Recognizing and Managing the Complications of Dementia: Behavioral & Psychological Symptoms of Dementia (BPSD)

Kiran Rabheru MD, CCFP, FRCP, ABPN
Professor
University of Ottawa
Geriatric Psychiatrist
The Ottawa Hospital
Objectives

Participants will be able to:

• Identify symptoms and clusters of behavioral disturbances in patients with dementia

• Plan treatment strategies of common behavioral disturbances in various settings: Home, LTC facility, inpatient unit or the ER

• Understand the role of pharmacological management in the treatment planning
What is BPSD?

• Occurs in all types of dementia

• Some types of dementias present with characteristic symptoms
  • e.g. Lewy Body - visual hallucinations
  • Frontotemporal dementia – disinhibition

• BPSD leads to earlier institutionalization, hospitalization, decreased quality of life
“Psychosis” in the elderly is a symptom, NOT a disorder

- Delirium
- Schizophrenia
- Delusional Disorder
- Mood Disorder
- Dementia
- Substance Abuse
- Drug-induced Psychosis
- Medical / Neurological Conditions

Presentation & Diagnosis: Highly variable
Key Principle: Comorbidity
Comorbidity is The Rule

Delirium often presents with psychotic / aggressive behavior.

Psychosis & aggression

Delirium
Depression
Personality
Parenting
Genetics
Environment
Dementia
Psycho-social
Psychosis & Aggression in the Elderly
Phases of Treatment

**ACUTE** → SAFETY → patient, staff, residents

**MEDIUM** → ASSESS → 1) rule out delirium
2) medicate or not?

**LONG-TERM** → MAINTENANCE → 1) on what?
2) how long?
Placebo response in studies of major depression: variable, substantial, and growing.

Walsh BT, Seidman SN, Sysko R, Gould M.
Non-Pharmacological Interventions

**Approach**  A kind, unrushed, non-confrontational, face-to-face approach may work better

**Schedules**  Patient-centred care schedules

**Demands**  Reduce demands on patient

**Communication**  Communicate more effectively

**Personal Care**  Meticulous attention to good personal care is essential

**Activity and Environment**  Appropriate daytime activity and environment
Psychotic symptoms in Late Life
Prevalence by Setting

- Community: 4%
  - Christenson 1984
- Outpatient Clinics: Approximately 20%
  - Molinari 1983
- Long-term care: Up to 50%
  - Wragg / Jeste 1989
The top 10 most frequent drug events in long-term care by drug type

Use caution when prescribing atypical antipsychotics: They're often administered in error. A nine-month study of two large long-term care facilities found that 11% of adverse drug events involved atypical antipsychotics—second only to warfarin—and 12% of those were deemed preventable.

<table>
<thead>
<tr>
<th>Drug class</th>
<th>% of total (n=815)</th>
<th>% preventable (n=338)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>15%</td>
<td>12%</td>
</tr>
<tr>
<td>Atypical antipsychotic agents</td>
<td>11%</td>
<td>12%</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>8%</td>
<td>10%</td>
</tr>
<tr>
<td>Opioids</td>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td>Antiplatelets</td>
<td>6%</td>
<td>7%</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td>Antidepressants (non-SSRI, nontricyclic)</td>
<td>5%</td>
<td>7%</td>
</tr>
<tr>
<td>Laxatives</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Benzodiazepines (intermediate-acting)</td>
<td>5%</td>
<td>9%</td>
</tr>
<tr>
<td>Insulins</td>
<td>5%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Source: American Journal of Medicine, March 2005.
Expert warning on dementia drugs

Experts have ruled drugs used to treat schizophrenia should not be given to elderly patients with dementia.

The antipsychotic drugs risperidone and olanzapine are used to control behavioural problems.

But the Committee on Safety of Medicines said patients with dementia were three times more likely to have a stroke if they were taking the drugs.

The CSH estimated that around 40,000 over-65s were prescribed the drugs last year.

Around 30,000 were given risperidone, and 9,000 olanzapine.

Both drugs are atypical antipsychotics, which are also used to treat agitation, anxiety, mania and aggression.

Some doctors prescribed the drugs for patients with dementia, even though they were not specifically licensed for that use, if they believed they could help the individual patient.
Parker & Waichman Files Claims Against Eli Lilly and Company on Behalf of Three Individuals Claiming Injuries Caused by Zyprexa; Plaintiffs Diagnosed with Serious Cases of Diabetes and Pancreatitis

Additional Claims vs. Eli Lilly & Co. Expected to be Filed

03/19/01 - Parker & Waichman LLP (www.yourlawyer.com) filed claims against Eli Lilly and Company (NYSE: LLY - News) on behalf of three individuals who claim to have sustained severe side-effects from Zyprexa. The claims were filed in Federal District Court in the Eastern District of New York. Two plaintiffs have been diagnosed with serious cases of diabetes, and another plaintiff has required lengthy intensive care hospitalization due to a diagnosis of acute pancreatitis. Zyprexa is currently the most popular atypical antipsychotic medication, and is Eli Lilly and Company’s best-selling pharmaceutical. Zyprexa users can visit www.zyprexa-side-effects.com for more information on these claims.

The British Medical Control Agency and the Japanese Health and Welfare Ministry have both warned about the risk of diabetes in patients who are prescribed Zyprexa. In 2002, a study at Duke University showed a connection between Zyprexa and diabetes. This study documented nearly 300 cases of diabetes in people using Zyprexa. Only recently has Eli Lilly and Company added some language to their labeling in the United States concerning the risk of diabetes from Zyprexa.
FDA Calls for Warning on Antipsychotic Drugs

04/11/05 - The U.S. Food and Drug Administration ordered new warnings on antipsychotic drugs, alerting physicians to a higher death rate when the medicines are prescribed for atypical use of treating dementia in elderly patients.

The black box warning affects Eli Lilly and Co.'s Zyprexa and Symbyax, AstraZeneca Pharmaceuticals LP's Seroquel, Johnson & Johnson's Risperdal, Novartis AG's Clozaril, Pfizer Inc.'s Geodon, and Bristol-Myers Squibb Co.'s and Otsuka America Pharmaceutical's Abilify.

The FDA said it is asking the companies to add the boxed warning to their labels describing the heightened risk and noting the drugs are not approved to treat symptoms of dementia in the elderly.

The FDA said after reviewing 17 studies of four drugs in the class, the death rate for elderly patients on the medication were 1.6 to 1.7 times greater than those on a placebo. Most of the deaths were either heart related or from infections, the FDA said.

Because the FDA believes it is a class effect, it is ordering the warnings on all drugs in the category, it said.

Eli Lilly spokeswoman Carole Copeland said the Zyprexa label...
Dementia Drugs May be Risky

May 28, 2009 | Parker Waichman Alonso LLP

We have long been writing about the serious side effects associated with some popular dementia drugs. Now, ScienceDaily is reporting that these adverse effects could be placing the elderly at risk, citing Sudeep Gill, a geriatrics professor at Queen’s University who is also an Ontario Ministry of Health and Long-term Care Career Scientist working at Providence Care’s St. Mary’s of the Lake Hospital in Kingston.

Aricept, Exelon, and Reminyl are in a class of drugs called cholinesterase inhibitors and are typically prescribed for Alzheimer’s disease patients and patients with related dementias, said Science Daily, explaining that the drugs increase the brain chemical thought to aid in memory. The drugs also seem to decrease heart rate and prompt...
Aricept, Zantac, Detrol, other Anticholinergic Drugs Lined to Mental Impairment in Elderly

May 6, 2008 | Parker Waichman Alonso LLP

Two separate reports written by researchers at Wake Forest University School of Medicine support findings released recently concerning anticholinergic medications like Aricept, Zantac and Detrol. The studies found that anticholinergic drugs may be adversely affecting the thinking skills of older patients, a phenomenon not observed in those patients studied who do not take these medications. The studies also indicate that anticholinergics may cause older patients to experience a decrease in their daily physical activities.
Use of Antipsychotics in Elderly Dementia Patients: Benefits out-weighed by adverse events

Cochrane Review

Randomized, double-blind, placebo-controlled trial
Atypical antipsychotics

Observational Study with 37,241 subjects
Conventional vs Atypical

Health Canada
Drugs for BPSD

• If drugs are bad……..
• Why do we still use them?
• If we have to use them, how do we use them safely?
• Goal is to:
  – Maximize benefit
  – Minimize risk
  – Explain these to patient & family
  – Consent
CONCEPT:

1. SYMPTOMS

2. CLUSTERS OF SYMPTOMS
Symptoms of BPSD

- Agitation
- Diurnal rhythm
- Irritability
- Wandering
- Aggression
- Hallucinations
- Mood change
- Socially unacc.
- Delusions
- Social withdrawal
- Anxiety
- Socially unacc.
- Accusatory
- Suicidal ideation
- Mood change
- Agitation
- Wandering
- Socially unacc.
- Hallucinations
- Sexually inappropriate

Jost and Grossberg, 1996
Clusters of BPSD

- 'Aggression'
  - Aggressive resistance
  - Physical aggression
  - Verbal aggression

- 'Agitation'
  - Walking aimlessly
  - Pacing
  - Trailing
  - Restlessness
  - Repetitive actions
  - Dressing/undressing
  - Sleep disturbance

- 'Apathy'
  - Withdrawn
  - Lack of interest
  - Amotivation

- 'Depression'
  - Sad
  - Tearful
  - Hopeless
  - Low self-esteem
  - Anxiety
  - Guilt

- 'Psychosis'
  - Hallucinations
  - Delusions
  - Misidentifications

Adapted from McShane R. Int Psychogeriatr 2000; 12(Suppl 1): 147–54
Measurement of vital signs
Identifying & Measuring BPSD

“Behavioural Vital Signs” or “BVS” Tool

Target Symptoms & Clusters
  • Frequency
  • Severity
  • Impact
BVS Tool: www.cagp.ca

• Click: “LINKS”
• Click: “ASSESSMENT TOOLS”
• Click: “BVS TOOL”

“Behavioral Vital Signs” Tool
BEHAVIOURAL-VITAL-SIGNS (BVS)

1. The primary caregiver or treatment team is to refer to each target symptom listed below.
2. Then rate their overall severity, frequency and impact and chart these findings.
3. Can be done per shift, daily, weekly or monthly as ordered.

<table>
<thead>
<tr>
<th>Delusions (off)</th>
</tr>
</thead>
<tbody>
<tr>
<td>People stealing things</td>
</tr>
<tr>
<td>Not recognizing one's own house or surroundings</td>
</tr>
<tr>
<td>Not recognizing spouse (or other caregivers)</td>
</tr>
<tr>
<td>False belief of abandonment (e.g., to an institution)</td>
</tr>
<tr>
<td>Suspiciousness</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>--------------</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hallucinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visuospatial</td>
</tr>
<tr>
<td>Auditory</td>
</tr>
<tr>
<td>Hallucinations of smell</td>
</tr>
<tr>
<td>Hallucinations of touch or other surface sensation</td>
</tr>
<tr>
<td>Other hallucinations</td>
</tr>
<tr>
<td>---------------</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Depression - Anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agitated</td>
</tr>
<tr>
<td>Depressed mood</td>
</tr>
<tr>
<td>Not participating in activity</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>--------------</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Manic States</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elation</td>
</tr>
<tr>
<td>Grandiosity</td>
</tr>
<tr>
<td>Irritability</td>
</tr>
<tr>
<td>Scleral jaundice</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>------------</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sleep - Wake Cycle Disturbance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difficulty</td>
</tr>
<tr>
<td>Falling asleep</td>
</tr>
<tr>
<td>Waking up too early</td>
</tr>
<tr>
<td>Waking up too late</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>------------</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Agitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physically Aggressive</td>
</tr>
<tr>
<td>Unagitated</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>------------</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Agitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal Aggressive</td>
</tr>
<tr>
<td>Verbal Non-Aggressive</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>------------</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Agitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physically Non-Aggressive</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>------------</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Agitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal Non-Aggressive</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>------------</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Apathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inappropriate</td>
</tr>
<tr>
<td>Lack of interest</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>------------</td>
</tr>
</tbody>
</table>

Definition of Agitation:
- Some patients have symptoms that do not neatly fit into the better-defined symptom complexes of BPSD (e.g., psychosis, depression or anxiety).
- These symptoms are assigned to the "grab bag" category of agitation.
- Agitation can be defined as inappropriate verbal, vocal or motor activity that is not judged by an outside observer to result directly from the needs, or confusion, of the person.
<table>
<thead>
<tr>
<th>Behaviour Frequency</th>
<th>Severity</th>
<th>Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate 1-5</td>
<td>How much difficulty is it to distract or redirect the patient?</td>
<td>Rate 1-5</td>
</tr>
<tr>
<td>5: Constant</td>
<td>5: Extreme (not directable)</td>
<td>5: Extreme (serious harm)</td>
</tr>
<tr>
<td>4: Several times a day</td>
<td>4: Intense (major problem)</td>
<td>4: Intense (significant harm)</td>
</tr>
<tr>
<td>3: At least once daily</td>
<td>3: Moderate (moderate problem)</td>
<td>3: Moderate (moderate harm)</td>
</tr>
<tr>
<td>2: At least once a week</td>
<td>2: Minimal (minor problem)</td>
<td>2: Minor (minor harm)</td>
</tr>
<tr>
<td>1: Less than once a week</td>
<td>1: Negligible (insignificant problem)</td>
<td>1: Negligible (no notable harm)</td>
</tr>
<tr>
<td>0: Almost never</td>
<td>0: None</td>
<td>0: None</td>
</tr>
</tbody>
</table>

Please place appropriate X, □, or — symbols in chart below according to your assessment based on the above criteria.
Approach to BPSD:

The SMART Approach:

- **S**afety: remove patient to safe environment
- **M**edical: organic workup to treat reversible causes; reduce medication load
- **A**ssess Competency: personal care decisions, financial, driving; protect assets
- **R**est, nutrition, hydration; pain ambulation, vision, hearing, constipation
- **T**rial of medication: cholinesterase inhibitor / antipsychotic / antidepressant / mood stabilizer

Rabheru K. Can Family Physician Vol 49 March 2003 pg. 389
Algorithm For Management of Psychosis In Late-Life

Identify and document target cluster(s) / symptom(s); consider BVS Tool

Rule out new medical and psychiatric causes
New onset behavioural problem = delirium until proven otherwise

Implement caregiver-led non-pharmacologic interventions and monitor closely

Initiate pharmacological treatment if target symptom(s) severe, persistent and disturbing or dangerous enough

Start appropriate initial and maintainance pharmacotherapy
Monitor efficacy & side effects
If not meeting therapeutic goals, consider switching agents, adjunctive therapy or consult geriatric psychiatry

Antipsychotics for BPSD

• **Goal:**
  - Reduce psychotic symptoms & aggression.
  - Increase the safety & comfort for patient and caregiver.

• **Prerequisites:**
  - Monitor target symptoms / clusters.
  - Consider need for drug Rx only if risk is significant.
  - Monitor impact of Rx.
On improving the quality of mental health care in nursing homes:

“Appropriate first-line pharmacological treatment of residents with severe behavioral symptoms with psychotic features, such as hallucinations and delusions that are causing distress, consists of atypical antipsychotics.”

Efficacy and Adverse Effects of Atypical Antipsychotics for Dementia: Meta-analysis of Randomized, Placebo-Controlled Trials

Lon S. Schneider, M.D., M.S., Karen Dagerman, M.S., Philip S. Insel, M.S.

Am J Geriatr Psychiatry 2006; 14:191–210

Objective: Atypical antipsychotic medications are widely used to treat delusions, aggression, and agitation in people with Alzheimer disease (AD) and other dementia. Several clinical trials have not shown efficacy, and there have been concerns about adverse events. The objective of this study was to assess the evidence for efficacy and adverse events of atypicals for people with dementia Methods: MEDLINE, the Cochrane Register of Controlled Trials, meetings, presentations, and information obtained from sponsors were used in this study. Published and unpublished randomized, placebo-controlled, double-blind, parallel-group trials in patients with AD or dementia of atypical antipsychotics marketed in the United States were studied.
Schneider meta-analysis

- N= 16 trials AP vs. PBO
- 3,353 pts. On drug and 1,757 on PBO
- aripiprazole (k3), olanzapine (k5), quetiapine (k3), risperidone (k5)
- Variable reporting; 1/3 drop-outs
- Efficacy: aripiprazole and risperidone, but not for olanzapine
- Smaller effects for less severe dementia, outpatients, and patients selected for psychosis
Schneider meta-analysis

- A/E: somnolence & UTI / incontinence
- across drugs, EPS & abnormal gait with risperidone or olanzapine
- Cognition worsened
- No evidence for increased injury, falls, or syncope
- Significant risk for CVAEs, especially with risperidone. Increased mortality
Editors' note: Antipsychotics do not improve cognitive or neuropsychiatric outcomes in most patients with dementia, and serious concerns have been raised about their side effects in the very old. Increased mortality rate and risk of cerebrovascular events have been reported by previous studies of relatively short duration (usually 12 weeks). In this article, the DART-AD investigators report long-term mortality rates among patients with Alzheimer's disease in residential care after 12 months of neuroleptic treatment, adding to the growing evidence against the use of antipsychotics in this vulnerable population.

The dementia antipsychotic withdrawal trial (DART-AD): long-term follow-up of a randomised placebo-controlled trial

Clive Ballard MD FMedSci, Maria Luisa Hannen PhD, Megan Theodoulou MRCPsych C, Simon Douglas BSc, Rupert McShane MRCPsych, Kasia Kossakowski BSc, Randeep Gill MBBS, Edmund Juszczak MSc, Ly-Mee Yu MSc, Robin Jacoby DM, for the DART-AD Investigators
DART-AD RESULTS

- N=165
- 83 AP & 82 PBO

Survival:
- 70% vs 77% at 1 year
- 46 % vs. 72 % at 2 years
- 30% vs 59 % at 3 years
- Seek less harmful alternatives for the long-term treatment
Mortality: Atypicals vs. placebo

- Odds ratio of death all drugs pooled = 1.54 (1.06-2.23) vs PBO
- Black box warnings of death on atypicals: 4.5% vs 2.6% on PBO
- Causes: “cardiovascular, infection”
Mortality: Typicals vs. Atypical

• Typicals: higher mortality RR = 1.37
  • For every 100 patients treated with typicals….7 additional deaths….no black box warning for typicals

• Other medications have less evidence for efficacy or safety.

• Absence of evidence ≠ Evidence of absence
Cholinesterase Inhibitors for BPSD

- Treatment with cholinesterase inhibitors (ChEIs) has been reported to show behavioural benefits for AD patients in:
  - Mild-to-moderate AD\textsuperscript{1-3}
  - Moderate-to-severe AD\textsuperscript{4,5}
  - AD patients in nursing homes\textsuperscript{6}

- Unlike most psychotropics\textsuperscript{7}, ChEIs appear to treat multiple behavioural symptoms (eg, affective and psychotic)\textsuperscript{1-6}

Memantine Therapy of Behavioral Symptoms in Community-Dwelling Patients with Moderate to Severe Alzheimer’s Disease

George T. Grossberg a, Vojislav Pejovic b, Michael L. Miller b, Stephen M. Graham c

aDepartment of Neurology and Psychiatry, Saint Louis University School of Medicine, St. Louis, Mo,
bPrescott Medical Communications Group, Chicago, Ill., and cForest Research Institute, Jersey City, NJ, USA

Dement Geriatr Cogn Disord 2009;27:164–172

Key Words: a reduced severity or emergence of specific symptoms, Memantine, Alzheimer's disease, Behavioral disturbances, particularly agitation and aggression, Dementia, mild cognitive impairment.
MEMANTINE:

Mild to moderate: very small advantage over placebo. Individuals may consider….little risk.

In moderate to severe: evidence & indication given upto 6 months (APA) with or without a ChEI

---

Memantine in moderate to severe Alzheimer’s disease
Barry Reisberg, M.D., et al.
The New England Journal of Medicine April 2003

Memantine treatment in patients with moderate to severe AD already receiving donepezil
Pierre Tariot, M.D., et al.
JAMA, January 2004

Memantine in severe dementia:
Results of the M-BEST study
(Benefit and Efficacy in Severely Demented Patients During Treatment with Memantine)
Bengt Winblad, M.D., Ph.D., et al.
International Journal of Geriatric Psychiatry, 1999
Common Medical drugs with Anticholinergic Effects

- 14/25: detectable anticholinergic activity
- 10/25: activity with the potential to impair memory

Memory impaired in normal elderly

# Common Drugs Potentially Worsening Cognition

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Anticholinergic</td>
<td>Lomotil, ditropan, detrol</td>
</tr>
<tr>
<td>2</td>
<td>Antidepressants</td>
<td>Elavil, sinequan, prozac, lithium</td>
</tr>
<tr>
<td>3</td>
<td>Antipsychotic</td>
<td>Haldol, stelazine, mellaril</td>
</tr>
<tr>
<td>4</td>
<td>Antihypertensives</td>
<td>Betablockers, alpha-antagonists, calcium channel</td>
</tr>
<tr>
<td>5</td>
<td>Antibiotics</td>
<td>Cipro, flagyl, keflex</td>
</tr>
<tr>
<td>6</td>
<td>Anticonvulsants</td>
<td>Dilantin, tegretol, Velproic acid</td>
</tr>
<tr>
<td>7</td>
<td>Antiemetics</td>
<td>Antivert, phenergan, gravol</td>
</tr>
<tr>
<td>8</td>
<td>Antiparkinsonian</td>
<td>Cogentin, artane, sinemet, parlodel</td>
</tr>
<tr>
<td>9</td>
<td>Antihistamines</td>
<td>Benadryl, cough &amp; cold preparations (OTC)</td>
</tr>
<tr>
<td>10</td>
<td>Narcotics</td>
<td>Codeine, demerol, talwin</td>
</tr>
<tr>
<td>11</td>
<td>H₂ Receptor Antagonists</td>
<td>Cimetidine, ranitidine</td>
</tr>
<tr>
<td>12</td>
<td>NSAIDs</td>
<td>Motrin, naprosyn, indocid</td>
</tr>
<tr>
<td>13</td>
<td>Benzodiazepines</td>
<td>Valium, dalmane, ativan, halcion</td>
</tr>
</tbody>
</table>

AHCPR Clinical Practice Guidelines # 19 publication #97-0702
Washington – Dept. of Health and Wellness Services Nov 1956
Depression in Dementia

- No clear established & validated criteria

- citalopram, sertraline, venlafaxine, mirtazapine, & bupropion

- Treatment may help other neuropsychiatric symptoms eg. aggression or psychosis

- Rule out: alcohol, sedative-hypnotics, other drug dependence, CNS pathology, and medical problems eg hypothryroidism
Pharmacological Treatment of Neuropsychiatric Symptoms of Dementia
A Review of the Evidence

Kaypee M. Sink, MD
Karen E. Holden, MD
Kristine Yaffe, MD

Up to 20% of community-dwelling elderly individuals older than 85 years have dementia, with Alzheimer disease (AD), vascular dementia, and dementia with Lewy bodies accounting for most cases. Although cognitive deficits are the clinical hallmark of dementing illnesses, noncognitive...
No first-line recommended drug treatment for agitation without delusions

- **Typical antipsychotics:**
  - No clear evidence that typical AP are useful.
  - Haloperidol with aggression: too many adverse effects.
- **Serotonergics:** recommended only for depression.
- **Anticonvulsants:** Carbamazepine, Valproate: **Not recommended**
- **Cholinergic medications:**
  - Statistical significance of small magnitude & questionable clinical significance.
  - Only mild BPSD symptoms in all trials except two.
Benzodiazepines

- Better vs. PBO
- Equal IM olanzapine at 2 hours but inferior at 24 hours. No data beyond 8 weeks
- Sedation, ataxia, amnesia, confusion, delirium, paradoxical anxiety → falls, respiratory suppression.
- All are dose related
- With alcohol: may cause disinhibition or withdrawal
Benzodiazepines

- Useful if anxiety is prominent, occasional PRN s, procedures
- Use low dose, short t1/2,
- Clonazepam has longer t1/2...use with caution as ....falls ...increase
- Start SLOWLY...monitor.....taper very slowly.
Pharmacologic Options in Dementia

Possibly Prevent Emergence of BPSD

✓ Consider Cholinergic medication early in AD & Mixed AD /CVD

Mild/Moderate Agitation

✓ Consider Trazodone & Consider SSRIs

Aggressive / Psychotic

✓ Consider Atypical antipsychotics

CAUTION: AVOID LONG-TERM USE OF BENZODIAZEPINES
Non-Pharmacological Options for the Treatment of BPSD

- **Social contacts**: pets, one to one, family videos

- **Therapy**: music; Snoezelen (multi-sensory stimulation); bright light therapy; reminiscence therapy; validation therapy; aroma therapy; and, massage and touch therapy

- **Behavioral interventions**: redirection, distraction, supervision, routine, structure, rewards

- **Eliminate triggers**: assess cause of symptoms (environment, hearing aids, pain management, medications, infection, sleep hygiene)

- **Staff & Caregiver training**

Canadian Consensus Conference on Diagnosis and Treatment of Dementia
Alternative Pharmacological Options for the Treatment of BPSD

Anxiolytics

- Benzodiazepines should be used only for short periods as p.r.n. agents.

Antidepressants

- SSRIs can be used for the treatment of severe depression.
- Trazodone: Insufficient evidence to recommend for or against the use.

Atypical antipsychotics

- Risperidone and olanzapine can be used for severe agitation, aggression and psychosis. The potential benefit of all antipsychotics must be weighed against the potential risks such as cerebrovascular adverse events and mortality.

ChEIs & and memantine

- A trial of a cholinesterase inhibitor and/or memantine can be considered.

Canadian Consensus Conference on Diagnosis and Treatment of Dementia
CATIE-AD Study
NEJM, Oct 12 2006

• Multi-site, double-blind, placebo-controlled
• 421 outpatients with moderately severe Alzheimer Disease complicated by agitation, aggression, or psychosis
• Randomly assigned to olanzapine, risperidone, quetiapine, or placebo
CATIE Study

• Outcome Measures:
  – Time to discontinuation for any reason
  – At least minimal improvement on the Clinical Global Impression of Change (CGIC) scale at 12 weeks

• Results:
  – No significant differences among treatments
CATIE Study

• “Adverse effects offset advantages in the efficacy of atypical antipsychotic drugs for the treatment of psychosis, aggression, or agitation in patients with Alzheimer’s disease.”
Outcome - Results

• The median time to the discontinuation of treatment due to a lack of efficacy:
  – olanzapine 22.1 weeks
  – risperidone 26.7 weeks
  – quetiapine 9.1 weeks
  – Placebo 9.0 weeks
## Pharmacokinetics & Clinical Potency of Atypical Antipsychotic Agents

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Clozapine</th>
<th>Risperidone</th>
<th>Olanzapine</th>
<th>Quetiapine</th>
<th>Ziprasidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dibenzo-diazepine</td>
<td>Dibenzo-diazepine</td>
<td>Benzio-xazol</td>
<td>Thienobenzodiazepine</td>
<td>Dibenzo-thiazepine</td>
<td>Benzisothiazolyl piperazine</td>
</tr>
<tr>
<td>Potency</td>
<td>50</td>
<td>1</td>
<td>4.0</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>Time to peak plasma conc. (hrs)</td>
<td>3</td>
<td>1.5</td>
<td>5</td>
<td>1.5</td>
<td>4</td>
</tr>
<tr>
<td>Protein binding (%)</td>
<td>92 - 95</td>
<td>90</td>
<td>93</td>
<td>83</td>
<td>98 - 99</td>
</tr>
<tr>
<td>Active metabolites</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Metabolism</td>
<td>CYP1A2, CYP3A4</td>
<td>CYP2D6</td>
<td>CYP1A2, CYP2D6</td>
<td>CYP3A4</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Elimination half-life (hrs)</td>
<td>10 - 100</td>
<td>6 - 24</td>
<td>20 - 70</td>
<td>4 - 10</td>
<td>3 - 10¹</td>
</tr>
</tbody>
</table>

## Antipsychotic Agents
### Side Effect Profiles

<table>
<thead>
<tr>
<th>Conventional antipsychotics</th>
<th>Clozapine</th>
<th>Risperidone</th>
<th>Olanzapine</th>
<th>Quetiapine</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPS</td>
<td>+++++</td>
<td>0</td>
<td>0/+</td>
<td>0/+</td>
</tr>
<tr>
<td>TD</td>
<td>+++++</td>
<td>0/+</td>
<td>0/+</td>
<td>0/+</td>
</tr>
<tr>
<td>Seizures</td>
<td>0/+</td>
<td>+++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sedation</td>
<td>+++++</td>
<td>+++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Anticholinergic effects</td>
<td>+++++</td>
<td>+++</td>
<td>0</td>
<td>0/+</td>
</tr>
</tbody>
</table>

0 = none; + = mild; ++ = moderate; +++ = severe

Adapted from Masand PS et al. Handbook of Psychiatry in Primary Care 1998
### Antipsychotic Agents

**Side Effect Profiles (cont’d)**

<table>
<thead>
<tr>
<th></th>
<th>Conventional antipsychotics</th>
<th>Clozapine</th>
<th>Risperidone</th>
<th>Olanzapine</th>
<th>Quetiapine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>+/+++</td>
<td>+++</td>
<td>0/+</td>
<td>0/+</td>
<td>++</td>
</tr>
<tr>
<td>Liver transaminase</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>increase</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihistaminic effects</td>
<td>+/+++</td>
<td>+++</td>
<td>0</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Prolactin increase</td>
<td>+/++</td>
<td>0</td>
<td>++</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Weight gain</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>

0 = none; + = mild; ++ = moderate; +++ = severe

Adapted from Masand PS et al. *Handbook of Psychiatry in Primary Care* 1998
## Suggested Treatment in Acute/urgent Situations for Psychosis in Late Life with Atypical Antipsychotics

<table>
<thead>
<tr>
<th>Atypical Medication</th>
<th>Usual dose and formulation</th>
<th>Usual frequency</th>
<th>Maximum dose / 24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>0.25-1 mg, PO Tabs or Liquid / M-tab</td>
<td>Q2-4 hours as needed and tolerated</td>
<td>2 mg for many dementia patients Not DLB / PD May be higher in other conditions e.g. schizophrenia, bipolar disorder etc.</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>2.5-5 mg PO Tabs /Zydis</td>
<td>Q2-4 hours as needed and tolerated</td>
<td>10 mg for dementia patients May be higher in other conditions e.g. schizophrenia, bipolar disorder etc.</td>
</tr>
<tr>
<td></td>
<td>Note: IM formulation is available but there is little experience with its use in Canada with the elderly dementia population. Dosage 2.5 mg-5 mg IM, max 10 mg/24 hours. Not given IV.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>12.5 – 25 mg BID</td>
<td></td>
<td>75.0 mg BID (150.0 mg tab split = 2 X 75.0 mg)</td>
</tr>
</tbody>
</table>
# Guidelines for Maintenance Therapy of Psychosis in Late-Life with Atypical Antipsychotics

<table>
<thead>
<tr>
<th>Atypical Antipsychotic</th>
<th>Starting Dose (mg/day)</th>
<th>Usual Daily Dose (mg/day)</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risperidone</strong></td>
<td>0.25 mg</td>
<td>1 mg/day for most dementias - not for LBD/PDD</td>
<td>2.0 mg/day for most dementias - not for DLB/PDD</td>
</tr>
<tr>
<td></td>
<td>In very old, frail or LBD or PD patients</td>
<td>May be given as single dose or divided dose, as tolerated</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Usual starting dose is 0.5 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>May be increased Q3-5 days by 0.25 mg – 0.5 mg as tolerated</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Olanzapine</strong></td>
<td>1.25 - 2.5 mg</td>
<td>5-10 mg/day for most dementias – not for LBD/PDD</td>
<td>10 mg/day for most dementias – not DLB/PDD</td>
</tr>
<tr>
<td></td>
<td>In very old, frail or LBD or PD patients</td>
<td>May be given as single dose or divided doses as tolerated</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Usual starting dose is 2.5 – 5 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>May be increased Q3-5 days by 1.25-2.5 mg as tolerated</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Quetiapine</strong></td>
<td>6.25 – 12.5 mg</td>
<td>100 mg/day for most dementias – may be lower for LBD/PDD</td>
<td>150 mg/day – some dementia patients need higher doses</td>
</tr>
<tr>
<td></td>
<td>In very old, frail or LBD or PD patients</td>
<td>Wide range of dosing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Usual starting dose is 12.5 – 25 mg</td>
<td>May be given as single dose or divided doses as tolerated</td>
<td></td>
</tr>
<tr>
<td></td>
<td>May be increased Q3-5 days by 25-50 mg as tolerated</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Antipsychotic & EPS: DLB & PDD

Litmus Test for neuroleptic sensitivity: Dose Response Curves
Conventional antipsychotics contraindicated

Baskys A.
Psychotic Major Depression
ECT → first line Rx or AD + risperidone 0.75-2.25 mg/day
Olanzapine 5-10mg/day or quetiapine 50-200 mg/day
Duration of antipsychotic use: 6 Months

Delusional Disorder
Antipsychotic is the only treatment recommended
Risperidone 0.75-2.5 mg/day preferred
Olanzapine 5-10mg/day or quetiapine 50-200 mg/day
Duration of treatment: 6 months-indefinitely at the lowest effective dose

Late-life Schizophrenia
Risperidone (1.25-3.5 mg/day) preferred
Quetiapine (100-300 mg/day), olanzapine (7.5-15 mg/day) are high second line
Duration of treatment: indefinite treatment at the lowest effective dose
For Mild Geriatric Non-psychotic Mania
Mood stabilizer alone; D/C Antidepressant

For Severe Non-psychotic Mania
First: Mood stabilizer alone; D/C Antidepressant
Next: Add an antipsychotic / add or change mood stabilizer

For Psychotic Mania
Treatment of choice is a mood stabilizer plus an antipsychotic

Risperidone (1.25-3.0 mg/day) and olanzapine (5-15 mg/day) are first-line options in combination with a mood stabilizer for mania with psychosis

Quetiapine (50-250 mg/day) high second line
Duration: Mania with psychosis, 3 months
Diabetes, dyslipidemia, or obesity: Avoid clozapine, olanzapine, and conventional antipsychotics (especially low- and mid-potency).

Parkinson’s disease
Quetiapine is first line for a patient with Parkinson’s disease

QTC prolongation or congestive heart failure:
Avoid clozapine, conventionals (especially low- and mid-potency) and ziprasidone antipsychotics

For patients with cognitive impairment, constipation, diabetes, diabetic neuropathy, dyslipidemia, xerophthalmia, and xerostomia
Risperidone, with quetiapine high second line