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 maintainace pharmacotherapy
Monitor efficacy & side effects
If not meeting therapeutic goals, consider switching agents, adjunctive therapy or consult geriatric psychiatry

Adapted from Mintzer JE, Browman-Mitzer O. J Clin Psychiatry 1996;5(7):55-63

Antipsychotics for BPSD

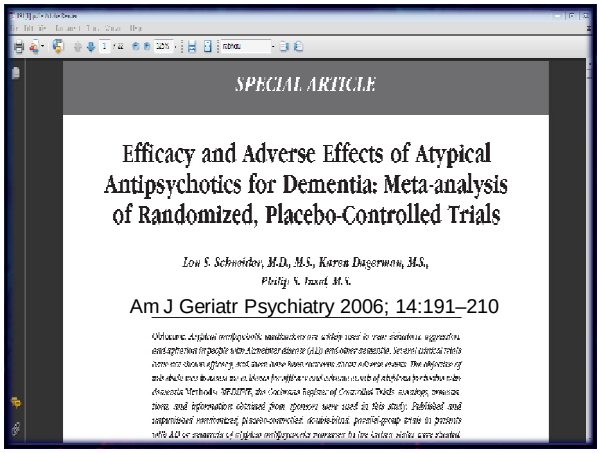
- **Goal:**
  - Reduce psychotic symptoms & aggression.
  - Increase the safety & comfort for patient and caregiver.
- **Prerequisites:**
  - Monitor target symptoms / clusters.
  - Consider need for drug Rx only if risk is significant.
  - Monitor impact of Rx.

Evidence-Based Recommendation From AGS-AAGP Consensus Panel in 2002-2003

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."*

American Geriatrics Society, American Association for Geriatric Psychiatry. *J Am Geriatr Soc.* 2003; 51:1287-1298.



SPECIAL ARTICLE

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 N. Insel, M.A.

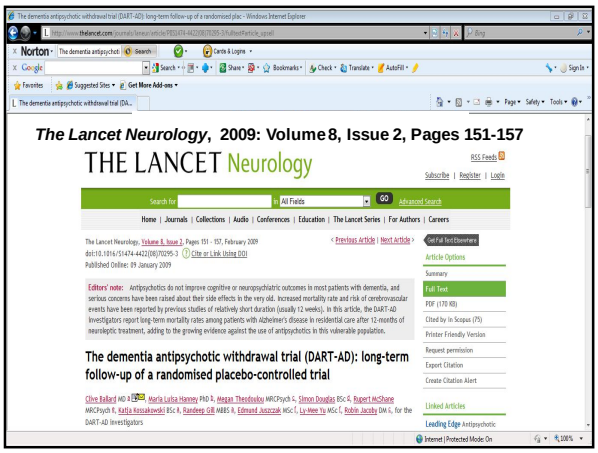
Am J Geriatr Psychiatry 2006; 14:191–210

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



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".

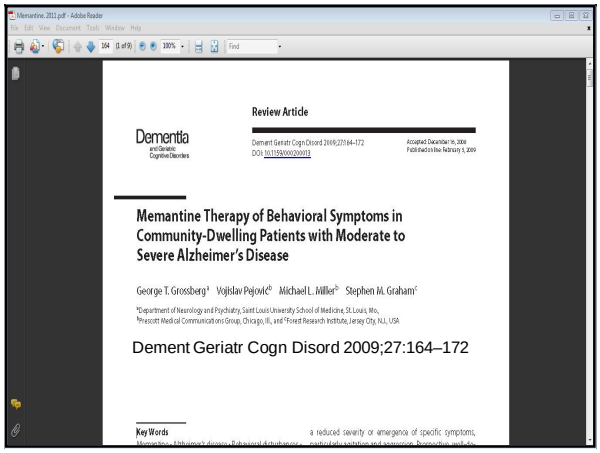
Mortality: Typicals vs. Atypicals

- 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[1-3]
  - Moderate-to-severe AD[4,5]
  - AD patients in nursing homes[6]
- Unlike most psychotropics[7], ChEIs appear to treat multiple behavioural symptoms (eg, affective and psychotic)[1-6]

[1]Holmes C et al. *Neurology*. 2004;63:214-9; [2]Cummings et al. *Am J Psychiatry*. 2004;161:532-8; [3]Finkel et al. *Int J Geriatr Psychiatr*. 2004;19:9-18; [4]Feldman H et al. *Neurology*. 2001;57:613-21; [5]Gauthier S et al. *Int J Psychogeriatr*. 2002;14:389-404; [6]Hatoum et al. *J Am Med Dir Assoc*. 2005;6:238-45; [7]Lee et al. *BMJ*. 2004;329:75; [8]Pratt et al. *Int J Clin Prac*. 2002;56:710-7.



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

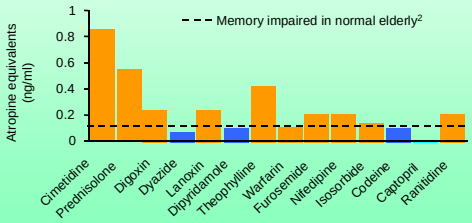
Memantine in moderate to severe Alzheimer's disease
Barry Reisberg, M.D., *et al.*
The New England Journal of Medicine April 2003

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[1]
- 10/25: activity with the potential to impair memory[2]



1. Tune L *et al.* Am J Psychiatry 1992; 149: 1393–4
2. Miller PS *et al.* Am J Psychiatry 1988; 145: 342–5

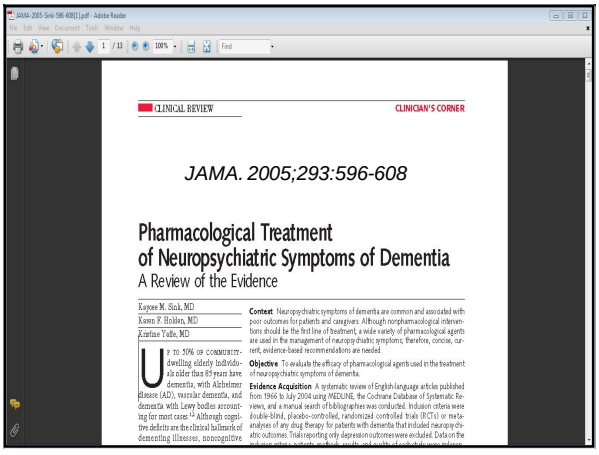
Common Drugs Potentially Worsening Cognition

1.	Anticholinergic	Lomotil, ditropan, detrol
2.	Antidepressants	Elavil, sinequan, prozac, lithium
3.	Antipsychotic	Haldol, stelazine, mellaril
4.	Antihypertensives	Betablockers, alpha-antagonists, calcium channel
5.	Antibiotics	Cipro, flagyl, keflex
6.	Anticonvulsants	Dilantin, tegretol, Velproic acid
7.	Antiemetics	Antivert, phenergan, gravol
8.	Antiparkinsonian	Cogentin, artane, sinemet, parlodel
9.	Antihistamines	Benadryl, cough & cold preparations (OTC)
10.	Narcotics	Codeine, demerol, talwin
11.	H_2 Receptor Antagonists	Cimetidine, ranitidine
12.	NSAIDs	Motrin, naprosyn, indocid
13.	Benzodiazepines	Valium, dalmane, ativan, halcion

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 hypothyroidism



CLINICAL REVIEW — CLINICIAN'S CORNER

JAMA. 2005;293:596-608

Pharmacological Treatment of Neuropsychiatric Symptoms of Dementia
A Review of the Evidence

Kaycee M. Sink, MD
Karen P. Holden, MD
Alistair Yaffe, MD

Up to 50% 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.[1,2] Although cognitive deficits are the clinical hallmark of dementing illnesses, noncognitive

Context Neuropsychiatric symptoms of dementia are common and associated with poor outcomes for patients and caregivers. Although nonpharmacological interventions should be the first line of treatment, a wide variety of pharmacological agents are used in the management of neuropsychiatric symptoms; therefore, concise, current, evidence-based recommendations are needed.

Objective To evaluate the efficacy of pharmacological agents used in the treatment of neuropsychiatric symptoms of dementia.

Evidence Acquisition A systematic review of English-language articles published from 1966 to July 2004 using MEDLINE, the Cochrane Database of Systematic Reviews, and a manual search of bibliographies was conducted. Inclusion criteria were double-blind, placebo-controlled, randomized controlled trials (RCTs) or meta-analyses of any drug therapy for patients with dementia that included neuropsychiatric outcomes. Trials reporting only depression outcomes were excluded. Data on the

JAMA Review

❑ **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

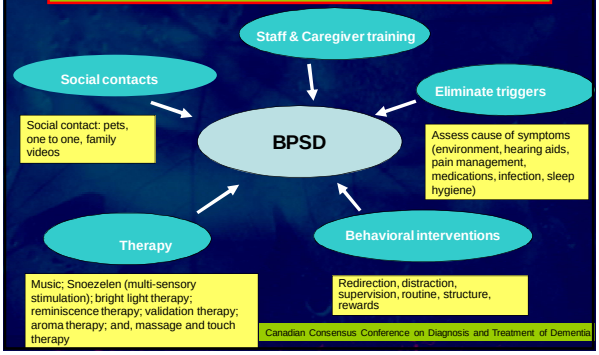
✓ Consider Trazodone & Consider SSRIs

Aggressive / Psychotic

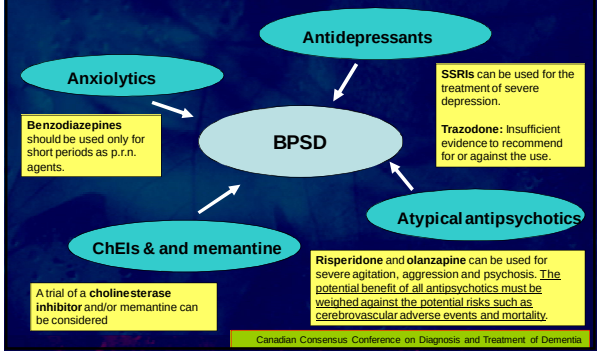
✓ Consider Atypical antipsychotics

CAUTION: AVOID LONG-TERM USE OF BENZODIAZEPINES

Non-Pharmacological Options for the Treatment of BPSD



Alternative Pharmacological Options for the Treatment of BPSD



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

	Clozapine	Risperidone	Olanzapine	Quetiapine	Ziprasidone
Drug class	Dibenzo-diazepine	Benzio-xazol	Thienoben-zodiazepine	Dibenzo-thiazepine	Benziso-thiazolyl piperazine
Potency	50	1	4.0	80	20
Time to peak plasma conc. (hrs)	3	1.5	5	1.5	4
Protein binding (%)	92 - 95	90	93	83	98 - 99
Active metabolites	No	Yes	No	No	No
Metabolism	CYP1A2, CYP3A4	CYP2D6	CYP1A2, CYP2D6	CYP3A4	CYP3A4
Elimination half-life (hrs)	10 - 100	6 - 24	20 - 70	4 - 10	3 - 10[1]

MD Jibson. J Psychiatric Research 32 (1998) 215-228

Antipsychotic Agents Side Effect Profiles

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

	Conventional antipsychotics	Atypical Antipsychotics			
		Clozapine	Risperidone	Olanzapine	Quetiapine
EPS	+/+++	0	0/+	0/+	0
TD	+/+++	0/+	0/+	0/+	0/+
Seizures	0/+	+++	0	0	0
Sedation	+/+++	+++	+	++	++
Anticholinergic effects	+/+++	+++	0	0/+	0

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

Antipsychotic Agents
Side Effect Profiles *(cont'd)*

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

Atypical Antipsychotics

	Conventional antipsychotics	Clozapine	Risperidone	Olanzapine	Quetiapine
Hypotension	+/+++	+++	0/+	0/+	++
Liver transaminase increase	+	+	0	+	+
Antihistaminic effects	+/+++	+++	0	+	++
Prolactin increase	+/++	0	++	+	0
Weight gain	+	+++	+	++	+

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

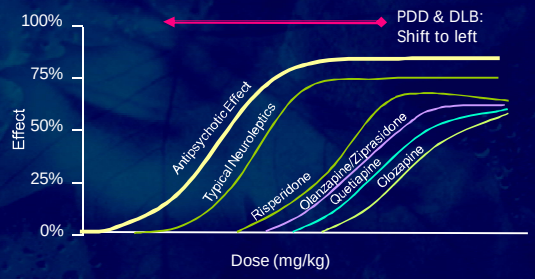
Atypical Medication	Usual dose and formulation	Usual frequency	Maximum dose / 24 hours
Risperidone	0.25-1 mg, PO Tabs or Liquid / M-tab	Q2-4 hours as needed and tolerated	2 mg for many dementia patients Not DLB / PD May be higher in other conditions e.g. schizophrenia, bipolar disorder etc.
Olanzapine	2.5-5 mg PO Tabs /Zydis 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.	Q2-4 hours as needed and tolerated	10 mg for dementia patients May be higher in other conditions e.g. schizophrenia, bipolar disorder etc.
Quetiapine	12.5 – 25 mg BID		75.0 mg BID (150.0 mg tab split = 2 X 75.0 mg)

Guidelines for Maintenance Therapy of Psychosis in Late-Life with Atypical Antipsychotics

Atypical Antipsychotic	Starting Dose (mg/day)	Usual Daily Dose (mg/day)	Maximum Dose
Risperidone	0.25 mg In very old, frail or LBD or PD patients Usual starting dose is 0.5 mg May be increased Q3 -5 days by 0.25 mg – 0.5 mg as tolerated	1 mg/day for most dementias - not for LBD/PDD May be given as single dose or divided dose, as tolerated	2.0 mg/day for most dementias - not for DLB/PDD Doses may be higher (e.g. schizophrenia) or lower (e.g. LBD, PD) Official indication for BPSD in Canada
Olanzapine	1.25 -2.5 mg In very old, frail or LBD or PD patients Usual starting dose is 2.5 – 5 mg May be increased Q3-5 days by 1.25-2.5 mg as tolerated	5-10 mg/day for most dementias – not for LBD/PDD May be given as single dose or divided doses as tolerated	10 mg/day for most dementias – not DLB/PDD Doses may be higher (e.g. schizophrenia) or lower (e.g. LBD or PDD)
Quetiapine	6.25 – 12.5 mg In very old, frail or LBD or PD patients Usual starting dose is 12.5 – 25 mg May be increased Q3-5 days by 25-50 mg as tolerated	100 mg/day for most dementias – may be lower for LBD/PDD Wide range of dosing May be given as single dose or divided doses as tolerated	150 mg/day – some dementia patients need higher doses Wide range of dosing Consider first with LBD or PDD patients Doses may be higher (e.g. for schizophrenia) or lower (e.g. LBD or PDD)

Antipsychotic & EPS: DLB & PDD

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



MD Jibson. J Psychiatric Research 32 (1998) 215-228;
Lewy body dementia: the litmus test for neuroleptic sensitivity and extrapyramidal symptoms.J Clin Psychiatry. 2004;65 Suppl 11:16-22 .Baskys A.

2004 Alexopoulos Guidelines

Recommended Treatments

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

2004 Alexopoulos Guidelines

Recommended Treatments

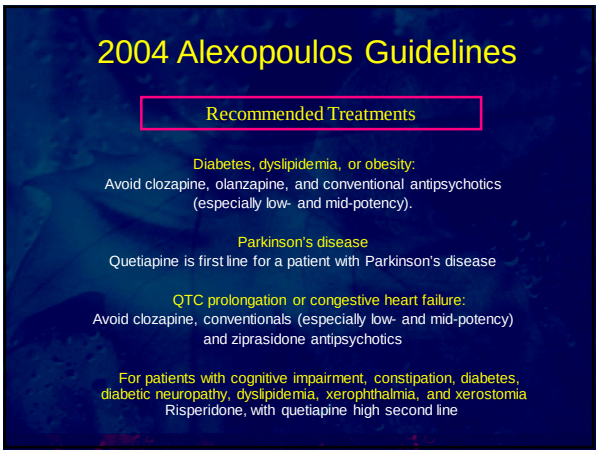
For Mild Geriatric Non-psychotic Mania
Mood stabilizer alone; D/C Antidepressant

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


2004 Alexopoulos Guidelines
Recommended Treatments
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