Update on Pharmacologic Approaches to Agitation in Dementia

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Goals

- Review basic principles in the management of dementia-related agitation
- Discuss recent APA guidelines on antipsychotic use in dementia patients with agitation and psychosis
- Introduce emerging medication treatment options

Provisional definition

- Meets criteria for cognitive impairment/dementia
- At least 1 of the following, associated with emotional distress, recurrent/persistent for 2+ weeks:
  - Excessive motor activity
  - Verbal aggression
  - Physical aggression
- Severe enough to produce disability in at least 1 of the following
  - Interpersonal relationships, social functioning, ADL's

Cummings, et al. 2015

Characterize and quantify symptoms

- Type, frequency, pattern, timing
- Likert scale
- Family or staff logs
- Rating scales
  - Neuropsychiatric Inventory Questionnaire (NPI-Q)
  - Section E of the Minimum Data Set
  - Cohen-Mansfield Agitation Inventory

Assess for modifiable contributors and other factors

- Pain
- Health conditions
- Medications
- Dementia subtype (e.g. Dementia with Lewy Bodies or Parkinson Disease Dementia)

Nonpharmacologic interventions

- Interventions for family caregivers
  - Caregiver: Education and support, stress reduction, stress reduction, cognitive reframing, problem solving skills
  - Skills: Communication, environment, simplifying tasks
- Environmental modifications
  - Overstimulation, understimulation
  - Lack of activity and structure
  - Lack of established routines

Brasure, et al. 2016; Kales, et al. 2015

What do I do in my clinic?

- Alzheimer's Association referral

  http://www.alz.org/alzwa/
- Encourage caregivers to get support; provide education
- Get a history and problem solve triggers, if possible
- Discuss structure/routine (this could include placement)
- Referral to geriatric psychology, social work

Medication Rules of Thumb

- Start a low dose and titrate slowly to the minimum effective dose
- Balance potential benefit with potential side effects
  - This includes assessing the risk of under-treatment
- Keep in line with the patient and family's goals of care

Medications

- **Antipsychotics**
- **Citalopram**
- Benzodiazepines
- Cholinesterase inhibitors
- Memantine
- Anticonvulsants
  - valproate
  - carbamezapine
- **Dextromethorphan-quinidine**
- **Prazosin**

TABLE A–1. Research evidence for efficacy of second-generation antipsychotics (SGAs) from placebo-controlled trials

Antipsychotic	Symptom domain	Confidence	Effect	SMD (95% CI)
Aripiprazole	BPSD	Moderate	Small	0.20 (0.04, 0.35)
Aripiprazole	Agitation	Low	Small	—
Aripiprazole	Psychosis	Low	Nonsignificant	0.14 (–0.02, 0.29)
Olanzapine	Overall BPSD	Low	Very small	0.12 (0.00, 0.25)
Olanzapine	Agitation	Moderate	Very small	0.10 (0.07, 0.31)
Olanzapine	Psychosis	Insufficient	Nonsignificant	0.05 (–0.07, 0.17)
Quetiapine	Overall BPSD	Low	Nonsignificant	0.13 (–0.03, 0.28)
Quetiapine	Agitation	Insufficient	Nonsignificant	0.06 (–0.14, 0.25)
Quetiapine	Psychosis	Insufficient	Nonsignificant	0.04 (–0.11, 0.19)
Risperidone	Overall BPSD	Moderate	Very small	0.19 (0.00, 0.38)
Risperidone	Agitation	Moderate	Small	0.22 (0.09, 0.35)
Risperidone	Psychosis	Moderate	Small	0.20 (0.05, 0.36)
SGAs overall	Overall BPSD	High	Very small	—
SGAs overall	Agitation	Moderate	Small	—
SGAs overall	Psychosis	Low	Very small	—

Note. BPSD=behavioral and psychological symptoms of dementia; CI=confidence interval; SMD=standardized mean difference.
Source. Adapted from Maglione et al. 2011.

Reus, et al. 2016

Black box warning

"FDA ALERT [6/16/2008]: FDA is notifying healthcare professionals that both conventional and atypical antipsychotics are associated with an increased risk of mortality in elderly patients treated for dementia-related psychosis."

For atypical antipsychotics, there was an approximately 1.6- to 1.7-fold increase in mortality rate (4.5 percent, compared with 2.6 percent in the patients taking placebo)

APA Guidelines

- Use for symptoms that are severe, dangerous, and/or cause significant distress to the patient
- Potential risks/benefits discussed with patient, surrogate decision maker, with input from family or others involved
- If no clinically significant response after a 4-week trial, taper and discontinue

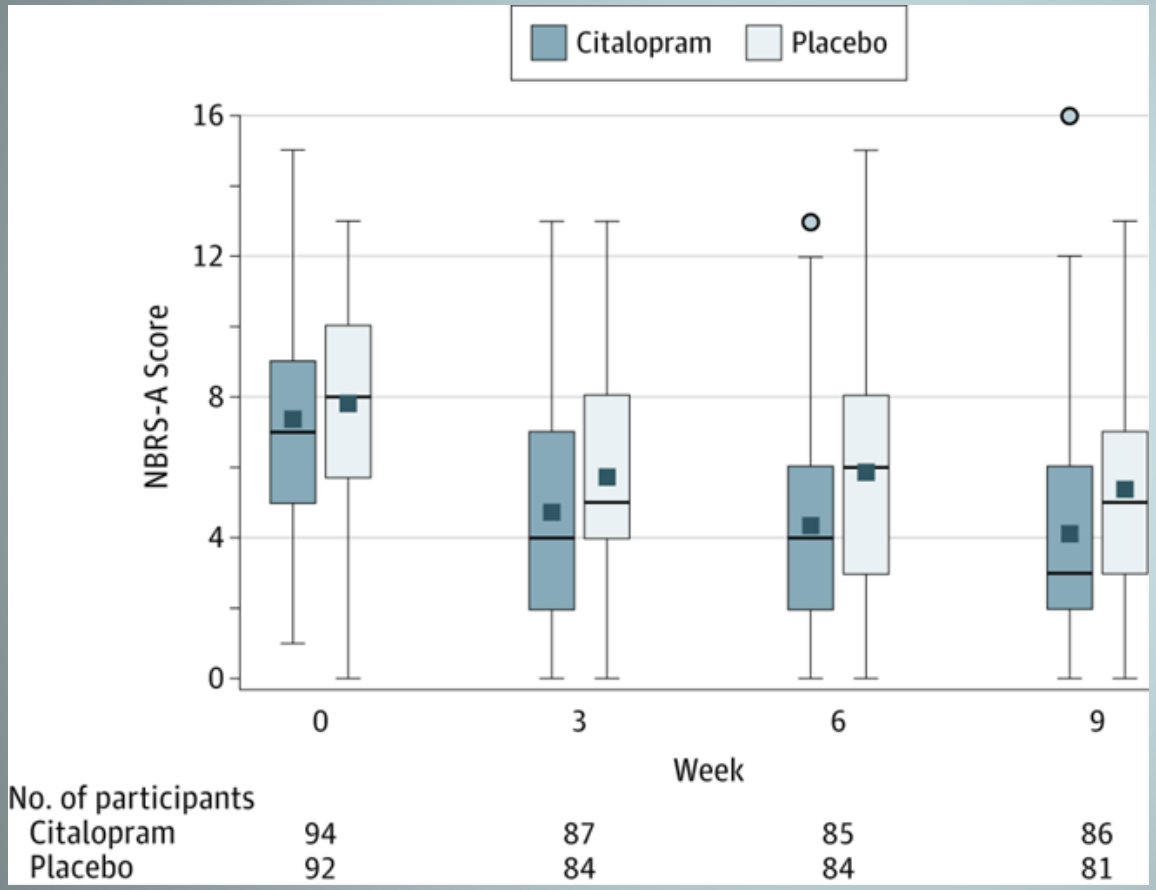
APA Guidelines

- If positive response, attempt to taper and withdraw within 4 months of initiation
  - Patient, family, and surrogate decision maker involvement
  - Exception: prior attempts resulted in recurrence of symptoms
- If tapered, assess for recurrence at least monthly for 4 months after medication discontinuation.

APA Guidelines

- For nonemergency situations, haloperidol should not be a first-line agent
- Long-acting injectables should not be used unless indicated for a co-occurring chronic psychotic disorder

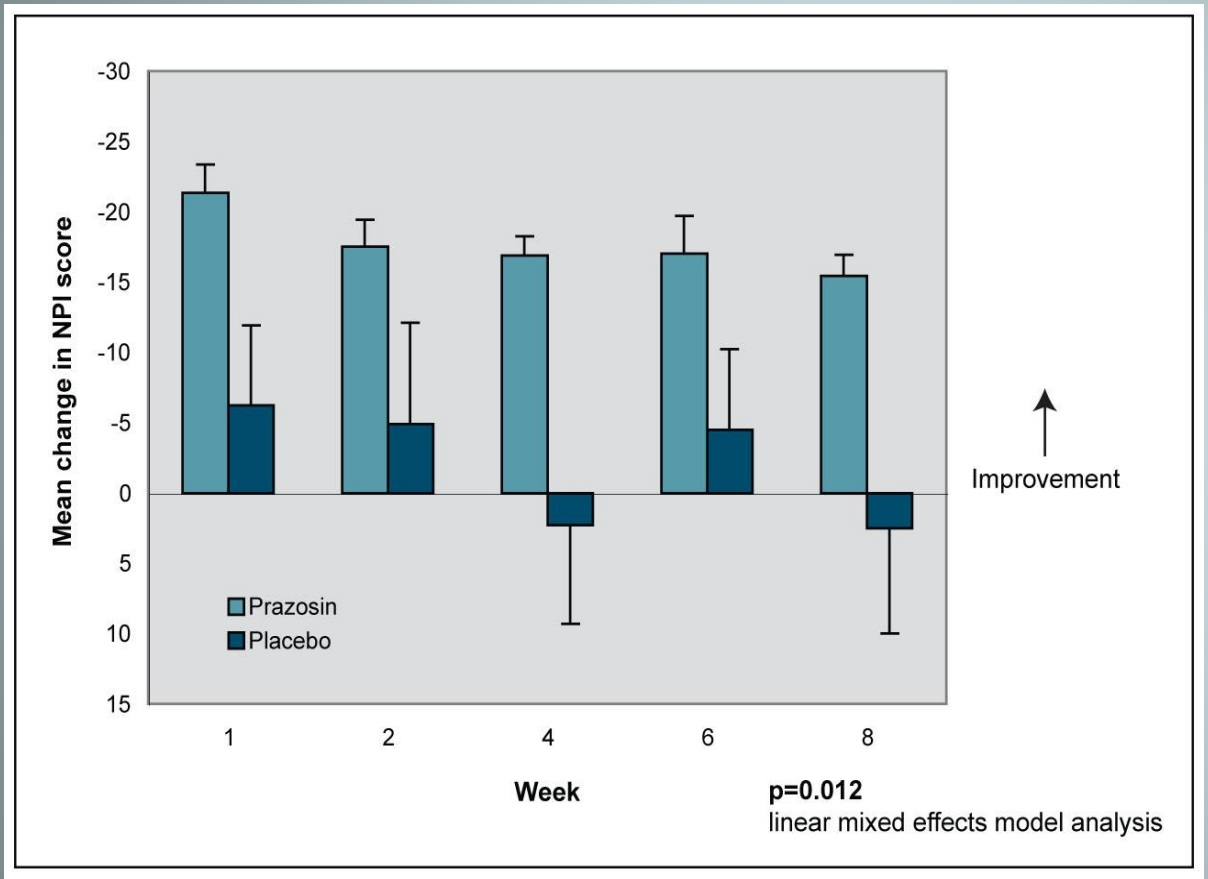
Citalopram



- 30mg daily
- QT changes
- MMSE decline
- moderate agitation and lower levels of cognitive impairment more likely to benefit

Porsteinsson, et al. 2014

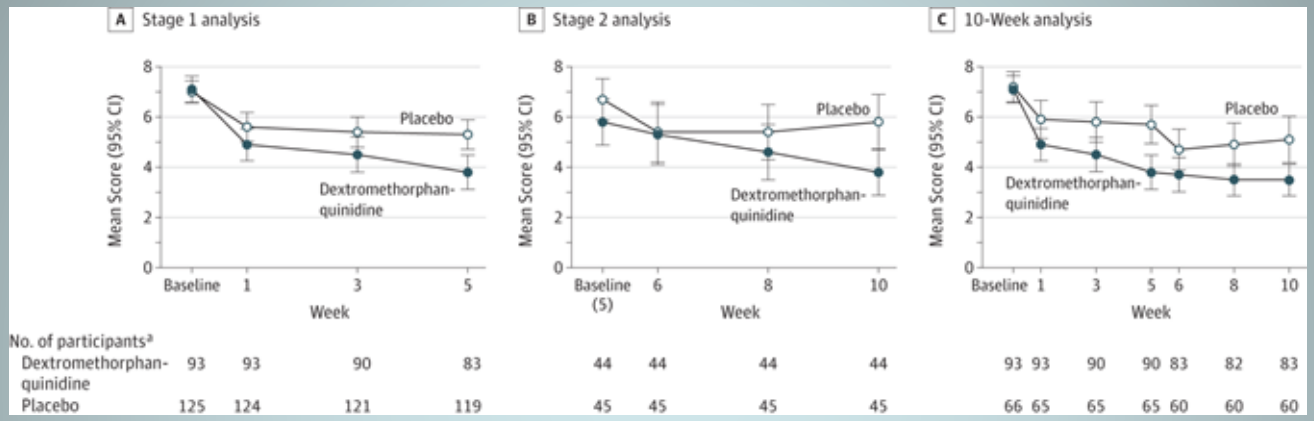
Prazosin



- 2mg qam and 4mg qhs
- Twelve participants in each arm (11 included in analysis)
- No differences in BP

Wang, et al. AJGP 2009

Dextromethorphan-Quinidine



- sequential parallel, comparison design
- 30/10mg twice daily
- Falls, diarrhea, UTI

Cummings, et al. JAMA 2015

What do I do in my clinic?

Agitation characteristics	Medication choices	Time frame
Infrequent Minimal distress	Cholinesterase inhibitors Memantine	Weeks to months
Frequent Significant distress Interferes with necessary care	SSRIs Prazosin Atypical antipsychotics	Days to weeks
Emergent Safety of the patient or others at risk	Atypical antipsychotic Benzodiazepines	Days

Consider anticonvulsant if above agents not effective;
Consider second agent if a first agent is partially effective

Summary

- Treatment planning is tailored to the patient
- Both nonpharmacologic and pharmacologic approaches are included
- New guidelines are in place for the prescription of and discontinuation of antipsychotic medications
- This continues to be an active area of research

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