Assessment and Management of Neuropsychiatric Symptoms in Dementia: Evidence and Recent Advances
FACULTY/PRESENTER DISCLOSURE

• Faculty: Dr. Corinne Fischer

• Relationships with financial sponsors:
  - Grants/Research Support: Hoffman LaRoche, Vielight Inc.
MITIGATING POTENTIAL BIAS

• None of the content of this presentation relates to the research funding
Faculty/Presenter Disclosure

- Faculty: Dr. Dallas Seitz

- Relationships with commercial interests:
  - Grants/Research Support: CIHR, Alzheimer’s Association, Queen’s University, CABHI
  - Clinical Trials: Hoffmann La Roche
Disclosure of Commercial Support

• Off-label use of medication will be discussed in this presentation
Epidemiology and factors associated with neuropsychiatric symptoms of dementia

• Provide a definition of Neuropsychiatric symptoms in dementia
• Review the epidemiology of neuropsychiatric symptoms (NPS) in dementia with a focus on symptoms at various dementia stages and different dementia subtypes
• Review our knowledge of existing risk factors for the development of NPs in dementia
Epidemiology and factors associated with neuropsychiatric symptoms of dementia

• Neuropsychiatric symptoms refer to the “non-cognitive” symptoms of dementia

• Previously referred to as “Behavioural and Psychological Symptoms of Dementia”

• Consist of a broad variety of symptoms including agitation, aggression, apathy, agitation, increased motor behaviour, psychosis, wandering and socially inappropriate behaviour
Epidemiology and factors associated with neuropsychiatric symptoms of dementia

- Symptoms have been studied most consistently in AD with much more limited study in other disorders
- Greater rates of apathy and disinhibition in FTD where NPS are often a presenting feature
- Symptoms such as psychosis very prevalent in Parkinson’s disease related dementia and dementia with Lewy bodies
- Seen with high frequency in Huntington’s disease related dementia though fewer studies conducted
Epidemiology and factors associated with neuropsychiatric symptoms of dementia

**Neuropsychiatric Inventory Domains**

- The original NPI included 10 neuropsychiatric domains; two others,
  - Hallucinations
  - Delusions
  - Agitation/aggression
  - Dysphoria /depression
  - Anxiety
  - Irritability
  - Disinhibition
  - Euphoria
  - Apathy
  - Aberrant motor behavior
  - Sleep and night-time behavior change
  - Appetite and eating change
Epidemiology and factors associated with neuropsychiatric symptoms of dementia

- Study examined the trajectory of NPS over a 3 year period among patients attending a memory clinic (Brodaty, Connors et al. 2015)
- 970 patients were followed over 3 years
- Delusions, hallucinations, agitation, anxiety, apathy, disinhibition, irritability, and aberrant motor behavior increased over the 3 years
- Subjects with FTD had greater NPS at baseline while patients with DLB had more hallucinations while patients with AD had less NPS at baseline
Epidemiology and factors associated with neuropsychiatric symptoms of dementia

• Study used data from the NACC database to quantify NPS based on measures of pathology (Leger and Banks 2014)
• 149 patients with bvFTD (20% had AD pathology)
• Patients with AD pathology were more likely to have hallucinations, delusions, or agitation
• Tau negative cases were more likely to have depression, delusions, and changes in appetite and eating
Epidemiology and factors associated with neuropsychiatric symptoms of dementia

• 223 subjects were followed over the course of 12 years (Vik-Mo, Giil et al. 2019)
• 113 patients had AD, 84 had DLB and 16 with PDD
• The following symptoms were most common among patients with AD: aberrant motor behaviour, aggression/agitation, delusions and irritability
• DLB was characterized by unstable symptoms
• 57% of patients with Alzheimer's disease and 84% of patients with DLB had reoccurring psychotic symptoms
Epidemiology and factors associated with neuropsychiatric symptoms of dementia

Dag Aarsland et al, 2012
Epidemiology and factors associated with neuropsychiatric symptoms of dementia

Review Article

Neuropsychiatric signs and symptoms of Alzheimer’s disease: New treatment paradigms

Krista L. Lanctôt\textsuperscript{a,\,*}, Joan Amatniek\textsuperscript{b}, Sonia Ancoli-Israel\textsuperscript{c,d}, Steven E. Arnold\textsuperscript{e}, Clive Ballard\textsuperscript{f,g}, Jiska Cohen-Mansfield\textsuperscript{h}, Zahinoor Ismail\textsuperscript{i}, Constantine Lyketsos\textsuperscript{j}, David S. Miller\textsuperscript{k}, Erik Musiek\textsuperscript{l}, Ricardo S. Osorio\textsuperscript{m}, Paul B. Rosenberg\textsuperscript{n}, Andrew Satlin\textsuperscript{o}, David Steffens\textsuperscript{p}, Pierre Tariot\textsuperscript{q}, Lisa J. Bain\textsuperscript{r}, Maria C. Carrillo\textsuperscript{s}, James A. Hendrix\textsuperscript{s}, Heidi Jurgens\textsuperscript{s}, Brendon Boot\textsuperscript{t,u}
Epidemiology and factors associated with neuropsychiatric symptoms of dementia

• NPS occur in an estimated 97% of patients with dementia (Lanctot, Amatniek et al. 2017)
• Symptoms fluctuate in intensity (Tschanz, Corcoran et al. 2011)
• Most are persistent (Tschanz, Corcoran et al. 2011)
• Cross-sectional study looking at 4,571 patients with MCI and AD at various stages (Siafarikas, Selbaek et al. 2018)
• Frequency of NPS was 87.2% with 91.2% in AD and 79.5% in MCI
Epidemiology and factors associated with neuropsychiatric symptoms of dementia

• NPS increased in prevalence with increased severity of cognitive decline
• Depression was the most frequent symptom in MCI and apathy was the most frequent symptom in AD
• Subgroups of symptoms were consistent across the spectrum
• Another study looked at data from the NACC data set
• 540 patients with MCI aged 60 or above (Forrester, Gallo et al. 2016)
• NPS were clustered (severe, affective, asymptomatic)
Epidemiology and factors associated with neuropsychiatric symptoms of dementia

- 56% were classified as asymptomatic, 37% affective (depression, anxiety, irritability, nighttime behaviors), 7% severe (agitation, anxiety, apathy, nighttime behaviors, inhibition)

- The severe class had more than twice the hazard of progression to dementia and the affective class had 1.5 times the risk

- NPS in MCI may exhibit a vast range from 35 to 85% (Gallagher, Fischer et al. 2017)
Epidemiology and factors associated with neuropsychiatric symptoms of dementia

**Figure 1.** Presence of neuropsychiatric symptoms in patients with AD according to severity of disease (Adapted from Mega et al., 1996).
Epidemiology and factors associated with neuropsychiatric symptoms of dementia

<table>
<thead>
<tr>
<th>Name of patient:</th>
<th>Date:</th>
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</thead>
</table>

**Informer:** Spouse | Child | Other |

Please answer the following questions based on changes that have occurred since the patient first began to experience memory problems. Circle "yes" only if the symptom has been present in the past month. Otherwise, circle "no."

For each item marked "yes":
- Rate the severity of the symptom (how it affects the patient): 1 = Mild (noticeable, but not a significant change); 2 = Moderate (significant, but not a dramatic change); 3 = Severe (very marked or prominent; a dramatic change)
- Rate the distress you experience because of that symptom (how it affects you): 0 = Not distressing at all; 1 = Minimal (slightly distressing, not a problem to cope with); 2 = Mild (not very distressing, generally easy to cope with); 3 = Moderate (very distressing, not always easy to cope with); 4 = Severe (very distressing, difficult to cope with)

Please answer each question honestly and carefully. Ask for assistance if you are not sure how to answer any question.

### Delusions
- Does the patient believe that others are stealing from him or her, or planning to harm him or her in some way?
  - Yes
  - No

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<thead>
<tr>
<th>Severity</th>
<th>Distress</th>
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<tr>
<td>1</td>
<td>2</td>
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### Hallucinations
- Does the patient act as if he or she hears voices? Does he or she talk to people who are not there?
  - Yes
  - No

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### Agitation or aggression
- Is the patient stubborn and resistive to help from others?
  - Yes
  - No

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### Depression or dysphoria
- Does the patient act as if he or she is sad or in low spirits? Does he or she cry?
  - Yes
  - No

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### Anxiety
- Does the patient become upset when separated from you? Does he or she have any other signs of nervousness, such as shortness of breath, sighing, being unable to relax, or feeling excessively tense?
  - Yes
  - No

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### Elation or euphoria
- Does the patient appear to feel too good or act excessively happy?
  - Yes
  - No

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</table>

### Apathy or indifference
- Does the patient seem less interested in his or her usual activities and in the activities and plans of others?
  - Yes
  - No

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### Disinhibition
- Does the patient seem to act impulsively? For example, does the patient talk to strangers as if he or she knows them, or does the patient say things that may hurt people's feelings?
  - Yes
  - No

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### Irritability or lability
- Is the patient impatient and cranky? Does he or she have difficulty coping with delays or waiting for planned activities?
  - Yes
  - No

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### Motor disturbance
- Does the patient engage in repetitive activities, such as pacing around the house, handling buttons, wrapping string, or doing other things repeatedly?
  - Yes
  - No

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### Nighttime behaviors
- Does the patient awaken you during the night, rise too early in the morning, or take excessive naps during the day?
  - Yes
  - No

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### Appetite and eating
- Has the patient lost or gained weight, or had a change in the food he or she likes?
  - Yes
  - No

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Epidemiology and factors associated with neuropsychiatric symptoms of dementia

• Meta-analyses of NPS in AD (Zhao, Tan et al. 2016)
• Examined all studies published between 1964 and 2014
• 48 articles in total, examined 12 NPI domains
• Apathy was most frequent (48%) followed by depression (42%), aggression (40%), anxiety (39%), sleep disorders (39%)
• Other symptom domains were less prevalent
Epidemiology and factors associated with neuropsychiatric symptoms of dementia

Gulla et al, 2016
Epidemiology and factors associated with neuropsychiatric symptoms of dementia

Perspective

Neuropsychiatric symptoms as early manifestations of emergent dementia: Provisional diagnostic criteria for mild behavioral impairment

Zahinoor Ismail\textsuperscript{a,b,c,d,\textdagger}, Eric E. Smith\textsuperscript{b,d}, Yonas Geda\textsuperscript{e,f}, David Sultzer\textsuperscript{g,h}, Henry Brodaty\textsuperscript{i}, Gwenn Smith\textsuperscript{j}, Luis Agüera-Ortiz\textsuperscript{k}, Rob Sweet\textsuperscript{l,m}, David Miller\textsuperscript{n}, Constantine G. Lyketsos\textsuperscript{o}, for the ISTAART Neuropsychiatric Symptoms Professional Interest Area
Epidemiology and factors associated with neuropsychiatric symptoms of dementia

• Based on the idea that NPS increase rates of conversion to dementia (Ismail, Smith et al. 2015)
• Is it possible that onset of NPS may be a harbinger of dementia in the absence of cognitive/functional decline
• Describes NPS of any severity, that persist for 6 months and occur in advance or in conjunction with MCI
• Five MBI domains of 1) decreased motivation; 2) emotional dysregulation; 3) impulse dyscontrol; 4) social inappropriateness; and 5) abnormal perception or thought content
Epidemiology and factors associated with neuropsychiatric symptoms of dementia

| Mild Behavioral Impairment Checklist (MBI-C) | Label |
| Date: | |
| Rated by: | ☐ Clinician ☐ Informant ☐ Subject |
| Location: | ☐ Clinic ☐ Research |
| Circle “Yes” only if the behavior has been present for at least 6 months (continuously, or on and off) and is a change from her/his longstanding pattern of behavior. Otherwise, circle “No”.
| Please rate severity. 1 = Mild (noticeable, but not a significant change); 2 = Moderate (significant, but not a dramatic change); 3 = Severe (very marked or prominent, a dramatic change). If more than 1 item in a question, rate the most severe. |

| This domain describes interest, motivation, and drive | YES | NO | SEVERITY |
| Has the person lost interest in friends, family, or home activities? | Yes | No | 1 2 3 |
| Does the person lack curiosity in topics that would usually have attracted her/his interest? | Yes | No | 1 2 3 |
| Has the person become less spontaneous and active — for example, is she/he less likely to initiate or maintain conversation? | Yes | No | 1 2 3 |
| Has the person lost the motivation to do anything, including obligations or interests? | Yes | No | 1 2 3 |
| Is the person less affectionate and/or lacking in emotions when compared to her/his usual self? | Yes | No | 1 2 3 |
| Does she/he no longer care about anything? | Yes | No | 1 2 3 |

| This domain describes mood or anxiety symptoms | YES | NO | SEVERITY |
| Has the person developed sadness or appear to be in low spirits? Does she/he have episodes of tearfulness? | Yes | No | 1 2 3 |
| Has the person become less able to experience pleasure? | Yes | No | 1 2 3 |
| Has the person become discouraged about their future or feel that she/he is a failure? | Yes | No | 1 2 3 |
| Does the person view herself/himself as a burden to family? | Yes | No | 1 2 3 |
| Has the person become more anxious or worried about things that are routine (e.g. events, visits, etc.)? | Yes | No | 1 2 3 |

| This domain describes the ability to delay gratification and control behavior, impulses, oral intake and/or changes in reward | YES | NO | SEVERITY |
| Has the person become agitated, aggressive, irritable, or temperamental? | Yes | No | 1 2 3 |
| Has she/he become unreasonably or uncharacteristically argumentative? | Yes | No | 1 2 3 |
| Has the person become more impulsive, seeming to act without considering things? | Yes | No | 1 2 3 |
| Does the person display sexually disinhibited or intrusive behaviour, such as touching (herself/others), hugging, groping, etc., in a manner that is out of character or may cause offence? | Yes | No | 1 2 3 |

© 2016 For more information contact: zahinoor email MD email: MBlchecklist@gmail.com
Epidemiology and factors associated with neuropsychiatric symptoms of dementia

• Role of APO-E4 unclear, though may be an association with some domains: agitation/aggression, hallucinations, delusions, and late-life depression or anxiety (Panza et al. 2011)

• Recent study examined 1226 patients who met criteria for MBI from the Personality and Total health through Life Project (Andrews, Ismail et al. 2018)

• A higher genetic risk score and APO-E4 score were associated with a greater likelihood of affective regulation
Epidemiology and factors associated with neuropsychiatric symptoms of dementia

• Among 220 patients with AD individuals with higher TC had elevated NPS and psychosis (Hall et al 2014)

• Possible association with hypertension (Moon et al 2014, Steinberg et al 2014, Hwang et al 2017)

• NPS domains associate differentially with CVS risk factors (Fischer et al 2019)

• Multiple studies showed no association or mostly in affective domains
Epidemiology and factors associated with neuropsychiatric symptoms of dementia

- Limited study of risk factors related to NPS (Poulin, Bergeron et al. 2017)
- Study looked at 181 subjects from the ADNI data set
- Symptoms were classified as minimal, fluctuating or persistent
- Examined past psychiatric history, imaging and biomarkers
- No relationship with biomarkers but greater probability of past psychiatric history, dorsolateral prefrontal atrophy and worse cognitive and ADL functioning
Epidemiology and factors associated with neuropsychiatric symptoms of dementia

- Risk factors associated with the presence of agitation in patients with autopsy confirmed AD (Sennik et al 2017)
- Agitation was more common among patients with high pathology load and inversely related to vascular pathology load
- Smoking, TBI and phosphorylated TDP-43 were positively correlated with agitation in AD
Epidemiology and factors associated with neuropsychiatric symptoms of dementia

• Possible association with sociodemographic factors (Nagata et al. 2017)
• 421 AD outpatients enrolled in the CATIE-AD trial
• Examined the relationship between NPI domains and sociodemographic factors
• Found that among the four NPS clusters apathy/eating problems and emotion/disinhibition were associated with clinical and sociodemographic factors
Epidemiology and factors associated with neuropsychiatric symptoms of dementia

• NPS are very common among patients with dementia
• Profile and stability of symptoms varies depending on the disorder (NPS are more common in early stage FTD and become more frequent with progression of AD while psychosis is common in PDD)
• NPS may occur in advance of cognitive impairment and when present increase conversion to dementia (MBI)
• Risk factors have yet to be confirmed but some association with pathology, APO-E4, cerebrovascular disease, psychiatric history and sociodemographic risk factors
Evidence-Based Non-Pharmacological and Pharmacological Treatment of Behavioural Symptoms of Dementia

Dr. Dallas Seitz MD PhD FRCPC
Associate Professor of Psychiatry, University of Calgary

October, 2019
Canadian Conference on Dementia
General Principles To Managing NPS

• Non-pharmacological treatments should be used first whenever available

• Even when NPS are caused by specific etiologies (pain, depression, psychosis) non-pharmacological interventions should be utilized with medications

• All non-pharmacological interventions work best when tailored to individual needs and background

• Family and caregivers are key collaborators and need to involved in treatment planning
Nonpharmacological Interventions

• Training caregivers or
• Mental health consultations
• Participation in pleasant events
• Exercise
• Music
• Sensory stimulation (e.g. touch, Snoezelen, aromatherapy)

Livingston, Am J Psychiatry, 2005
Seitz, JAMDA, 2012
Training Caregivers and Staff

• Some staff and caregiver training approaches are effective in reducing NPS\(^1-3\)
• Also referred to as patient-centred care
• Most training programs involve education about dementia symptoms
• Communication strategies to avoid confrontation
• Strategies for redirection and distraction
• Often incorporate *personalized* pleasant events into interactions

Effects OF Caregiver Training on Agitation

Participation in Pleasant Events

• 1-to-1 interaction with personalized pleasant events has been demonstrated to reduce NPS\(^1\)
  – Given 3X/week – 20 – 30 minutes/session

• Participation in group “validation therapy” may also be beneficial\(^2\)

1. Lichtenberg, *Gerontologist*, 2005
Exercise

- Exercise programs have been demonstrated to reduce NPS in LTC residents\textsuperscript{1-3}
- Training caregivers in behavioral management and exercise program improved physical functioning of person with dementia and depressive symptoms\textsuperscript{4}
  - 30 minutes/day was recommended
  - Exercise program included strength, flexibility, aerobic activity, balance

2. Landi, Arch Gerontol Geriatr, 2004
4. Teri, JAMA, 2003
Music

• Group music with movement or individualized music therapy are effective in reducing NPS\textsuperscript{1,2}

• 30 minutes 2 – 3 times/ week
  – May use prior to times of increased agitation

• \textit{Personalized} music more effective than generic music

2. Raglio, \textit{Alzheimer Dis Assoc Disord}, 2008
Sensory Stimulation

• Therapeutic touch or gentle massage may relieve symptoms of agitation\(^1,2\)

• Snoezelen (multisensory stimulation) providing tactile, light, olfactory, or auditory stimulation\(^3\)

• Aromatherapy with massage
  – 1 positive\(^4\) and 1 negative\(^5\) RCT

2. Woods, Alter Ther Health Med, 2005
5. Burns, Dementia Geriatr Cogn Disord, 2011
Limitations of Psychosocial Treatments

• Modest effects of treatments
• Effectiveness for aggression and psychosis may be limited
  – Agitation, depressive symptoms, apathy may be more likely to respond
• May required prolonged and sustained implementation for effects to be realized
• Many interventions have only been evaluated in small studies, methodological quality is limited
Feasibility of Non-Pharmacological Interventions

Seitz, JAMDA, 2012
Pharmacological 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
NPS that May Respond to Medications

• Aggression*
• Agitation*
• Psychosis*
• Depression
• Anxiety
• Apathy
• Sleep
Atypical Antipsychotics

- **Risperidone, aripiprazole,** and olanzapine have the strongest evidence to treat psychosis and agitation in dementia\(^1,2\)
- Number needed to treat for significant improvement: 5 – 14
- Odds ratio for significant improvement compared to placebo: 1.5 – 2.5

5. Verhey, Dementia Geriatr Cogn Disord, 2006
NPS that Respond to Antipsychotics

• Olanzapine and risperidone associated with overall improvement in NPS
  – Hostility, psychosis, agitation most likely to improve

Atypical Antipsychotics Dosing

<table>
<thead>
<tr>
<th></th>
<th>Initial Dose</th>
<th>Titration Schedule</th>
<th>Maximum dosage</th>
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<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>
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Consider switching antipsychotics if no benefit or limited benefit observed after 2 weeks of therapeutic dose
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
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 symptoms\(^1\)
  - Risperidone
- Weight gain, dyslipidemia\(^2,3\)
  - 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
  - Equivalent to approximately 1 year additional decline
- MMSE -1 point over 8 – 12 week trials
  - Often LTC population with low MMSE at baseline

Typical Antipsychotics

• Effective in reducing symptoms of aggression, agitation and psychosis\textsuperscript{1-3}

• Adverse event rates higher with typicals when compared to atypical

• Risk of stroke\textsuperscript{4,5} and death\textsuperscript{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
Citalopram for Agitation: CITAD

• RCT of citalopram (10 – 30 mg daily) or placebo for AD patient with significant agitation
  – Majority received 30 mg of citalopram*

• Significant improvements on NBRS-A, CMAI with citalopram compared to placebo

• 40% of citalopram vs 26% of individuals with placebo had moderate or marked improvement

• Worsening of cognition noted with citalopram

Porsteinsson, JAMA, 2014
Predictors of Response to Citalopram

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>CGIC 1-2</th>
<th>CGIC 1-7</th>
<th>CGIC 1-2</th>
<th>CGIC 1-7</th>
<th>Test of Interaction</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visitation</td>
<td>LR test p=0.015</td>
<td>2.78 (1.14, 6.76)</td>
<td>0.11 (0.10, 1.26)</td>
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</tr>
<tr>
<td>Long-term care</td>
<td>LR test p=0.649</td>
<td>2.21 (0.86, 5.66)</td>
<td>1.62 (0.64, 4.41)</td>
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<tr>
<td>Neuropsychiatric Inquiries</td>
<td>LR test p=0.541</td>
<td>2.45 (0.75, 8.64)</td>
<td>2.39 (0.79, 7.24)</td>
<td>1.06 (0.33, 3.41)</td>
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<tr>
<td>ADL Activities of Daily Living</td>
<td>LR test p=0.541</td>
<td>4.20 (0.15, 15.97)</td>
<td>1.15 (0.40, 3.18)</td>
<td>1.67 (0.40, 6.23)</td>
<td></td>
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</tr>
<tr>
<td>MMSE</td>
<td>LR test p=0.054</td>
<td>4.20 (0.15, 15.97)</td>
<td>1.15 (0.40, 3.18)</td>
<td>1.67 (0.40, 6.23)</td>
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</tr>
<tr>
<td>Age group (years)</td>
<td>LR test p=0.287</td>
<td>1.15 (0.23, 5.81)</td>
<td>0.79 (0.25, 2.54)</td>
<td>1.47 (0.55, 3.95)</td>
<td></td>
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<tr>
<td>Gender</td>
<td>LR test p=0.607</td>
<td>2.19 (0.87, 5.55)</td>
<td>1.55 (0.60, 3.98)</td>
<td></td>
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<tr>
<td>Mecamylamine</td>
<td>LR test p=0.468</td>
<td>1.57 (0.68, 3.69)</td>
<td>2.63 (0.87, 7.60)</td>
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<tr>
<td>Lorazepam</td>
<td>LR test p=0.204</td>
<td>2.36 (1.12, 4.54)</td>
<td>0.26 (0.02, 2.77)</td>
<td></td>
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<tr>
<td>Trazodone</td>
<td>LR test p=0.579</td>
<td>1.99 (0.59, 6.63)</td>
<td>1.11 (0.16, 7.5)</td>
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<tr>
<td>Predictors of Response</td>
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<tr>
<td>Community-dwelling (vs. LTC)</td>
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<tr>
<td>MMSE &gt; 21 (vs. lower)</td>
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<tr>
<td>Moderate symptoms (vs. Severe)</td>
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</tbody>
</table>

Schneider, Am J Psychiatry, 2016
Which Symptoms Improve with Citalopram?

- Individuals treated with citalopram less likely to report delusions (OR: 0.4), anxiety (OR: 0.4), irritability (OR: 0.4), and had reductions in symptoms of hallucinations

- Worsening of sleep problems was greater with citalopram compared to placebo

Citalopram or Escitalopram?

• S-entantiomer of Citalopram (Escitalopram) was associated with improvement in NPS, R-entantiomer associated with adverse effects
  – Escitalopram (Cipralex) 5 to 10 mg may be a better choice than Citalopram (Celexa)

Ho, Br J Pharmaco, 2016
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 (+5 points worsening on the CMAI)

• Trazodone associated with a similar risk of falls and fractures when compared to antipsychotics in dementia\(^4\)

1. Teri, Neurology, 2000
4. Watt, CMAJ, 2018
Cannabinoids to Treat Agitation in Dementia

• Systematic review of natural and synthetic cannabinoids for agitation and aggression in Alzheimer’s disease
• N = 6 studies, 2 THC, 3 dronabinol, 1 nabilone
• No difference in agitation noted with cannabinoids compared to placebo (SMD -0.69, 95% CI: -1.5 to 0.13, p=0.1) or neuropsychiatric symptoms overall
  – Heterogeneity between studies
• Higher risk of sedation with cannabinoids compared to placebo (RR = 1.73, P=0.04)

Cannabinoids for Agitation in Dementia

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Standardized Mean Difference</th>
<th>Standardized Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean SD Total</td>
<td>Mean SD Total</td>
<td>IV, Random (95% CI)</td>
<td>IV, Random (95% CI)</td>
</tr>
<tr>
<td>THC</td>
<td></td>
<td></td>
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<tr>
<td>van den Elen et al [10]</td>
<td>-1.2 5.6 24</td>
<td>-1.8 6.1 25</td>
<td>18.0%</td>
<td>0.10 (-0.45 to 0.66)</td>
</tr>
<tr>
<td>van den Elen et al [10] (first phase data)</td>
<td>-4.45 3.21 20</td>
<td>-5.02 4.65 20</td>
<td>17.7%</td>
<td>0.14 (-0.48 to 0.76)</td>
</tr>
<tr>
<td>van den Elen et al [10] (second phase data)</td>
<td>-3.43 4.91 20</td>
<td>-4.02 6.21 20</td>
<td>17.7%</td>
<td>0.10 (-0.52 to 0.72)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>64</td>
<td>66</td>
<td>53.4%</td>
<td>0.11 (-0.23 to 0.46)</td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 0.00; p = 0.99; I^2 = 0%$</td>
<td></td>
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<tr>
<td>Test for overall effect: $Z = 0.65 (p = 0.52)$</td>
<td></td>
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<tr>
<td>Synthetic Cannabinoid</td>
<td></td>
<td></td>
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<tr>
<td>Lanctôt et al [42]</td>
<td>-11.86 15.13 36</td>
<td>-2.46 13.72 35</td>
<td>18.4%</td>
<td>-0.64 (-1.12 to -0.17)</td>
</tr>
<tr>
<td>Vollier et al [31]</td>
<td>-32.5 7.5 15</td>
<td>3 6.5 15</td>
<td>11.7%</td>
<td>-4.02 (-4.44 to -3.41)</td>
</tr>
<tr>
<td>Waithier et al [38]</td>
<td>0.5 0.5 2</td>
<td>-1 1 2</td>
<td>1.5%</td>
<td>1.08 (-5.36 to 7.52)</td>
</tr>
<tr>
<td>Waithier et al [40]</td>
<td>-4 2.78 6</td>
<td>-2 4.54 10</td>
<td>15.0%</td>
<td>-0.47 (-1.50 to 0.56)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>59</td>
<td>62</td>
<td>46.6%</td>
<td>-1.67 (-3.65 to 0.30)</td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 2.99; p = 0.0001; I^2 = 90%$</td>
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<tr>
<td>Test for overall effect: $Z = 1.56 (p = 0.10)$</td>
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<tr>
<td>Total (95% CI)</td>
<td>123</td>
<td>128</td>
<td>100.0%</td>
<td>-0.69 (-1.50 to 0.13)</td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 0.88; p = 0.36; I^2 = 86%$</td>
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<tr>
<td>Test for overall effect: $Z = 1.66 (p = 0.10)$</td>
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<tr>
<td>Test for subgroup differences: $\chi^2 = 3.05 (p = 0.08); I^2 = 67.3%$</td>
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</tbody>
</table>

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
Dextromethorphan/Quinidine for Agitation in Dementia

• Participants with AD and agitation (N=220) treated with DXM/Q 20mg/10mg OD → 30 mg/10mg BID
• Change in NPI Agitation/Aggression score DXM/Q vs Placebo: -1.5 (95%CI: -0.7 to 2.3, P<0.001)
  – NPI total score: -3.8 to -4.2
• Increased risk of falls (9% vs 4%), diarrhea (6% vs 3%), UTIs (5% vs 4%) and dizziness (5% vs 2%)
• No change significant changes noted in cognition, functioning during treatment

1. Cummings, JAMA, 2015
Antidepressants for Depression in Dementia

• Antidepressants for depression in dementia failed to find statistically significant benefit over placebo\(^1\):
  – 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

2. Carmargos, Am J Geriatr Psychiatry, 201
Medications for Sleep in Dementia

• Melatonin most extensively studied, inconclusive\(^1\)

• RCT of trazodone 50 mg or placebo for AD patients with sleep disturbance (N=30)
  – Trazodone improved sleep duration by 42.5 minutes and 8.5% increase in nighttime sleep
  – No significant cognitive or other adverse events noted between groups

Apathy

• Cholinesterase inhibitors may be associated with improvements in apathy\textsuperscript{1,2}

• Recent trial of methylphenidate (10 – 20 mg daily) demonstrated significant reduction in apathy with 21% of treated patient significantly improved compared to 3% of placebo (P=0.02)\textsuperscript{3}

2. Cummings, Am J Psychiatry, 2004
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. See CCSMH Pocket Card In Resources Section.

Identify target symptoms.

- Depression/Axiety
  - Cholinesterase Inhibitor
  - Memantine
  - SSRI (See Table 1)
  - Also refer to CCSMH Depression Pocket Card in Resources Section

- Sleep Disturbance
  - Lorazepam (See Table 2)
  - Trazodone
  - Zopiclone

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

**Main Pathway**
- Risperidone
- Aripiprazole/Quetiapine
- Carbamazepine
- Citalopram
- Gabapentin
- Prazosin
- Combination or ECT

**SUMMARY OF DRUGS**
- PRNS for Agitation/Aggression
  - Trazodone
  - Lorazepam

**Alzheimer’s Treatments**
- Acetylcholinesterase inhibitors
- Memantine

Davies, J Clin Psychopharm, 2018
4 Don't use antipsychotics as first choice to treat behavioural and psychological symptoms of dementia.

People with dementia often exhibit aggression, resistance to care and other challenging or disruptive behaviours. In such instances, antipsychotic medicines are often prescribed, but they provide limited benefit and can cause serious harm, including premature death. Use of these drugs should be limited to cases where non-pharmacologic measures have failed and patients pose an imminent threat to themselves or others. Identifying and addressing causes of behaviour change can make drug treatment unnecessary.
Prevalence of Antipsychotic Use

In Canadian long-term care homes, **1 in 5** residents is taking antipsychotic drugs without a diagnosis of psychosis. **62%** of seniors in Canadian long-term care have been diagnosed with dementia. **1 in 7** residents to **3 in 7** residents.

(Source: CIHI, 2017)

Regional variation between long-term care homes in use of antipsychotic drugs.

http://yourhealthsystem.cihi.ca/
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
Relapse Risk After Antipsychotic Discontinuation

• Responders to 16 weeks of open label treatment of risperidone were randomized to either continuation or placebo at 16 and 32 weeks

• Relapse rates at 16 weeks following randomization:
  – Risperidone continuation: 23/70 (33%)
  – Placebo: 24/40 (60%)

• Relapse rate at 32 weeks after randomization:
  – Risperidone continuation: 2/13 (15%)
  – Placebo: 13/27 (48%)

Predictors of Relapse

• Severe hallucinations at baseline associated with greater risk of relapse (HR: 2.96)
  – 77% relapse hallucinations vs. 39% no hallucinations
  – Auditory hallucinations associated with greater risk than visual
  – More severe hallucinations associated with greater risk than less severe hallucinations

Staffing and Antipsychotic Use

Correlation Between Total Staffing Hours and Antipsychotic Prescribing Rate

Chappell, Kirkham, Seitz 2019 (unpublished)
Conclusions

• Management of NPS in dementia must include thorough assessment of potential contributors

• There are several medications that have been demonstrated to be of benefit in NPS

• The risks and benefits of starting and continuation of medications for NPS need to be carefully considered for on an individual basis
Acknowledgements

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Dr. Colleen Maxwell (Waterloo)
Dr. Nathan Herrmann (Sunnybrook)
Dr. Krista Lanctot (Sunnybrook)
Victoria Chappell (Queen’s University)
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Brodaty H; Connors MH; Xu J; Woodward M; Ames D; PRIME study group. The course of neuropsychiatric symptoms in dementia: a 3-year longitudinal study. Journal of the American Medical Directors Association. 16(5):380-7, 2015 May 01.


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Peters ME; Schwartz S; Han D; Rabins PV; Steinberg M; Tschanz JT; Lyketsos CG. Neuropsychiatric symptoms as predictors of progression to severe Alzheimer's dementia and death: the Cache County Dementia Progression Study. American Journal of Psychiatry. 172(5):460-5, 2015 May.

Siafarikas N; Selbaek G; Fladby T; Saltyte Benth J; Auning E; Aarsland D. Frequency and subgroups of neuropsychiatric symptoms in mild cognitive impairment and different stages of dementia in Alzheimer’s disease. International Psychogeriatrics. 30(1):103-113, 2018 01.


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