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Neurocognitive Disorders - Behavioral and Psychiatric Symptoms

The Elephant in the Room: Sensitive Subjects in Dementia Care
UCI-MIND Research Conference

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Auguste Deter, age 51
- Confusion, delusions, hallucinations
- Plaques, tangles, arteriosclerosis

“She screams that the doctor wants to cut her open... She fears him as a threat to her honor as a woman.”
- Alois Alzheimer
November 1906, Frankfurt

Patient distress and compromised safety
Recurrence
Institutionalization
Caregiver burden
Increased healthcare utilization and costs

Relative Rate or Risk

0 1 2 3 4
0 1 2 3 4
ED Visits Acute Hospitalization Medicare Expenditures

Maust 2017

Neuropsychiatric Symptoms

Consequences
- Patient distress and compromised safety
- Recurrence
- Institutionalization
- Caregiver burden
- Increased healthcare utilization and costs

Brain Imaging and Neurobiology

Neuropsychiatric Symptoms in AD

OFF-State AChE (U/L)

- Delusions in AD
- PET metabolic activity
- Aggression in AD mice
- Genetics
- Amyloid transgenics vs Wildtype
- Agitation in AD
- PET cholinergic receptors in anterior cingulate

Sultzer 2014, Pugh 2007, Sultzer 2017

Psychosis

Neurocognitive Disorders

- Prevalence: 20–40%
- Delusions: paranoid/threat and misidentifications
- Hallucinations less common; usually visual
- Associated with:
  - More rapid cognitive decline
  - Agitation/aggression

Management
- Consider delirium
- Address sensory deficits
- Reassurance and support
- Med treatment - rarely
  - Consider if distress or behavioral impact
  - Re-evaluate frequently, consider d/c after 3 months

Lewy body dementia
- 80% with visual hallucinations
- Associated with cortical spread and density of Lewy bodies
- Cholinesterase inhibitor medications may be beneficial

Parkinson’s disease
- Visual hallucinations are common
- Dopamine replacement therapy often contributes, but is necessary for control of motor symptoms of PD
- Consider delirium
- If meds are necessary:
  - Quetiapine
  - Pimavanserin
  - Clozapine

Dementia with Lewy Bodies and Parkinson’s Disease

Psychosis

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Definition
- Heterogeneous behaviors
  - Non-aggressive physical, aggressive physical, verbal
  - Related to anxiety, fear, confusion, irritability, impulsivity
  - Prevalence
  - Agitation 20–70%: Physical aggression 10–25%
  - Associated with:
    - Premorbid aggression
    - Rapid decline

Prevalence
- Agitation 20-70%; Physical aggression 10-25%

Associated with:
- Premorbid aggression
- Rapid decline

What's the behavior?
- Talk with patient and carers
- Context and spectrum of behaviors
- Are there "medical" causes?
  - Pain, delirium, sensory deficits
- Are there other contributors?
  - Boredom, communication, misinterpretation, environment, anxiety, psychosis
- What’s the acute risk?
  - Safety measures

Psychosocial Interventions
1. Caregiver
   - Problem-solving: avoiding triggers, routines, reassurance, distraction, managing affect, let it go
   - Emotion-focused: support, time for themselves
   - Education: link to neurocognitive disorder
   - Respite care
   - Support groups
2. Patient
   - Repetition, redirection, reassurance
   - Improve communication, pleasant activities, social engagement
3. Environment
   - Stimulation, wandering paths, visual barriers

Current evidence gaps:
Severe symptoms, symptoms that best respond, implementation

Addressing Agitated Behaviors
- What’s the behavior?
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Medication Interventions
- Agitation/Aggression in AD
  - Antipsychotics
  - Cholinesterase Inhibitors or Memantine
  - Anticonvulsants
    - Valproate
    - Carbamazepine
  - Serotoninergics
    - Trazadone
    - Citalopram
  - Antidepressants
    - Trazodone
    - Citalopram
  - Others
    - Prasozin
    - Cabapent
    - Buproprine
    - Propranolol

US - No medication is approved in the U.S. for the treatment of agitation in AD.
EMA - Risperidone for short-term treatment of persistent aggression in moderate to severe AD with risk of harm, and unresponsive to non-pharmacological approaches.

Atypical Antipsychotic Efficacy
- Agitation in AD
  - Effect size -
    - Agitation = 0.20
    - Psychosis = 0.11
  - Total behavioral symptoms = 0.16

Adverse Effects
- Somnolence
- Extrapyramidal effects
- Gait difficulty
- Edema
- Urinary symptoms
- Metabolic syndrome
- Weight gain
- Cognitive decline
- Cerebrovascular events
- Mortality

AHRQ 2011
Maher 2011
Schneider 2006
Maust 2015

Schneider 2008
Mauri 2015
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Hostility, suspiciousness, uncooperativeness
Symptoms improved by 30%
Greatest improvement among behavioral measures

Citalopram for Agitation in AD

- N=186, mean MMSE 16
- 9-week, placebo-controlled trial
- Citalopram target dose: 30mg/day
- 78% reached target dose
- Adverse effects in citalopram group
  - Anorexia, diarrhea, fever, falls
  - MMSE 1.05 point decline vs placebo
  - QTc interval
  - % vs in each group
  - Mean of max increase vs placebo
  - 7 vs 1 with QTc increase >30msec

Antipsychotic Discontinuation

- Design
  - AD with agitation-psychosis
  - Rx risperidone x 16 weeks (open)
  - Responders randomized to continue risperidone or not x 16 weeks (blind)

- Time to relapse* and risk of relapse favored risperidone
  - Placebo 60%
  - Risperidone 33% (p<.004)
  - Relative hazards ratio 1.94 (CI 1.09-3.45; p=.02)

- Relapse - increased NPI core by >30% or 5-point increase from end of Phase A, and CGI-C much worse or very much worse

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- Behavioral Interventions, including pain management
  - S-citalopram
  - Dextromethorphan
  - Pimavanserin
  - Brexpiprazole
  - Aripiprazole
  - Lithium
  - Prazosin

Antipsychotic Review and Behavioral Intervention
WHELD Program in Nursing Homes

- 9-month intervention, person-centered care and
  - Antipsychotic review, social interaction, or exercise
  - Antipsychotic review
    - Reduced antipsychotics by 50%
    - Non-significant decline in mortality
    - Significant decline in mortality when combined with social interaction (35% neither, 19% both)
    - Total neuropsychiatric symptoms worsened
    - Not significant when combined with social interaction
  - EXERCISE
    - Improved total neuropsychiatric symptoms
    - No change in depression
  - Implications
    - Reducing meds alone may not be optimal
    - Real-life, practical interventions can improve outcomes and reduce antipsychotic use
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**Apathy in AD**
- Common and persistent
- Promotes disability
- Central aspect of the neurodegenerative disorder
- Neurobiology
  - Brain – behavior relationships
  - Refine nosology
  - Treatment target

**Apathy in AD Assessment and Management**
- Delirium or other medical contribution?
- Behavioral interventions
  - Enhanced activities: 23/26 studies found benefit
  - WHILD study: Antipsychotic review combined with social activity or exercise improved apathy
- Medications
  - Cholinesterase inhibitors - mixed findings; no robust benefit
  - Antidepressants - mixed findings; depression confound
  - Methylphenidate
    - ADMET (2013): 21% improved on methylphenidate 20mg/d; 3% on placebo
    - ADMET 2 in progress

**Depression and Anxiety**
- Variable frequency
- Depression is a risk factor for dementia
  - Risk seen in longitudinal studies of depression
  - Links to brain amyloid on imaging
- Anxiety promotes increased dementia risk in those with memory complaints and brain amyloid
- Depression is particularly common in vascular dementia
- Management
  - Psychological - Mixed evidence of mild benefit
  - Exercise
  - Other PSI – mild benefit
  - Antidepressant meds
    - Little evidence of benefit in AD
  - Sertraline in vascular dementia

**Resources**
- Alzheimer’s Association Caregiver Center
  [www.alz.org/care](http://www.alz.org/care)
- Approaches to individual neuropsychiatric symptoms
- Practical Dementia Care
  - Rabins, Lyketsos, and Steele, 2006
  - Appendix A: Dementia Family Care Guidelines
- Problem-oriented, brief: not as much info on agitated behaviors
- Caregiver’s Guide to Understanding Dementia Behaviors
  - Family Caregiver Alliance
    [www.caregiver.org](http://www.caregiver.org)
- Problem-oriented, brief
Better-defined syndromes, particularly “agitation”
Biomarkers for distinct symptoms
Medication development guided by neurobiology
Prevention
Practical, effective, and safe management
- Integrated psychosocial and pharmacological
- Person-centered
- Practice guides and easy implementation
- Healthcare system alliance