Dementia in Distress, Behavioral Disturbances related to Dementia

Mehrdad Ayati, MD
Geriatric Medicine
Financial Disclosure

Unfortunately Not
IF YOU ASK US HOW TO SEDATE YOUR DEMENTED PATIENTS
You are sitting in the wrong place.
Behavioral Disturbance

- Shadowing a caregiver
- Arguing/Complaining
- Becoming easy upset
- Repetitive questioning
- Pacing
- Hoarding
- Rejection of care
- Inappropriate crying out/screaming
- Verbal or Physical aggression
- Sleep disturbance
- Wandering
- Inappropriate sexual behavior
My biggest challenge: No tool to Measure
### Cohen-Mansfield Agitation Inventory (CMAI)

**Instructions:** For each of the behaviors below, check the rating that indicates the average frequency of occurrence over the **last 2 weeks**.

<table>
<thead>
<tr>
<th>Behavior</th>
<th>Never</th>
<th>Less Than Once a Week</th>
<th>Once or Twice a Week</th>
<th>Several Times a Week</th>
<th>Once or Twice a Day</th>
<th>Several Times a Day</th>
<th>Several Times an Hour</th>
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</thead>
<tbody>
<tr>
<td>1. Hitting (including self)</td>
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<td>2. Kicking</td>
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<td>3. Grabbing onto people</td>
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<td>4. Pushing</td>
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<td>5. Throwing things</td>
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<td>6. Biting</td>
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<td>7. Scratching</td>
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<td>8. Spitting</td>
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<td>9. Hurt self or others</td>
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<td>10. Tearing things or destroying property</td>
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<td>11. Making physical sexual advances</td>
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<td>12. Paces, aimless wandering</td>
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<td>13. Inappropriate dress or disobeying</td>
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<td>14. Trying to get to a different place</td>
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<td>15. Intentional falling</td>
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<td>16. Eating/drinking inappropriate substances</td>
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<td>17. Handling things inappropriately</td>
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<td>18. Hiding things</td>
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<td>19. Hoarding things</td>
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<td>☐</td>
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<td>20. Performing repetitious mannerisms</td>
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<td>21. General restlessness</td>
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<td>22. Screaming</td>
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<tr>
<td>23. Making verbal sexual advances</td>
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<td>24. Cursing or verbal aggression</td>
<td>☑</td>
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<td>25. Repetitive sentences or questions</td>
<td>☑</td>
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<td>26. Strange noises (weird laughter or crying)</td>
<td>☑</td>
<td>☐</td>
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<td>☐</td>
<td>☐</td>
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<td>27. Complaining</td>
<td>☑</td>
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<td>☐</td>
<td>☐</td>
<td>☐</td>
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<td>28. Negativism</td>
<td>☑</td>
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<td>☐</td>
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<tr>
<td>29. Constant unwarranted request for attention or help</td>
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</tbody>
</table>

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**Name of Rater:**

**Name of Primary Caregiver/Informant:**
## NPI-Q Summary

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Severity</th>
<th>Caregiver Distress</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delusion</td>
<td>0</td>
<td>1 2 3</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td>Hallucination</td>
<td>0</td>
<td>1 2 3</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td>Agitation/Aggression</td>
<td>0</td>
<td>1 2 3</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0</td>
<td>1 2 3</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td>Euphoria/Elation</td>
<td>0</td>
<td>1 2 3</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td>Apathy</td>
<td>0</td>
<td>1 2 3</td>
<td>0 1 2 3 4 5</td>
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<tr>
<td>Disinhibition</td>
<td>0</td>
<td>1 2 3</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td>Irritability</td>
<td>0</td>
<td>1 2 3</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td>Aberrant Motor</td>
<td>0</td>
<td>1 2 3</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td>Nightmare Behavior</td>
<td>0</td>
<td>1 2 3</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td>Appetite</td>
<td>0</td>
<td>1 2 3</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
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</tbody>
</table>
Non-pharmacologic intervention is first and superior step in treatment of BDRD.
Evidence Based Medicine
Non-Pharmacologic Interventions

LET ME KISS IT TO MAKE IT ALL BETTER.

DON'T LISTEN! IT'S NO BETTER THAN A PLACEBO!

DR. MILFORD HAD A PASSION FOR EVIDENCE BASED MEDICINE
Snoezelen: limited conflicting evidence for efficacy in dementia

- Cochrane review of 3 RTC
- 245 demented patients
- Improved behavioral rating scale but not maintain at follow up
- Help with cognition but decrease attention during and immediately post session.


¹Superscript indicates that the author is possibly referring to a specific edition or publication of the work.
Virtual Reality

Effectiveness of a Virtual Reality Forest on People With Dementia: A Mixed Methods Pilot Study

Wendy Moyle, PhD, MHSc, BN, RN,1, 2, 7, 8 Cindy Jones, PhD, GDipPsych, GCertHigherEd, BA (Psych), BB (HRM),1, 2, 7 Toni Dwan, B Psych (Hons),1 and Tanya Petrovich, PhD, BSc(Hons), Grad Dip Ed8
Music therapy and Sensory interventions (Snoezelen or Massage) may improve immediate agitation in patients with dementia without lasting effects.

Aromatherapy, Light therapy, and Home-like care in care homes may have no effects.

Based on Systemic review of 160 studies

Music therapy and Sensory interventions had no change in follow up after 3 weeks (3-8 w for Music and 1-3 w for sensory)

Don’t hate me, let’s just keep it off the records!

- Interventions involving music, bright light therapy, and aromatherapy with lavender appear no more effective than placebo or no intervention for decreasing aggression among assisted living and nursing home residents.
Aromatherapy

• **Limited and inconsistent evidence of efficacy**


  • Cochrane review of trials with methodologic limitations
  • 7 randomized trials evaluating aromatherapy in 428 patients
  • No significant differences in agitation, behavioral symptoms, activities of daily living, and quality of life in 1 trial with 114 patients
  • Only one trial showed improvement with [Lemon Balm](#) in 72 patients
Music-based therapies do not appear to improve agitation or other behavioral disturbances although it may reduce depressive symptoms in patients with dementia.

- Review of 17 randomized trials
- Residing in institutions
- Decrease in depressive symptoms in analysis of 9 trials with 376 patients
- No significant differences in anxiety, agitation, emotional well-being and cognition

Massage and Touch

• 2 trials with 110 patients

• Hand massage significantly reduced agitated behavior on CMA score vs no treatment in 1 trial with 34 patients

• Addition of touch to verbal encouragement to eat significantly increased mean caloric and protein intake in 1 trial with 42 patients

Let’s come to our business
Target Symptoms

Start Low, go Slow but go

Instruction for Caregivers

Avoid Polypharmacy

Change only one medication at a time

Set a Realistic Expectation

Important Roles for Pharmacologic Therapy
Antidepressant

Depression in ½ of patient with Alzheimer or MCI (Di Lulio et al 2010).

SSRIs: relatively safe, high efficacy

Treatment of Depression will not resolve the Cognitive deficits
Antidepressant

- **SSRIs**: Citalopram, Escitalopram, Sertraline, Fluoxetine, Paroxetine
- **SNRIs**: Venlafaxine, Duloxetine, Desvenalfaxine
- **Serotonin Agonist**: Trazodone, Nefazodone
- **Specific serotonergic**: Mirtazapine, Buspirone
Citalopram (CitAD Trial)

- Addition of Citalopram to psychosocial intervention appears to slightly reduce agitation (Dose > 20 mg)
- But:
  - QT interval prolongation
  - Worsening of Cognition
Participant Flow in Randomization to Citalopram vs Placebo for Agitation in Alzheimer

Primary outcomes
- NBRS-A analysis
- 94 Slope model
- 90 Shown in table 2
- mADCS-CGIC analysis
- 94 Sensitivity analysis
- 85 Shown in table 2

Primary outcomes
- NBRS-A analysis
- 92 Slope model
- 85 Shown in table 2
- mADCS-CGIC analysis
- 92 Sensitivity analysis
- 81 Shown in table 2

Figure Legend:
Participant Flow in Randomization to Citalopram vs Placebo for Agitation in Alzheimer
Neurobehavioral Rating Scale (NBRS)-Agitation Subscale Higher NBRS scores indicate more severe symptoms. The horizontal bar inside the boxes indicates the median, the square in the boxes indicates the mean, and the lower and upper ends of the boxes are the first and third quartiles. The whiskers indicate values within 1.5 × the interquartile range from the upper or lower quartile (or the minimum and maximum if within 1.5 × the interquartile range of the quartiles) and data more extreme than the whiskers are plotted individually as outliers.
| 01 | Sertraline associated with significant improvement in agitation (Cohen-Mansfield Agitation Inventory scores). |
| 02 | Comparing sertraline 200 mg/day vs. placebo in 1 trial with 244 patients (p<0.05) |
| 03 | No significant difference in total Neuropsychiatric Inventory scores (including agitation, delusion, and hallucination subscales) |
| 04 | Cochrane Database Syst Rev. 2011 Feb 16 |
Antidepressants associated with
- Improved symptoms in 48.1% of patients and worsened symptoms in 12.6% of patients
- Decreased mortality risk
- No significant difference in behavioral symptom change or in comparison of antipsychotics vs. antidepressants

Treated Behavioral Symptoms and Mortality in Medicare Beneficiaries in Nursing Homes with Alzheimer's Disease and Related Dementias, J Am Geriatr Soc. 2015 Sep;63(9):1757-65.
Treated Behavioral Symptoms and Mortality in Medicare Beneficiaries in Nursing Homes with Alzheimer's Disease and Related Dementias

Treated Behavioral Symptoms and Mortality in Medicare Beneficiaries in Nursing Homes with Alzheimer's Disease and Related Dementias, Volume: 63, Issue: 9, Pages: 1757-1765, First published: 27 August 2015, DOI: (10.1111/jgs.13606)
Escitalopram versus risperidone for the treatment of behavioral and psychotic symptoms associated with Alzheimer’s disease: a randomized double-blind pilot study

Yoram Barak, Igor Plopski, Shelly Tadger and Diana Paleacu

Abarbanel Mental Health Center and the Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel
• Decrease in the NPI scores in both groups
• Risperidone > Escitalopram
• Less Withdraw from Escitalopram
• Risperidone group shows an effect sooner
• Limitation if study: small size, single center study, high SD in NPI scores.
Sertraline or mirtazapine for depression in dementia (HTA-SADD): a randomised, multicentre, double-blind, placebo-controlled trial

Sube Banerjee, Jennifer Helie, Michael Dewey, Renee Romeo, Clive Ballard, Robert Baldwin, Peter Bentham, Chris Fox, Clive Holmes, Cornelius Katona, Martin Knapp, Claire Lawton, James Lindesay, Gill Livingston, Niall McCre, Eime MacAra-Cook, Joanna Murray, Shirley Nwok, Martin Orell, John O’Brien, Michaela Popp, Alan Thomas, Rebecca Walsh, Kenneth Wilson, Alastair Rums

Figure 2: Unadjusted mean CSDD scores by treatment group
Lowest score is best. Error bars show 95% CIs. CSDD=Cornell scale for depression in dementia.
Major Side Effects

• GI upset (Nausea) in first few days
• SIADH (Hyponatremia): first couple weeks of treatment
• Platelet activation (cautious when use with NSAIDs or ASA)
• Should we use prophylactic acid reducer medications?


SNRIs

• Not many evidence of Behavioral Disturbances related to Dementia
• One trial in combating depression in Huntington's Disease
• Venlafaxine may induce Myoclonic Jerks
• Venlafaxine in Preexisting Heart Disease (need EKG baseline)
• Cautious combining Venlafaxine and Mirtazapine (QT prolongation)
  • National Collaborating Centre for Mental Health: Management of Depression in Primary and Secondary Care (Clinical Guideline 23). London, National Institute for Clinical Excellence, 2004
Trazodone

• Insufficient Evidence (except early 1990s)
• 1 RTC in Alz and 1 RTC in FTD
• No significant differences with placebo.
• Some efficacy in sleep disorder of Alzheimer cases in small RTC
• Metabolize by CYP3A4
• Alpha1 adrenergic blocker

Mirtazapine

- Induce 5HT, Type 1A 5-HT1A (Sleep enhancer)
- Block 5-HT2 and 5HT3 (like Ondansetron)
- Less sexual dysfunction, Nausea and Tremor
- Anxiolytic (dual antagonism at 5-HT2 and 5-HT3 receptors and its enhanced activity at 5-HT)
- Effective in treatment of Depression in case series
Mirtazapine

• Higher risk of Stroke and Mortality
• Increase risk of QT prolongation
• Sedative at lower doses (Delirium)
• Weight gain and Lipid Disorder
• Be aware of Akathisia
• Rarely Neutropenia or Agranulocytosis


Other Antidepressants/Anxiolytics

- **Buspirone**: limited data, no double blind studies
- **Dextromethorphan-Quinidine**:  
  - Improved NPI scores (agitation and aggression) in 5 weeks of trial  
  - Increased risk of fall  
  - Although statistically significant, the observed between-group difference of 1.5 points on the NPI agitation/aggression domain is of uncertain clinical significance.


Gabapentin

- Efficacy is unproven.
- Limited benefit in prospective case series design.
- 12 patients for 8 weeks, only 2 patients were much improved on CGI
- One case report of women with nocturnal agitation and vascular dementia.
Valproate

• No significant differences in agitation in analysis of 3 trials with 216 patients.

• Systemic review of RTCs >>> neither short or long acting were effective

• May be associated with increased adverse events (sedation, nausea, vomiting, diarrhea, GI upset, infection and Thrombocytopenia)

Cognitive Enhancers

- Cholinesterase Inhibitor: Very small benefit in meta-analysis
- Rivastigmine in DLB
- No clinically significant effect of Memantine


Pain Management

• Stepwise Protocol (AGS)
• Acetaminophen, Low dose Morphine, Buprenorphine patch, Pregabalin
• After 8 weeks: reduced neuropsychiatric symptoms
• No effect on cognition and daily function
• Agitation score were similar at 12 weeks.
Fig 2  Cohen-Mansfield agitation inventory scores, with 95% confidence intervals, over study period.

Bettina S Husebo et al. BMJ 2011;343:bmj.d4065
Lithium

- Inhibitory effects on glycogen synthase kinase-3 and tau
- One case series showed reduction of Agitation.
- In older adults: Higher permeability of blood-brain – barrier >> higher serum concentration
- Need to keep the level low: 0.4-0.8 meq/L

Zonisamide

- 1, 2-benzisoxazole-3-methane sulfonamide
- Same mechanism like Valproate or Lamotrigine.
- Effective and well tolerated in one case report with DLB.

Successful treatment of extrapyramidal and psychotic symptoms with zonisamide in a patient with dementia with Lewy bodies. Progress in Neuro-Psychopharmacology and Biological Psychiatry, Volume 34, Issue 6, 2010
Cannabinoids

- Medical cannabis oil in 11 patients with ALZ type
- THC 2.5 mg, titrate up to 7.5 mg bid
- Improve in NPI score from 44.4 to 12.8 (p<0.01)
- Improve in CGI score from 6.5 to 5.7 (P<0.01)
- No significant changes in Mini-Mental State Examination score or Clinical Global Impression-Improvement at 4 weeks
- 1 patient reported confusion with 5 mg/day THC dose and improved with dose reduction to 2.5 mg/day

Cannabinoids

- Small RTC (50 patients)
- THC 1.5 mg TID vs Placebo
- Not significant changes in NPI agitation/aggression or aberrant motor behavior subscale scores, activities of daily living, or quality of life.
  - Tetrahydrocannabinol for neuropsychiatric symptoms in dementia, Neurology 2015 June 9;84(23):2338
Nabilone (Cannabidiol Receptor Agonist)

- 72 yo, male, Alz type
- Aricept for 6 months, no effect
- Gabapentin 700 mg TID
- Trazodone 37.5 mg BID + 62.5 mg QHS
- Seroquel 100 mg QAM, 100 mg QHS
- Zyprexa 7.5 mg daily
- Lorazepam 0.5 mg before ADLs
Prazosin

- Small Trial
- 22 patients
- 1 mg daily, titrate up to 6 mg daily for 8 weeks
- Mean change in both NPI and Brief Psych rating scale
- No difference in blood pressures

ECT

• Can reduce symptoms of aggression and agitation
• Based on systematic review of observational studies of 122 patients.
• Clinically significant improvement as measured by Clinical Global Impression, Cohen Mansfield Agitation Inventory, Neuropsychiatric Inventory, or other scales reported in 88% of patients

Take Home Point

• Always try Non-Pharmacological first
• If there are no dangerous symptoms: Start with ChEI +- Memantin
• If symptoms persist, consider SSRIs
• If no improvement, consider switching if at Max dosage, consider combination therapy later, Trazodone or Mirtazpin for sleep issue
• If you need urgent management, you can use AP.
• Avoid Benzodiazepine Do not make cocktails, avoid anecdotal, do not sedate your patients.
Thank You

- mayati@stanford.edu

- “Humans are the limbs of the same body and are from the same essence in their creation. When the conditions of the time hurt one of these parts, other parts will suffer from discomfort as well. If you are indifferent about the misery of others, it is not deserving to call you a human being.”

Saadi Shirazi, 1210-1290, Shiraz, Iran