Evaluation and Management of Neuropsychiatric Symptoms in Neurocognitive Disorders: A Clinical Review and Research Update

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DISCLOSURES
Dr. Forester serves as President of the American Association for Geriatric Psychiatry

Grants and research support in past 3 years:
- NIA
- Rogers Family Foundation
- Spier Family Foundation
- Biogen
- Eli Lilly
- Eisai

Consulting in past 3 years:
- Biogen
- Acadia Pharmaceuticals

Dr. Forester will discuss unapproved or investigational use of pharmaceutical compounds.

OUTLINE

- Define behavioral symptoms of dementia
- Review diagnostic assessment and formulation of treatment plan
- Present non-pharmacological strategies to address behavioral disturbances
- Investigating novel therapeutics for agitation and anxiety in AD
- Cannabinoids and ECT

POLLING QUESTION

BACKGROUND

Neuropsychiatric disturbances are common in patients with dementia (prevalence 60–80%, lifetime risk of nearly 100%) and are associated with significant morbidity and a more rapid functional decline 1,2. No first-line recommendations for agitation without delusions. Antipsychotics are a high-risk option along with mood stabilizers 3. There is no FDA approved medication for the management of BPSD. 1.

2.
3.

BPSD DEFINITIONS
- The Psychosis of AD (Ueste and Finke) 2
- Neuropsychiatric Symptoms of AD
- BPSD (Behavioral and Psychological Symptoms of Dementia)

- Includes:
  - Agitation, aggression, wandering, delusions, hallucinations, repetitive vocalizations, mood disturbances.
EVALUATION OF BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

- **Medical:** Pain, confusion, constipation, electrolyte disturbance, unstable medical illness, poor sleep
- **Environmental:** Caregiver interactions, time of day, change in routines, noise, cultural issues
- **Psychiatric:** Prior history of psychiatric illness (depression, anxiety disorder, bipolar disorder, substance use disorder)

BEHAVIORAL INTERVENTIONS:

- **First Line Treatment**
  - Behavioral analysis: Identify precipitants and response
  - Assure safety/adequate supervision
  - Treatment should not exceed patient's capacity to learn/remember
  - Behavioral interventions can include:
    - Caregiver education
    - Prosthetic (habilitative) environment
    - Activity/exercise
    - Reminiscence therapies
    - Music therapy
    - Aromatherapy/massage
    - Bright light therapy

PHARMACOLOGICAL APPROACHES TO THE TREATMENT OF BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

- **Antipsychotics**
  - Conventional agents
  - Atypicals
  - CATIE-AD study
  - SAE and mortality warnings
  - Informed consent issues
  - Mood stabilizing anticonvulsants
  - Antidepressants
  - Cholinesterase inhibitors/Memantine
  - Novel interventions: Cannabinoids and ECT

CONVENTIONAL ANTIPSYCHOTICS IN DEMENTIA

- Limited efficacy, substantial toxicity
- Associated with a risk of falls
- Cardiac toxicity (i.e., thioridazine)
- Associated with EPS
  - Parkinsonism (bradykinesia, rigidity, tremor)
  - Akathisia
  - Tardive dyskinesia: 28% after 1 year, 50% after 2 years, 63% after 3 years


ATYPICAL ANTIPSYCHOTIC DOSING IN DEMENTIA

- Risperidone: 0.5-2.0 mg/day
- Olanzapine: 2.5 mg-10 mg/day
- Quetiapine: 25 mg-200 mg plus per day
- Aripiprazole: 5-10 mg/day
- Clozapine, Ziprasidone, Paliperidone, Asenapine, Iloperidone, Lurasidone: Insufficient data
- Brexpiprazole: One positive and one negative Phase III trial; third Phase III trial ongoing
- Pimavanserin FDA rejected application for dementia related psychosis (April 5, 2021)
- TD incidence:
  - Risperidone: 5.3% 1 year, 7.2% 2 year
  - Olanzapine: 6.7% 1 year, mean dose 4.3 mg/day, 11% 2 year

Woerner MG et al., Neuropsychopharmacology. April 2021
POLLING QUESTION

CATIE-AD STUDY

- 42-site, DBPCT, 421 Outpatients (including ALF residents) with AD and psychosis, aggression or agitation, 36-week study
- Randomized to:
  - Olanzapine (mean dose 5.5 mg/day)
  - Risperidone (mean dose 1.0 mg/day)
  - Quetiapine (mean dose 56.5 mg/day)
  - Placebo

Schneider LS, Tariot PN et al., NEJM 2006;355:1525-1538

CATIE-AD Secondary Outcomes
Support Modest Beneficial Effect

Significant difference between medications and placebo in time to discontinuation for inefficacy (p=0.002)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Time to Discontinuation (wk)</th>
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</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>26.7 wk</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>22.1 wk</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>9.1 wk</td>
</tr>
<tr>
<td>Placebo</td>
<td>9.0 wk</td>
</tr>
</tbody>
</table>

Schneider LS et al. NEJM 2006;355:1525-38

CATIE-AD: SIDE EFFECTS

- EPS: Olanzapine & risperidone > quetiapine
- Sedation: All drugs > placebo
- Body weight: elevated with risperidone
- Falls: drugs > placebo
- CVA: 5/421 (1.1%): drugs > placebo
- Deaths: 7/421: drug-placebo
- Placebo less often discontinued due to adverse effects

Schneider LS et al. NEJM 2006;355:1525-38

Antipsychotic Medications - Adverse Events

- CVAEs
  - Cerebrovascular Adverse Events
- Mortality

Schneider LS et al. NEJM 2006;355:1525-38
CEREBROVASCULAR ADVERSE EVENTS

- Class warning for elevated risk of cerebrovascular adverse events
- Risperidone (3.8%) vs. Placebo (1.5%); N=1230
- Olanzapine (1.3%) vs. Placebo (0.4%); N=1882
- Aripiprazole (1.3%) vs. Placebo (0.6%); N=938
- Quetiapine (0.3%) vs. Placebo (1.9%); N=568

FDA WARNING ON MORTALITY

- Announced April 11, 2005
- Boxed Warning: Atypical antipsychotics used to treat dementia-related psychosis carry an "increased risk of death compared with placebo"
- 17 PCTs reviewed enrolling 5,377 elderly pts with dementia-related behavioral disorders (3631 drug, 1766 placebo)
- Rate of death in drug treated patients was 4.5% vs. 2.6% in placebo group
- Risk of death 1.6 to 1.7 times that seen in placebo group
- Cause of death – heart-related or infectious
- Six drugs involved in trials: aripiprazole (3), olanzapine (5), risperidone (7), quetiapine (2), ziprasidone (1), haloperidol (2)
- 7 medications have warning including clozapine, ziprasidone, and Symbyax (olanzapine/fluoxetine)
- FDA Alert [6/16/2008]: FDA added conventional antipsychotics to warning

2016 APA Practice Guideline

- Use antipsychotics only if benefits outweigh the risks
- Initiate treatment at a low dose and titrate to the minimum effective dose as tolerated
- If adverse effects occur, risks vs. benefits should be reviewed to determine if taper and discontinuation of the medication is indicated
- If there is no response after a 4-week trial on an adequate dose, taper and discontinue the medication
- When there is adequate response, an attempt to taper and withdraw the medication should be made within 4 months of initiation of treatment unless there is a recurrence of symptoms with previous attempts at tapering the medication
- While tapering the medication, assess symptoms at least every month during the taper and for at least 4 months after medication discontinuation
- In the absence of delirium, haloperidol should not be used as a first-line agent
- Long-acting injectable antipsychotic medication should not be used unless for a co-occurring chronic psychiatric illness

DIVALPROEX IN BPSD

- Divalproex has been studied in case series and four placebo-controlled trials in patients with dementia and agitation
- In three trials, benefit seen in secondary outcomes addressing agitated behaviors.
- Trial sponsored by Alzheimer’s Disease Cooperative Study Group (ADCS): treatment with divalproex did not show benefit on any primary or secondary measure of agitation associated with Alzheimer’s Dementia in nursing home residents
- Divalproex in combination with atypical antipsychotics is common in routine clinical practice, and likely creates different neurochemical effects than divalproex monotherapy. Consequently, combination therapy may be effective in treating BPSD even when monotherapy is not.

EFFECT OF CITALOPRAM ON AGITATION IN ALZHEIMER’S DISEASE: CITAD STUDY

- 186 subjects with AD plus agitation
- Psychosocial intervention plus citalopram or placebo for 9 weeks
- Citalopram dose range 10mg to 30mg/day
- Reduction of agitation and caregiver distress noted in Citalopram group
- Neuropsychiatric Rating Scale-Agitation subscale, CMAI, NPI-total score and CGI-C
- Adverse effects at 30 mg/day: Worsening cognition (MMSE declined by 1.05 points) and QTc prolongation (18.1 ms)

Benzodiazepines

- Minimal efficacy data
- Sedating
- Further inhibit learning and memory
- Cause falls
- Paradoxical disinhibition
NEUROPSYCHIATRIC EFFECTS OF CHOLINERGIC AGENTS

- Tacrine, Donepezil, Rivastigmine, Galantamine
- Effects important in some individuals, modest at group level
- Perhaps most notable benefit in Lewy Body Dementia
- Key effects
  - Decrease psychosis (visual hallucinations)
  - Decrease apathy
  - Decrease agitation but occasional increase
  - Decrease ? Anxiety, depression
- Donepezil not effective in reducing CMAI agitation in 12-week DBPCT in AD patients who had not responded to a psychosocial intervention


Novel Therapeutic Approaches

- Electroconvulsive Therapy (ECT)
- Cannabinoids

PEC TOAGITATION IN AD:

- 67-year-old female admitted for severe agitation
- Diagnosed with Alzheimer’s Dementia 10 years prior
- MRI 8 years prior demonstrated diffuse severe cortical atrophy and bilateral hippocampal atrophy
- Now with advanced dementia with little meaningful speech, aggressive at home with spouse caregiver
- 12 failed medication trials
- She remained aggressive and essentially impossible to place at home or in a facility

THE INDEX PATIENT

- Approximately 2 months into the hospitalization, she began ECT with her husband’s consent (HCP)
- She received 8 inpatient bilateral ECT treatments
- Reduced agitation/aggression noted after first treatment with continued improvement thereafter
- No further episodes of aggression or assaultiveness
- Appetite improved, calm during daily care
- Only side effect was mild headache - No significant memory or cognitive AEs
- Discharge psychiatric meds: Escitalopram 20mg, Haloperidol PRN severe agitation
- Patient was able to go home with in-home services

IMPACT OF ECT ON QUALITY OF LIFE

“My mother was a petite 5’3” 115-pound terror when her aggression reared; she was uncontrollable. Her medications were losing efficacy and it became so dangerous for our in-home aide, my father and me that we had no option but to place her inpatient at McLean Hospital. From the very first ECT treatment, the medical teams, my father and I were rendered speechless. Walking down South Belknap hall after that first treatment, she came at me like previously when severely aggressive. However, this time, she reached her arms out, rubbed my cheek lovingly with a smile from ear to ear. Tears rolled down my cheeks. Behaviors that we thought were robbed long ago returned; my mother was using words and sentences instead of gibberish. Her agitation and aggression nearly disappeared. She went from 31 medications to one. We were able to bring my mom back home and were blessed with another 10 years with her. This treatment gave my mother tremendous quality of life and gave my family, her husband and me, our mother. Without ECT, she never would have seen me get married, a day where she was so cognizant of everything that was happening even standing on her own. She always said “Here comes the bride” to start to play.”

Quotation from daughter, Karen
SAFETY AND UTILITY OF ACUTE ELECTROCONVULSIVE THERAPY FOR AGITATION AND AGGRESSION IN DEMENTIA


ECT-AD

5-Year, NIA-funded R01 RCT  
Individuals with AD complicated by severe agitation/aggression  
ECT plus Usual Care vs Simulated ECT: 9 treatments, 3 weeks  
Open-label extension up to 12 months  
PIs: Drs. Petrides and Forester

Protocol Review: Aims

Aim 1: To compare the relative efficacy of up to 9 ECT treatments plus usual care (ECT+UC) versus Simulated ECT plus Usual Care (S-ECT+UC) in reducing severe agitation in 200 participants with moderate to severe AD.

Aim 2: To compare the relative tolerability/safety outcomes of ECT+UC versus S-ECT+UC in 200 participants with moderate to severe AD.

Exploratory Aim: To explore the stability of agitation reduction (Cohen Mansfield Agitation Inventory) and global functioning (Clinical Global Impression [CGI-S]) with assessments at 1, 3 and 6 months following the randomized phase, and then for a fourth visit within 12 months after the randomized phase.

Study Design

Table: Scale Schedule

Screening: 7 days max between Screening and Day 0
Baseline aka Day 0: Within 24 hours prior to 1st ECT/S-ECT
POLLING QUESTION

Cannabinoids for Agitation in Dementia?

Medical Use: Approved Meds

- Dronabinol (Marinol cap): Synthetics liquid: Synthetic THC
  - FDA approved in 1985 as appetite stimulant for people with AIDS, and as antiemetic for people receiving chemotherapy
- Nabilone (Cesamet cap): Racemic mixture of THC analog
  - FDA approved in 2006 for chemotherapy-induced nausea/vomiting
- Cannabidiol extract (Epidiolex liquid)
  - FDA approved 6/2018 AED for Lennox-Gastaut & Dravet syndromes (ages 2+)
DRONABINOL

- Synthetic cannabinoid (THC)
- Most prevalent active ingredient of marijuana (schedule I)
- Also an FDA-approved schedule III drug (dronabinol, Marinol)
- Approved for anorexia, particularly at end-of-life
- Benign safety profile and low dependence potential
- CB1 and CB2 agonist
  - CB1 likely to mediate anxiolytic effects
  - CB2 may mediate anti-inflammatory effects, much more speculative
- Short-term effects of THC include euphoria, relaxation, and sedation

RATIONALE

- Neurotransmitter Regulation – serotonin, dopamine
- Neuroprotection and Neuroinflammation – limit oxidative stress, reduce TNF-α, inhibit glutamate release, block amyloid generation, increase available acetylcholine, limit microglial and cytokine production
- Improve Circadian Rhythm Disturbances – sleep/activity cycling, appetite, body temp.
- Related Comorbidities – pain, anxiety, insomnia, & others
- Vascular Disease – increase vasodilation & cerebral blood flow

STUDY CRITERIA

- Inclusion Criteria
  - Dementia due to AD
  - Severe agitation (IPA)
  - Age 60-95
- Exclusion Criteria
  - Serious or unstable illness
  - Seizures; delirium
  - Use of lithium
  - Inability to swallow a pill
- Blood Collection
  - CR receptor polymorphisms
  - Inflammatory markers

Cannabinoids for Agitation in Alzheimer’s Disease

Johannes D. Stans, H.L. Rehman, Rehmanah, R., Ryan, Houston, F.D.,
Eldred, Ryan, F.D., H.R., Rehman, R., Ryan, Houston, F.D.,
Bongard, Ryan, F.D., H.R., Rehman, R., Ryan, Houston, F.D.

THC-AD

- NIA R01, 5-year RCT, Funded: June 2016
  - PIs: Forester (McLean), Rosenberg (J Hopkins); Co-PI Agronin (Miami Jewish Home)
- Aim #1 – To compare efficacy of 3-week dronabinol treatment to placebo in treating agitation in AD
  - Primary outcome: Neuropsychiatric Inventory – Clinician Version (NPI-C) Agitation and Aggression subscales, Pittsburgh Agitation Scale (PAS)
- Aim #2 – To compare safety of a 3-week dronabinol treatment to placebo in patients with agitation and AD

Design Overview

- 4 visits over the course of a 3-week trial
- Placebo-controlled, randomized, double-blind
- 25 mg BID dose increased to 50 mg BID dose after 1 week (administered at 8 AM and 2 PM. Half life is 4 hours)
- Target 80 participants total (McLean Hospital, North Shore Medical Center, Johns Hopkins, Miami Jewish)
- Inpatient, outpatient and long-term care settings
- Blood biomarkers also collected
  - Cytokines and DNA testing
RECRUITMENT SUMMARY

<table>
<thead>
<tr>
<th>Assessment</th>
<th>n (%)</th>
<th>Mean ± SD (percentile)</th>
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</thead>
<tbody>
<tr>
<td>Total</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>78.0, 7.1 [65 – 94]</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>32 (72.7)</td>
<td></td>
</tr>
<tr>
<td>Education (years)</td>
<td>13.3, 3.4 [3 – 19]</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>38 (88.3)</td>
<td></td>
</tr>
<tr>
<td>Family History</td>
<td>20 (44.2)</td>
<td></td>
</tr>
<tr>
<td>HDR screen Agitation</td>
<td>10 (23)</td>
<td></td>
</tr>
<tr>
<td>Short CAM-Alert</td>
<td>20 (83.3)</td>
<td></td>
</tr>
</tbody>
</table>

➢ Our cohort is significantly agitated and cognitively impaired, but not delirious.
➢ Health corresponds to an often frail & elderly population in AD.

Medical Marijuana and Alzheimer’s Dementia

After marijuana edibles helped dying Holocaust survivor battle Alzheimer’s, his family’s foundation pushes for more research

By FORD VOX
ABC News
Dec 9, 2018, 1:50 PM ET

An Open Label Trial of Cannabidiol for the Treatment of Behavioral Symptoms in Older Adults with Alzheimer’s Dementia

Geriatric Psychiatry Research Program

Outpatient 8-week open-label clinical trial using a custom-formulated high-CBD/low-THC full spectrum sublingual solution derived from industrial hemp to treat anxiety and agitation in older adults with mild to moderate Alzheimer’s disease.

Rationale:
• CBD may have anxiolytic properties
  • CBD mitigated anxiogenic effects of THC (Zuardi et al., 1982)
  • CBD reduced anxiety in patients with anxiety disorder (Bergamaschi et al., 2009)

• Total amount of THC will not exceed 0.3% by weight
• Target dose of CBD per day will be 45mg with approximately 1mg THC

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Description of CBD-AD

1. 8 Week Treatment Phase
   • Assess anxiety/agitation reduction
   • Assess safety and tolerability of study product
   • Assess reduction in caregiver burden

2. Optional 12-Month Observational Follow-Up Phase
   • Assess durability of reduction in anxiety/agitation and caregiver burden with commercially available similar cannabinoid products

MEMORY CARE INITIATIVE
Mass General Brigham
A Primary Care-based Collaborative Care Team
• Collaborative Dementia Care
• Establish care team which collaborates with PCP to provide:
  • Timely & regular patient assessment & severity stratification
  • Assist with diagnosis, disclosure and difficult conversations
  • Care Planning
  • Medication management
  • Caregiver support
  • Connection to specialists (Neurology, geri psych) and other Population Health programs (Collaborative Care, Care Management)
  • Connection to community resources
• Outcome: Reduction in caregiver stress and improvement in the behavioral and psychological symptoms of dementia

Collaborative Dementia Care Program

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Collaborative Dementia Care Program
SUMMARY

• Distressed behaviors are clues to the diagnosis
• Unless urgent, the complete assessment (not just the symptoms) determines the working diagnosis
• Use non-pharmacologic interventions in every case
• The working diagnosis determines management approach and medication class used
• Consider side effects and tolerability in all medication choice
• Treatment goals to enhance quality of life of patient and caregiver