

Pharmacological Treatment of Aggression in Dementia

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Pharmacological Treatment of Aggression in Dementia



- Self-assessment questions
- Definitions and biological correlates
- Prevalence of aggression & its concomitants
- Typical antipsychotics
- Atypical antipsychotics
- Antidepressants
- Anticonvulsants
- Cholinesterase inhibitors
- Other medications

Self-assessment Question 1:

The most frequent behavioral concomitant of psychosis in Alzheimer's Disease is

- A. Suicide
- B. Wandering
- C. Shadowing
- D. Aggression and agitation
- E. Disrobing



Self-assessment Question 2

Behavior which places patients at risk for being assaulted includes all of the following except

- A. Wandering
- B. Verbally abusive
- C. Self-destructive
- D. Physically abusive
- E. Socially disruptive
- F. Resisting care



Self-assessment Question 3

Randomized Clinical Trials of Cholinesterase Inhibitors in the Treatment of Dementia Demonstrate



- A. Robust improvement of assaultive and agitated behavior
- B. Prevention of cognitive decline for 5 years
- C. Improved cognition over pre-treatment
- D. Full remission of psychotic symptoms
- E. All of the above
- F. None of the above

Self-assessment Question 4

The Medication Class with the Most Expert Consensus and RCT Evidence of Benefit in Treatment of Aggression or Agitation of Dementia is

- A. Antipsychotic
- B. Anticonvulsant
- C. Antidepressant
- D. Stimulant
- E. Beta-blocker
- B. Cholinesterase inhibitor

Self-assessment Question 5

RCTs have Demonstrated Efficacy
of the following Anticonvulsants in
the Treatment of Agitation or
Assaultive Behavior of Dementia

- A. Lamotrigine
- B. Gabapentin
- C. Topiramate
- D. A,B,C
- E. B only
- F. None of the above



Pharmacological Treatment of Aggression in Dementia



- Aggression, agitation, and Behavioral & Psychological Symptoms of Dementia are common (BPSD)
- Underlying medical causes of aggression in the demented patient need be ruled out.
- Behavioral approaches should be considered prior to pharmacotherapy whenever possible
- No pharmacotherapy has an indication by the FDA for treatment of aggression in dementia
- Data support several pharmacologic approaches

Prevalence of Aggressive Behavior in Dementia Ranges from



23.7% to 96%

Lyketsos et al. Am J Psychiatry 2000;157:708-714

Delusions in Alzheimer's Disease have been Associated with



- Anosognosia
- Depression
- Overt Aggression

- Mizrahi R. Am J. Geriatr Psychiatry 2006; 14:573-581

Aggressive behavior

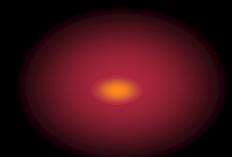


- Verbal or physical behavior intended to harm others.
- Not all aggressive behavior is dangerous or injurious.

Assaultive behavior



- Unwelcome physical contact



Disruptive behavior



- Verbal or motor activity which interferes with the functioning of the environment or interferes with the functioning of others.
- Disruptive behavior may not necessarily be assaultive or aggressive.

Agitation



- Motor or verbal activity that is purposeless, excessive, unresponsive to suggestion, and does not advance any goal that is in the person's interest.
- A manifestation of an underlying serious mental illness or cognitive impairment.
- Disruptive of some aspect of daily functioning
- Not necessarily assaultive, aggressive, or disruptive to others

Components of Agitation that can Escalate into Aggression



- Restlessness
- Pacing
- Repetition
- Cursing
- Verbal aggression
- Requests for attention

Behaviors in Dementia that can Lead to Aggressive Incidents



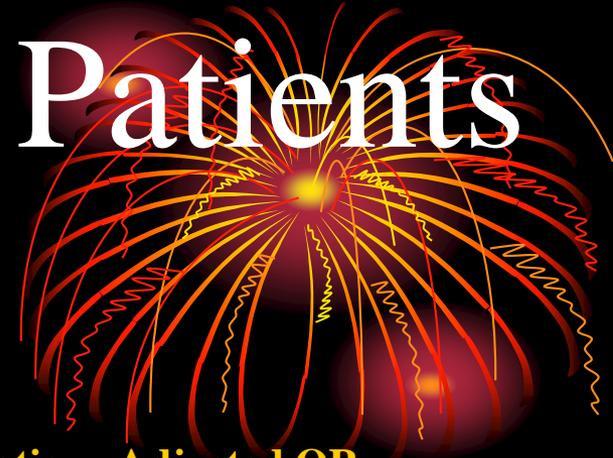
- Wandering
- Sundowning
- Shadowing
- Modeling
- Exit seeking
- Resistance to bathing-dressing
- Move to new surroundings

Resident-on-Resident Violent Incidents



- Cases N=250 (median age 81)
- Controls N=486 (median age 83)
 - 39 Fractures
 - 6 Dislocations
 - 105 bruises or hematomas
 - 113 lacerations

Characteristics of Patients at Risk of Injury



	Crude Odds Ratio	Adjusted OR (age, ADLs, cognition)
• Wandering	7.2	2.8
• Verbally abusive	5.7	1.9
• Physically abusive	5.0	1.1
• Socially disruptive	5.0	1.6
• Resists care	3.2	1.0

Biological Correlates of Aggression in Alzheimer's I



- 5HTTPR* Allele and L*/*L genotype (1)
- Choline acetyltransferase activity in midfrontal and superior frontal cortex (2)
- Left anterior temporal, bilateral dorsofrontal, right parietal cortex hypoperfusion (3)
- Medial temporal hypoperfusion (4)

1. Sukonick et al: Arch Neurol 2001; 58:1425-1428

2. Minger et al. Neurology 2000;55:1460-1467

3. Hirono et al: Arch Neur 2000;57:861-866

4. Lanctot et al.: Arch Neurol 2004;61:1731-1737.

Biological Correlates of Aggression in Alzheimer's II



- Aggressive behavior and antipsychotic medications (AP) associated with increase in number of Alpha 1-adrenoceptors (1-ADR)
- Correlation between Alpha 1-ADR density in frontal cortex and Alpha 1-ADR affinity and aggression in Alzheimer's Disease
- If AP medications excluded, correlation persists
- APs cause up-regulation of alpha 1-and alpha 2-ADR, compromising long term efficacy of APs

Psychopathological Correlates in Dementia



- Depression (1)
- Pain (2)
- Psychosis explains 22% of variance in aggression scores
- Disorientation--verbal aggression

1. Lyketsos,CG. Am J Psychiatry 1999; 156:66-71

2. Cohen-Mansfield et al. J Gerontol Psychol Sci 1998; 53B:P300-P330

Instruments to Assess Agitation and Assault in Dementia



- Social Dysfunction and Aggression Scale-9 (SDAS-9)
- Nurses Observation Scale for Inpatient Evaluation (NOSIE)
- Cohen-Mansfield Agitation Inventory (CMAI)
- Brief Psychiatric Rating Scale (BPRS)
- Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD)

Pharmacological Treatment of Aggressive Behavior in Dementia



- Treat acute medical conditions which can contribute to agitation or aggressive behavior
- Rule out adverse medication effects
- Add only one new agent at a time
- Increase doses in tiny increments
- Use lowest effective dose
- Consider drug-drug interactions
- Monitor for changes in: gait, respiration, depression, movements, level of arousal

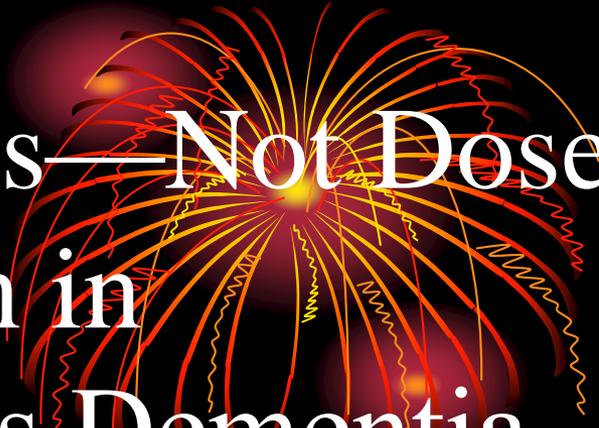
Typical Antipsychotics

- Meta-analysis of 12 trials of haloperidol, thioridazine, thiothixine, chlorpromazine, trifluoperazine: no clear benefit for Typical APs in treatment of neuropsychiatric symptoms of dementia. (1)
- Systematic review found haloperidol beneficial for dementia patients with aggression, but not for general agitation (2)

1. Sink, KM, JAMA 2005; 293:596-608

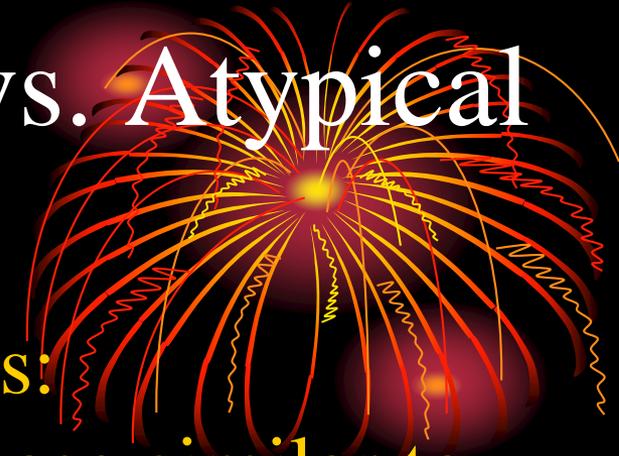
2. Lonergan,E, Cochrane Database Syst Rev 2002; CD002852.

Plasma Haloperidol Levels—Not Dose Correlated with Reduction in Aggression in Alzheimer's Dementia



- Plasma haloperidol levels 1.45 to 1.65 ng/ml correlated with 20% reduction in BPRS
- Oral haloperidol dose did not correlate with reduction in BPRS
- Psychosis, suspiciousness, aggression responded to haloperidol at therapeutic levels

Risk of Death: Typical vs. Atypical Antipsychotics



- Haloperidol vs. Placebo in 2 RCTs: Odds Ratio 1.7 (CI 0.7-3.9)--increase similar to average increase in risk of death for Atypical APs vs. placebo (1)
- Typical APs in 22,890 patients age >65 associated with significantly higher adjusted risk of death than Atypical APs at all intervals (retrospective study) (2)

1. Schneider LS et al. J Am Med Assoc. 2005 294:1934-1943.

2. Wang PS, et al. (2005). N Engl J Med. 2006_353:2335-2341

Atypical Antipsychotics



Advantages

Disadvantages

- Risperidone depot hypotension, DMII
- Olanzapine IM weight gain, DMII
- Quetiapine PD, LBD prolonged QTc
- Aripiprazole PD EPS
- Clozapine Resistant anticholinergic
- Ziprasidone IM prolonged QTc

PD = Parkinson's Dementia

LBD = Lewy Body Dementia

Atypical Antipsychotics: Review of 15 RCTs



- Modest efficacy in treating BPSD (1,2)
- Efficacy in treatment of agitation versus efficacy in treatment of psychosis difficult to discern.(2)
- Psychosis scores improved significantly only for risperidone (2)
- Neuropsychiatric symptoms improved with active treatment in pooled analysis of aripirazole and risperidone, not olanzapine (2)

Atypical Antipsychotics: CATIE-AD Trial Findings



- N=421 outpatients:dementia+agitation/aggression
- Rx: Olanzapine, quetiapine, risperidone, placebo
- Outcomes: 1) time to discontinuation for any reason
2) Clinical Global Improvement (CGI)
- Results: 1) Adverse effects offset efficacy of Atypical APs for treatment of psychosis, aggression, or agitation in Alzheimer's Disease
2) Atypical APs no better than PBO on
CGIC

FDA Warning (May 2004)

All atypical antipsychotics based on published and unpublished proprietary clinical trials data:

'Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg heart failure, sudden death) or infectious (eg pneumonia) in nature. These drugs are not approved for the treatment of patients with dementia related psychosis.'

Typical vs. Atypical Antipsychotics

- 4 RCTs compared Typical APs to Atypical APs in treatment of dementia
- No focus on Aggression (3 compared risperidone with haloperidol; 1 compared quetiapine with haloperidol)
- One of four RCT found significantly more efficacy with Atypical AP than Typical APs
- In all four RCTs, Atypical APs were less likely to cause EPS or TD.

Chan WC e al. Int J Geriatr Psychiatry. 2001; 16: 1156–1162.

Anticonvulsants Used for Rx of Agitation/aggression in Dementia

Results Inconclusive



Advantages

Disadvantages

- | | | |
|-----------------|-----------------|---------------------------------------|
| • Valproate | modest efficacy | 3-5 day onset |
| • Carbamazepine | tolerable | Enzyme induction |
| • Gabapentin | Rx: pain | No evidence of efficacy for agitation |
| • Lamotrigine | Rx: depression | No evidence of efficacy for agitation |
| • Topiramate | Rx: obesity | Weight loss |

Antidepressants

- Aggressive behavior associated with moderate to severe depression in N=541 patients with dementia (1)
- Citalopram 10 to 20 mg and perphenazine 6.5mg +/- 1.7 mg--both better than placebo (2)
- Trazodone about equal to haloperidol (3)
- Citalopram versus risperidone; 12 week RCT in non-depressed dementia patients with behavioral symptoms: no statistical difference in behavior noted between agents. (4)

1. Raskin et al. J Geriatr Psychiatry Neurol 2003 16 (1): 4-7

2. Pollock et al. Am J Psychiatry;159;460-465;

3. Sultzer et al. Am J Geriatr Psychiatry 1997; 5: 60-69;

4. Pollock et al. Am J Geriatr Psychiatry. 2007 Sep 10;

Acetylcholinesterase inhibitors/NMDA agents



- Donepezil N=120: 62% of demented subjects had 30% reduction in NPI (1)
- Galantamine No conclusive data
- Rivastigmine 2 year trial: reduced aggression (2)
- Memantine + Donepezil significantly lowered NPI total scores vs. placebo (3)

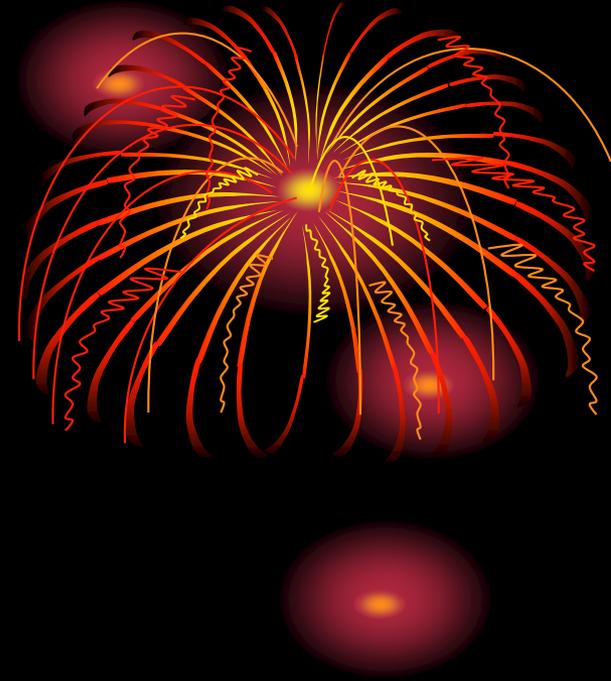
1) Cummings JL, et al. Am J Geriatr Psychiatry. 2006 Jul;14(7):605-12.

2) Rosler M, et al: Neuropsychiatry Neuropsycholo Behav Neurol 1998/1999; 11:211-216

3) Cummings JL 2006: Neurology. 2006 Jul 11;67(1):57-63.

Other agents

- Buspirone
- Trazodone
- Benzodiazepines
- Beta-blockers
- Lithium
- Anti-androgenic agents



Trazodone



- Two RCTs found no efficacy of Trazodone vs. placebo (1)
- No differences between Haloperidol mean dose of 1.8mg/d vs. Trazodone mean dose 200mg/d (2)
- No differences between Haloperidol dose of 1-5mg/day for 9 weeks vs. Trazodone 50-250mg/day.(2)

1: Martinon-Torres G. Cochrane Database Syst Rev. 2004 Oct 18;(4):CD004990

2. Teri L. Neurology. 2000 Nov 14; 55(9):1271-8.

3. Sultzer DL Am J Geriatr Psychiatry. 1997 Winter;5(1):60-9.

Anti-androgenics



- No RCTs of anti-androgenics in treatment of agitation of dementia patients could be found

Lithium

No RCTs of lithium in treatment of agitation of dementia could be found

Beta blockers

- Propranolol added to stable doses of antipsychotic in disruptive treatment-resistant behaviors in Alzheimer's patients
 - Mean dose 106 +/- 38 mg/day
 - Improvement was significant for agitation/aggression and anxiety on NPI (1)
 - Pindolol used for aggressive behavior (2)
1. Peskind ER et al. Alzheimer Dis Assoc Disord. 2005 Jan-Mar;19(1):23-8.
2: Herrmann N et al J Psychopharmacol. 2004 Jun;18(2):215-20.

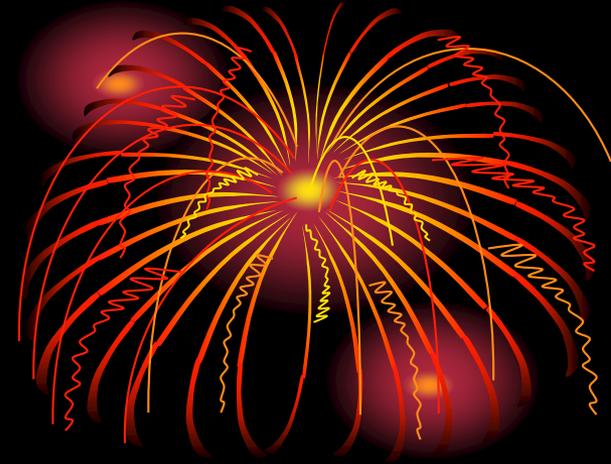
Benzodiazepines



- Anecdotal reports of short-term benefit for acute agitation of dementia
- Significant evidence for increased risk of gait disturbance and hip fractures in the elderly.
- No significant differences were observed between patients using haloperidol or alprazolam in terms of disruptive behavioral episodes per week.(1)

1) Christensen DB. J Am Geriatr Soc. 1998 May;46(5):620-5.

Buspirone



- Anecdotal case reports of benefit
- No randomized clinical trials could be found

Summary: Pharmacological Treatment of Aggressive Behavior in Dementia



- Identify risk of assault—or risk of provocation of assault—and treat proactively
- Identify treatable medical conditions
- Choose least harmful interventions
- Share risk-benefit ratio with surrogates and/or family
- Consider side effects and medication interactions before beginning treatment
- Adhere to principles of psychopharmacologic treatment in elderly

Answers to Self-Assessment Questions



1. A
2. C
3. F
4. A
5. F