Pharmacological Management of Neuropsychiatric Symptoms of Dementia

Dr. Dallas Seitz MD FRCPC
Assistant Professor and Clinician Scientist,
Department of Psychiatry
Queen’s University

Department of Psychiatry Webinar
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Objectives

• By the end of this session participants should be able to:

• 1.) Review the neuropsychiatric symptoms (NPS) encountered in various types of dementia;

• 2.) Develop an approach to the use of medications in NPS; and

• 3.) Understand the safety and efficacy of pharmacological treatments for NPS.
Neuropsychiatric Symptoms

• Non-cognitive symptoms associated with dementia

• Also known as Behavioral and Psychological Symptoms of Dementia (BPSD)
  – International Psychogeriatrics Association 1996
    “Signs and symptoms of disturbed perception, thought content, mood, or behavior that frequently occur in patients with dementia”

1. Finkel, Int Psychogeriatr, 1996; 8(suppl 3):497-500
What are Neuropsychiatric Symptoms?

- Delusions\(^1\)
- Hallucinations
- Anxiety
- Elevated mood
- Apathy
- Depression
- Irritability
- Sleep Changes

- Agitation\(^2\):
  - Restlessness
  - Requests for help or repetitive questioning
  - Screaming or vocalizations
  - Hitting, pushing, kicking
  - Sexually disinhibited behavior

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Clusters of Neuropsychiatric Symptoms

- **Cohen-Mansfield Agitation Inventory (CMAI)**\(^1\):
  - **Verbal agitation** (yelling, repetitive vocalizations)
  - **Non-aggressive physical agitation** (restlessness, pacing)
  - **Aggressive physical agitation**

- **Neuropsychiatric Inventory (NPI)**\(^2\):
  - **Psychotic symptoms** (delusions/hallucinations)
  - **Mood/Apathy** (depression/apathy/eating/sleep)
  - **Hyperactivity**
    - (agitation/irritability/euphoria/disinhibition)

2. Aalten, Dement Geriatr Cogn Disord, 2003
Management of Neuropsychiatric Symptoms

• Differential Diagnosis:
  – Delirium (medication-induced, other causes)
  – Depression
  – Pain or discomfort
  – Other medical causes
  – Environment causes

1. Sink, JAMA, 2005
NPS that May Respond to Medications

- Aggression*
- Agitation*
- Psychosis*
- Depression
- Anxiety
- Apathy
General Principles for Management of NPS

• Medications should be used for severe NPS or patient safety, in conjunction with non-pharmacological approaches

• Prescribing requires assessment of capacity and informed consent

• Dosages are lower than that used in younger populations and need to be adjusted cautiously

• Elderly with dementia are more susceptible to some side-effects such as sedation, cognitive decline, EPS
Pharmacological Treatments

- Atypical antipsychotics
- Antidepressants
- Cholinesterase inhibitors
- Memantine
- Other medications
Atypical Antipsychotics

• Risperidone (N=5), aripiprazole (N=3), and olanzapine (N=5) have the strongest evidence to treat psychosis and agitation in dementia\textsuperscript{1,2}
  – Quetiapine (N=3) trials have largely been negative

• Comparison trials:
  – risperidone = olanzapine\textsuperscript{3}
  – olanzapine = haloperidol\textsuperscript{4}
  – Neither quetiapine or haloperidol superior to placebo\textsuperscript{5}

5. Verhey, Dementia Geriatr Cogn Disord, 2006
Clinical Antipsychotic Trials of Intervention Effectiveness – Alzheimer’s Disease (CATIE-AD)

• RCT (N=421) of outpatients with Alzheimers comparing risperidone, olanzapine, quetiapine and placebo for psychosis, agitation or aggression over 36 weeks

• Outcomes:
  – Time to discontinuation due to any cause
  – Global impression
  – Adverse events

CATIE-AD

- No difference in groups on time to discontinuation due to any cause
- Olanzapine and risperidone > placebo and quetiapine on discontinuations due to lack of efficacy
  - Overall discontinuation rate of 63% by 12 weeks
- Discontinuations due to adverse events favored placebo
- No difference in rates of global clinical improvement

NPS that Respond to Antipsychotics

• Olanzapine and risperidone associated with overall improvement in NPS\(^1\)
  – Hostility, psychosis, agitation most likely to improve

• Olanzapine demonstrated worsening ADL functioning and depression/withdrawal symptoms

• No overall benefit in clinical impression with any antipsychotic

## Atypical Antipsychotics Dosing

<table>
<thead>
<tr>
<th></th>
<th>Initial Dose</th>
<th>Titration Schedule</th>
<th>Maximum dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>0.5 mg total (given OD or BID)</td>
<td>0.25 - 0.5 mg every 3 – 7 days</td>
<td>2 mg</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>2.5 – 5.0 mg OD</td>
<td>2.5 – 5.0 mg every 3 – 7 days</td>
<td>10 mg</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>2 – 5 mg</td>
<td>2 – 5 mg every 3 – 7 days</td>
<td>10 mg</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>12.5 mg BID</td>
<td>25 mg in divided doses every 3 – 7 days</td>
<td>200 mg</td>
</tr>
</tbody>
</table>

Switch antipsychotics if no benefit or limited benefit observed after 2
Serious Adverse Events

• Mortality: OR=1.6, absolute risk ~1\%\textsuperscript{1,2}
  – Number needed to harm: 100
  – Infections, cardiovascular events
• Stroke: RR=2.7, absolute risk~1\%\textsuperscript{2,3}
• Any serious adverse events within 30 days\textsuperscript{4}
  – Atypical: 13.9\% (OR: 3.5, 3.1 – 4.1)
  – Typical: 16\% (OR=4.2, 95\% CI: 3.7 – 4.8)
  – No antipsychotic: 4.4\%

1. Schneider, JAMA, 2005
2. Schneider, Am J Geriatr Psychiatry, 2006
3. Herrmann, CNS Drugs, 2005
## Mortality Risk with Individual Atypicals

<table>
<thead>
<tr>
<th></th>
<th>Kales, 2012 Hazard ratio (95%CI)</th>
<th>Huybrecht, 2012 Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>0.99 (0.89 – 1.10)</td>
<td>1.03 (0.97 – 1.09)</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>0.73 (0.67 – 0.80)*</td>
<td>0.81 (0.75 – 0.88)*</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>--</td>
<td>0.88 (0.73 – 1.07)</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>1.54 (1.38 – 1.73)*</td>
<td>2.37 (1.89 – 2.26)*</td>
</tr>
</tbody>
</table>

Mortality Risk Atypicals vs Other Medications

- Risk of mortality in outpatients with dementia (compared to typical antipsychotic):
  - Atypical (HR, 95% CI): 0.93 (0.75 – 1.16)
  - SSRI: 0.49 (0.39 – 0.62)
  - Anticonvulsant: 0.79 (0.51 – 1.24)
  - Sedative/hypnotic: 0.76 (0.59 – 0.98)
  - No medication: 0.66 (0.53 – 0.82)

Common Adverse Events

- Somnolence: OR=2.8, absolute risk~10%¹
- Gait changes: OR=3.2, AR=10%¹
- Falls and fractures: OR = 1.5 – 2.0
- Extrapyramidal symptoms¹
  - Risperidone
- Weight gain, dyslipidemia²,³
  - Greatest risk with olanzapine and quetiapine, women at highest risk

Cognitive Effects of Antipsychotics

• Atypical antipsychotics associated with a MMSE score -2.4 over 36 weeks compared to placebo\(^1\)
  – Equivalent to approximately 1 year additional decline

• MMSE -1 point over 8 – 12 week trials\(^2\)
  – Often LTC population with low MMSE at baseline

Discontinuing Antipsychotics

• A large proportion of currently stable individuals on antipsychotics can have antipsychotics safely withdrawn\(^1,2\)
  – Withdrawal associated with 30% increase risk of behavioral worsening compared to placebo\(^1,2\)

• Predictors of successful discontinuation:
  – Less severe NPS at initiation of treatment\(^2\)
  – Lower dose of antipsychotic required to treat NPS\(^1\)

1. Van Reekum, Int Psychogeriatr, 2002
ADAD Trial

- Responders to 16 weeks of treatment randomized to either continuation or placebo
  - Acutely symptomatic population compared to previous studies of chronic antipsychotic treatment
  - Relapse rates at 16 weeks:
    - Risperidone continuation: 2/13 (15%)
    - Placebo: 13/27% (45%)

1. Devanand, American Association for Geriatric Psychiatry Annual Meeting, 2012
Discontinuing Antipsychotics

- RCT of antipsychotic continuation or placebo (N=165) in LTC residents with dementia, 12 – 54 month follow-up¹
  - Received antipsychotic treatment for 3 months
- No difference noted with cognitive impairment, global impression, or NPS
- Subgroup analysis of individuals with greater NPS (NPI > 15) showed trend towards decreased NPS with continuation of treatment

Effects of Discontinuing Antipsychotics on Mortality

![Graph showing cumulative survival over time with placebo and continue treatment groups.]

Log-rank p=0.03

Number at risk (deaths)
- Continue treatment: 29 (3)
- Placebo: 34 (1)

Time since randomisation (months)
0 6 12 18 24 30 36 42 48 54

Cumulative survival (%) 100 90 80 70 60 50 40 30 20 10 0

Ballard, Lancet Neurology, 2009
Typical Antipsychotics

• Effective in reducing symptoms of aggression, agitation and psychosis\(^1-3\)
• Adverse event rates higher with typicals when compared to atypicals
• Risk of stroke\(^4,5\) and death\(^6,7\) similar to atypical antipsychotics

2. Lanctot, J Clin Psychiatry, 1988
3. Lonergan, Cochrane Data Syst Rev, 2002
4. Gill, BMJ, 2005
5. Herrmann, Am J Psychiatry, 2004
Selective Serotonin Reuptake Inhibitors

- SSRIs have some benefits in treating agitation, psychosis and other NPS\(^1\) (N=7)
- Citalopram more effective than placebo in reducing NPS\(^2\)
  - Doses of 20 – 30 mg daily (Note: FDA warning about citalopram doses above 20 mg daily)
- Sertraline had modest effect on agitation compared to placebo\(^3\)
  - Doses 25 – 100 mg daily

1. Seitz, Cochrane Data Syst Rev, 2011
3. Finkel, Int J Geriatr Psychiatry, 2004
Selective Serotonin Reuptake Inhibitors

• No significant difference noted between SSRIs and typical antipsychotics\(^1\) or citalopram compared to risperidone\(^2\) on NPS

• Similar results found for escitalopram (10 mg daily) compared to risperidone\(^3\)

SSRI Adverse Events

• Trial withdrawals and trial withdrawals due to adverse events similar for SSRIs when compared to placebo\(^1\)

• No increased rate major adverse events for SSRIs when compared to antipsychotics
  – EPS decreased with citalopram compared to risperidone\(^2\)

• Risk of stroke and death\(^3,4\) associated with antidepressants in dementia unclear

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1. Seitz, Cochrane Data Syst Rev, 2011
4. Huybrechts, CMAJ, 2011
Antidepressants for Depression in Dementia

• Meta-analysis of antidepressants for depression in dementia failed to find statistically significant benefit over placebo:
  – Response OR (95% CI): 2.12 (0.95 – 4.70)
  – Remission: 1.97 (0.85 – 4.55)
  – Adverse event rates were relatively low 9% vs. 6% with placebo

HTA-SADD Study

• RCT of sertraline, mirtazapine and placebo in mild to moderate dementia (N=326)¹
• No benefit for either drug over placebo on depression outcomes, all groups improved
• Some early benefit for mirtazapine over sertraline on behavioral symptoms and caregiver quality of life
• Higher adverse event rates for sertraline (GI) and mirtazapine (drowsiness) compared to placebo

Trazodone

- 2 small RCTs of trazodone for NPS found no significant difference between trazodone and either placebo\(^1\) or haloperidol\(^1-3\)
  - Trazodone treated individuals had **numerically worse outcomes** when compared to placebo and haloperidol

- Trazodone was not associated with increased risk of major adverse events

1. Teri, Neurology, 2000
Cholinesterase Inhibitors

• Cholinesterase inhibitors may provide some modest benefits in NPS\(^1\)
  – RCTs designed for cognitive outcomes, low baseline NPS

• Apathy, depression, anxiety may be most likely to improve\(^2\)

• Cholinesterase inhibitors may reduce the emergence of certain NPS\(^3\)
  – Apathy, disinhibition, aberrant motor symptoms

2. Gauthier, Int Psychogeriatr, 2002
Cholinesterase Inhibitors for Agitation

- Donepezil had no effect in reducing agitation among individuals with significant agitation\(^1\)
- Cholinesterase inhibitors not superior to antipsychotics in treating agitation\(^2,3\)

3. Ballard, BMJ, 2005
Memantine

- Memantine is associated with reductions in NPS in RCTs$^{1,2}$
  - Studies with cognition as primary outcome, low levels of NPS at baseline
  - Delusions, hallucinations, agitation/aggression
- Open label study (N=31) of memantine for treatment of agitation in LTC residents demonstrated benefit on agitation/aggression and overall NPS
  - 14/31 experienced an AE, somnolence being most common

3. Herrmann, CNS Drugs, 2011
Memantine in DOMINO Trial

• RCT of donepezil treated patients randomized to donepezil continuation, memantine alone, combination, or placebo in outpatients with moderate to severe dementia (N=295)¹

• Donepezil continuation was associated with greatest cognitive benefit

• At 52 weeks memantine associated with reduction in NPS (-5.7 on NPI, ns)

¹. Howard, NEJM, 2012
Benzodiazepines

- RCT comparing IM lorazepam 1 mg, IM olanzapine (2.5 mg or 5 mg), or placebo for acute agitation in dementia (N=272)
  - Could receive up to 3 doses in 24 hours
- Most individuals received a single dose of olanzapine or lorazepam
- 66% of active treatment group had response at 2 hours
  - Olanzapine 5 mg IM had most rapid onset
- Olanzapine associated with improvements at 24 hours following first injection
- No statistically significant increase in adverse events
  - Somnolence numerically higher with lorazepam (10%) compared to olanzapine (3%)

1. Meehan, Neuropharmacology, 2002
Sleep Disturbances in Dementia

- Limited evidence for any agent in dementia
- Melatonin most extensively studied, inconclusive
- Untreated insomnia associated with increased falls in LTC residents when compared to treated insomnia
- Little difference in efficacy and safety between benzodiazepines and BZD agonists (e.g. zopiclone) for insomnia in older adults
- Less evidence for trazodone than BZDs
- Sleep guidelines, primary insomnia, adults:
  - Short-intermediate BZD (i.e. temazepam) or BZD agonist (e.g. zopiclone)

3. Glass, BMJ, 2005
## Medications for Sleep

<table>
<thead>
<tr>
<th>Medication</th>
<th>Initial Dose</th>
<th>Titration and Maximum Dose</th>
<th>Formulations</th>
<th>Adverse Events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam</td>
<td>0.25-0.5mg</td>
<td>0.5mg every 3-7 days, max 2mg</td>
<td>Tablet, IM</td>
<td>Sedation, Confusion</td>
<td>Short-term use only, tolerance may develop</td>
</tr>
<tr>
<td>Zopiclone</td>
<td>3.75mg PO QHS</td>
<td>3.75mg every 3-7 days, max 15mg</td>
<td>Tablet</td>
<td>Sedation, Confusion</td>
<td>Short-term use only, tolerance may develop</td>
</tr>
<tr>
<td>Trazodone*</td>
<td>25mg PO QHS (sleep)</td>
<td>25mg every 3-7 days, max 100mg</td>
<td>Oral Tablet</td>
<td>Sedation, orthostatic hypotension</td>
<td>Short-term use only for sleep.</td>
</tr>
</tbody>
</table>

* May also be used in the treatment of frontotemporal dementia
Anticonvulsants

- **Carbamazepine**
  - Two small RCTs showing some benefit\(^1,^2\)
  - 1 negative RCT with oxcarbazepine

- **Valproic acid derivatives**
  - 5 RCTs, no benefit in NPS\(^3\)
  - Divalproex sodium acid prophylaxis of NPS was not effective and resulted in increased brain atrophy over 12 months\(^4\)

- **Case reports of gabapentin, lamotrigine**

4. Tariot, Arch Gen Psychiatry, 2011
Approach to Use of Psychotropic Medications for Neuropsychiatric Symptoms of Dementia

Older Adult with Neuropsychiatric Symptoms

Assessment of Neuropsychiatric Symptoms:
- Rule out pain, delirium or recent medication changes
- Evaluate for environmental contributors

Obtain Informed Consent from Patient or Substitute Decision Maker

Initiate Non-pharmacological treatments.

Identify target symptoms

Depression/Anxiety
- Cholinesterase Inhibitor
- Memantine
- SSRI or Other Antidepressant

Sleep Disturbance
- Lorazepam
- Zopiclone
- Trazodone

Agitation/Aggression/Psychosis
- Mild symptoms (not physically aggressive or causing significant distress):
  - SSRI
- Severe symptoms or non-response to SSRI:
  - Risperidone (See Table 1)
  - Olanzapine
  - Aripiprazole

If symptoms persist
- If non-responsive:
  - Haloperidol
  - Carbamazepine

(Note: Table 1 contains additional medications and dosages.)
Analgesia to Treat Neuropsychiatric Symptoms

• RCT of standardized pain protocol for LTC residents with dementia and significant agitation (N=352)$^1$

• Received standardized pain protocol for 8 weeks or usual care
  – Withdrawn at week 8 - 12

• Evaluated agitation, aggression, pain, ADL, and cognition

## Pain Treatment Protocol

<table>
<thead>
<tr>
<th>Step</th>
<th>Pain Treatment at Baseline</th>
<th>Study Treatment</th>
<th>Dosage</th>
<th>Number (%) of residents (N=175)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No analgesia, or low dose acetaminophen</td>
<td>Acetaminophen</td>
<td>Max 3g/day TID</td>
<td>120 (69)</td>
</tr>
<tr>
<td>2</td>
<td>Full dose acetaminophen or low-dose morphine</td>
<td>Morphine</td>
<td>5 mg BID, max 10 BID</td>
<td>4 (2)</td>
</tr>
<tr>
<td>3</td>
<td>Low-dose buprenorphine or unable to swallow</td>
<td>Buprenorphine patch</td>
<td>5 mcg/h, max 10 mcg/h</td>
<td>39 (22)</td>
</tr>
<tr>
<td>4</td>
<td>Neuropathic pain</td>
<td>Pregabalin</td>
<td>25 mg OD, max 300 OD</td>
<td>12 (7)</td>
</tr>
</tbody>
</table>
CMAI Total Score

- Benefits also noted on overall NPS, and pain
- No effect on cognition or ADL functioning
- 9/175 (5%) treatment group withdrew d/t AE

Medications Withdrawn
Other Potential Pharmacological Treatments

Randomized Controlled Trials:
• Prazosin\(^1\)
• Cyproterone acetate\(^2\)
• Estrogen\(^3\)

Open label studies or case series:
• Cannabinoids, propranolol

Treatment Tools

• Use of Antipsychotics and Other Medications for Urgent Treatment of Severe Agitation, Aggression or Psychosis

• Tool on Pharmacological Treatment of Behavioral Symptoms of Dementia in Long Term Care Facilities for Older Adults

http://dallasseitz.webs.com/neuropsychiatric-symptoms
Conclusions

- Neuropsychiatric symptoms are common in dementia and have an important impact on patients and caregivers
- A comprehensive assessment of NPS is important and informs treatment strategies
- Both non-pharmacological and pharmacological interventions have important roles in the management of NPS
Resources

• PIECES Website

• Canadian Coalition for Seniors’ Mental Health
  – www.cccsmh.ca

• International Psychogeriatrics Association
  BPSD Guides
  – http://www.ipa-online.net/ipaonlinev4/main/programs/task/task_BPSD.html

• Links to webinars
  – www.dallasseitz.web.com
  – Research ➔ Neuropsychiatric Symptoms
Questions

• Questions
• Cases to discuss
• Contact information
  – Email: seitzd@providencecare.ca