 weeks and one-month post group compared to pretest. For physically aggressive behaviors the experimental group scored an average 0.23, 0.02, and 0.21 points lower, respectively.	Significant improvement compared to usual care both immediate and at end of 1 month 60% of both groups were established as moderate severity dementia
Light therapy Dowling et al (2007)	N= 70 Daily activities in bright light for 1hr over 11 wks Morning and afternoon light groups compared to control	Residents of two large long-term care facilities in San Francisco, California, who experienced rest–activity disruption. excluded if they had other neurological diagnoses taking valerian, melatonin, or sleeping pills. Average MMSE 7	Neuropsychiatric Inventory–Nursing Home (NPI-NH) scores after one week and at the end of 11 weeks Morning group had an increase in agitation of t = –2.70, p = .009	No long-term benefits in reducing agitation. Increases seen for some of experimental group. Statistically significant changes are not necessarily clinically significant
Memantine Reisberg et al (2003)	N= 181 Memantine v placebo in moderate to severe AD	345 patients screened between August 1998 and April 1999 at 32 U.S. centers, 252 were randomly assigned to study groups and 71 dropped out. Average MMSE 7.9	No significant change on NPI scale however for ADCS-ADLsev (P=0.02) and CIBIC-Plus ratings at the end point between the groups (0.3; P=0.06) and week 28 (0.3; P=0.03)	Mixed results from previous studies however does not support benefit for NPS and inconclusive for improvement in ADL
Sertraline Finkel et al (2004)	N=245 Sertraline (avg dose= 126mg) compared to placebo for 12 wks	Patients experiencing any type of behavior symptoms Average MMSE 16.9 Patients were also taking donepezil	No significant difference between groups on NPI, CGIC, CGIS, CMAI, orBEHAVE-AD	No significant difference Funded by Phizer

Table E:
Effects of dextromethorphan-quinidine on Agitation in Patients with Alzheimer's disease dementia[31]

Purpose	Evaluate dextromethorphan-quinidine for efficacy and safety for use in reducing agitation	
Design	Phase 2 randomized double blind controlled trial	
Population	Inclusion: Aged 50-90; AD diagnosis and recent Clinically significant agitation (CGI-Severity agitation score ≥4) or MMSE score of 8 to 28. Other psychotropic agents (if stable for at least 1-2 months)	Exclusion: Abnormal ECG, hx of heart block, family hx of QT Non AD dementia, non AD agitation Inpatient hospitalization or significant depression Previous use of trial med Hx of substance abuse in past 3 years Hx of syncope Myasthenia gravis
Outcomes	Change in score on NPI-agitation scale from baseline score	
Methods	In stage 1, 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 re-randomized in a 1:1 ratio to dextromethorphan-quinidine (n = 59) or placebo (n = 60). Dextromethorphan-quinidine was dosed as 20/10 mg once daily in the morning (with placebo in the evening) for week 1. Dextromethorphan-quinidine was increased to twice daily for weeks 2 and 3 and then increased to 30/10 mg twice daily for weeks 4 and 5. In stage 2, patients receiving dextromethorphan-quinidine continued to receive 30/10 mg twice daily.	

Results

Outcome and stage	N (N placebo)	Change from baseline- treatment	Change from baseline - control	P value
NPI -agitation				
Stage 1	93 (125)	-3.3	-1.7	<0.001
Stage 2	44 (45)	-2.0	-0.8	0.02
10 weeks	93 (66)	-3.6	-1.9	0.001
NPI – total				
Stage 1	93 (125)	-13.5	-8.5	0.03
Stage 2	44 (45)	-6.0	-2.5	0.15
10 weeks	93 (66)	-16.0	-10.1	0.02
ADCS clinical global impression- agitation				
Stage 1	88 (123)	3.0	3.6	<0.001
Stage 2	42 (42)	3.3	3.7	0.07
10 week	82 (59)	2.7	3.3	0.02

Authors conclusion	• In 10-weeks 55.9% of patients treated with only dextromethorphan- quinidine experienced an average 50% reduction in the NPI Agitation/Aggression score from baseline compared with 37.9% of patients receiving only placebo (*P* = .03)
Critique	Inclusion of other psychotropic medications (if stable) makes study generalizable however placebo arm at baseline had more concomitant medications (except antidepressants) Range of MMSE incorporating moderate to severe agitation was not controlled for in this study
Take home	-Still need additional studies to truly assess impact as study was small. -May have reduced irritability however did not significantly impact caregiver distress nor ADL.