Pharmacologic treatment of behavioral disturbances in dementia

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Objectives

- Discuss common behavioral and psychiatric symptoms (BPSD) in dementia
- List common pharmacologic treatments of behavioral problems in demented patients
- Discuss limitations in the use of antipsychotic agents in treatment of BPSD

Background

- Dementia
  - 20-50% of individuals over the age of 80
  - Behavioral issues in 50-90% of patients at some point in their illness
    - Even greater in institutionalized patients
- The Aging imperative "Global Aging"
  - Individuals over the age of 80 are fastest growing segment

Small GW et al. *JAMA*. 1997;278:1363-1371.

Common Behavioral Disturbances

- Agitation
- Insomnia
- Aggression
- Depression
- Anxiety
- Disinhibition
- Delusions
- Wandering

Sink KM. JAMA, February 2, 2005—Vol 293, No. 5

Clinical significance

- Associated with rapid cognitive and physical decline
- Increased mortality
- Increased caregiver burden and stress
- Increased risk of institutionalization
- Increase cost of care- expected to triple in next 10 years
  - 30% of cost due to neuropsychiatric symptoms

Taylor DH *J Gerontol A Biol Sci Med Sci.* 2004;59:762-766
Herrmann N, Lactot KL. *Can J Psychiatry* 2007;52:630–646

BPSD

- New onset may be due to delirium
- Full physical and metabolic analysis needs to be done to rule out organic cause
- Review of medications to rule out as cause

Cohen-Mansfield J, et al. Gerontology. 1990;36:150–158.
Kiely DK, et al. Int J Geriatr Psychiatry. 2000;15:1013–1020.

Treatment Strategies

- Non-pharmacologic
- Pharmacologic

Non-pharmacologic Therapy

- Environmental
- Behavioral
- Sensory
- Physical activity
- Social contact
- Psychotherapeutic
- Staff training

Cohen-Mansfield J. Am J Geriatr Psychiatry.2001;9:361–381.

Medications used for treatment

- Antipsychotics
  - Typical
  - Atypical
- Anxiolytics
- Antidepressants
- Benzodiazepines
- Cognitive enhancers
- Anticonvulsants
- Cannabinoids
- Estrogens

Target symptoms

- Apathy
- Depression*
- Anxiety
- Hallucinations*
- Delusions
- Agitation
- Aggression*

American Geriatrics Society and American Association for Geriatric Psychiatry. Consensus statement on improving the quality of mental health care in US nursing homes: management of depression and behavioral symptoms associated with dementia. J Am Geriatr Soc. 2003;51:1287–1298.

Antipsychotics

- Most widely studied
- Typical antipsychotics clinically efficacious
- Comparison of 17 RCTs with over 500 dementia patients, 237 placebo showed 60% response rate
  - Clinical efficacy rates and adverse events rates are about equal
  - Increased risk for extrapyramidal side effects, akathisia (Ballard 1999b), QT prolongation (Reilly 2000), tardive dyskinesia, Parkinsonism (Tune 1991) and stroke (CMO 2004)

Lanctot KL. J Clin Psychiatry. 1998;59:550–561
Ballard C, et al. **Atypical antipsychotics for aggression and psychosis in Alzheimer's disease (Review) 2008 The Cochrane Collaboration.**

Atypical Antipsychotics

- Of the atypicals, risperidone (dose 1mg) and olanzapine (dose 5-10mg) have been shown to be the most efficacious for aggression, and risperidone for psychosis
- Clinical Antipsychotic Trial of Intervention Effectiveness- Alzheimer's Disease (CATIE-AD)
- Increased risk of CVAE's and mortality: 2.2% of treated vs 0.8% placebo (relative risk 2.7; 95%CI, 1.4 to 5.3)

Herrmann N, Lanctot KL. CNS Drugs. 2005;19:91–103.

Table 1 RCTs of atypical antipsychotics

Reference	Patients, *n*	Duration	Residence	Drugs	Outcome	Comment
Katz et al[138]	625	12 weeks	Nursing home	Risperidone (0.5, 1, or 2 mg daily), placebo	BEHAVE-AD,[a] BEHAVE-AD Psychosis subscale, CMAI, CGI-S; improvement in primary outcome with 1 and 2 mg daily vs placebo	Significant improvement in aggressive behaviour; no worsening of extrapyramidal symptoms vs placebo with 1 mg dose
De Deyn et al[139]	229	12 weeks	Nursing home	Risperidone (mean 1.1 mg daily), haloperidol (mean 1.2 mg daily), placebo	BEHAVE-AD,[a] CMAI, CGI-S; no significant improvement vs placebo on primary outcome	Significant reduction in secondary measures such as aggressive behaviour
Street et al[140]	206	6 weeks	Nursing home	Olanzapine (5, 10, or 15 mg daily), placebo	NPI–NH core total,[a] NPI total, NPI subscales, BPRS; significant improvement with 5 and 10 mg daily vs placebo in primary outcome	Improvement in BPRS with 5 mg daily vs placebo; somnolence, abnormal gait observed in drug group; lower dosage showed greatest effect
Meehan et al[126]	272	24 hours	Nursing home, hospital	Olanzapine intramuscular (2.5 or 5 mg daily), lorazepam intramuscular (1 mg daily), intramuscular placebo	PANSS-EC,[a] CMAI, ACES; significant improvement in PANSS-EC with 2.5 and 5 mg olanzapine at 2 hours and 24 hours postinjection	Significant improvements with 5 mg olanzapine and 1 mg lorazepam vs placebo on ACES; effect of olanzapine was longer-lasting than lorazepam
Brodaty et al[141]	345	12 weeks	Nursing home	Risperidone (mean 0.95 mg daily), placebo	CMAI,[a] BEHAVE-AD, CGI-S, CGI-C; risperidone showed significant improvements vs placebo group in CMAI-Aggression ($P < 0.001$)	Significant improvements in secondary outcomes
De Deyn et al[142]	652	10 weeks	Nursing home	Olanzapine (1, 2.5, 5, or 7.5 mg daily), placebo	NPI-NH Psychosis subscale,[a] CGI-C,[a] NPI-NH total and subscales, BPRS; no significant improvement with any dosage vs placebo with primary outcome	Secondary measures showed 7.5-mg daily dosage had some benefit with individual items of NPI, BPRS; occurrence of adverse events not significantly different between groups

Table 1 continued

Reference	Patients, *n*	Duration	Residence	Drugs	Outcome	Comment
Deberdt et al[143]	494	10 weeks	Nursing home, community	Olanzapine (mean 5.2 mg daily), risperidone (mean 1 mg daily), placebo	NPI–NPI-NH Psychosis subtotal,[a] CGI-S Psychosis,[a] NPI subscales, BPRS, CMAI, PDS, CSDD; no significant improvement with drug groups vs placebo on all outcome measures	Significant improvement noted in all groups, including placebo
Ballard et al[144]	93	26 weeks	Nursing home	Rivastigmine (3 to 6 mg), quetiapine, (25 to 50 mg), placebo	CMAI[a] and SIB[a]; no significant improvements in drug vs placebo	Quetiapine group experienced greater cognitive decline vs placebo
De Deyn et al[145]	208	10 weeks	Community	Aripiprazole (mean 10 mg daily), placebo	NPI-Psychosis subscale,[a] NPI total, BPRS; no significant improvement in drug group vs placebo at endpoint with primary outcome	Significant improvement in some secondary outcomes
Tariot et al[146]	284	10 weeks	Nursing home	Quetiapine (mean 96.9 mg daily), haloperidol (mean 1.9 mg daily)	BPRS,[a] CGI-S,[a] BPRS factors, NPI, MOSES and PSMS; no significant improvement in any measures	Significant placebo response noted
Schneider et al[22]	421	12 weeks	Community	Olanzapine (mean 5.5 mg daily), quetiapine (56.5 mg daily), risperidone (1 mg daily), placebo	Time until discontinuation of treatment for any reason,[a] CGI-C; no significant differences between treatment groups in primary outcome	Time to discontinuation for lack of efficacy significantly greater for olanzapine and risperidone; time to discontinuation for adverse events significantly greater for placebo
Zhong K et al[147]	333	10 weeks	Nursing home	Quetiapine (100 or 200 mg daily), placebo	PANSS-EC,[a] CGI-C, NPI-NH, CMAI; significant change in primary outcome with higher dosage vs placebo	Significant change in CGI-C with higher dosage vs placebo; gait abnormalities reported only in drug group

[a]Primary outcome measure

ACES = Agitation-Calmness Evaluation Scale; BEHAVE-AD = Behavioural Pathology in Alzheimer's Disease; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impression; CGI-C = Clinical Global Impression-Change; CGI-S = Clinical Global Impression-Severity; CMAI = Cohen-Mansfield Agitation Inventory; CSDD = Cornell Scale for Depression in Dementia; MOSES = Multidimensional Observation Scale for Elderly Subjects; NPI = Neuropsychiatric Inventory; NPI-NH = Neuropsychiatric Inventory-Nursing Home; PANSS-EC = Positive and Negative Syndrome Scale-Excited Component; PDS = Progressive Deterioration Scale; PSMS = Physical Self-Maintenance Scale; SIB = Severe Impairment Battery

Herrmann N, Lactot KL. *Can J Psychiatry* 2007;52:630–646

Antipsychotics

- Can safely be withdrawn after period of behavioral stabilization without exacerbating the behavior

Cohen-Mansfield, et al. Arch Intern Med. 1999;159:1733–1740.
Van Reekum R, et al. Int Psychogeriatr. 2002;14:197–210.
Ballard CG, et al. J Clin Psychiatry. 2004;65:114–119.

Take home points

- Treatment of BPSD should include both a pharmacologic and non-pharmacologic approach depending on symptoms
- Use of antipsychotics is effective, but not without side effects
- Withdrawal of antipsychotics should be attempted once symptoms are under control
- Appropriate drug therapy should be tailored to patient symptoms