Pharmacological Treatment of Aggression in Dementia

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Pharmacological Treatment of Aggression in Dementia

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

Self-assessment Question 1:

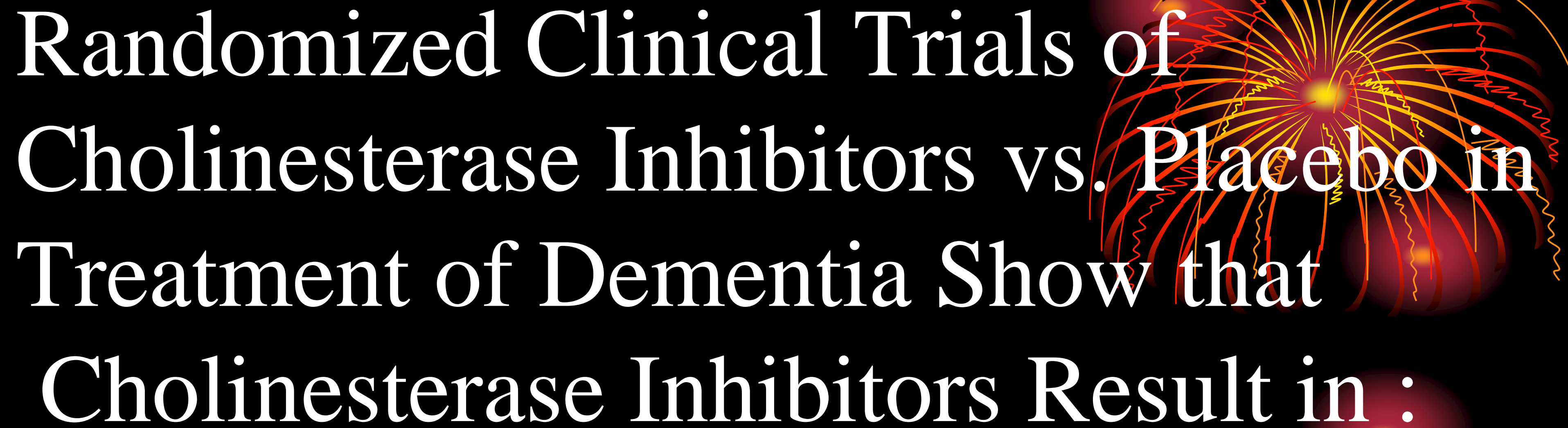
The most significant behavioral correlation with delusions in Alzheimer's Disease is

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

Self-assessment Question 2

Behavior found to increase risk of being injured by another patient in a nursing home includes all except:

A. Wandering
B. Verbal abusive
C. Self-destructive
D. Socially inappropriate
E. None of the above



Self-assessment Question 3

Randomized Clinical Trials of Cholinesterase Inhibitors vs. Placebo in Treatment of Dementia Show that Cholinesterase Inhibitors Result in :

A. Full remission of assaultive /agitated behavior

B. Prevention of cognitive decline for 5 years

C. Improved cognition over pre-treatment

D. Improvement of psychotic symptoms

E. All of the above

F. None of the above

Self-assessment Question 4

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

A. Antipsychotics

B. Anticonvulsants

C. Buspirone

D. Stimulants

E. Beta-blockers

Self-assessment Question 5

RCTs have Proven Efficacy of these Anticonvulsants for Agitation/Assaultive Behavior of Dementia

A. Lamotrigine

B. Gabapentin

C. Topiramate

D. A,B,C

E. B only

F. None of above

Aggressive behavior

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

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

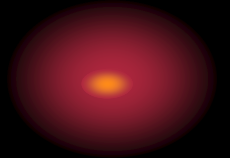
- Motor or verbal activity that is purposeless, excessive, unresponsive to suggestion, and does not advance any goal that is in the person's interest.
- A manifestation of an underlying serious mental illness or cognitive impairment.
- Disruptive of some aspect of daily functioning
- Not necessarily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



Assessment Instruments

- Neuropsychiatric Inventory (NPI) (12 items/total score 144)
- Neuropsychiatric Inventory Caregiver Distress Scale(total 46)
- Behavioral Rating Scale for Geriatric Patients (BGP)
- 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)

Neuropsychiatric Inventory (NPI)

- Delusions
- Hallucinations
- Agitation/Aggression
- Dysphoria/Depression
- Anxiety
- Euphoria/Elation
- Apathy/indifference
- Disinhibition
- Irritability/lability
- Aberrant motor
- Nighttime disturbances
- Appetite and eating abnormalities

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

Prevalence of Behavioral Symptoms -Aggression, agitation, anxiety, irritability, aberrant motor behavior

- >80 % of patients with dementia demonstrate agitation sometime during course of illness
- 60%-98% of patient over course of AD have at least one behavioral symptom
- 50% have psychotic symptoms (30-40% have delusions; 15-30% have hallucinations)
- 30% of cost of caring for AD attributed to management of NP symptoms.

Delusions in Alzheimer's Disease have been Associated with

- Overt Aggression
- Anosognosia
- Depression

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

Resident-on-Resident Violent Incidents in Nursing Homes

- Injured patients N=250 (median age 81)

  39 Fractures

  6 Dislocations

  105 bruises or hematomas

  113 lacerations

- Non-injured patients N=486 (median age 83)

Shinoda-Tagawa et al: Resident to Resident violent Incidents in Nursing Homes <u>JAMA</u> **2004; 291:591-598**

Assaulted Patients are More likely Behaviorally Disruptive

	Injured	Non-injured
• Wandering	42%	15%
• Verbally abusive	28%	9%
• Socially disruptive	30%	13%

Being physically abusive and resisting care were NOT significant.

Shinoda-Tagawa et al.Resident-toResident Violent Incidents in Nursing Homes
JAMA 2004; 291:591-598

Characteristics of Nursing Home Patients at Risk of Injury

	Crude Odds Ratio	Adjusted OR (age, ADLs,cognition)
• Wandering	7.2	2.8
• Verbally abusive	5.7	1.9
• Socially disruptive	5.0	1.6

Shinoda-Tagawa et al. JAMA 2004; 291:591-598

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 AD

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

Sharp SI ,et al. Aggressive behavior and Neuroleptic Medication Associated with Increased number of Alpha 1-adrenocepters,**Am J Geriatric Psychiatry 15:5, May 2007. 435-437**

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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

Principles of Pharmacological Treatment of Aggression in Dementia

- Rule out and address underlying medical causes of aggression or agitation
- Behavioral approaches should be considered prior to pharmacotherapy when possible
- Consider the risk-benefit ratio of each medication
- No pharmacotherapy has an indication by the FDA for treatment of aggression in dementia

Interventions for Aggressive Behavior of Dementia

- Typical antipsychotics: short-term efficacy
- Atypical Antipsychotics: evidence for efficacy
- Anticonvulsants: no conclusive evidence
- Cholinesterase inhibitors: possibly preventive
- Memantine: preliminary evidence for efficacy
- Buspirone: no conclusive evidence for efficacy
- Trazodone: no conclusive evidence for efficacy
- Benzodiazepines: no efficacy
- Beta-blockers: no efficacy

Algorithm for Treatment of Assaultive Behavior in Dementia

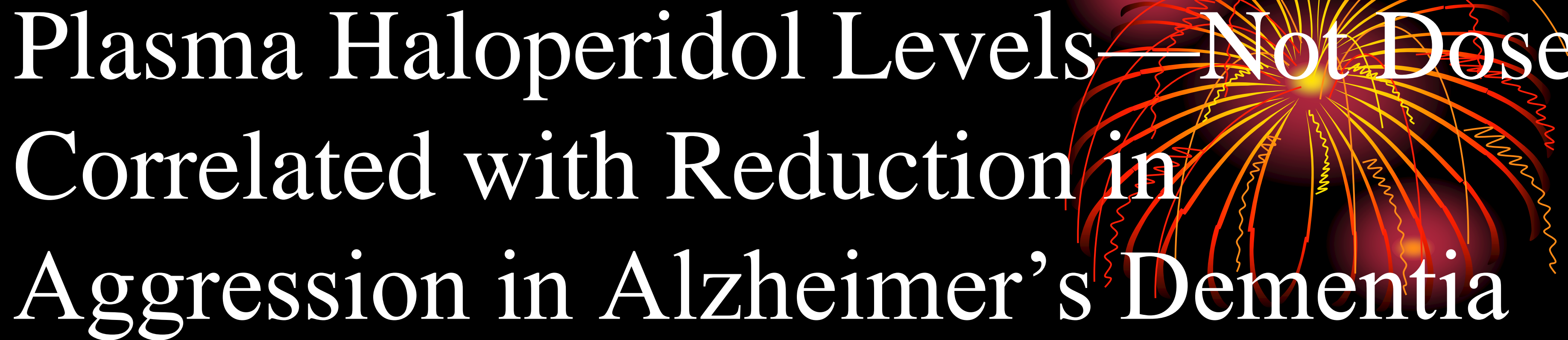
- Dementia + Behavioral Problems-> Need to Intervene
- Manage delirium, pain, acute medical problems
- Evaluate and define behavior and symptoms
- Begin with nonpharmacological interventions
- If no improvement, consider depression/anxiety dx
- Rx AcetylCholinesterase inhibitor
- Rx Memantine
- Trial of Atypical AP
- Trial of SSRI
- Referral to specialist

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

Pelton et al. Am J Geriatr Psychiatry 2003;11:186-193

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 Atypicals 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

	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)

1. Aupperle P. Am J Alzehimers Dis Other Demen 2006; 21:101-108
2. Schneider LS. Am J Geriatr Pychiatry 2006; 14:191-210

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

Schneider LS. N Engl J Med 2006;355:1525-38

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. <u>These drugs are not approved for the treatment of patients with dementia related psychosis.'</u>

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 signficantly 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 for Agitation/aggression in Dementia: Results Inconclusive

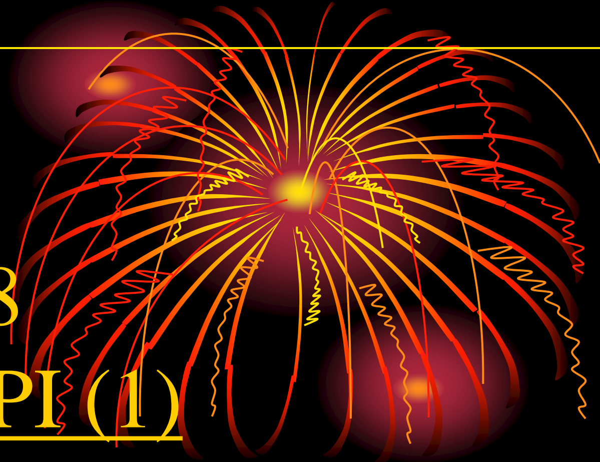
	Indications	Efficacy for Aggression
• Valproate	labile mood	Minimal; 3-5 day onset
• Carbamazepine	labile mood	Minimal
• Gabapentin	pain	None
• Lamotrigine	bipolar depression	None
• Topiramate	Seizures, Weight loss	None

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;

Cholinesterase inhibitors



Donepezil vs. Placebo X 12 weeks

N=272 patients with AD and MMSE 8

Results: no benefit in agitation nor NPI (1)

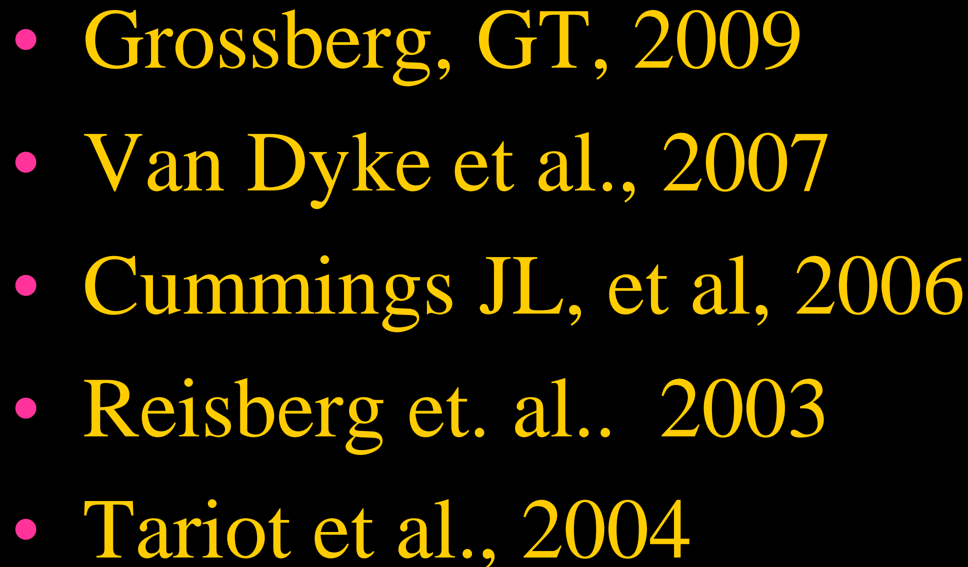
Galantamine v. Placebo X 5 months

Results: 2 point difference NPI; no statistical signif (2)

Rivastigmine: Parkinson's and Lewy Body: no improvement (3, 4)

1) Howard RJ, et al. Donepezil for treatment of agitation in Alzheimer's Disease N Engl J Med 2007; 357:1382-1392
2) Tariot PN, Solomon PR, Morris JC, et al. A 5-month randomized, placebo-controlled trial of galantamin in AD. Neurology 2000; 54:2269-2276.
3) Emre M, Aarsland D, Albanese A, et al. Rivastigmine for dementia associated with Parkinson's disease N Engl J Med 2004; 351:2509-2518
4) McKeith I, Del Ser T, Spano Pa et al. Efficacy of rivastigmine in dementia with Lewy bodies: Lancet. 2000; 356:203102036

RCTs of Memantine for Aggression/agitation in Community-Dwelling with Moderate-to-Severe AD



- Grossberg, GT, 2009
- Van Dyke et al., 2007
- Cummings JL, et al, 2006
- Reisberg et. al.. 2003
- Tariot et al., 2004

RCT of Memantine + Donepezil

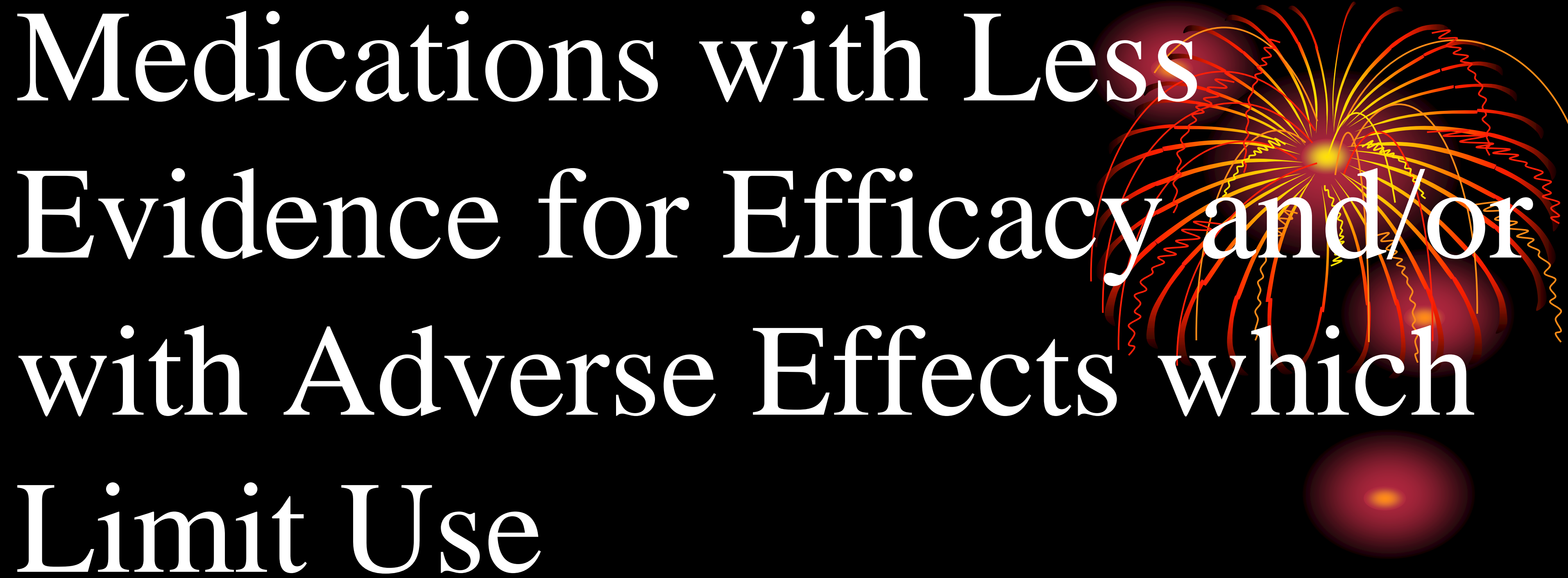
- Design: double blind, placebo controlled, Rx: Memantine 20mg/day + stable doses of donepezil vs. placebo X 24 weeks
- Subjects: Moderate- to Severe AD
- Outcome: MEMANTINE arm had significantly lower NPI scores than patients treated with PLACEBO at weeks 12 and 24.
- MEMANTINE arm: Reduction of agitation/aggression, irritability, appetite/eating disturbances.
- Conclusions: MEMANTINE reduced agitation/aggression in patients who were agitated at baseline and delayed its emergence in those free of agitation at baseline

Cummings JL, Schneider E, Tariot PN, et al. Behavioral effects of memantine in Alzheimer disease patients receiving donepezil treatment Neurology 2006;67:57-63

Pooled Analysis: 3 trials of Memantine-Agitation/Aggression/Psychosis

- Subjects: Moderate to Severe Alzheimer's disease
- Outcome: NPI sub-item cluster of agitation and psychosis
- Duration: 12, 24, 28 weeks
- Results: significant treatment advantage for memantine over placebo
- Tolerability: good
- Memantine believed to improve glutamatergic neurotransmission, reduce damaging effects of excessive glutamate stimulation.

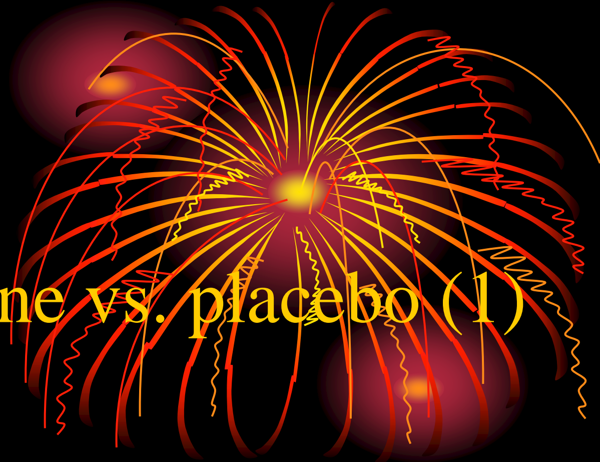
- Wilcock GK, Ballard CG, Cooper JA, Loft, Memantine for agitation/aggression and psychosis in moderately servere to severe Alzheimer's Disease: A pooled analysis. J. Clin Psychiatry 2008; 69: 341-348



Medications with Less Evidence for Efficacy and/or with Adverse Effects which Limit Use

- Buspirone
- Trazodone
- Benzodiazepines
- Beta-blockers

Trazodone



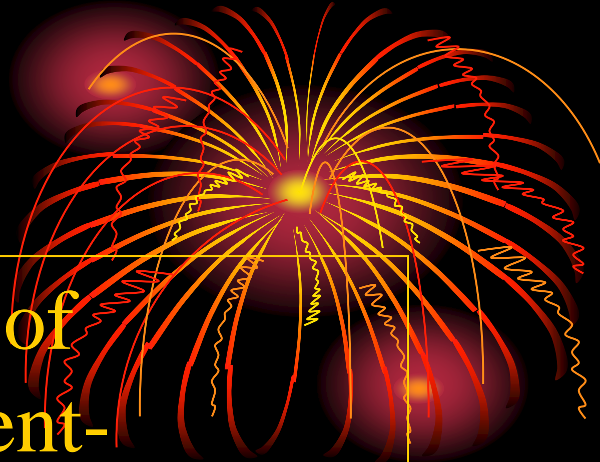
- Two RCTs found no efficacy of Trazodone vs. placebo (1)
- No differences between Haloperidol mean dose of 1.8mg/d v Trazodone mean dose 200mg/d (2)
- No differences between Haloperidol dose of 1-5mg/day for 9 weeks vs. Trazodone 50-250mg/day.(2)

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.

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

- 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 found

Summary: Principles of Pharmacological Treatment of Aggressive Behavior in Dementia

- Identify risk of assault—or risk of provocation of assault—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

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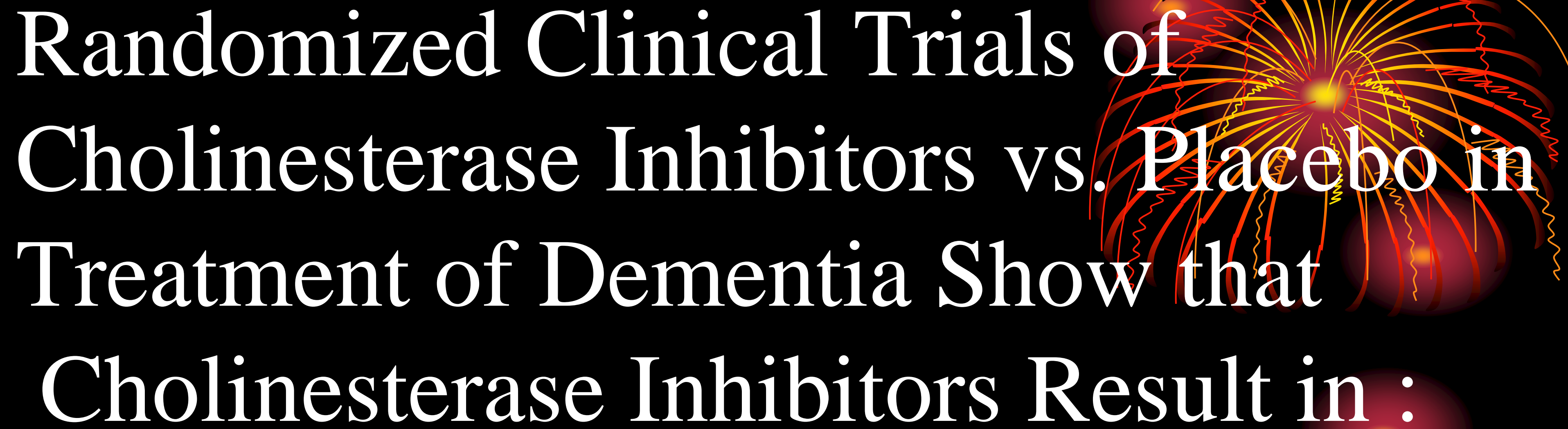

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D. A,B,C

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Answers to Self-Assessment Questions

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