

MAD, SAD, SCARED, AND IMPAIRED:

The Recognition and Treatment of Neuropsychiatric Symptoms in Geriatric Psychiatry

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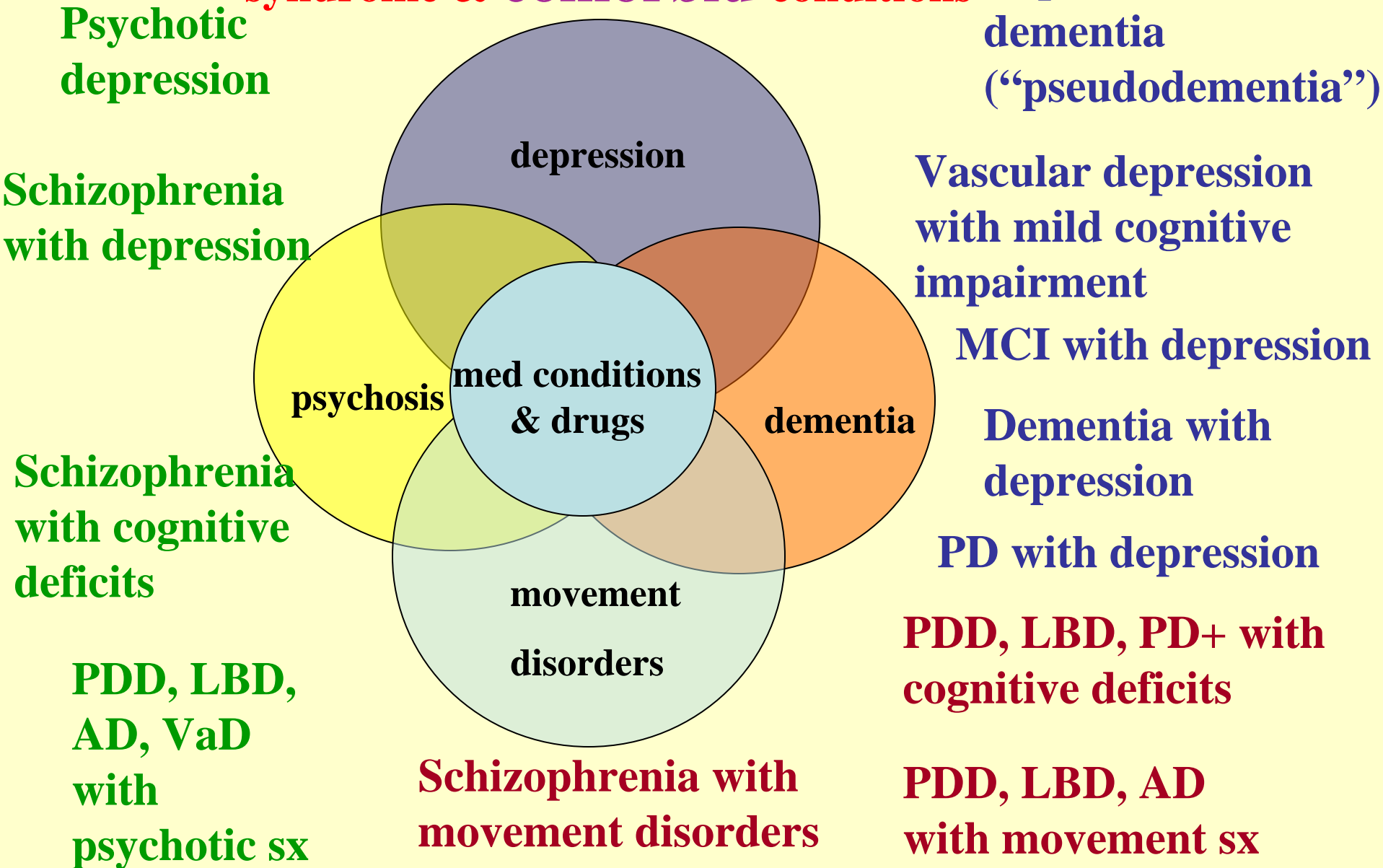
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OVERVIEW: Consider main

syndrome & comorbid conditions



THE BASICS

“MA⁶” Mnemonic for Dementia

Memory impairment; and one of the following four items:

Apraxia

Aphasia

Agnosia

Abstraction and other executive functioning
plus

Absence of clouding of consciousness

Ability to function is impaired

Causes of dementia:

AD>>VaD=LBD=Mixed>FTD>other

Diagnostic Criteria of Mild Cognitive Impairment vs Alzheimer's Disease

Mild Cognitive Impairment

Memory impairment
(subjective, objective
[1.5 × standard deviation,
corroborated])

General cognitive function
intact

Activities of daily life intact

Alzheimer's Disease

Memory impairment

Aphasia, agnosia, apraxia,
and/or impaired executive
function present

Activities of daily life
impaired

Insidious onset, gradual
progression

Other potential causes
ruled out

**Prevalence: about 10% of those in aged 70-79
to nearly 20% aged 80-89**

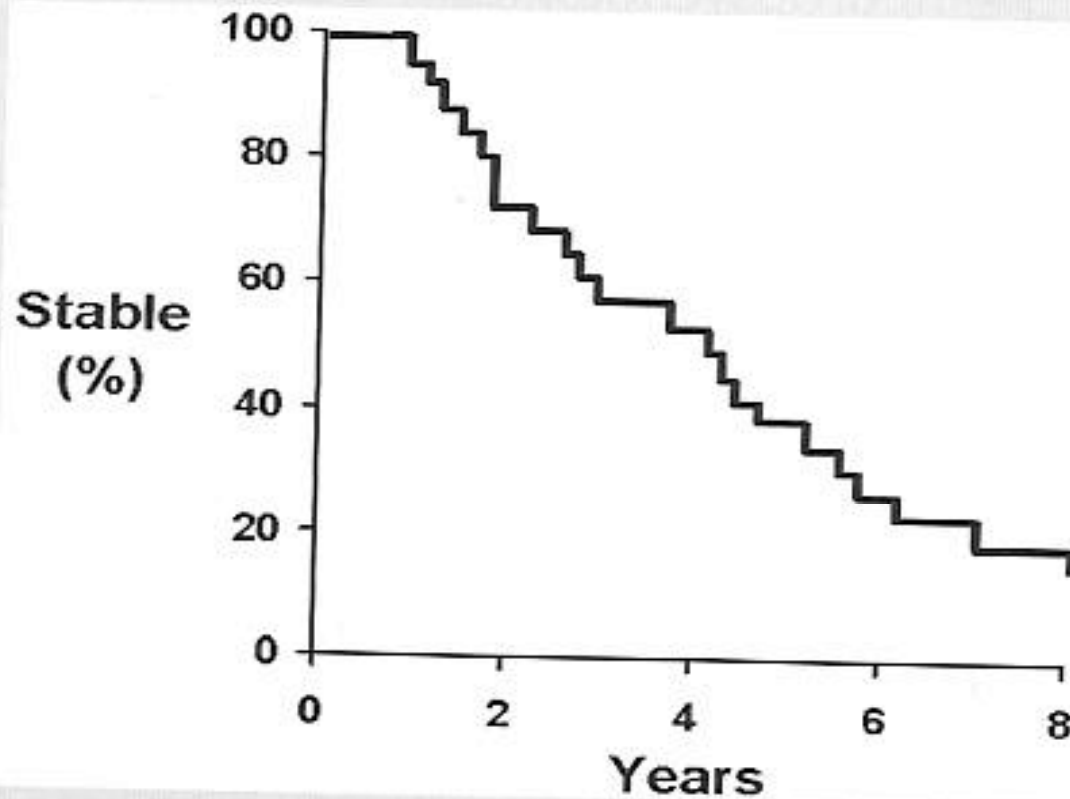
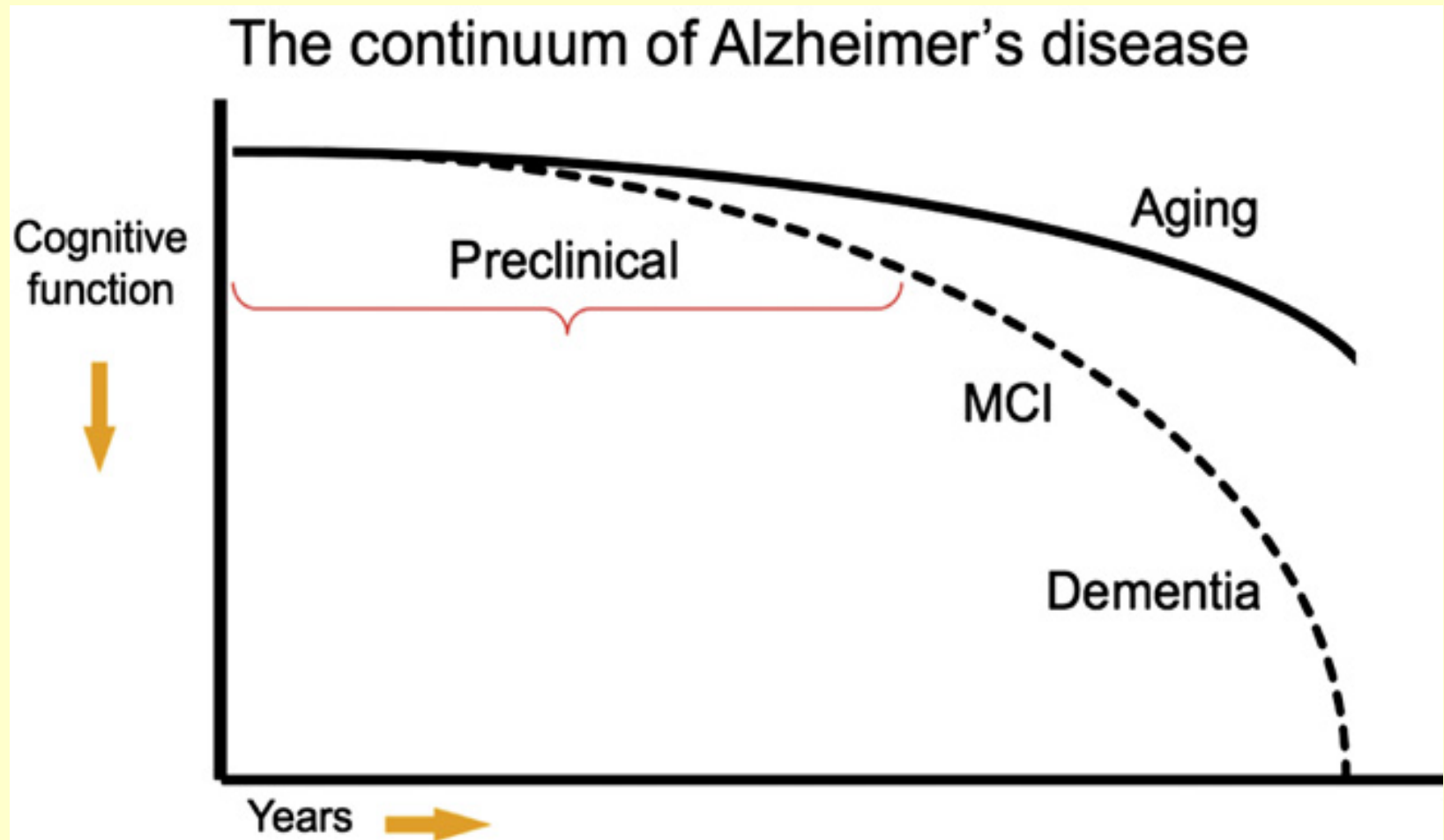


FIGURE 1-7

Survival curve of subjects with mild cognitive impairment after 8 years of follow-up.

About 5 to 16% conversion per year

Model of the clinical trajectory of Alzheimer's disease (AD)



["I'm fine; I'm just waiting for my disease"]

The new and growing class of presymptomatic patients. Kwon & Steiner, 2011]

Graphic representation of the proposed staging framework for preclinical AD

Stage 1

Asymptomatic amyloidosis

- High PET amyloid tracer retention
- Low CSF $A\beta_{1-42}$

Stage 2

Amyloidosis + Neurodegeneration

- Neuronal dysfunction on FDG-PET/fMRI
- High CSF tau/p-tau
- Cortical thinning/Hippocampal atrophy on sMRI

Stage 3

Amyloidosis + Neurodegeneration + Subtle Cognitive Decline

- Evidence of subtle change from baseline level of cognition
- Poor performance on more challenging cognitive tests
- Does not yet meet criteria for MCI

MCI → AD dementia

Causes of Dementia (and most defining features)

Alzheimer's disease 60-70% (insidious onset; memory deficits early; consistency in loss of various cognitive functions)

Vascular 10-30% (sudden onset, stepwise; less consistency ("patchy") in cognitive deficits)

Mixed (AD + Vascular) 10%

Lewy Body 10-25% (central feature: dementia & Need 2 of 3 core sx: ***parkinson sx; fluctuating cognition with variations in attention and alertness; visual hallucinations***) also milder cognitive deficits; falls; visuospatial deficits; neuroleptic sensitivity; REM sleep behavior

Depression 5-15%

6. Frontotemporal 5-10% : executive or language (semantic/primary progressive aphasia) prominent early; memory less impaired early in disorder.

Three types of cellular inclusions:

- a. *Tar-DNA binding protein of 43kDa (TDP-43) --most common*
- b. *Tau*
- c. *Fused in sarcoma (FUS) protein*

Both Tau and TDP are associated with diverse pathologic subtypes including CBD, Pick's, PNP ALS, PD types and semantic dementia

7. Other 10-20% e.g. Parkinson's disease
(movement disorder early--1-yr before dementia)

Causes of Dementia by Neuropathology

- Neurodegenerative syndromes

E.g. AD, FTD, LBD, PD

- Vascular syndromes

E.g. infarcts, vasculitis, Binswanger

- Nondegenerative, non-vascular

E.g., TBI, infections, substance induced, metabolic syndromes

Table 2. Behavioral domains
assessed by the NPI (Cummings
et al., 2006b)
NPI ITEM

- 1. Delusions**
- 2. Hallucinations**
- 3. Agitation/aggression**
- 4. Depression/dysphoria**
- 5. Anxiety**
- 6. Euphoria/elation**
- 7. Apathy/indifference**
- 8. Disinhibition**
- 9. Irritability/lability**
- 10. Aberrant motor behavior**
- 11. Night-time behavior**
- 12. Appetite/eating changes**

NPI = Neuropsychiatric Inventory

Neuropsychiatric Symptoms and Cognitive Disorders

- 75% (62% clinically significant) of dementia patients exhibited neuropsychiatric symptoms in past month
- 43% (29% clinically significant) of MCI patients exhibited neuropsychiatric symptoms in the past month

Prevalence of Neuropsychiatric Symptoms(i.e., Psychiatric and Behavioral Problems) in AD

Physical Aggression: 42%

Verbal Aggression/threats: 54%

Restlessness:38%

Wandering: 29%

Sleep disturbances:38%

Apathy/Withdrawal: 27%

Hallucinations:24%

Delusions:50%

Paranoia/suspiciousness:30%

Emotional lability: 8%

Mood disturbances(depression,tearfulness):29%

About half

Cause of caregiver distress

Psychoses:
about half

About one-quarter

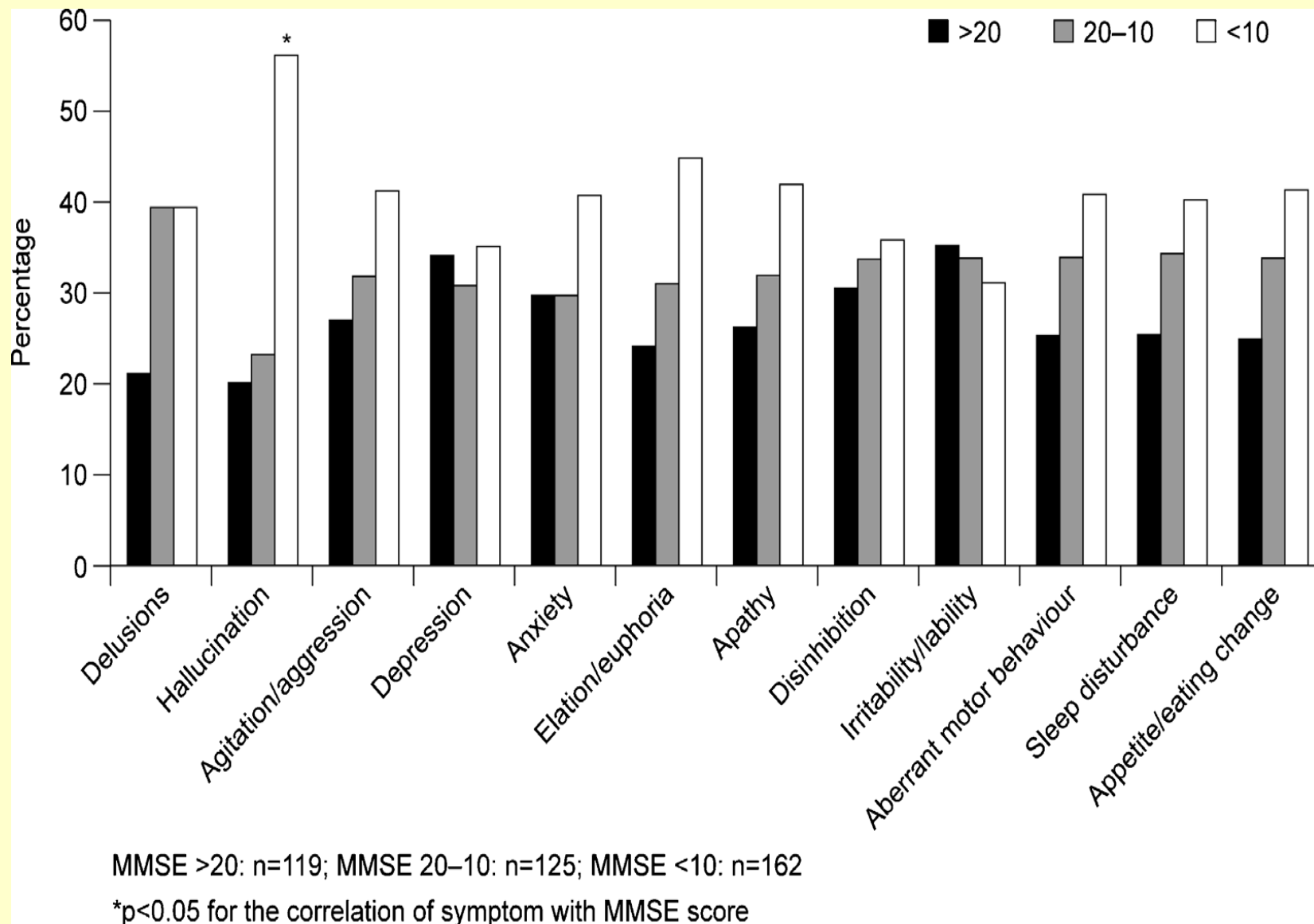
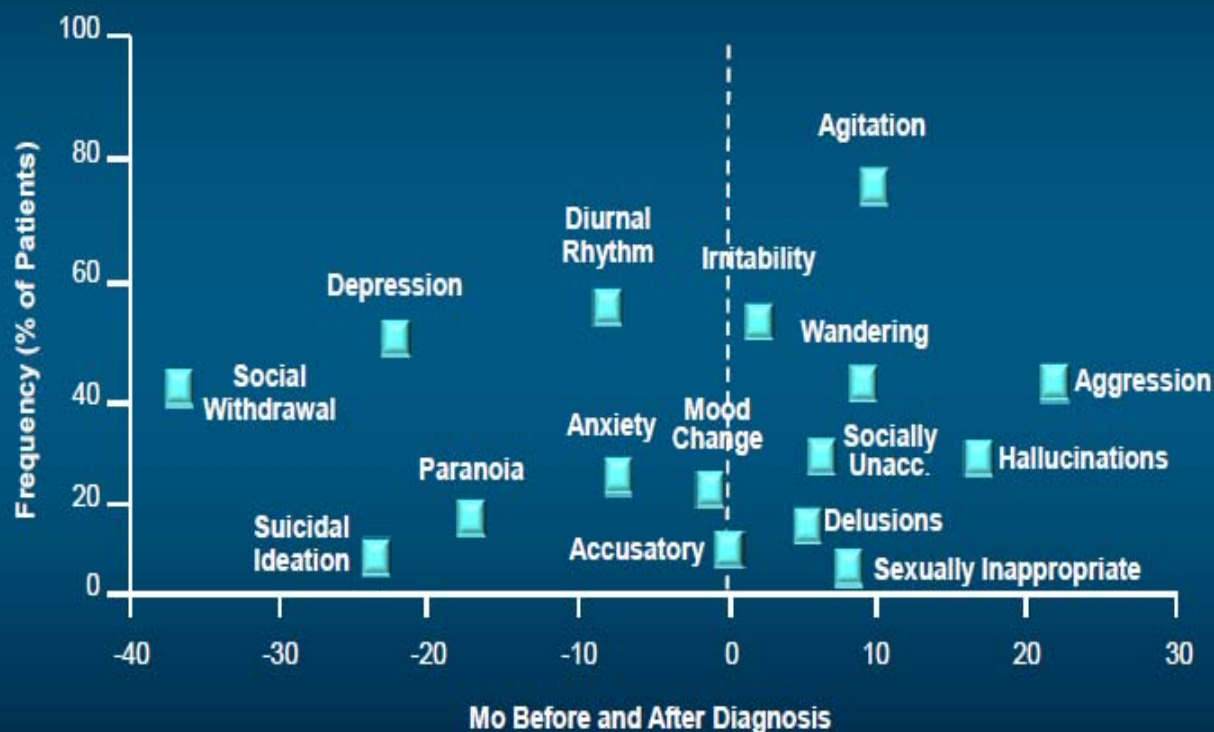


Figure 2. NPI symptoms in AD, by MMSE groupings (mild, moderate, severe) (Craig *et al.*, 2005).

Peak Frequency of Behavioral Symptoms as AD Progresses



Depression vs Dementia

- ***Persons with depression:***
- ***Symptoms of shorter onset (weeks or months vs years); progress more rapidly***
- ***Family more aware of disabilities***
- ***Patient is more distressed by disability,***
- ***Says “I don’t know” to questions, and are more irritable and do not want to answer the question***
- ***Often history of depression;***
- ***No problems with agnosia or apraxia.***

Neuropsychiatric Symptoms of MCI

(Lyketsos et al, 2002; Geda et al, 2008)

Depression: 20% to 27% (1/4)

Apathy: 15 to 19% (1/6)

Irritability: 15 to 19% (1/6)

Psychosis: 5% (1/20)

Hallucinations in PD, DLB, PDD

- $\frac{1}{4}$ Parkinson's Disease
- $\frac{1}{2}$ Dementia Lewy Body
- $\frac{3}{4}$ Parkinson's Disease Dementia

- In PD and PDD medications may contribute to psychotic sx

Depression and Parkinson's Disease

- In Parkinson's disease about 40-50% have depression; about 1/3 have anxiety disorder
- Depression precedes motor dysfunction in 12 to 37% of PD patients

Distinguishing AD, LBD, & PDD

Obtain good history:

- **AD=dementia first and parkinsonian sx later, most typically rigidity and bradykinesia. No response to L-dopa.**
- **PDD=movement disorder first and then cognitive deficits (at least 1 year separation). Classic PD sx: tremors, bradykinesia, rigidity; responds to L-dopa.**
- **LBD= movement disorder & cognitive deficits within 1 year. Rarely responds to L-dopa. Tremor less common than rigidity/bradykinesia.**

Five “Ds” of Psychiatric Care in Older Adults

Think of these possibilities and consider course:

- Delirium: **days to weeks**
- Drugs: **days to months**
- Disease: **days to months**
- Depression: **weeks to months**
- Dementia: **months to years**

CASE 1

A daughter reports that her mother, an 82-year-old woman with 4 year history of AD whose psychotic symptoms and agitation have been well-controlled on 50mg of quetiapine (Seroquel) at bedtime, has become suddenly more agitated and more psychotic. What should you do?

- 1. Increase quetiapine to 75mg daily.**
- 2. D/C quetiapine and try risperidone.**
- 3. Stop all medications.**
- 4. None of the above**

Delirium and Dementia

- Delirium in a patient with pre-existing dementia is a common problem that may have life-threatening complications.
- Delirium occurs 4-5 times more often in persons with dementia.

Delirium episode as a sign of undetected dementia
among community dwelling elderly subjects:
a 2 year follow up study

Terhi Rahkonen, Riitta Luukkainen-Markkula, Satu Paanila, Juhani Sivenius,
Raimo Sulkava

J Neurol Neurosurg Psychiatry 2000;69:519–521

- **Dementia was diagnosed immediately after delirium symptoms had subsided in 14 of 51 subjects (27%) and an additional 14 subjects were diagnosed as being demented during the 2 year follow up, 28 of 51 patients (55%) altogether.**
- **A delirium episode is often the first sign of dementia requiring attention from medical and social professionals.**

Delirium and Dementia (cont)

- **Acute changes in mental status in older adults with dementia are often attributed to the underlying dementia or “sundowning.”**
- **Delirium superimposed on dementia is less likely to be recognized and treated than is delirium without dementia.**
- **May be a sign of treatable medical problems or serious underlying illnesses such as a myocardial infarction, urinary tract infection, pneumonia, pain, or dehydration.**
- **Medications causing delirium include diphenhydramine, benzodiazepines, anti-depressants, and anti-psychotics.**

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1. Increase quetiapine to 75mg daily.
2. D/C quetiapine and try risperidone.
3. Stop all medications.
4. None of the above

CASE 2

A 68-year-old man presents with major depression and cognitive deficits. The depression responds to escitalopram (Lexapro), although he continues to show some mild cognitive impairment. What should you do?

1. Continue escitalopram.
2. Continue escitalopram and add donepezil(Aricept).
3. Discontinue escitalopram.
4. None of the above

•**Pseudodementia**—“depression with reversible dementia” syndrome: dementia develops during depressive episode but subsides after remission of depression.

•Mild cognitive impairment in depression ranges from 25% to 50%, and cognitive impairment often persists 1 year after depression clears.

Even if depression and cognitive problems clear, they may be prodromal for eventual irreversible dementia (40% on 3-year follow-up).

Maintenance Treatment of Depression in Old Age: A Randomized, Double-blind, Placebo-Controlled Evaluation of the Efficacy and Safety of Donepezil Combined with Antidepressant Pharmacotherapy

Reynolds CF et al Arch Gen Psychiatry. 2011 January ; 68(1): 51–60.

- In post-hoc analyses, 57 participants formerly depressed persons with Mild Cognitive Impairment, 3 of 30 on donepezil (10%) and 9 of 27 (33%) on placebo converted to dementia (primarily Alzheimer's) over 2 years (Fishers exact $p = 0.05$). However, the MCI subgroup also had a 44% recurrence of depression rate on donepezil versus 12% on placebo (LR = 4.91, $p = .03$).
- The cognitively normal subgroup ($n = 73$) showed no cognitive benefit or change in depression recurrence on donepezil.
- **The use of donepezil as augmentation treatment of late-life depression depends upon a careful weighing of risks and benefits in those with MCI, while no apparent benefit accrues in those with normal cognition**

CASE 2

A 68-year-old man presents with major depression and cognitive deficits. The depression responds to escitalopram (Lexapro), although he continues to show some mild cognitive impairment. What should you do?

- 1. Continue escitalopram.**
- 2. Continue escitalopram and add donepezil(Aricept).**
- 3. Discontinue escitalopram.**
- 4. None of the above**

CASE 3

A 72-year-old man with a 6 month history of vascular dementia (MMSE = 22) reports feeling sad, losing interest in activities and friends, and some difficulty sleeping. His health is good and all laboratory tests are normal. What would you do next?

1. Begin sertraline 50 mg daily.
2. Consider some form of psychotherapy.
3. Begin mirtazapine 15mg at bedtime.
4. None of the above.

Antidepressants for treating depression in dementia(Cochrane, 2009)

Authors' conclusions

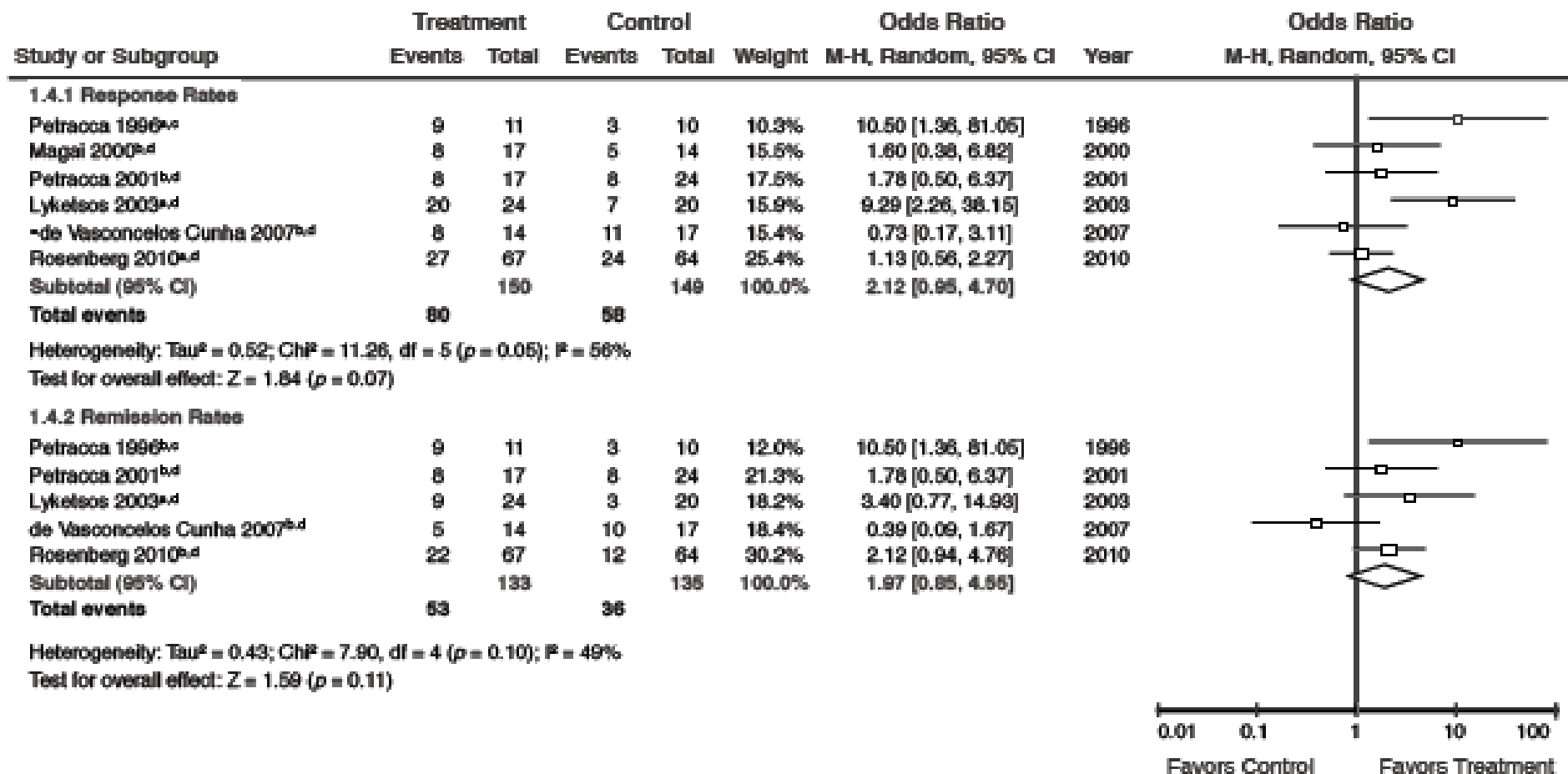
- **Available evidence offers weak support to the contention that antidepressants are effective for patients with depression and dementia.**
- However, only four studies are included in the meta-analysis relating to efficacy, and sample sizes are small. Moreover, only two included studies investigated the properties of the more commonly used SSRIs and no studies investigated the properties of newer classes of antidepressants (e.g. selective noradrenergic reuptake inhibitors). This review draws attention to the paucity of research.

Table 2. Primary Outcomes and Results of the Placebo-Controlled Studies of Patients with Dementia and Depression

| Study | Primary Outcome | Results |
|----------------------------------|--|--|
| Reifler et al. 1989 | Not defined | No significant difference between treatment groups in improvement on HDRS. |
| Petracca et al. 1996 | Not defined | Patients taking clomipramine had significantly lower HDRS scores than those on placebo ($P = .01$). Remission greater with drug than placebo ($P = .02$). |
| Magai et al. 2000 | Not defined | ANOVA showed no significant effect of treatment group on change in CSDD scores. Response rates did not differ significantly. |
| Petracca et al. 2001 | Not defined | ANOVA showed no effect of treatment group on change in HDRS. No significant difference in remission rates. |
| Lyketsos et al. 2003 | Global response as rated by 2 psychiatrists | Sertraline was significantly superior to placebo on the global ratings and on ANOVAs of change on HDRS and CSDD. |
| de Vasconcelos Cunha et al. 2007 | Repeated-measures ANOVA using the MADRS | No significant difference between treatment groups in the ANOVA of change on the MADRS or in the 50% improvement rates. |
| Rosenberg et al. 2010 | Logistic regression of Wk 12 mood domain ratings on the mADCS-CGIC | No significant differences on the mADCS-CGIC mood ratings at Week 12 according to treatment group. No difference in median CSDD scores during 12 wks or in remission rates according to treatment group. |

HDRS = Hamilton Depressive Rating Scale; CSDD = Cornell Scale for Depression in Dementia; ANOVA = analysis of variance; MADRS = Montgomery and Asberg Depression Rating Scale. mADCS-CGIC = modified Alzheimer's Disease Cooperative Study—Clinical Global Impression of Change.

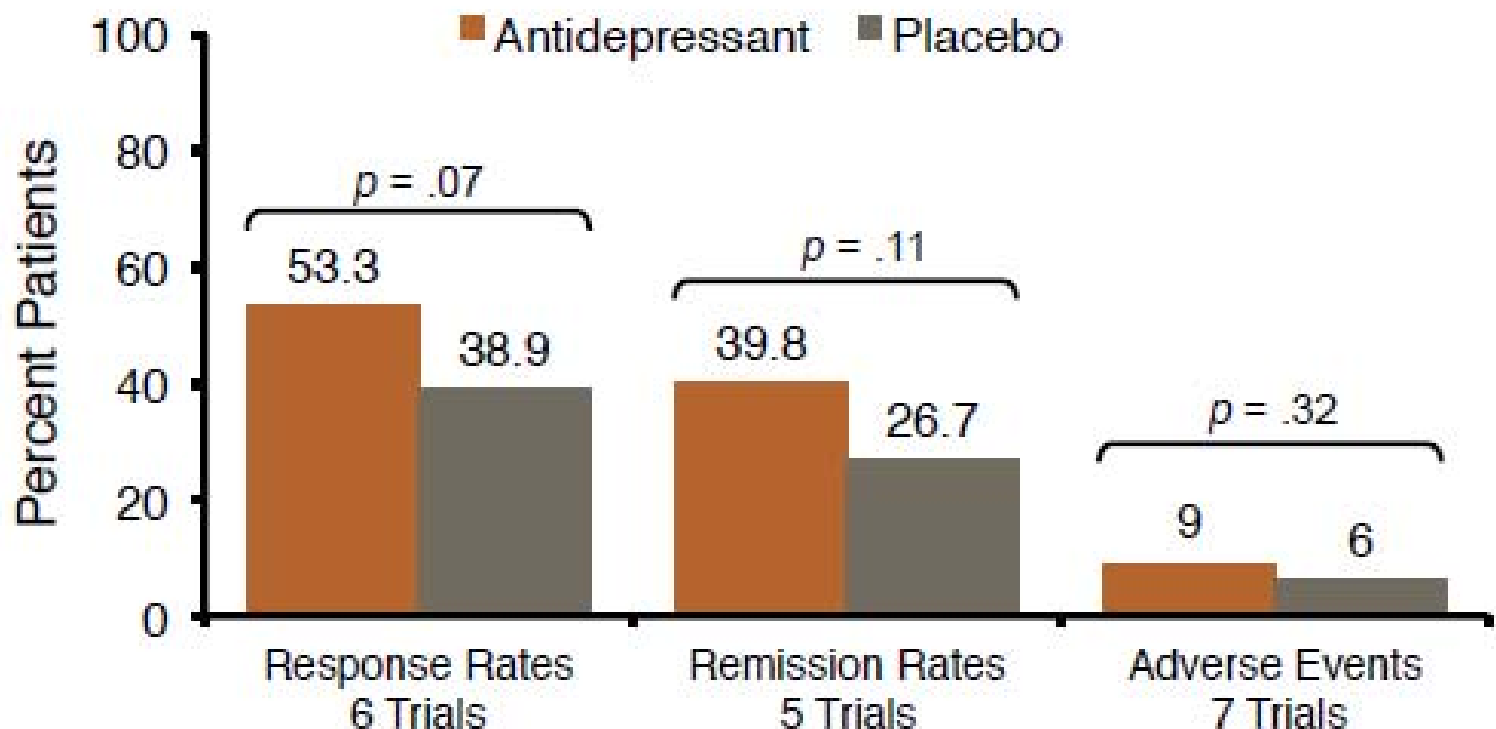
Antidepressant Trials in Depressed Patients with Dementia



Nelson JC, et al. *J Am Geriatr Soc.* 2011;59(4):577-585. PMID: 21453380.



Antidepressant Outcomes in Depressed Patients with Dementia



Response = $\geq 50\%$ improvement;
Remission = ≤ 7 Hamilton Depression Rating Scale or equivalent

Nelson JC, et al. *J Am Geriatr Soc.* 2011;59(4):577-585. PMID: 21453380.

A Systematic Review and Meta-Analysis of Placebo-Controlled Antidepressant Studies in People with Depression and Dementia

JC Nelson & DP Devanand J Am Geriatr Soc 59:577–585, 2011.

RESULTS: Seven trials with 330 participants met selection criteria. The odds ratio (OR) for six trials reporting response rates with antidepressant and placebo was 2.12 (95% CI 0.95–4.70; $P=.07$). The OR for five trials reporting remission rates was 1.97 (95% CI 0.85–4.55; $p=.11$).

- Adverse event discontinuation rates (9.0%) were not significantly higher with drug than placebo (6.0%), and were low.

CONCLUSION: The evidence for antidepressant treatment of people with depression and dementia, although suggestive, does not confirm efficacy. All of the trials were significantly underpowered to detect differences, resulting in inconclusive findings. Variable trial methods, comorbid conditions, and differences in antidepressants employed further confounded findings.

Sertraline or mirtazapine for depression in dementia (HTA-SADD): a randomised, multicentre, double-blind, placebo-controlled trial

Sube Banerjee, Jennifer Hellier, Michael Dewey, Renee Romeo, et al
Lancet 2011; 378: 403–11

- **Findings** Decreases in depression scores at 13 weeks did not differ between 111 controls and 107 participants allocated to receive sertraline or mirtazapine or between participants in the mirtazapine and sertraline groups (these findings persisted to 39 weeks. Fewer controls had adverse reactions than did participants in the sertraline group or mirtazapine group and fewer serious adverse events rated as severe. Five patients in every group died by week 39.
- **Interpretation** Because of the absence of benefit compared with placebo and increased risk of adverse events, the present practice of use of these antidepressants, with usual care, for first-line treatment of depression in Alzheimer's disease should be reconsidered.

Behavioral treatment of depression in dementia patients: a controlled clinical trial.

L. Teri et al, [J Gerontol B Psychol Sci Soc Sci.](#) 1997; 52:P159-66.

Abstract

The current study is a controlled clinical investigation of two nonpharmacological treatments of depression in patients with Alzheimer's disease. Two active behavioral treatments, **one emphasizing patient pleasant events** and **one emphasizing caregiver problem solving**, were compared to an equal-duration typical care condition and a wait list control. 72 patient-caregiver dyads were randomly assigned to one of four conditions and assessed pre-, post-, and at 6-months follow-up. Patients in both behavioral treatment conditions showed significant improvement in depression symptoms and diagnosis as compared with the two other conditions. These gains were maintained at 6-month follow-up.

If you use antidepressants:

- Among antidepressants, citalopram, sertraline, venlafaxine, mirtazapine, bupropion, and duloxetine have minimal drug-drug interactions. Paroxetine and fluoxetine have most. **Try to avoid the latter two drugs with older persons.**
- **Citalopram prolongs QT interval (esp >20 mg in elderly).**
- Venlafaxine, duloxetine, fluoxetine and bupropion are most activating, sertraline is slightly activating, citalopram is neutral, and paroxetine is mildly sedating, and mirtazapine and trazadone are very sedating.
- Paroxetine may cause mild anti-cholinergic effects and mirtazapine causes more pronounced effects.
- Mirtazapine(moderate) and trazadone(high) have higher rates of orthostatic hypotension.

Risk of SSRIs

- 1. Possible increased risk of bleeding
- 2. Hyponatremia –SIADH
- 3. Osteoporosis
- 4. Prolonged QT interval for citalopram (>20mg)

- Sertraline (Zoloft): my first choice SSRI
- Duloxetine(Cymbalta): my first choice for persons with contraindications to SSRIs and/or persons with pain due to neuropathies or osteoarthritis.

CASE 3

A 72-year-old man with a 6 month history of vascular dementia (MMSE = 22) reports feeling sad, losing interest in activities and friends, and some difficulty sleeping. His health is good and all laboratory tests are normal. What would you do next?

1. Begin sertraline 50 mg daily
2. Consider psychotherapy
3. Begin mirtazapine 15mg at bedtime
4. None of the above.

CASE 4

An 85-year-old-woman with midstage AD(MMSE=15) with Type 2 diabetes and hypertension has become increasingly more agitated and aggressive towards her home attendant, seeing dead relatives, and is also keeping her spouse awake at night. There have been no changes in her medical condition and all lab tests are essentially within normal limits.

What would you do first?

- 1. Try an antidepressant. Which one?**
- 2. Try antipsychotic agent –which one?**
- 3. Try psychosocial approach**
- 4. None of the above**

(b) Would your strategy change if the woman has Lewy Body Dementia?

Antipsychotic Efficacy (Cochrane) 2008

Main results

Sixteen placebo controlled trials have been completed with atypical antipsychotics although only nine had sufficient data to contribute to a meta-analysis and only five have been published in full in peer reviewed journals. No trials of amisulpiride, sertindole or zotepine were identified which met the criteria for inclusion.

The included trials led to the following results:

1. There was a significant improvement in aggression with risperidone and olanzapine treatment compared to placebo.
2. There was a significant improvement in psychosis amongst risperidone treated patients.
3. Risperidone and olanzapine treated patients had a significantly higher incidence of serious adverse cerebrovascular events (including stroke), extrapyramidal side effects and other important adverse outcomes.
4. There was a significant increase in drop-outs in risperidone (2 mg) and olanzapine (5-10 mg) treated patients.
5. The data were insufficient to examine impact upon cognitive function.

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

L S. Schneider, M.S., K. Dagerman, P S. Insel, Am J Geriatr Psychiatry 2006; 14:191–210

Results: Quality of the reporting of trials varied. Efficacy on rating scales was observed by meta-analysis for aripiprazole and risperidone, but not for olanzapine. Response rates were frequently not reported. There were smaller effects for less severe dementia, outpatients, and patients selected for psychosis. Approximately one-third dropped out without overall differences between drug and placebo. Adverse events were mainly somnolence and urinary tract infection or incontinence across drugs, and extrapyramidal symptoms or abnormal gait with risperidone or olanzapine. Cognitive test scores worsened with drugs. There was no evidence for increased injury, falls, or syncope. There was a significant risk for cerebrovascular events, especially with risperidone; increased risk for death overall was reported elsewhere.

Conclusions: Small statistical effect sizes {approx 0.20} on symptom rating scales support the evidence for the efficacy of aripiprazole and risperidone. Incomplete reporting restricts estimates of response rates and clinical significance. Dropouts and adverse events further limit effectiveness. Atypicals should be considered within the context of medical need and the efficacy and safety of alternatives.

Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. Schneider LS et al NEJM 355:1325-1328,2006

In this 42-site, double-blind, placebo-controlled trial, 421 outpatients with Alzheimer's disease and psychosis, aggression, or agitation were randomly assigned to receive olanzapine (mean dose, 5.5 mg per day), quetiapine (mean dose, 56.5 mg per day), risperidone (mean dose, 1.0 mg per day), or placebo. Doses were adjusted as needed, and patients were followed for up to 36 weeks. The main outcomes were the time from initial treatment to the discontinuation of treatment for any reason and the number of patients with at least minimal improvement on the Clinical Global Impression of Change (CGIC) scale at 12 weeks.

RESULTS: There were no significant differences among treatments with regard to the time to the discontinuation of treatment for any reason: olanzapine (median, 8.1 weeks), quetiapine (median, 5.3 weeks), risperidone (median, 7.4 weeks), and placebo (median, 8.0 weeks) ($P=0.52$). The median time to the discontinuation of treatment due to a lack of efficacy favored olanzapine (22.1 weeks) and risperidone (26.7 weeks) as compared with quetiapine (9.1 weeks) and placebo (9.0 weeks) ($P=0.002$). The time to the discontinuation of treatment due to adverse events or intolerability favored placebo. Overall, 24% of patients who received olanzapine, 16% of patients who received quetiapine, 18% of patients who received risperidone, and 5% of patients who received placebo discontinued their assigned treatment owing to intolerability ($P=0.009$). No significant differences were noted among the groups with regard to improvement on the CGIC scale. Improvement was observed in 32% of patients assigned to olanzapine, 26% of patients assigned to quetiapine, 29% of patients assigned to risperidone, and 21% of patients assigned to placebo ($P=0.22$).

CONCLUSIONS: 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.

Numbers Needed to Treat and Harm in CATIE Trial

- $NNT = 100 / 32(d) - 21(pl) = 9$ (improvement)
- $NNH = 100 / 24(d) - 5(pl) = 5$ (d/c due to intolerability)

Haloperidol for agitation in dementia (cochrane)

Conclusions

- 1. Evidence suggests that haloperidol was useful in reducing aggression, but was associated with adverse effects; there was no evidence to support routine use of this drug for other manifestations of agitation in dementia.
- 2. Similar drop-out rates among haloperidol and placebo treated patients suggested that poorly controlled symptoms, or other factors, may be important in causing treatment discontinuation.
- 3. **The present study confirmed that haloperidol should not be used routinely to treat patients with agitated dementia. Treatment of agitated dementia with haloperidol should be individualized and patients should be monitored for adverse effects of therapy.**

Valproate preparations for agitation in dementia (Cochrane 2010)

- The updated review corroborates the earlier findings that valproate preparations are ineffective in treating agitation among demented patients, and that valproate therapy is associated with an unacceptable rate of adverse effects. **On the basis of current evidence, valproate therapy cannot be recommended for management of agitation in dementia.**
- **Valproate treatment (DBRCT) did not delay emergence of agitation or psychosis or slow cognitive decline in moderate AD** (Tariot et al, 2011).

The association between dementia and long-term use of benzodiazepine in the elderly: nested case-control study using claims data.

[Wu CS](#), [Wang SC](#), [Chang IS](#), [Lin KM](#).

[Am J Geriatr Psychiatry](#). 2009 Jul;17(7):614-20.

- **PARTICIPANTS:** Cases (N = 779) were patients who were identified with dementia at least two times in their outpatient claims. They were individually matched to six comparison subjects (N = 4,626) based on age and gender.
All subjects were aged 45 and older and enrolled in the National Health Insurance Research Database in Taiwan, 1997-2004.
- **MEASUREMENTS:** BZD usage (average dosage per year, average days per year, and cumulative dose and periods) and potential confounding comorbidities, including cardiovascular and psychiatric diseases.
- **RESULTS:** Subjects with dementia had higher cumulative dose, longer duration of BZDs exposure, and more likelihood to be long-term BZDs users.
- **CONCLUSION:** Our findings suggest that long-term use of BZDs is associated with an increased risk for dementia, but the underlying mechanisms remain unclear, and further investigations are needed. Long-term use of BZDs should be avoided among the elderly, who may be at a higher risk for developing dementia, in addition to other health problems.

Clinical Symptom Responses to Atypical Antipsychotic Medications in Alzheimer's Disease: Phase 1 Outcomes from the CATIE-AD Effectiveness Trial

David L. Sultzer, MD, Sonia M. Davis, DrPH, Pierre N. Tariot, MD, Karen S. Dagerman, MS, Barry D. Lebowitz, PhD, Constantine G. Lyketsos, MD, MHS, Robert A. Rosenheck, MD, John K. Hsiao, MD, Jeffrey A. Lieberman, MD, and Lon S. Schneider, MD

- **Results**—At the last observation in Phase 1 compared to placebo, there was greater improvement in patients treated with olanzapine or risperidone on the Neuropsychiatric Inventory total score, with risperidone on the Clinical Global Impression of Change, with olanzapine or risperidone on the Brief Psychiatric Rating Scale (BPRS) Hostile Suspiciousness factor, and with risperidone on the BPRS Psychosis factor. There was worsening with olanzapine on the BPRS Withdrawn Depression factor. Among patients continuing Phase 1 treatment at 12 weeks, there were no significant antipsychotic –placebo group differences on measures of cognition, functional skills, care needs, or quality of life, except for worsening of functional skills in the olanzapine treatment group compared to placebo.
- **Conclusion**—In this descriptive analysis of clinical outcomes in AD outpatients in usual care settings, some clinical symptoms improved with atypical antipsychotic treatment. Antipsychotic medications may be more effective for particular symptoms, such as anger, aggression, and paranoid ideas. Functional abilities, care needs, or quality of life do not appear to improve with antipsychotic treatment.

Table 1

Pharmacological alternatives to antipsychotics with at least 1 positive randomized controlled trial for agitation and/or psychosis in patients with dementia

| Medication | Evidence and limitations |
|--|---|
| Citalopram (Celexa) | 2 positive studies: more effective for agitation than placebo in nondepressed patients; efficacy equivalent to that of risperidone (mean dose, 1.25 mg/d) for psychosis and agitation and citalopram (mean dose, 29.4 mg/d) with better tolerability (no placebo group) ^{18,19} |
| Trazodone (Desyrel) | 1 positive study; 1 negative study: trazodone (mean dose, 218 mg/d) had efficacy for agitation equivalent to that of haloperidol (mean dose, 2.5 mg/d) and was better tolerated (no placebo group); trazodone (mean dose, 200 mg/d) was equivalent to placebo for treating agitation ^{20,21} |
| Carbamazepine (Tegretol) | 2 positive trials but problems with tolerability in both: modal dose of 300 mg/d superior to placebo for agitation and aggression; adverse effects (eg, ataxia, postural instability, disorientation) 59% for carbamazepine vs 29% for placebo; 400 mg/d superior to placebo for aggression/hostility but worrisome trend for increased hallucinations with active treatment ^{22,23} |
| Cognitive enhancers (cholinesterase inhibitors, memantine [Namenda]) | Some evidence of modest benefit for psychosis and/or agitation in mostly post hoc data analysis in trials designed to assess cognitive variables; however, prospective studies of rivastigmine and donepezil specifically designed to assess neuropsychiatric symptoms showed no difference between the drugs and placebo ^{24–26} |
| Propranolol (Inderal) | A small study showed propranolol (average dose, 106 mg/d) was superior to placebo for agitation/aggression but was added to other psychotropics; benefits waned during 6-month open-label follow-up, and many older adults would have contraindications to this medication at this dose ²⁷ |
| Topiramate (Topamax) | A small study showed topiramate (mean dose, 44 mg/d) was equivalent to risperidone (mean dose, 1.9 mg/d) in reduction of global neuropsychiatric symptoms and, more specifically, agitation; no cognitive deterioration was detected but 50% of topiramate-treated patients reported fatigue and 50% reported decreased appetite ²⁸ |

PRAZOSIN FOR THE TREATMENT OF BEHAVIORAL SYMPTOMS IN ALZHEIMER'S DISEASE PATIENTS WITH AGITATION AND AGGRESSION

L Y. Wang et al, 2009

Intervention

Randomization to placebo (n=11) or prazosin (n=11). Medication was initiated at 1mg/day and increased up to 6mg/day using a flexible dosing algorithm.

Results

Participants taking prazosin (mean dose 5.7 ± 0.9 mg/day) had greater improvements than those taking placebo on the NPI (mean change -19 ± 21 versus -2 ± 15 , $p=0.01$) and BPRS (mean change -9 ± 9 versus -3 ± 5 , $p=0.04$) based on linear mixed effects models, and the CGIC (mean 2.6 ± 1.0 versus 4.5 ± 1.6 , $Z=2.57$, $p=0.01$). Adverse effects and blood pressure changes were similar between prazosin and placebo groups.

Conclusion

Prazosin was well tolerated and improved behavioral symptoms in patients with agitation and aggression in AD.

Increased Mortality Rates

All atypical antipsychotics and Haloperidol now carry warning about increased mortality rate. (Also seems to be true for older antipsychotic agents, e.g., Haldol.) Most deaths were due to cardiovascular and infectious(e.g, pneumonia) causes. Although death rates were 1.6 to 1.7 times greater than placebo, the absolute risk was about 2%--i.e., about 1 in 50 greater likelihood of death: 2.6% vs 4.5%)

Bleeding

Meta-analysis

OR 1.24 (2.04)
OR 1.24 (0.64)
OR 1.24 (2.04)

Results

Test for heterogeneity: $\chi^2=2.11$, $df=2$, $p=0.33$
Test for Overall Effect: $Z=1.14$, $p=0.25$

Confidence

95% CI
95% CI
95% CI
95% CI
95% CI

Results

Test for heterogeneity: $\chi^2=2.11$, $df=2$, $p=0.33$
Test for Overall Effect: $Z=1.14$, $p=0.25$

Confidence

95% CI
95% CI
95% CI

Results

Test for heterogeneity: $\chi^2=2.11$, $df=2$, $p=0.33$
Test for Overall Effect: $Z=1.14$, $p=0.25$

Confidence

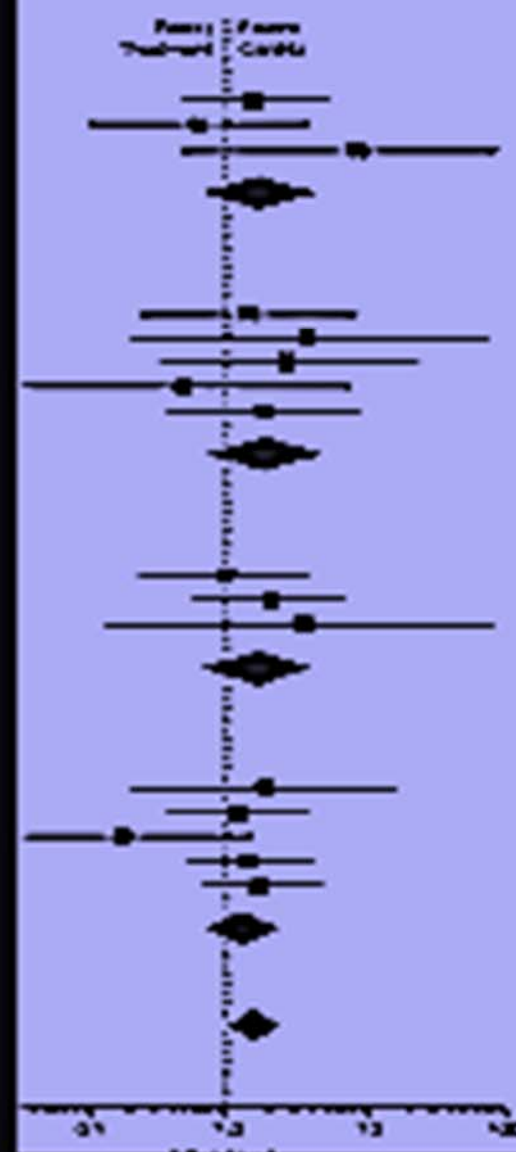
95% CI
95% CI
95% CI
95% CI
95% CI

Results

Test for heterogeneity: $\chi^2=2.11$, $df=2$, $p=0.33$
Test for Overall Effect: $Z=1.14$, $p=0.25$

Confidence

Test for heterogeneity: $\chi^2=2.11$, $df=2$, $p=0.33$
Test for Overall Effect: $Z=1.14$, $p=0.25$



No individual study is statistically significant.
In the meta-analysis, No individual drug is statistically significant.

Weighted of 4 drugs, Multiple studies, Statistically significant.

But new data

Efficacy and Comparative Effectiveness of Atypical Antipsychotic Medications for Off-Label Uses in Adults

A Systematic Review and Meta-analysis

JAMA Sept 28, 2011

Alicia Ruelaz Maher, MD

Margaret Maglione, MPP

Steven Bagley, MD

Marika Suttorp, MS

Jian-Hui Hu, MPP

Brett Ewing, MS

Zhen Wang, MS

Martha Timmer, MS

David Sultzer, MD

Paul G. Shekelle, MD, PhD

Side effects from meta-analysis

| | No. of Studies | Sample Size | Pooled OR (95% CI) |
|-----------------------------------|----------------|-------------|--------------------|
| Cardiovascular event ^a | | | |
| Aripiprazole | 1 | 366 | 1.20 (0.58-2.5) |
| Olanzapine | 5 | 778 | 2.30 (1.08-5.6) |
| Quetiapine | 3 | 355 | 1.10 (0.53-2.3) |
| Risperidone | 6 | 1757 | 2.10 (1.38-3.2) |
| Cerebrovascular accident | | | |
| Aripiprazole | 3 | 340 | 0.70 (0.05-10.) |
| Olanzapine | 2 | 278 | 1.50 (0.33-7.4) |
| Quetiapine | 2 | 185 | 0.70 (0.10-3.0) |
| Risperidone | 4 | 1099 | 3.12 (1.32-8.2) |

Are all commonly prescribed antipsychotics associated with greater mortality in elderly male veterans with dementia?

Rossom et al, 2010 JAGS

Participants: VA medical ctrs; predominantly male, aged 65+, dementia dx.

Results: During the first 30 days, there was a significant increase in mortality in subgroups prescribed a daily dose of haloperidol greater than 1 mg (HR=3.2); olanzapine greater than 2.5 mg (HR=1.5), or risperidone greater than 1 mg (HR=1.6) 95% CI=1.1-2.2, P=.01) adjusted for demographic characteristics, comorbidities, and medication history. After controlling for confounding effects, risperidone no longer had higher rates. Greater mortality was not seen when a daily dose of quetiapine at above (HR=1.2) or below 50mg (HR=0.7). No antipsychotic was associated with greater mortality after the first 30 days.

Conclusion: (1) Commonly prescribed doses of haloperidol, olanzapine, and risperidone, but not quetiapine, were associated with a short-term increase in mortality.

(2) Lower doses are not associated with greater mortality.

(3) Risperidone is not higher after controlling for confounds.

Differential risk of death in older residents in nursing homes prescribed specific antipsychotic drugs: population based cohort study

K F Huybrechts et al BMJ, 2012

Participants: 75 445 new users of antipsychotic drugs (haloperidol, aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone).

Results: Compared with risperidone, users of haloperidol had an increased risk of mortality (hazard ratio 2.07, 95% confidence interval 1.89 to 2.26) and users of quetiapine a decreased risk (0.81, 0.75 to 0.88). The effects were strongest shortly after the start of treatment, remained after adjustment for dose, and were seen for all causes of death examined. No clinically meaningful differences were observed for the other drugs. There was no evidence that the effect measure modification in those with dementia or behavioural disturbances. There was a dose-response relation for all drugs except quetiapine.

Conclusions: The data suggest that the risk of mortality with these drugs is generally increased with higher doses and seems to be highest for haloperidol and least for quetiapine.

Risk of Mortality Associated With Antipsychotics in Patients With Dementia: A Prospective Cohort Study

(Arai et al, 2013)

- **Methods:** 5148 patients in Japan followed up to 10 weeks; persons with unstable/uncontrolled medical conditions were excluded.
- **Findings:** 10 week mortality for total sample was 1.2% with no significant differences between persons who received and did not receive anti-psychotic medications.
- **Conclusions:** No significant differences in groups and mortality rate was lower than in meta-analyses (3.5%; Schneider et al, 2005) suggesting that “real world” mortality rates may not be so high (at least in Japan).

Effects of Medications on Cognition and the Brain

- Fleisher et al: Neurology 2011: 12 month follow-up , AD patients on **divalproex** had **significantly smaller brain volumes** (total, hippocampus) than placebo recipients and MMSE scores were also lower.
- Vigen et Am J Psychiatry, 2011): AD patients taking **antipsychotics** showed **significantly greater cognitive decline** than those given placebo over 1 year (from CATIE trial).

Psychosocial Approaches

- **Behavioral oriented**—e.g., breakdown behaviors into smaller components and addressing specific component
- **Emotion oriented**—e.g., validation of emotional feelings, reminiscence therapy, supportive psychotherapy
- **Cognition oriented**—e.g., reality orientation(to time and place), skills training, and other mind-stimulating activities
- **Stimulation oriented**—activity, recreational, art and socialization groups (e.g., day programs), music therapy
- **Other non-specific interventions**—e.g., reassurance, distraction, touch or massage therapy, bright light therapy, exercise
- **Caregiver oriented interventions**—e.g., support groups, education, respite care

Effectiveness of Non-Pharmacological Treatment

Key points

- Interventions found to be effective for use with particular symptoms of dementia included music or music therapy, hand massage or gentle touch and physical activity/exercise.
- The majority of interventions fell into the category of non-drug treatments that *might* work but research yielded inconclusive results due to conflicting results and weakness in study design.

If You Use An Antipsychotic Medication

Dosing
easier

Most commonly used

TABLE 11-1. Atypical antipsychotic side effects and dosage ranges in elderly patients

| | Clozapine (6.25-200.00 mg) | Risperidone (0.5-4.0 mg) | Olanzapine (5-20 mg) | Quetiapine (25-250 mg) | Aripiprazole 5-10mg |
|-------------------------|-------------------------------|-----------------------------|-------------------------|---------------------------|------------------------|
| Orthostasis | ++++ | ++++ | +++ | ++ | + |
| Sedation | +++++ | ++ | +++ | +++ | 0 |
| Prolactin increase | 0 | +++ | + | 0 | ? |
| Weight gain | ++++ | + | +++ | + | + |
| Extrapyramidal symptoms | 0/+ | ++ | + | 0/+ | + / ++ |
| Tardive dyskinesia | 0 | + | + | ? | ? |
| Anticholinergic effects | ++++ | + | + | 0 | 0 |
| Seizure risk | +++ | + | + | + | + |
| Hematological effects | +++ | + | + | + | + |

Note. +=minimal; ++=mild; +++=moderate; ++++=moderately severe; +++++=severe; 0=no effect; ?=not certain. Ziprasidone dosage and side effects in the elderly have not yet been determined.

Source. Data from Casey 1997 and Pickar 1995.

If you use medications—beware of side effects



Table 2

Suggested starting/target doses for atypical antipsychotics in patients with dementia

| Drug | Starting dose | Target dose |
|--------------|-----------------|-----------------|
| Aripiprazole | 2 - 5 mg/d | 7.5 - 12.5 mg/d |
| Olanzapine | 2.5 - 5 mg/d | 5 - 10 mg/d |
| Quetiapine | 12.5 - 25 mg/d | 50 - 200 mg/d |
| Risperidone | 0.25 - 0.5 mg/d | 0.5 - 1.5 mg/d |

CASE 4

An 85-year-old-woman with midstage AD(MMSE=15) with Type 2 diabetes and hypertension has become increasingly more agitated and aggressive towards her home attendant, seeing dead relatives, and is also keeping her spouse awake at night. There have been no changes in her medical condition and all lab tests are essentially within normal limits.

What would you do first?

1. Try an antidepressant. Which one?
2. Try antipsychotic agent –which one?
3. Try psychosocial approach
4. None of the above

(b) Would your strategy change if the woman has Lewy Body Dementia?

Case 5

83-year-old woman is having increasingly more problems with sleep. She has difficulty falling asleep and then awakes in the night, sometimes becoming agitated. Medical problems are ruled out. What do you do next?

1. Add quetiapine 25mg at bedtime.
2. Add trazadone 25mg at bedtime.
3. Add zolpidem 5mg at bedtime
4. Add melatonin 6mg at bedtime
5. None of the above

Sleep Disturbances

- **Cross-sectional studies suggest that approximately 25% to 35% of individuals with AD have problems sleeping.**
- **Sleep disturbances in AD may be a result of a progressive deterioration and decrease in the number of neurons in the suprachiasmatic nucleus, which cause fluctuations in neurohormones that are critical in the homeostatic maintenance of the circadian rhythm.**
[Light → SCN → Pineal Gland → Melatonin]
- **Common symptoms include nighttime sleep fragmentation, increased sleep latency, decreased slow-wave sleep, and increased daytime napping.**

A review of the evidence for the efficacy and safety of trazodone in insomnia.

WB Mendelson

J Clin Psychiatry. 2005; 66(4):469-76.

STUDY SELECTION: A total of 18 studies were identified from the literature search.

DATA SYNTHESIS:

1. Evidence for the efficacy of trazodone in treating insomnia is very limited
2. Side effects associated with trazodone are not inconsequential, with a high incidence of discontinuation due to side effects, such as sedation, dizziness, and psychomotor impairment, which raise particular concern regarding its use in the elderly.
3. There is also some evidence of tolerance related to use of trazodone.

CONCLUSION: Given the relative absence of efficacy data in patients with insomnia and the adverse events associated with trazodone's use in general, it is uncertain whether the risk/benefit ratio warrants trazodone's use in nondepressed patients with insomnia.

Melatonin and Ramelteon

Six randomized control trials with melatonin
2.5 mg to 10 mg:

- 3 not significant
- 1 increased sleep time
- 1 decreased nocturnal agitation
- 1 increased daytime wakefulness when used with light therapy
- Ramelteon(M1 and M2 agonist) may useful for reducing sleep latency

Sleep Treatments

- Usual sleep hygiene issues: Keep active and awake in day; no excessive liquids in evening; decrease noise and ambient light; avoid caffeine, alcohol, nicotine
- Address pain, uncontrolled blood glucose, CHF
- Light therapy –mixed results with 2 hours in AM or in PM; all day light may be better
- Physical exercise 15-30min daily reduced daytime sleepiness and increased nighttime sleep

Sleep treatment (cont)

- Zolpidem, zaleplon, eszopiclone: data are lacking in dementia
- Benzodiazepines may cause excessive sedation, amnesia, rebound insomnia, and some have very long half-lives
- Trazadone may cause dizziness, psychomotor impairment, over-sedation and may wear-off. Data lacking.
- Melatonin findings are mixed

Case 5

83-year-old woman is having increasingly more problems with sleep. She has difficulty falling asleep and then awakes in the night, sometimes becoming agitated. Medical problems are ruled out. What do you do next?

1. Add quetiapine 25mg at bedtime.
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3. Add zolpidem 5mg at bedtime
4. Add melatonin 6mg at bedtime
5. None of the above

CASE 6

An 85-year-old woman with 4-year history of AD starts showing agitation and increased confusion in early evening. After confirming the absence of physical causes of agitation, what would you do next?

- 1. Begin risperidone 0.5 mg.**
- 2. Develop an exercise and activity program.**
- 3. Try low dose lorazepam such as 0.5 mg.**
- 4. Consider bright light therapy in the morning.**

Sundowning

(10-25% prevalence in AD)

- A cyclical increase in agitation (which may include restlessness, confusion, disorientation, wandering, searching, escape behaviors, tapping or banging, vocalization, combativeness, and/or hallucinations) that takes place at roughly the same time every day.
- Despite the wide-spread belief that sundowning occurs in the late afternoon/early evening, the peak of sundowning activity is more likely to occur in the early- to mid-afternoon (e.g., around 1:00pm); in some patients, it may occur late at night or in the early morning.

Causes of Sundowning

- **Agitation:**
 - (1) Confusion, over-stimulation, and fatigue during the day, which results in increased disorientation, restlessness, and insecurity at night.
 - (2) Fear of the dark because of the lack of familiar daytime noises and activity and the lack of visual cues.
- **Sleep Disturbance** characterized by wandering and confusion
- **Chronobiological** phenomenon that is ***unrelated to sleep disturbances, i.e., a*** disturbance in the normal circadian rhythms, that is regulated the suprachiasmatic nucleus (SCN). The SCN deteriorates significantly in Alzheimer's disease, contributing to disruption of circadian rhythms that causes significant delays in peak body temperature and alterations in endogenous melatonin secretion.

Treatment of Sundowning

- R/O other causes for agitation
- Increase activities, especially physical exercise during the day to try to re-establish better sleep rhythms
- Avoid overstimulation, turn on lights at dusk
- Bright light therapy in AM –most studies negative
- Melatonin—studies mixed results (effect small) –may be more effective in early dementia
- Antipsychotics may help reduce **agitation** in select patients, but little evidence for other drugs such as benzodiazepines, antihistamines, anticonvulsants, or SSRIs.

[There is no published Class I (RCT) evidence that any of these drugs are useful for treating **sundowning** per se]

CASE 6

An 85-year-old woman with 4-year history of AD starts showing agitation and increased confusion in early evening. After confirming the absence of physical causes of agitation, what would you do next?

- 1. Begin risperidone 0.5 mg.**
- 2. Develop an exercise and activity program.**
- 3. Try low dose lorazepam such as 0.5 mg.**
- 4. Consider bright light therapy in the morning.**

CASE 7

A man comes for a visit with his wife who has mid-stage AD. He states that she believes the person she sees in the mirror is her mother, talks to people on the television as if they were in the home, and sometimes thinks the husband is her son.

Sometimes she talks to dead relatives, especially at night. He tells her she is mistaken about these things and she gets angry at him, and then starts to cry.

What would you do?

- 1. Try low dose of quetiapine.**
- 2. Try sertraline.**
- 3. Try low dose of lorazepam.**
- 4. None of the above**

Misidentification Syndromes

May be more cognitively- related:

- **Capgras Syndrome (imposters);**
- **Phantom Boarder Syndrome (guest in house);**
- **Mirror Sign (mistakes self in mirror for someone else;**
- **TV or Magazine Sign (believes people on TV or in magazine are real).**

CASE 7

A man comes for a visit with his wife who has mid-stage AD. He states that she believes the person she sees in the mirror is her mother, talks to people on the television as if they were in the home, and sometimes thinks he is their son. Sometimes she talks to dead relatives, especially at night. He tells her she is mistaken about these things and she gets angry at him, and then starts to cry.

What would you do?

1. Try low dose of quetiapine.
2. Try sertraline.
3. Try low dose of lorazepam.
4. None of the above

Key Points on Neuropsychiatric Symptoms

AGS Guidelines, 2011

- **Behavioral symptoms require evaluation of the specific symptoms, the patient's comfort, the care environment, the needs of the caregiver, and the degree of distress of all those involved in the life of the older adult with dementia.**
- **It is important to remember that the needs of the caregiver must be taken into account! Mortality rates and psychiatric illness are elevated among caregivers.**

- **Medication treatment of behavioral disturbances in dementia is of limited efficacy and should be used only after environmental and nonpharmacologic techniques have been implemented.**
- **No psychoactive medication prescribed to treat NPS of dementia should be continued indefinitely, and attempts at drug withdrawal should be made regularly (eg, every 3-6 months) but recognizing that symptoms may recur.**

In the CATIE-AD trial, among AD patients with symptoms of psychosis, agitation, or aggressive behavior, second-generation antipsychotic medication administered to the patient has a small but significant impact on caregiver burden (Mohamed et al, 2012)

- **Despite these FDA warnings, antipsychotic medications may be needed for treatment of distressing delusions and hallucinations, and antidepressants may be helpful if symptoms of depression are evident.**
- **It is also advisable to document the process of informing the family member and, if capable, the patient of any future risk of mortality, stroke, and metabolic syndrome weighed against the present risk posed by the psychosis.**

- Treatment of psychiatric and behavioral disturbances in dementia is complex and may require several interventions as part of a comprehensive care plan. The goal is reduction rather than elimination of the distressing behavior.

| | |
|---------------------|---------------|
| Socio-environmental | Interpersonal |
| Biological | Psychological |

Case 8

A 79-year-old man with AD who had severe behavioral problems was successfully stabilized on 1 mg of risperidone.

After 4 months, what would be the next treatment strategy?

1. Stop risperidone.
2. Continue risperidone
3. Taper and stop risperidone.

A Randomised, Blinded, Placebo-Controlled Trial in Dementia Patients Continuing or Stopping Neuroleptics (The DART-AD Trial)

Ballard et al Lancet, 2008

- Participants: Patients currently prescribed the neuroleptics thioridazine, chlorpromazine, haloperidol, trifluoperazine or risperidone for behavioural or psychiatric disturbance in dementia for at least 3 mo.
- **Results:** There was no significant difference between the continue treatment and placebo groups in the estimated mean change in SIB scores between baseline and 6 mo; estimated mean difference in deterioration (favouring placebo) -0.4 (95% confidence interval [CI] -6.4 to 5.5), adjusted for baseline value ($p = 0.9$). For neuropsychiatric symptoms, there was no significant difference between the continue treatment and placebo groups ($n = 56$ and 53 , respectively) in the estimated mean change in NPI scores between baseline and 6 mo; estimated mean difference in deterioration (favouring continue treatment) -2.4 (95% CI -8.2 to 3.5), adjusted for baseline value ($p = 0.4$). Both results became more pronounced at 12 mo. There was some evidence to suggest that those patients with initial NPI ≥ 15 benefited on neuropsychiatric symptoms from continuing treatment.
- **Conclusions** For most patients with AD, withdrawal of neuroleptics had no overall detrimental effect on functional and cognitive status. Neuroleptics may have some value in the maintenance treatment of more severe neuropsychiatric symptoms, but this benefit must be weighed against the side effects of therapy.

Relapse risk after discontinuation of risperidone

Devanand DP et al.. N Engl J Med 2012;367:1497-1507

Among responders to risperidone, relapse rate was 60% for persons on placebo(note: non-relapse rate 40%) and 33% for those remaining on risperidone after 4 months. In the next 4 months , 48% of persons who were on risperidone & who were switched to placebo relapsed(note: non-relapse rate 52%) versus 15% who continued risperidone. However, risperidone discontinuation rates were high (68% among those on drug for 32 weeks).

Case 8

A 79-year-old man was with AD who had severe behavioral problems was successfully stabilized on 1 mg of risperidone.

After 4 months, what would be the next treatment strategy?

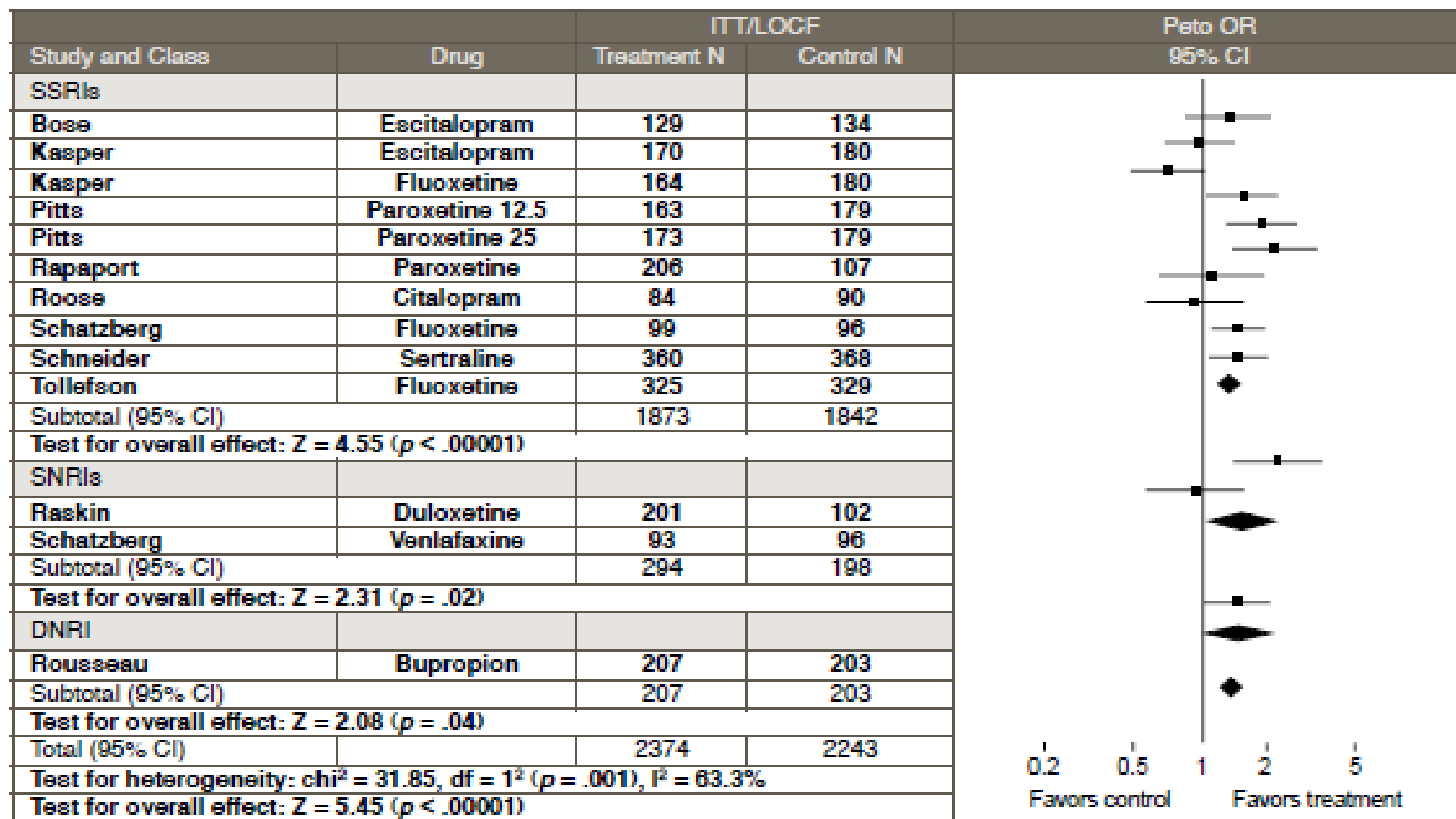
1. Stop risperidone.
2. Continue risperidone
3. Taper and stop risperidone.

Case 9

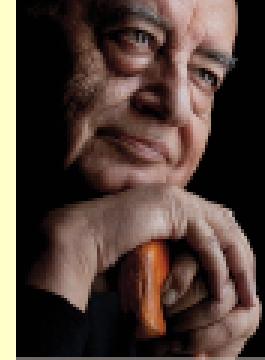
- A 72-year-old man with no history of depression reports symptoms of depression such as sadness, mild anhedonia, and mild insomnia. His HDRS score is 17. What would you recommend?
 1. Problem-solving therapy
 2. Antidepressant medication
 3. Combination treatment of psychotherapy and anti-depressant

Meta-analysis of Late-Life Depression Studies

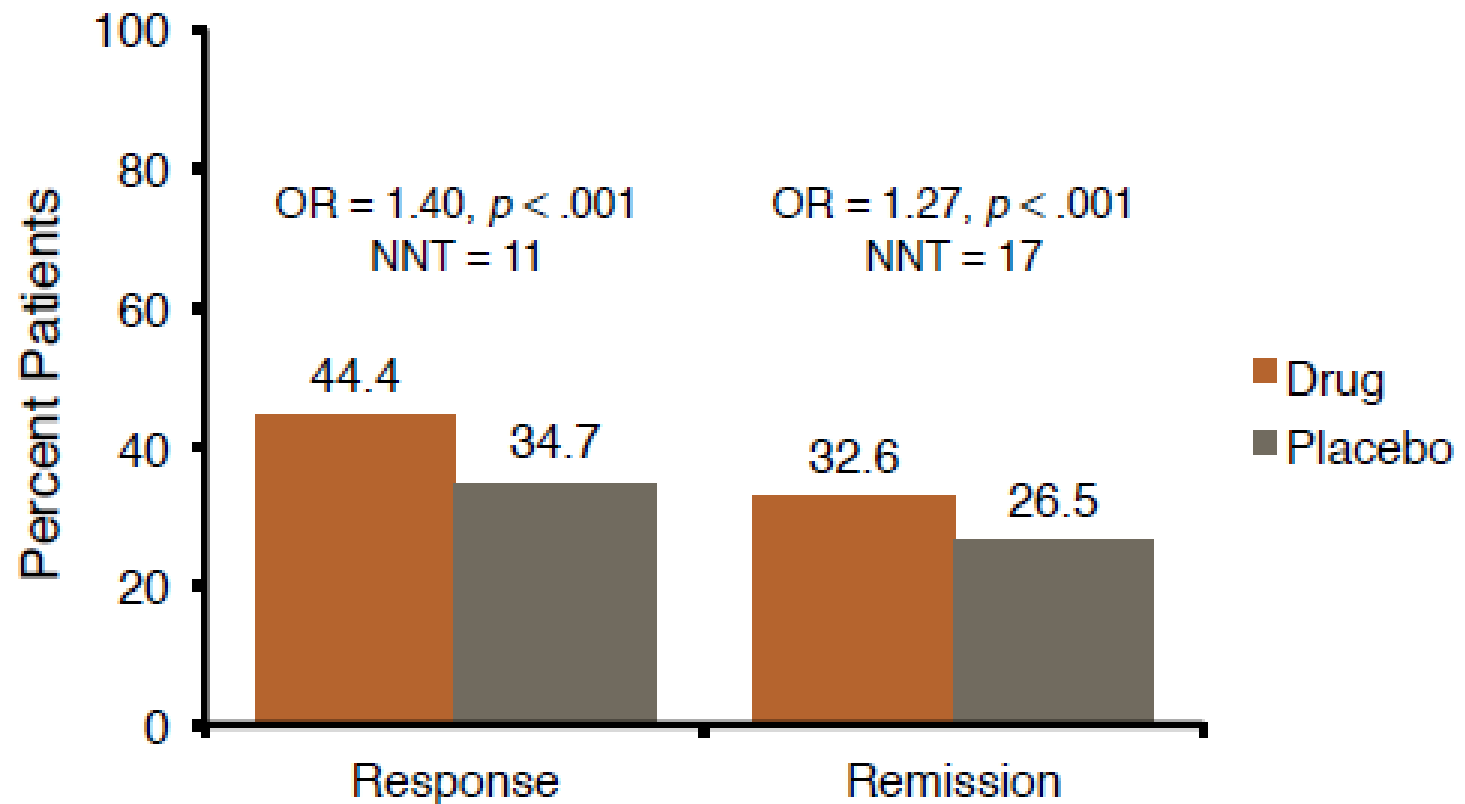
2nd Generation
Antidepressants



Nelson JC, et al. *Am J Geriatr Psychiatry*. 2008;16(7):558-567. PMID: 18591576.

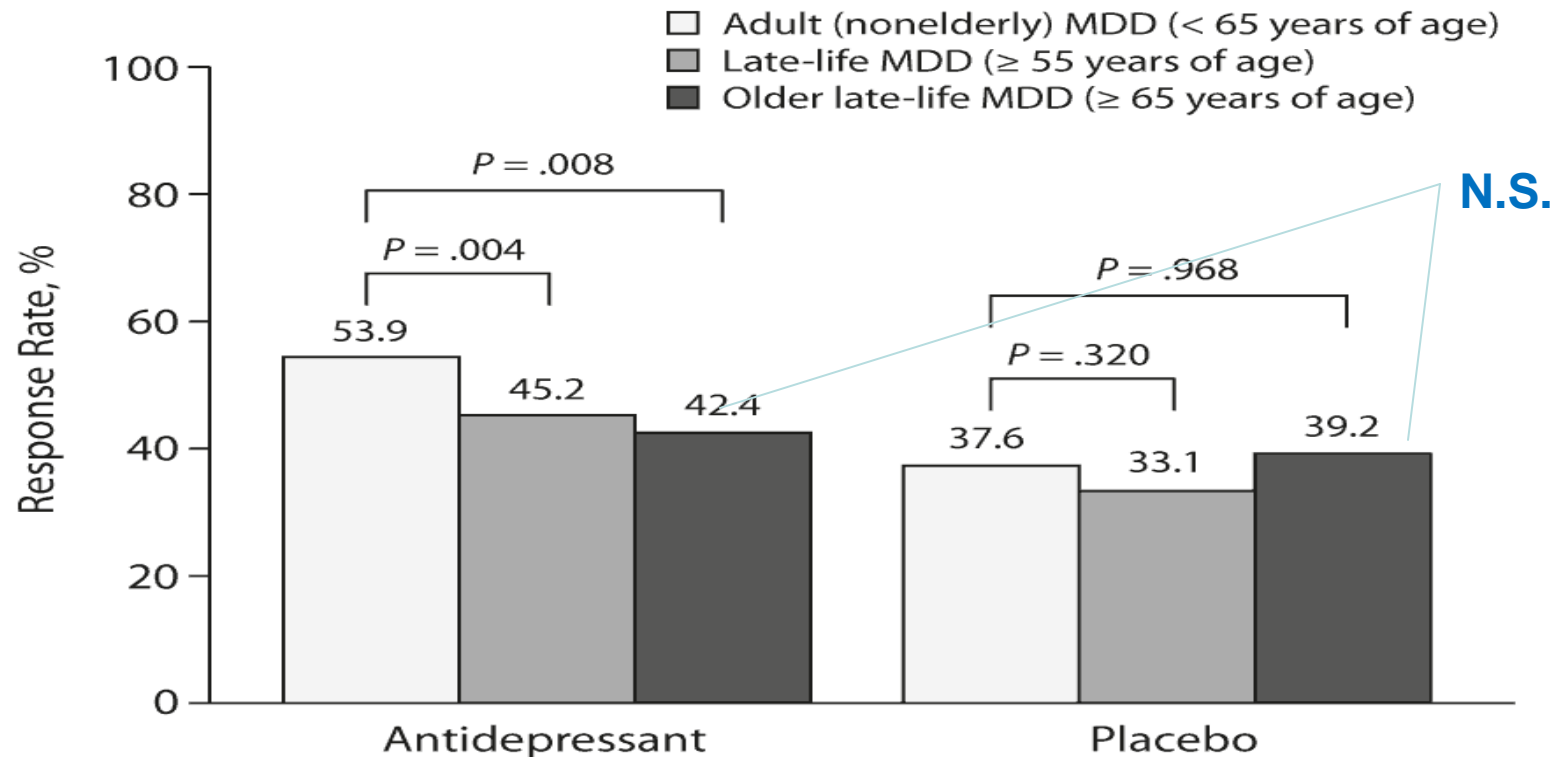


Mean Pooled Response and Remission Rates in 10 Studies With 13 Contrasts



Nelson JC, et al. *Am J Geriatr Psychiatry*. 2008;16(7):558-567. PMID: 18591576.

Figure 3. Comparison (using analysis of variance) of Antidepressant and Placebo Response Rates in Younger Adult and Older Adult Patients^a



^a $P = .450$ for meta-regression comparing the risk ratio of antidepressant response versus placebo response in adult MDD studies versus late-life MDD studies; $P = .036$ for meta-regression comparing the risk ratio of antidepressant response versus placebo response in adult MDD studies versus older late-life MDD studies.

Abbreviation: MDD = major depressive disorder.

Depression in Clinical Population of Depressed Persons Aged 55+

| | FOLLOW-UP: 33 MONTHS MEDIAN | | | |
|--|---|---|---|--|
| B A S E L I N E | | Not Depressed(CESD <8)at follow-up (n = 40) | Subclinical depression (CESD 8-15) at follow-up (n=37) | Clinical depression(CESD\geq 16) at follow-up (n=66) |
| | Not depressed (CESD<8) at baseline (n=88) | 38% | 31% | 32% |
| | Sub - Syndromally depressed (CESD 8-15) at baseline (n = 30) | 10% | 30% | 60% |
| | Syndromally depressed (CESD\geq16) at baseline (n = 25) | 16% | 4% | 80% |

Treatment of Depression in Older Adults

- **Use same antidepressants as younger patients—however, start low, go slow, keep going higher, and allow more time(if some response has been achieved, may allow up to 10-14 weeks before switching meds).**
- **Older patients may have a shorter interval to recurrence than younger patients. Thus, they may need longer maintenance of medication.**
- **Data are not clear if the elderly are more prone to relapse.**

KEY TREATMENT STUDIES

- **1. High risk older depressed pts(those with recurrent depression). Results:maintenance Rx with combination of meds & psychotherapy>meds alone >placebo. (Reynolds et al *JAMA*. 1999;281:39-45.)**
- **2 .Persons aged 70+ (mostly first episodes) who have responded to antidepressants, did better if maintained on medication(65% no recurrence) vs placebo(32% no recurrence) over 2 yrs. (note: psychotherapy didn't provide additional protection in this study). (Reynolds et al, *NEJM* 2006; 354:1130-38)**

3. Value of Collaborative Care: THE IMPACT STUDY

(Unutzer et al JAMA. 2002;288:2836-2845)

Rationale: Among primary care patients with depression, only a small fraction receives adequate treatment in primary care or sees a mental health specialist. Although treatment of depression in primary care has improved, few improvements deal with the specific needs of elderly patients.

IMPACT STUDY: Care team consisted of a depression care manager (usually a primary care nurse), the patient's primary care doctor, a consulting psychiatrist, and a liaison primary care doctor. For 12 months, IMPACT patients received proactive depression treatment in primary care. Treatment options included pharmacotherapy, and two behavioral therapy approaches. Consulting psychiatrists saw about 10% of patients, typically treatment non-responders.

RESULTS: *45% of intervention patients had a 50% or greater reduction in depressive symptoms from baseline compared with 19% of usual care participants.*

Psychotherapy

Originally thought to be ineffective over 50, e.g., Freud


Controlled trials indicated useful for:

- **Major and minor depression**
- **Recurrent depression, especially with meds**
- **Prevent depression after stroke**
- **Good evidence for Cognitive Behavior Therapy, Reminiscence and Life Review, Interpersonal Therapy, Problem Solving, Psychodynamic, Dialectical Behavioral Therapy (as adjunct to meds), Bibliotherapy (mild types) (Frazier et al, 2005)**



Clinical Connections

- Antidepressants more effective than placebo in late life MDD but effects are modest
- Effects more robust in moderate to severe patients with long duration of MDD illness
- Late onset depression responds well to placebo and supportive care

- 
- Antidepressants are not effective in dementia and depression
 - Cognitive enhancers not effective for acute depression treatment; in maintenance treatment may delay onset of dementia but may increase risk of depressive relapse
 - Antidepressants not effective in late life MDD with executive dysfunction
 - Novel agents may be of value as adjuncts
 - No recent prospective controlled acute phase adjunctive trials in late life MDD; open and retrospective trials support the use of aripiprazole

Case 9

- A 72-year-old man with no history of depression reports symptoms of depression such as sadness, mild anhedonia, and mild insomnia. His HDRS score is 17. What would you recommend?
 1. Problem-solving therapy
 2. Antidepressant medication
 3. Combination treatment of psychotherapy and anti-depressant

Case 10

A 57-year-old man with a 35 year history of schizophrenia who is taking risperidone 4mg daily reports that he is feeling more depressed and scores 12 on the Hamilton Depression Scale (i.e., subsyndromal depression). All labs are normal. Which of the following might be reasonable to consider:

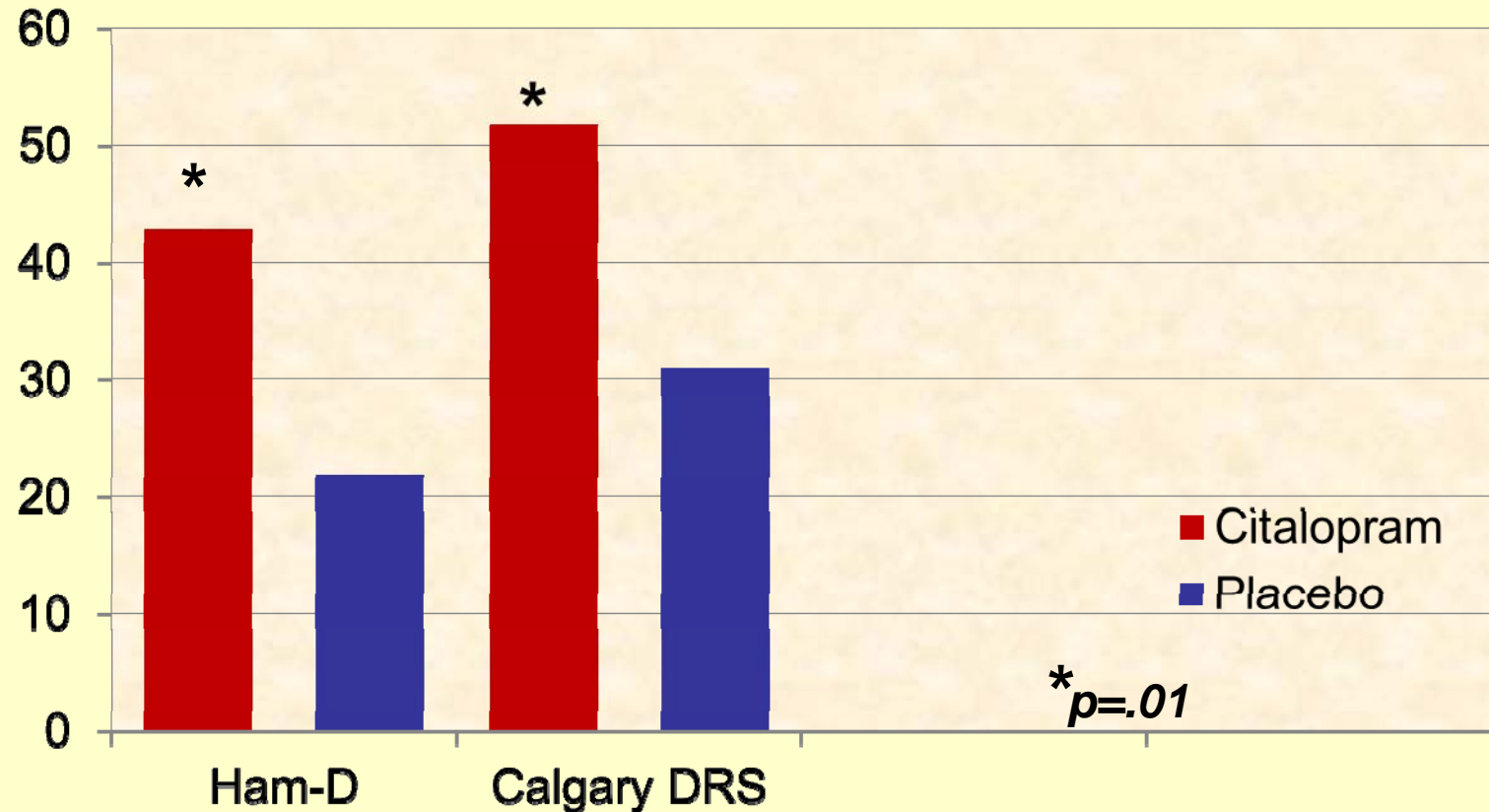
- 1.Trial of citalopram.**
- 2.Increase Risperdal dosage.**
- 3.Switch to olanzapine.**
- 4.Try CBT.**
- 5.All of the above.**
- 6.None of the above.**

There has been only been one large-scale randomized, double-blind controlled trial comparing atypical antipsychotics—
risperidone(1mg to 3mg/day, median dose 2mg/day) and olanzapine(5mg to 20mg/day, median dose 10mg/day)-- in adults older than 60 (Jeste et al, 2003).

Positive symptoms, negative symptoms, disorganized thoughts, and symptoms of anxiety/depression improved significantly from baseline in both groups. There were no significant differences in side effects except for more clinically significant weight gain in the olanzapine group.

Citalopram augmentation for subsyndromal symptoms of depression in middle-aged and older outpatients with schizophrenia and schizoaffective disorder: a randomized controlled trial.

Zisook et al, 2009



***Percent Responders
(>50% change from baseline)***

Cognitive Behavioral Social Skills Training(CBSST) in Middle-aged and Older Adults with Schizophrenia (Granholm et al, 2013)

- Improved everyday functioning
- Reduced depression and anxiety
- Increased motivation and self–esteem
- Improved life satisfaction
- Persons with most defeatist performance attitudes benefited the most
- CBSST does better than Tx as Usual and Goal-focused Supportive Contact (although latter also showed improvements in mood

Case 10

A 57-year-old man with a 35 year history of schizophrenia who is taking risperidone 4mg daily reports that he is feeling more depressed and scores 12 on the Hamilton Depression Scale (i.e., subsyndromal depression). All labs are normal. Which of the following might be reasonable to consider:

- 1.Trial of citalopram.**
- 2.Increase Risperdal dosage.**
- 3.Switch to olanzapine.**
- 4.Try CBT.**
- 5.All of the above.**
- 6.None of the above.**