Pharmacological Management of Neuropsychiatric Symptoms of Dementia

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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.

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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]

1. Finkel, Int Psychogeriatr, 1996; 8(suppl 3):497-500

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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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1. Cummings, *Neurology,* 1994
2. Cohen-Mansfield, *J Geronotol,* 1989

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)

1. Cohen-Mansfield, J Gerontol, 1989
2. Aalten, Dement Geriatr Cogn Disord, 2003

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Management of Neuropsychiatric Symptoms

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

1. Sink, JAMA, 2005

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NPS that May Respond to Medications

- Aggression*
- Agitation*
- Psychosis*
- Depression
- Anxiety
- Apathy

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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

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Atypical Antipsychotics

- Risperidone (N=5), aripiprazole (N=3), and olanzapine (N=5) have the strongest evidence to treat psychosis and agitation in dementia[1,2]
  - Quetiapine (N=3) trials have largely been negative
- Comparison trials:
  - risperidone = olanzapine[3]
  - olanzapine = haloperidol[4]
  - Neither quetiapine or haloperidol superior to placebo[5]

1. Schneider, Am J Geriatr Psychiatry, 2006
2. Ballard, Coch Database Syst Rev, 2008
3. Fontaine, *J Clin Psych,* 2003
4. Tariot, Am J Geriatr Psychiatry, 2006
5. Verhey, Dementia Geriatr Cogn Disord, 2006

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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

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1. Schneider, *New Eng J Med*, 2006

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

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1. Schneider, *New Eng J Med*, 2006

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

1. Sultzer, *Am J Psychiatry*, 2008

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Atypical Antipsychotics Dosing

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

Switch antipsychotics if no benefit or limited benefit observed after 2

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Serious Adverse Events

- Mortality: OR=1.6, absolute risk ~1%[1,2]
  - Number needed to harm: 100
  - Infections, cardiovascular events
- Stroke: RR=2.7, absolute risk~1%[2,3]
- Any serious adverse events within 30 days[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
4. Rochon, *Arch Intern Med*, 2008

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Mortality Risk with Individual Atypicals

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

1. Kales, Am J Psychiatry, 2012
2. Huybrechts, BMJ, 2012

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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)

1. Kales, Am J Psychiatry, 2007

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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

1. Schneider, Am J Geriatr Psychiatry, 2006
2. Schneider, N Eng J Med, 2006
3. Zheng, Am J Psychiatry, 2009

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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

1. Vigen, *Am J Psychiatry*, 2011
2. Schneider, *Am J Geriatr Psychiatry*, 2006

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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
2. Ruths, Int J Geriatr Psychiatry, 2008

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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

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Discontinuing Antipsychotics

- RCT of antipsychotic continuation or placebo (N=165) in LTC residents with dementia, 12 – 54 month follow-up[1]
  - 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

1. Ballard, PLoS Med, 2008

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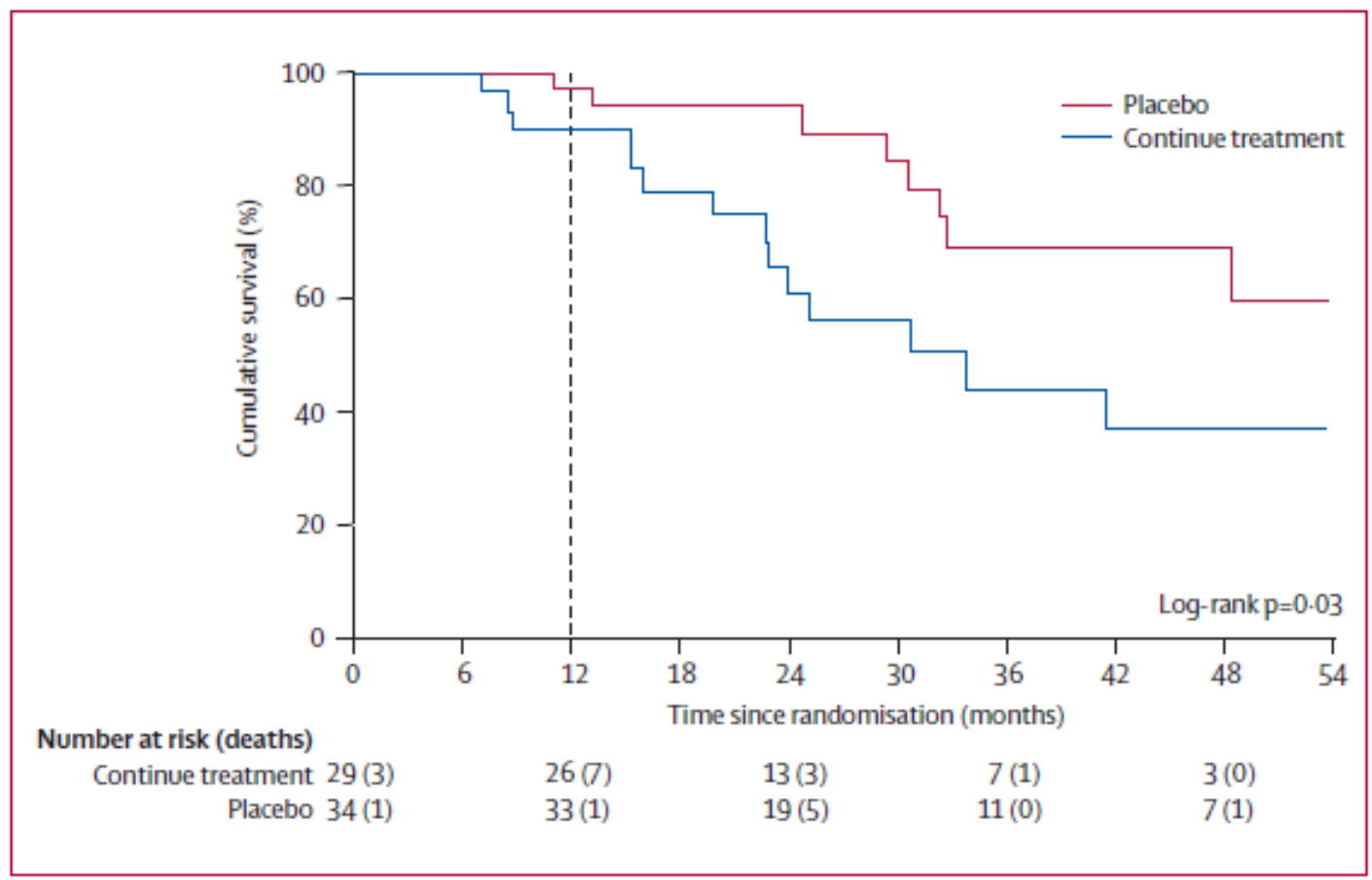
Effects of Discontinuing Antipsychotics on Mortality



Ballard, Lancet Neurology, 2009

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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

1. Schneider, J Am Geriatr Soc, 1990
2. Lanctot, J Clin Psychiatry, 1988
3. Lonergan, Cochrane Data Syst Rev, 2002
4. Gill, BMJ, 2005
5. Herrmann, Am J Psychiatry, 2004
6. Wang, N Eng J Med, 2005
7. Gill, Ann Intern Med, 2007

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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
2. Pollock, Am J Psychiatry, 2002
3. Finkel, Int J Geriatr Psychiatry, 2004

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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]

1. Seitz, Cochrane Database Syst Rev, 2011
2. Pollock, Am J Geriatr Psychiatry, 2007
3. Barak, Int Psychogeriatric, 2011

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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

1. Seitz, *Cochrane Data Syst Rev*, 2011
2. Pollock, *Am J Geriatr Psychiatry*, 2007
3. Kales, Am J Psychiatry, 2007
4. Huybrechts, CMAJ, 2011

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Antidepressants for Depression in Dementia

- Meta-analysis of 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

1. Nelson, J Am Geriatr Soc, 2011

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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

1. Banerjee, Lancet, 2011

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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
2. Sultzer, Am J Geriatr Psychiatry, 1997
3. Seitz, Cochrane Data Syst Rev, 2011

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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

1. Raina, Ann Intern Med, 2008
2. Gauthier, Int Psychogeriatr, 2002
3. Cummings, Am J Psychiatry, 2004

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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]

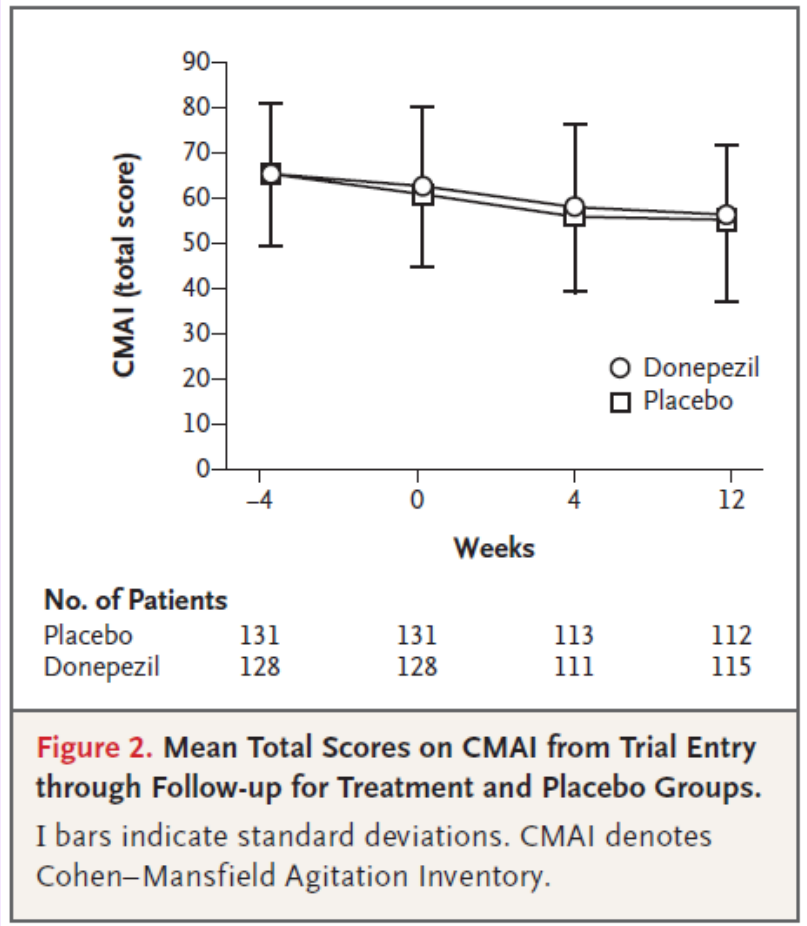

Figure 2. Mean Total Scores on CMAI from Trial Entry through Follow-up for Treatment and Placebo Groups.

I bars indicate standard deviations. CMAI denotes Cohen–Mansfield Agitation Inventory.

1. Howard, *New Eng J Med*, 2007
2. Holmes, Int J Geriatr Psychiatry, 2007
3. Ballard, BMJ, 2005

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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

1. Raina, Ann Intern Med, 2008
2. Gauthier, Int J Geriatr Psychiatry, 2008
3. Herrmann, CNS Drugs, 2011

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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)

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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%)

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1. Meehan, Neuropharmacology, 2002

Sleep Disturbances in Dementia

- Limited evidence for any agent in **dementia**
- Melatonin most extensively studied, inconclusive[1]
- Untreated insomnia associated with increased falls in LTC residents when compared to **treated** insomnia[2]
- Little difference in efficacy and safety between benzodiazepines and BZD agonists (e.g. zopiclone) for insomnia in older adults[3]
- Less evidence for trazodone than BZDs
- Sleep guidelines, primary insomnia, adults[4]:
  - Short-intermediate BZD (i.e. temazepam) or BZD agonist (e.g. zopiclone)

1. De Jonghe, Int J Geriatr Psychiatry, 2010
2. Avidan, J Am Geriatr Soc, 2005
3. Glass, BMJ, 2005
4. Rodin, J Clin Sleep Med, 2008

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Medications for Sleep

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

* May also be used in the treatment of frontotemporal dementia

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Anticonvulsants

- Carbamazepine
  - Two small RCTs showing some benefit[1,2]
  - 1 negative RCT with oxcarbazepine
- Valproic acid derivitatives
  - 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

1. Tariot, Am J Psychiatry, 1998
2. Olin, Am J Geriatr Psychiatry, 2001
3. Lonergan, Cochrane Database Syst Rev, 2009
4. Tariot, Arch Gen Psychiatry, 2011

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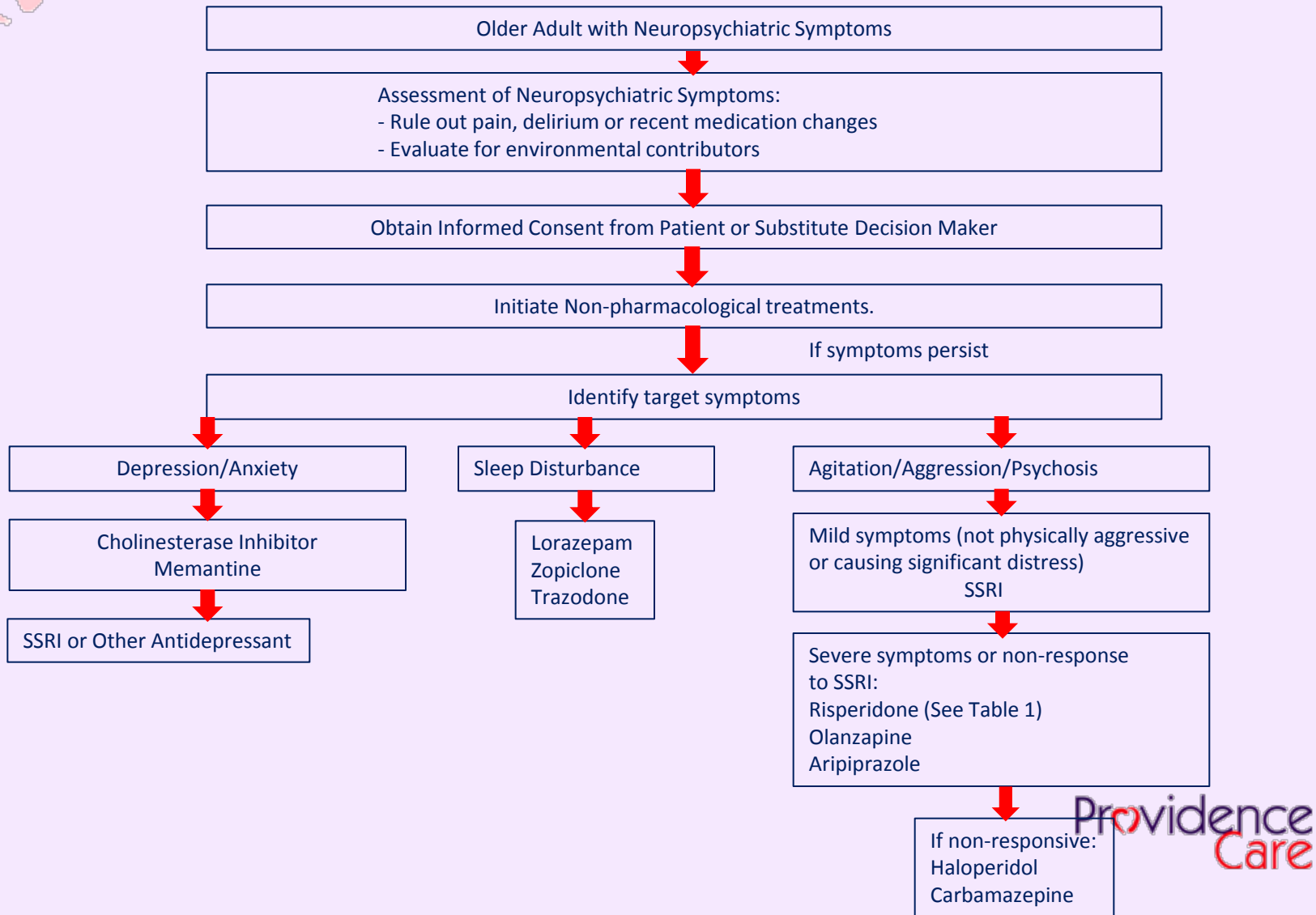
Approach to Use of Psychotropic Medications for Neuropsychiatric Symptoms of Dementia



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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

1. Husebo, BMJ, 2011

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Pain Treatment Protocol

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

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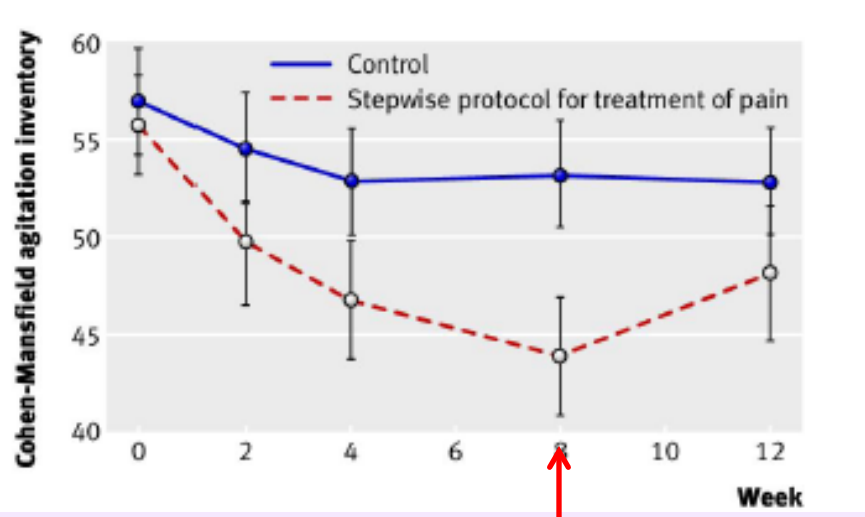
Pain Treatment Protocol

CMAI Total Score



Medications Withdrawn

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

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Other Potential Pharmacological Treatments

Randomized Controlled Trials:

- Prazosin[1]
- Cyproterone acetate[2]
- Estrogen[3]

Open label studies or case series:

- Cannabinoids, propranolol

1. Wang, Am J Geriatr Psychiatry, 2009
2. Huertas, J Clin Psychiatry, 2007
3. Kyomen, Am J Geriatr Psychiatry, 1999

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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

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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

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Resources

- PIECES Website
- Canadian Coalition for Seniors' Mental Health
  - www.ccsmh.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

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Questions

- Questions
- Cases to discuss
- Contact information
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