

Behandeling van gedragsproblemen bij personen met dementie

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Behavioral and Psychological Symptoms in Dementia (BPSD)

- **Relatively recent** interest in non-cognitive or neuropsychiatric symptoms in dementia

- **International Psychogeriatric Association** (IPA)

  (Consensus Statement, Finkel et al. Am J Geriatr Psychiatry 1998)

Neuropsychiatric Inventory Questionnaire (NPI-Q) *(J. Cummings 1994,1998)*

12 items:

Agitation/aggresion
Irritability
disinhibition
aberrant motor behavior
elation/euphoria
Delusions
Hallucinations
Anxiety
Depression
apathy
Sleep disturbance
Appetite changes

Name of patient: _____ Date: _____

Informant: Spouse: _____ Child: _____ Other: _____

Please answer the following questions based on *changes* that have occurred since the patient first began to experience memory problems. Circle "yes" only if the symptom has been present in the *past month*. Otherwise, circle "no".

For each item marked "yes":

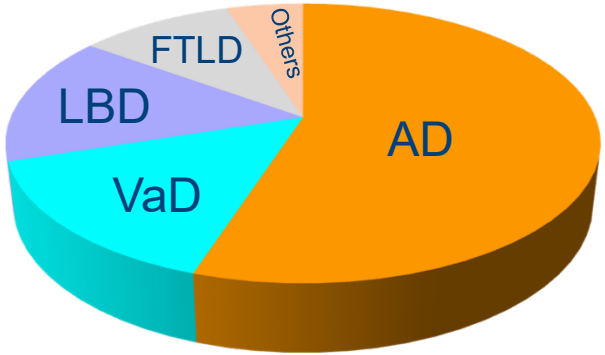
Rate the *severity* of the symptom (how it affects the patient):
1 = Mild (noticeable, but not a significant change)
2 = Moderate (significant, but not a dramatic change)
3 = Severe (very marked or prominent; a dramatic change)

Rate the *distress* you experience because of that symptom (how it affects you):
0 = Not distressing at all
1 = Minimal (slightly distressing, not a problem to cope with)
2 = Mild (not very distressing, generally easy to cope with)
3 = Moderate (fairly distressing, not always easy to cope with)
4 = Severe (very distressing, difficult to cope with)
5 = Extreme or very severe (extremely distressing, unable to cope with)

Please answer each question honestly and carefully. Ask for assistance if you are not sure how to answer any question.

Delusions	Does the patient believe that others are stealing from him or her, or planning to harm him or her in some way?										
Yes	No	Severity:	1	2	3	Distress:	0	1	2	3	4	5
Hallucinations	Does the patient act as if he or she hears voices? Does he or she talk to people who are not there?										
Yes	No	Severity:	1	2	3	Distress:	0	1	2	3	4	5
Agitation or aggression	Is the patient stubborn and resistive to help from others?										
Yes	No	Severity:	1	2	3	Distress:	0	1	2	3	4	5
Depression or dysphoria	Does the patient act as if he or she is sad or in low spirits? Does he or she cry?										
Yes	No	Severity:	1	2	3	Distress:	0	1	2	3	4	5
Anxiety	Does the patient become upset when separated from you? Does he or she have any other signs of nervousness, such as shortness of breath, sighing, being unable to relax, or feeling excessively tense?										
Yes	No	Severity:	1	2	3	Distress:	0	1	2	3	4	5
Elation or euphoria	Does the patient appear to feel too good or act excessively happy?										
Yes	No	Severity:	1	2	3	Distress:	0	1	2	3	4	5
Apathy or indifference	Does the patient seem less interested in his or her usual activities and in the activities and plans of others?										
Yes	No	Severity:	1	2	3	Distress:	0	1	2	3	4	5
Disinhibition	Does the patient seem to act impulsively? For example, does the patient talk to strangers as if he or she knows them, or does the patient say things that may hurt people's feelings?										
Yes	No	Severity:	1	2	3	Distress:	0	1	2	3	4	5
Irritability or lability	Is the patient impatient and cranky? Does he or she have difficulty coping with delays or waiting for planned activities?										
Yes	No	Severity:	1	2	3	Distress:	0	1	2	3	4	5
Motor disturbance	Does the patient engage in repetitive activities, such as pacing around the house, handling buttons, wrapping string, or doing other things repeatedly?										
Yes	No	Severity:	1	2	3	Distress:	0	1	2	3	4	5
Nighttime behaviors	Does the patient awaken you during the night, rise too early in the morning, or take excessive naps during the day?										
Yes	No	Severity:	1	2	3	Distress:	0	1	2	3	4	5
Appetite and eating	Has the patient lost or gained weight, or had a change in the food he or she likes?										
Yes	No	Severity:	1	2	3	Distress:	0	1	2	3	4	5

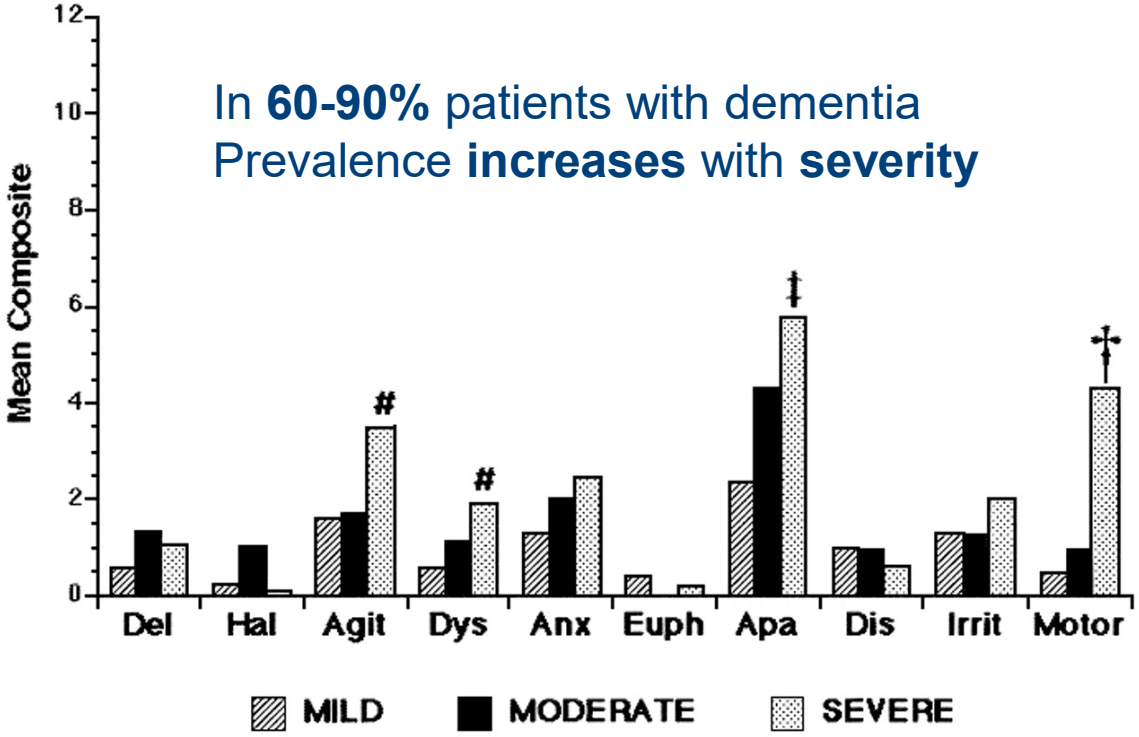
BPSD: type of dementia



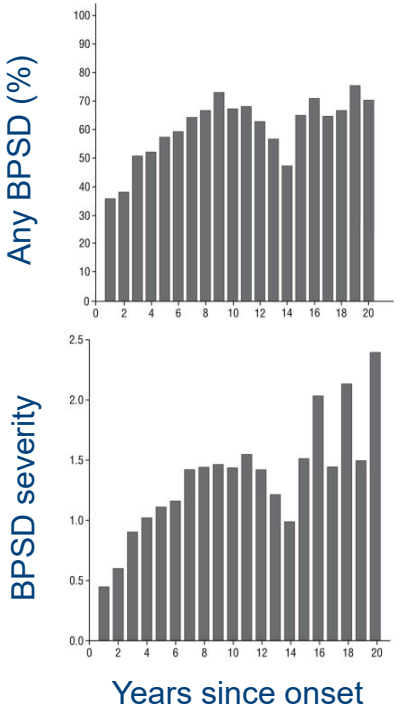
- Occurs independently of subtype of dementia
- Depression more common in vascular dementia
- Hallucinations: LBD > AD
- FTD: more often disinhibition, wandering, apathy

BPSD: prevalence

In **60-90%** patients with dementia
Prevalence **increases** with **severity**

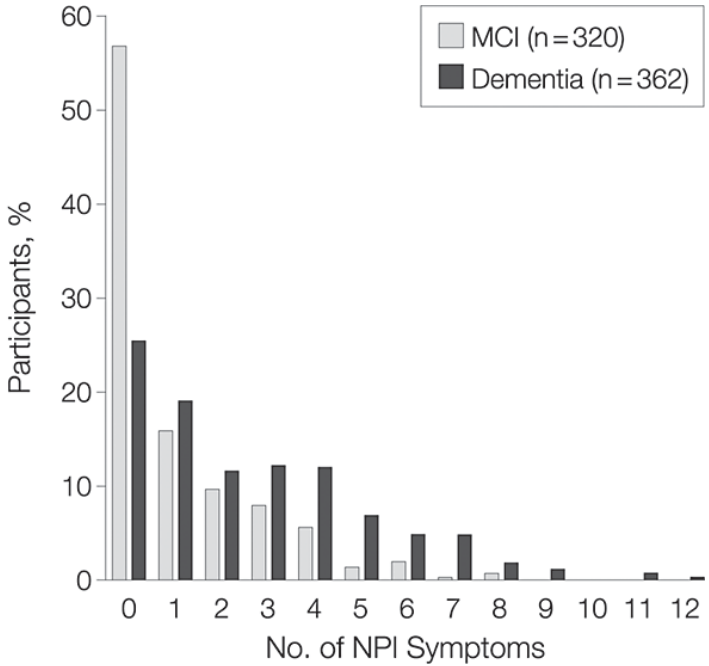


Mega et al. Neurology 1996



Scarmeas et al. Arch Neurol 2007

BPSD: prevalence



Symptoms	No. (%) MCI (n = 320)	No. (%) Dementia (n = 362)	χ^2_1 Test†
Delusions	15 (4.7)	109 (30.1)	75.6
Hallucinations	8 (2.5)	59 (16.3)	37.1
Agitation/aggression	47 (14.7)	145 (40.1)	54.4
Depression	84 (26.3)	158 (43.6)	23.0
Anxiety	33 (10.3)	92 (25.4)	27.9
Euphoria	4 (1.3)	11 (3.0)	
Apathy	58 (18.1)	164 (45.3)	61.2
Disinhibition	13 (4.1)	66 (18.2)	33.7
Irritability	53 (16.6)	123 (34.0)	28.3
Aberrant motor behavior	13 (4.1)	62 (17.1)	31.2

At least 1 NPI symptom from onset of cognitive symptoms:
80% in dementia
50% in MCI

Lyketsos et al. JAMA 2002

BPSD: fluctuations over time

- **BPSD** tend to last **long periods of time** but may **fluctuate** in **frequency** and **severity**

- Highly persistent overall, but **highly changeable in individuals**. Less severe symptoms more likely to improve. Elation, hallucinations, and appetite disorder most likely to improve. (*Ryu et al. Am J Geriatr Psychiatry 2005)*

BPSD: fluctuations over time

- **Mood disorders** (depression, elation, anxiety), may **not tend to persist**. *18% of participants with depression at baseline had depression after 2 years (14% for elation; 26% for anxiety). Incidence of these symptoms also very low (4% for depression; 8% for elation; 2% for anxiety)*.
- **Psychosis more persistent**. *Persecutory delusions persistent in 42% (misidentification in 50%). High incidence of misidentifications (28%). Hallucinations had lower incidence and persistence than other symptoms of psychosis.*

Savva et al. Br J Psychiatry 2009



BPSD: associations/consequences

- **Functional impairment** and **cognitive decline**
- Accelerate or lead to **nursing home placement, long-term hospitalization**

- "**Delusions and hallucinations** associated with increased risk for cognitive and functional decline; hallucinations predict institutionalization and death" (*Scarmeas et al. Arch Neurol 2005*)
- "**Disruptive behavior** (wandering, verbal outbursts, physical threats/violence, agitation/restlessness, and sundowning) predicts cognitive decline, functional decline, and institutionalization but not mortality" (*Scarmeas et al. Arch Neurol 2007*)



BPSD: impact on caregivers

- Impact of BPSD **greater than** of **cognitive symptoms** on 'caregiver burden' (*Van Den Wijngaart et al. Aging Ment Health* 2007)

- Caregivers of patients with behavioral symptoms are more **distressed** and **depressed** than those not managing behaviors. (*de Vugt et al. Int J Geriatr Psychiatry 2004)*

BPSD: initial approach

- What is the **underlying cause** of behavioral change?

- If ‘new onset’ or ‘deterioration’: infection? drug therapy (anticholinergics, benzodiazepines)?, pain?, sleep deprivation?, sensory deficits? => **delirium?!**

Non-pharmacological treatment

- What is the **underlying cause** of behavioral change?
- **Functional analysis:** understanding of the function or meaning behind the person's distressed behavior
- **Behavioral symptoms as expressions of:**

  -unmet needs (e.g., repetitive vocalizations for auditory stimulation) which are potentially modifiable (Gitlin et al. *J Am Geriatr Soc* 2010)

  -inadvertently reinforced behavior in response to environmental triggers (e.g. patient learns screaming attracts increased attention)

  -consequences of a mismatch between the environment and a patient's a abilities to process and act upon cues, expectations, and demands."

=> Tailored 'non-pharmacologic' plan → 'person-centered care'

+ essential to educate and support caregiver

Non-pharmacological treatment

Systematic review of RCTs

- Person-centered care (tailored > < impersonal, intrusive), communication skills training and adapted dementia care mapping **decreased symptomatic and severity of agitation** in care homes immediately and for **up to 6 months afterwards**
- **Activities and music therapy protocol** decreased overall agitation **sensory intervention** decreased clinically significant agitation immediately.
- Aromatherapy and light therapy: no efficacy.

Small effect sizes!

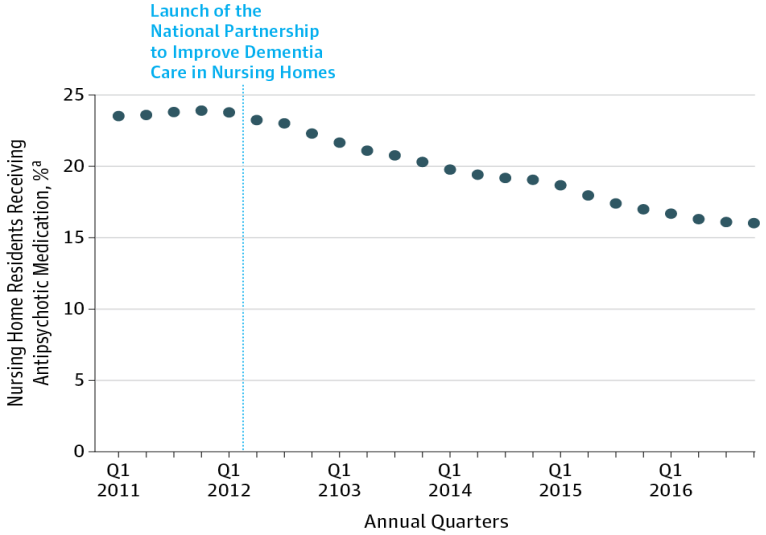
Livingston al. Br J Psychiatry 2014

Caregiver support decreases the odds of institutionalisation

- Meta-analysis of 13 studies (Spijker et al. J Am Geriatr Soc 2008)
- Most interventions were individualized, intensive interventions designed to meet the **unique needs of patients and their caregivers** at the appropriate time
- **Actively involving caregivers in making choices** about treatments distinguishes effective from ineffective support programs.

Effect of non-pharmacological approach on antipsychotic medication use

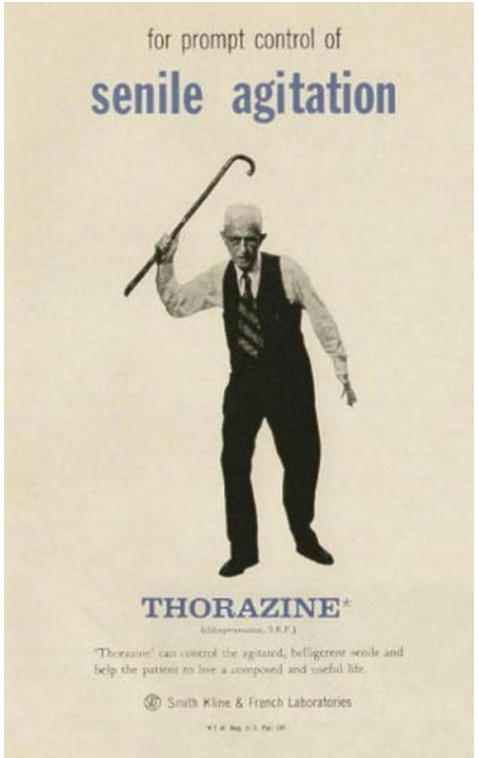
- **National Partnership to Improve Dementia Care in Nursing Homes**
- Use of non-pharmacologic approaches and person-centered dementia care practices



BUT: non-pharmacological approach is not a replacement for pharmacological treatment

Gurwitz et al. JAMA 2017

Pharmacological treatment of agitation/aggression



AchE-I for agitation/aggression

Systematic review and meta-analysis

- Small benefits with questionnable clinical significance as most studies included relatively mild BPSD.

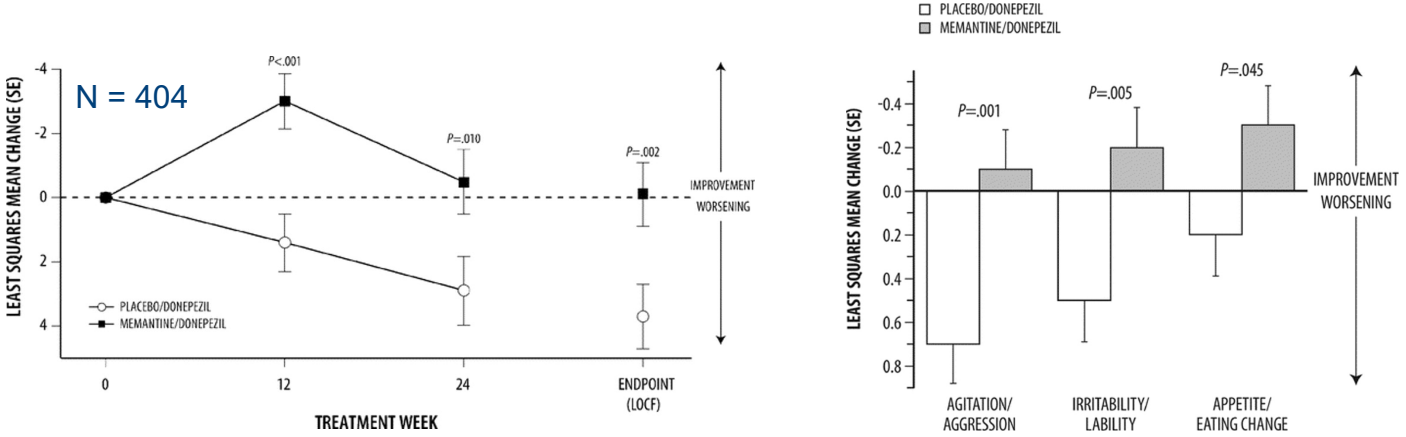
- Bad safety outcomes: drop-out due to adverse events (risk ratio (RR) 1.64; 95% CI 1.12 to 2.42)

- **Trial warranted in mild to moderate AD**

Wang et al. J Neurol Neurosurg Psychiatry 2015

Memantine for agitation/aggression

- **No clinically significant effect** in meta-analysis (Wang et al. *J Neurol Neurosurg Psychiatry 2015)*
- However: reduction of agitation/aggression (NPI-scores) in patients who were agitated at baseline and delayed its emergence in those who were free of agitation at baseline (Cummings et al. Neurology 2006); benefits on cluster of agitation/aggression/psychosis (Wilcock et al. J Clin Psychiatry 2008; post-hoc analysis 3 RCTs)



Cummings et al. Neurology 2006

SSRIs for agitation/aggression

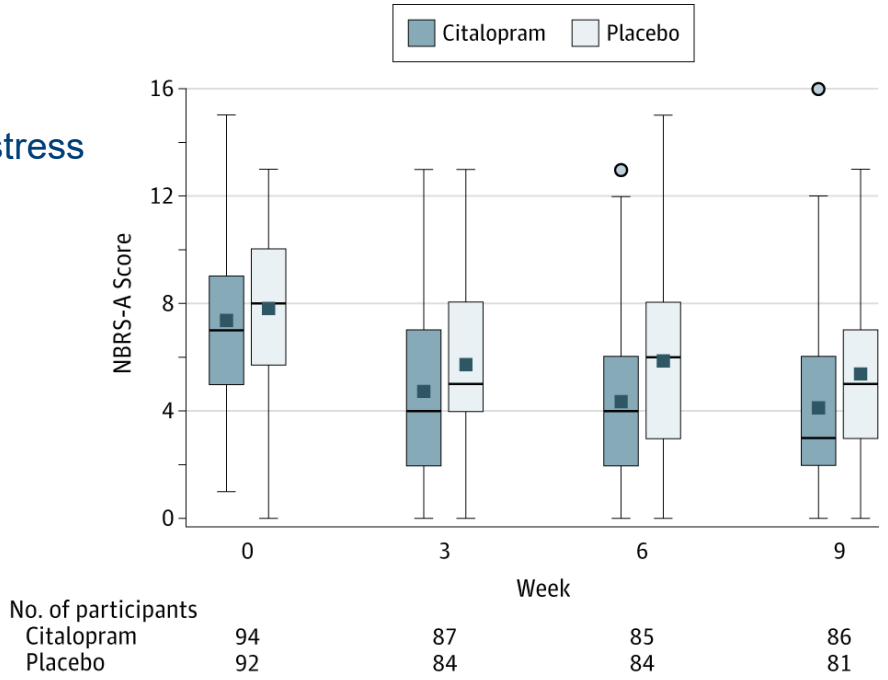
- Preference for Citalopram and Sertraline in elderly
- Limited evidence (meta-analysis: Seitz et al. Cochrane Database Syst Rev 2011), but well tolerated

Citalopram for Agitation in Alzheimer's Disease study (CitAD-study)

Significant reduction of agitation and caregiver distress

No increased withdrawal due to adverse events
BUT **cognitive** and **cardiac adverse effects**
at dosage of **30mg** (recommendation: 10 - 20mg)

Also reductions in the frequency
of irritability, anxiety, and delusions
(Leonpacher et al. Am J Psychiatry 2016)



Porsteinsson et al. JAMA 2014

Citalopram versus Risperidone

- **Double blind RCT** in 103 non-depressed patients with dementia hospitalized because of behavioral symptoms (including psychosis).

- **No statistical difference** was found after 12 weeks **in the efficacy** of citalopram and risperidone for the treatment of either agitation or psychotic symptoms BUT **greater side-effect burden for risperidone**

Pollock et al. Am J Geriatric Psychiatry 2007

Trazodone for agitation/aggression

- Little evidence
- Not superior to placebo in multicenter RCT with149 AD patients *(Teri et al. Neurology 2000)*

- Trial starting with 25mg (max. 150mg) warranted, especially if sleeping disturbances

Anti-epileptic drugs / mood stabilizers for agitation/aggression

- **Not recommended** by systematic review (Sink et al. JAMA 2005)

- Carbamazepine in nursing home patients with advanced dementia (modal dose 300mg; 5,3 mcg/mL) *(Tariot et al. Am J Psychiatry 1998)*
- Valproate: modest benefits *(Lindenmayer et al. J Clin Psychiatry 2000; Porsteinsson et al. Am J Geriatr Psychiatry 2001)*
- Gabapentin: open-label prospective study showed little benefit *(Herrmann et al. J Clin Psychopharmacol 2000)*, mild side effect profile
- Lamotrigine: No randomized controlled trials



Drugs to avoid in the treatment of agitation



- **Benzodiazepines**: paradoxal reactions, gait disturbance, dependency,…
- **Antihistaminic** drugs e.g. diphenhydramine (also anticholinergic) or promethazine

Atypical antipsychotics for agitation/aggression

- **Limited evidence** of clinically meaningful benefit / modest effects
- Limitations: heterogeneity of population, outcome measures (scales), setting

- **Most evidence for Risperidone**, no benefit for Quetiapine compared to placebo in meta-analysis of RCTs *(Schneider et al. Am J Geriatr Psychiatry 2006)*
- Modest effects for Olanzapine in systematic review *(Lee et al. BMJ 2004)* and for Aripiprazole in meta-analysis *(Maher et al. JAMA 2011)*
- **High placebo response rates** (45% vs 55% for risperidone) may indicate that benefit is often related to general benefits of good clinical practice, clinical review, treatment of comorbidity, and improved social interaction as a result of trial involvement.



- **CATIE-AD trial**

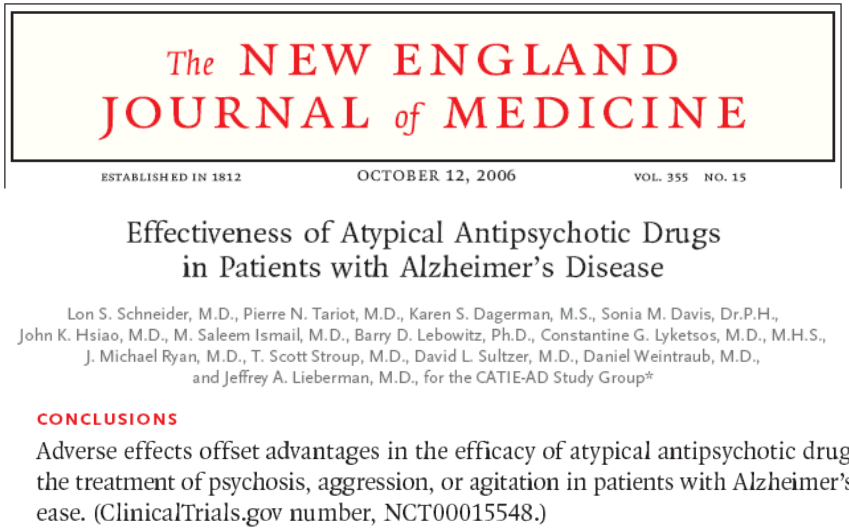
  -N = 421

  -Antipsychotic (mean) doses:

  Risperidone 1 mg
  Olanzapine 5.5 mg
  Quetiapine 56.5 mg

  -Side effects > efficacy (CGI-C)

  -Most help for suspicious thoughts, paranoid delusions, hostile/aggressive behavior



The NEW ENGLAND JOURNAL of MEDICINE

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Effectiveness of Atypical Antipsychotic Drugs in Patients with Alzheimer's Disease

Lon S. Schneider, M.D., Pierre N. Tariot, M.D., Karen S. Dagerman, M.S., Sonia M. Davis, Dr.P.H., John K. Hsiao, M.D., M. Saleem Ismail, M.D., Barry D. Lebowitz, Ph.D., Constantine G. Lyketsos, M.D., M.H.S., J. Michael Ryan, M.D., T. Scott Stroup, M.D., David L. Sultzer, M.D., Daniel Weintraub, M.D., and Jeffrey A. Lieberman, M.D., for the CATIE-AD Study Group*

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. (ClinicalTrials.gov number, NCT00015548.)

- More patients discontinued placebo for lack of efficacy than those on Olanzapine or Risperidone (70% vs 39% and 44%)
- No benefit for function, quality of life or caregiving time

Antipsychotics and mortality risk

- Systematic review of 15 RCTs of antipsychotics in AD reported **1% attributable risk of mortality over 12 weeks of treatment** *(Schneider et al. JAMA 2005)*

- A 12 month double blind RCT examining antipsychotic **discontinuation** in AD, with follow-up for up to five years, found a **significant reduction in mortality associated with discontinuation** with a risk difference in mortality of 29% after 36 months *(Ballard et al. Lancet Neurol 2009)*



Antipsychotics and mortality risk

- Excess mortality risk: **FGA > olanzapine > risperidone > quetiapine**
- **Higher doses** associated with **increased risk** (3.5% increase absolute risk in high-dose versus low-dose subgroup) *(Maust et al. JAMA Psychiatry 2015)*
- Also increased risk in short-term use *(Rochon et al. Arch Intern Med 2008)*
- Mechanisms unclear
- Causality? Overestimation?



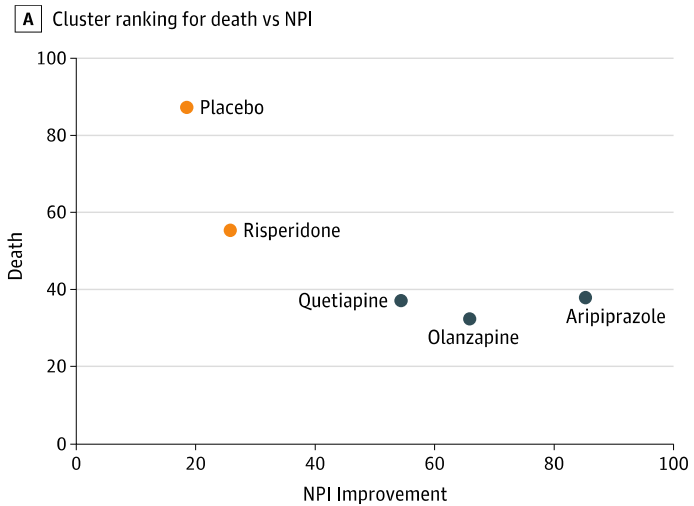
Antipsychotics and risk of stroke

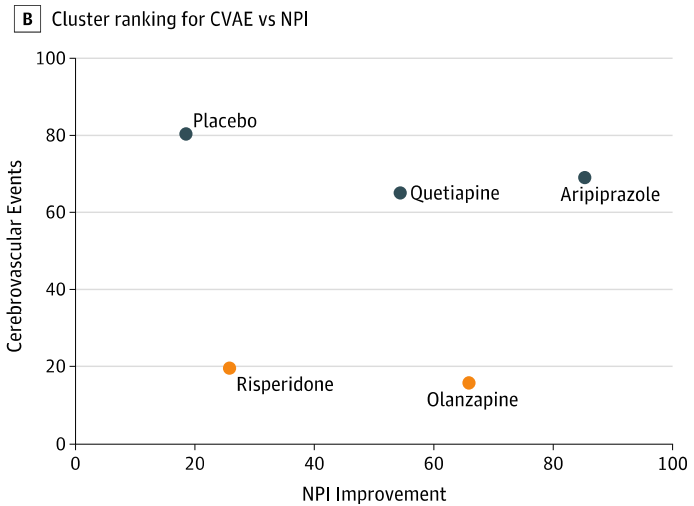
- Compared with placebo, risperidone (**OR, 3.85**; 95% CI, 1.55-9.55) and olanzapine (**OR, 4.28**; 95% CI, 1.26-14.56) are associated with increased risk of CVAEs.

(Yunusa et al. JAMA 2019)

Which SGA is most efficacious and safest?

-Network meta-analysis
-17 studies, 5373 patients

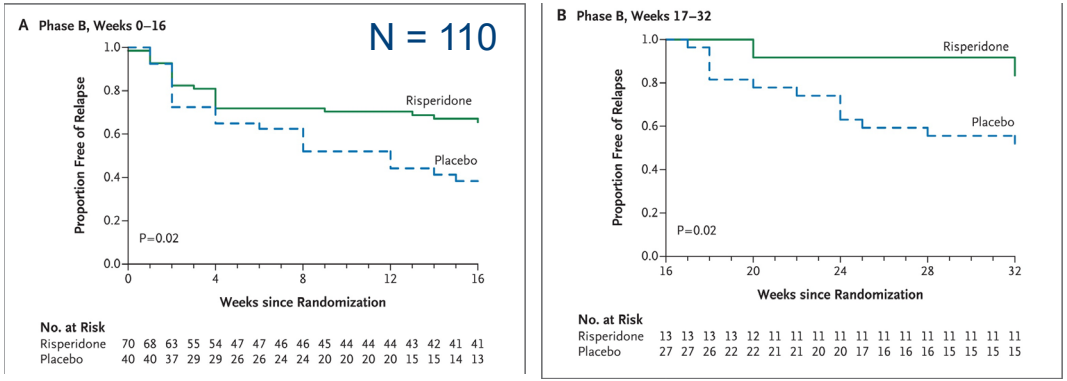




Yunusa et al. JAMA 2019

Discontinuation of antipsychotics?

- APA recommends discontinuation trial **after 4 months** if a previous trial did not cause relapse *(Reus et al. Am J Psychiatry 2016)*
- Patients with more severe symptoms at baseline could benefit from continuing their antipsychotic medication. *(Devanand et al. NEJM 2012)*



- Patients with severe baseline irritability/lability and severe auditory hallucinations may be at increased risk for relapse *(Patel AN et al Am J Psychiatry 2017)*

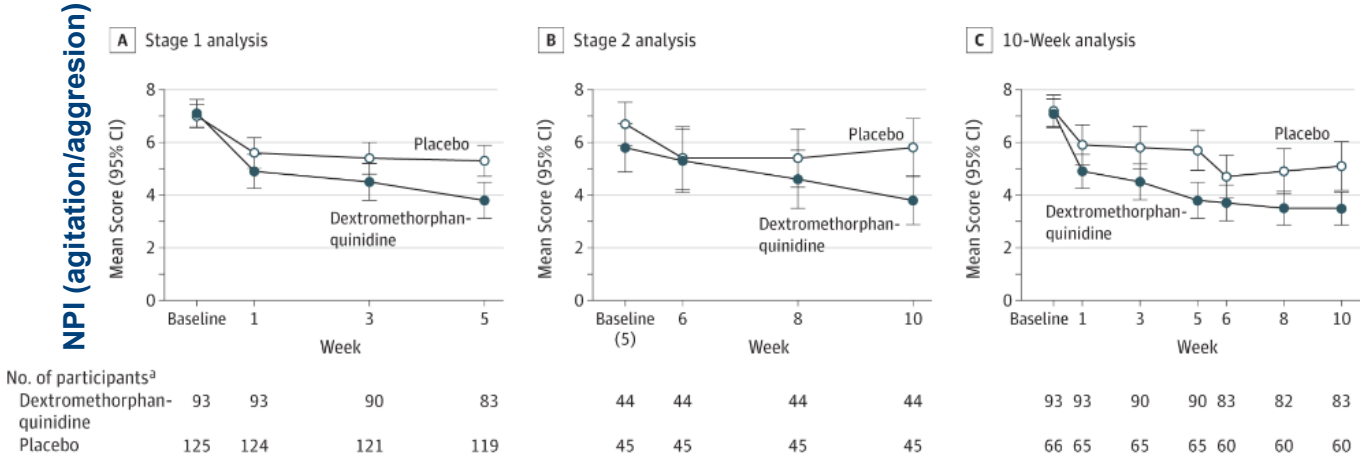
Discontinuation of SSRIs?

- Withdrawal of SSRI for indication other than depression was associated with significantly worse depressive symptoms and non-significant worsening of neuropsychiatric symptoms

  (DESEP study - *Bergh S et al BMJ 2012*)

Dextromethorphan-Quinidine for agitation

- Dextromethorphan-quinidine 20mg/10mg
- N = 220 AD patients with significant agitation (>90% outpatients mostly already on medication); Two consecutive 5 week stages
- Reduction of **1.5 point on the NPI** agitation/aggression domain (clinical significance?)



Cummings et al. JAMA 2015

ECT for agitation in dementia:
A promising option for the future?



- **No RCT available**

- **Evidence** so far **limited** by concomitant psychotropic medications, inconsistent use of rating scales, short follow-up, lack of a control group, small sample sizes, and publication bias *(Glass et al. Int Psychogeriatr 2017)*

Pharmacological treatment of depression



Depression in dementia

- Challenging diagnosis (Cornell Scale for Depression in Dementia)
- Lack of specific diagnostic criteria

  (Olin et al. Am J Geriatr Psychiatry 2002)

- If in doubt, therapeutic trial with antidepressant

Depression in dementia

- First-line treatment: SSRI (escitalopram, citalopram, sertraline)
- Avoid TCA due to anticholinergic/anti-adrenergic properties

- Systematic review of RCTs: "The available evidence does not provide strong support for the efficacy of antidepressants for treating depression in dementia, especially beyond 12 weeks. On the only measure of efficacy for which we had high-quality evidence (depression rating scales scores), antidepressants showed **little or no effect**".

  (Dudas et al. Cochrane Database Syst Rev 2018)



Depression in dementia

- Most evidence for citalopram (may also improve psychotic or other behavioral symptoms)

N = 98 Citalopram 10 – 30 mg

technique (*$P<0.05$, paired t-test; **$P<0.01$, paired t-test (within groups); ⊘ $P<0.05$, unpaired t-test (between groups); and ⊗ $P<0.10$, unpaired t-test (between groups).

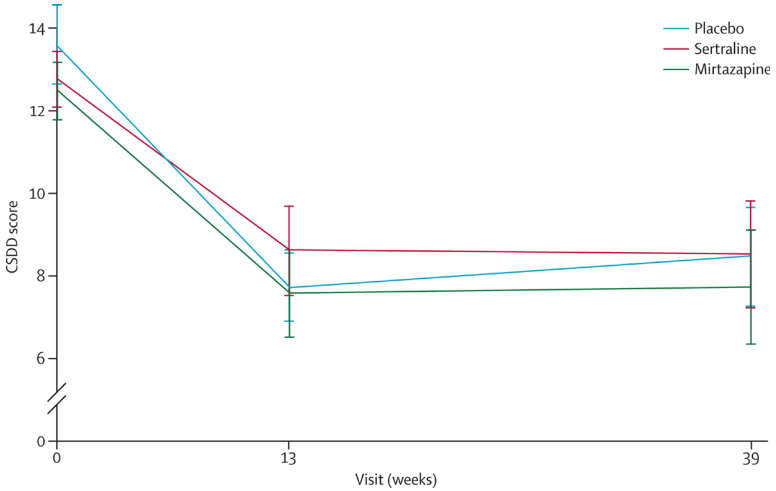
TABLE III

Average rating scores in patients with diagnosis AD/SDAT at baseline and at week 4 after treatment with double-blind technique

	Citalopram group Average score			*Placebo group Average score*			*Improvement: between group differences*		
	Baseline	*Week 4*	n	*Baseline*	*Week 4*	n	T	*d.f.*	P
CGI-severity of illness	3.897	3.897	29	3.909	4.032*	33	1.087	35[1]	0.284
Assessment of nursing situation	1.607	1.643	28	1.795	1.971	34	0.809	45[1]	0.423
GBS-ratings									
Subscale 1: motor impairment	7.408	6.667	27	8.282	7.813	32	0.346	48[1]	0.731
Subscale 2:									

Nyth et al. Br J Psychiatry 1990

Target dose: Sertraline 150mg, Mirtazapine 45mg



Banerjee et al. Lancet 2011

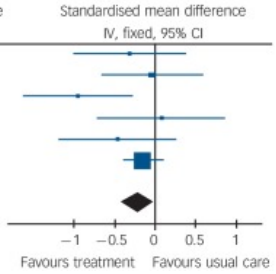
Depression in dementia

- Psychotherapy in mild to moderate dementia

Study or subgroup	Experimental Mean	s.d.	Total	Control Mean	s.d.	Total	Weight	Standardised mean difference IV, fixed, 95% CI
Burgener *et al*[33]	3.3	2.9	19	4.3	3.4	14	7.4%	−0.31 (−1.01, 0.38)
Burns *et al*[34]	5.4	2.6	20	5.5	3.1	20	9.3%	−0.03 (−0.65, 0.59)
Spector *et al*[35]	10.38	5.835	21	16.72	7.283	18	8.0%	−0.95 (−1.62, −0.28)
Stanley *et al*[36]	8.2	2.86	11	7.8	5.95	15	5.9%	0.08 (−0.70, 0.86)
Tappen & Williams[37]	15.13	9.54	15	19.13	7.37	15	6.8%	−0.46 (−1.18, 0.27)
Waldorff *et al*[38]	5.05	4.61	130	5.77	5.07	141	62.7%	−0.15 (−0.39, 0.09)
Total (95% CI)			216			223	100.0%	−0.22 (−0.41, −0.03)

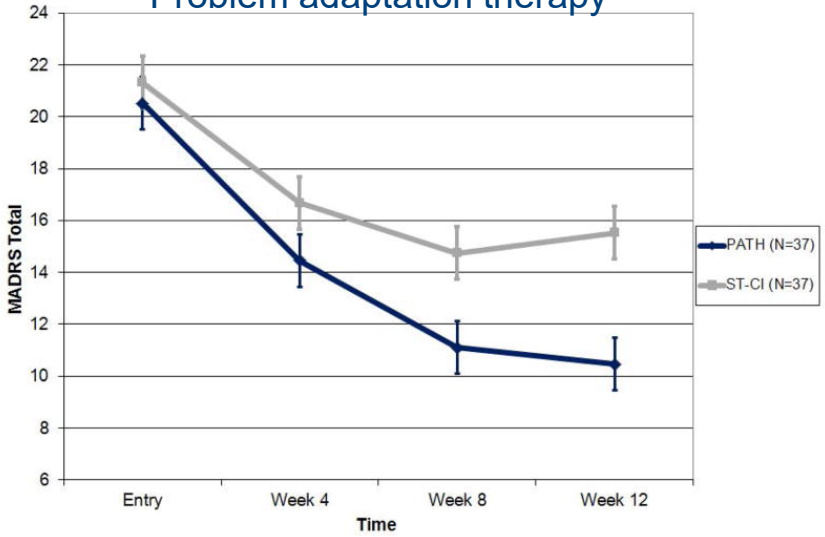
Heterogeneity: $\chi^2 = 6.33$, d.f. = 5 ($P = 0.28$); $I^2 = 21\%$

Test for overall effect: $Z = 2.30$ ($P = 0.02$)



Orgeta et al. Br J Psychiatry 2015

Problem adaptation therapy



Kiosses et al. JAMA Psychiatry 2015

Pharmacological treatment of apathy



Apathy in dementia

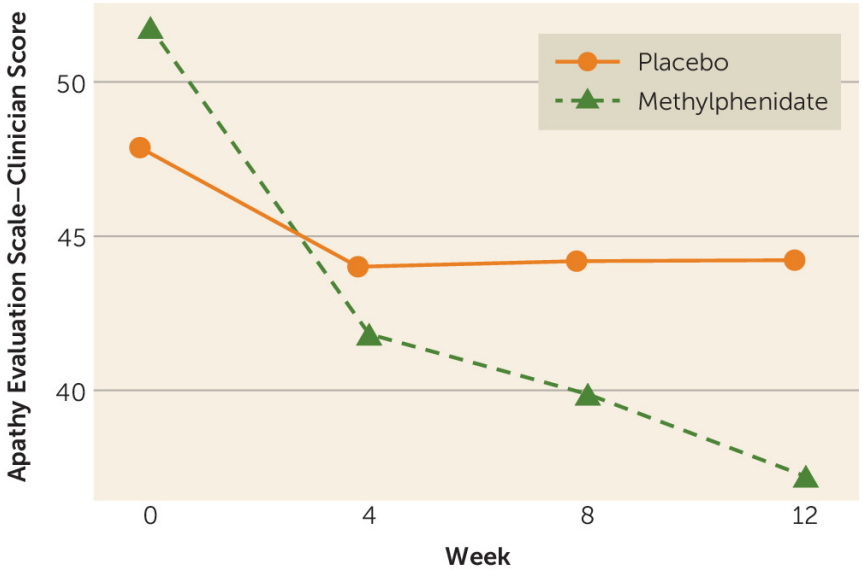
- DD with depression is challenging
- Functional impairment, **persistent over time**
- No well-studied non-pharmacological approach

- Stepwise approach: 1) AchE-I
  2) Antidepressant
  3) Methylphenidate

Apathy in dementia: methylphenidate

N = 60
Mild AD

Mean dose 10mg bd



Also improved cognition, functional status, caregiver burden, CGI scores, and depression

Well-tolerated
Cave: agitation, insomnia

Padala et al. Am J Psychiatry 2018

Take home message

- **BPSD** is highly **prevalent** and contribute to **great burden**
- Due to little evidence for efficacy and potential side-effects of drugs, **non-pharmacological approaches** need to be implemented **first**
- Targeted non-pharmacological approach however also have **little evidence for efficacy**
- Caution in using antipsychotics, SSRI as alternative, avoid benzodiazepines. **Weighing potential benefits vs risks**
- **Consider discontinuation** of pharmacological therapy

