Managing Noncognitive Behavioral Symptoms in Patients With Major Neurocognitive Disorders

James M. Ellison MD MPH

Swank Foundation Endowed Chair in Memory Care and Geriatrics
Christiana Care Health System, Wilmington, Delaware

Disclosures:

- Dr. Ellison reports no relevant conflicts of interest.
- Dr. Ellison will discuss unapproved or investigational uses of products during this presentation.

Agenda:

- Definitions
  - What are ***Major Neurocognitive Disorders***?
  - What are ***Noncognitive Behavioral Symptoms***?
- Nonpharmacologic Management
- Medications:
  - How are they used?
  - How helpful are they?
  - What harm can they do?

Major Neurocognitive Disorder (MND): The New Name for Dementias

Acquired loss of one or more *cognitive* abilities sufficient to *interfere* with independence.

DSM 5 "Major Neurocognitive Disorder"

A. Evidence of significant cognitive decline in **1 or more cognitive domains** based on
   1. Expressed concern, AND
   2. Substantial cognitive impairment (assessed quantitatively)

B. Cognitive deficits interfere with **independence** in everyday activities

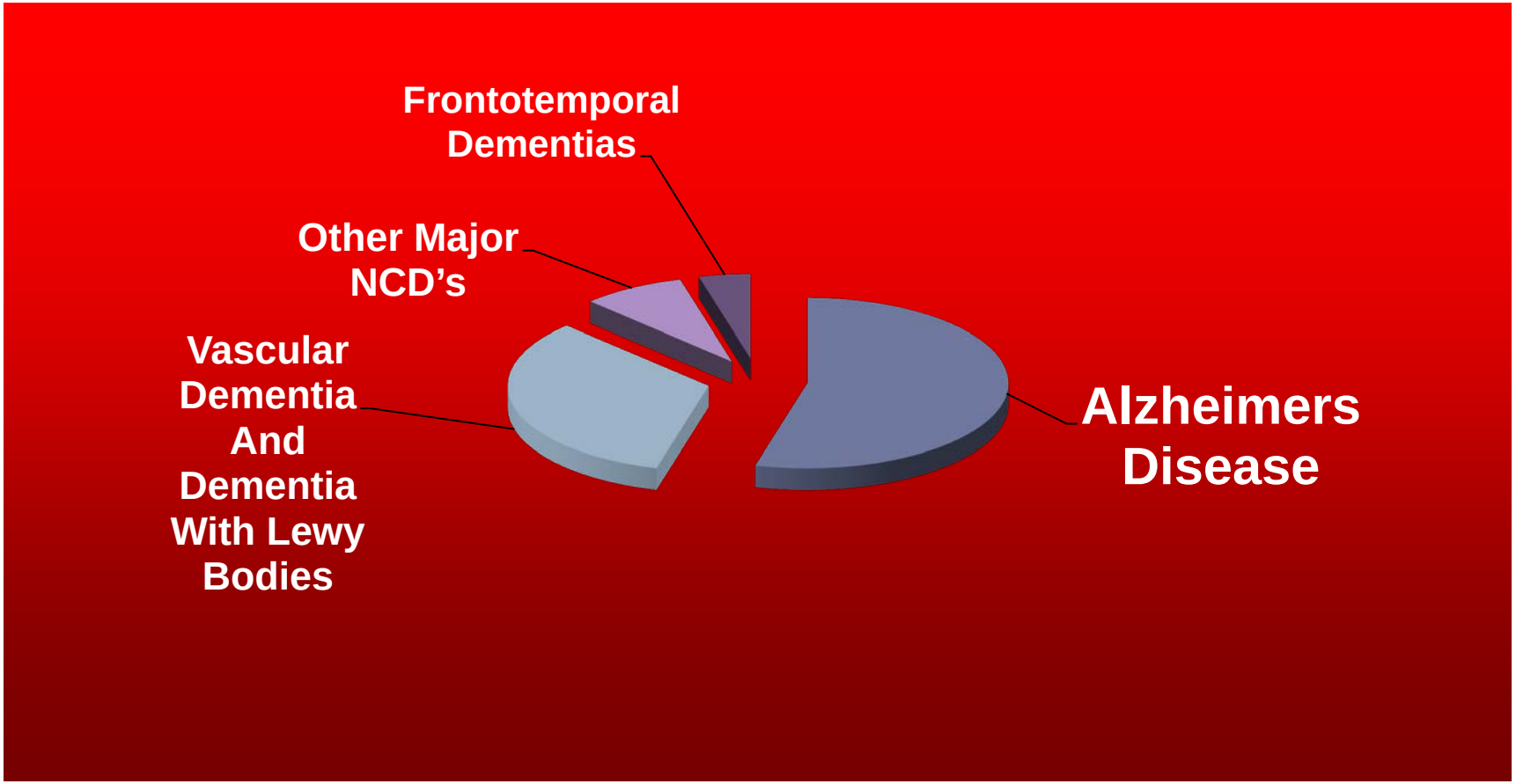
C. Not Delirium

D. Not another mental disorder

**Specify: AD, FTLD, LBD, VD, TBI, SUD, HIV, prion, PD, HD, other, multiple, unspecified*

Adapted from APA: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA, APA, 2013, p 602.

Alzheimer's Disease: The Most Prevalent MND



Other Maj. ND's include: PD, NPH, Alcohol dementia, TBI, Undetermined

modified from Plassman BL, Langa KM, Fisher GG, et al. Neuroepidemiology 2007;29:125–132.

Some Other, Potentially Modifiable Medical Causes of Cognitive Impairment

- Substances
  - Recreational drugs
  - Toxins
  - Medications: Prescribed/Abused
- Depression
- Sleep Disorders
- Post-surgical (post-anesthesia) impairment
- Infectious Diseases
- Cardiopulmonary Disorders
- Nutritional/Metabolic
- Endocrine Disorders
- Autoimmune Disorders
- Neoplasms

The Physician's Map of Dementia

Medications: Cognitive Enhancers
Better for Cognitive Symptoms Than for NCBS

Specific Agentsor	Evidence Says	Suggested Use
Cholinesterase Inhibitors		
Donepezil	Modest benefits in cognition, ADLs, Caregiver Burden, but questionable benefit for NCBS	Begin with 5 mg/d Increase to 10 mg/d (23 mg/d?)
Rivastigmine		Begin with 1.5 mg bid po Increase up to 6 mg bid po Or begin 4.6 mg patch and increase up to one 9.5 or 13.3 mg/patch per day
Galantamine ER		Begin with 8 mg ER q d Increase up to 24 ER q d
NMDA Receptor Antagonist		
Namenda (memantine) or Namenda XR	Modest benefits in cognition, ADLs, Caregiver Burden, but questionable benefit for NCBS	Begin with 5 mg IR bid and increase to 10 mg bid Begin with 7 mg q d and Increase to 28 mg q d

The Cholinesterase Inhibitors: Differentiating Characteristics

	Donepezil (Aricept)	Rivastigmine (Exelon, Exelon Transdermal)	Galantamine and "ER" (Razadyne)
Dosage strengths (mg)	5,10, 23 mg +ODT*	1.5, 3, 4.5, 6 mg	4, 8, 12 mg ER: 8, 16, 24 mg
Oral solution	1 mg/mL	2 mg/mL	4 mg/mL
Transdermal	NA	4.6 mg/24 hr, 9.5 mg/24 hr 13.3 mg/24 hr	NA
$T_{1/2}$ (hours)	73	5	6-8
Plasma protein binding	96%	40%	18%
CYP450 substrate of	2D6/3A4	NA	2D6/3A4
Monthly cost – Brand/Generic		**Can be high!**	

*ODT=orally disintegrating tablet.

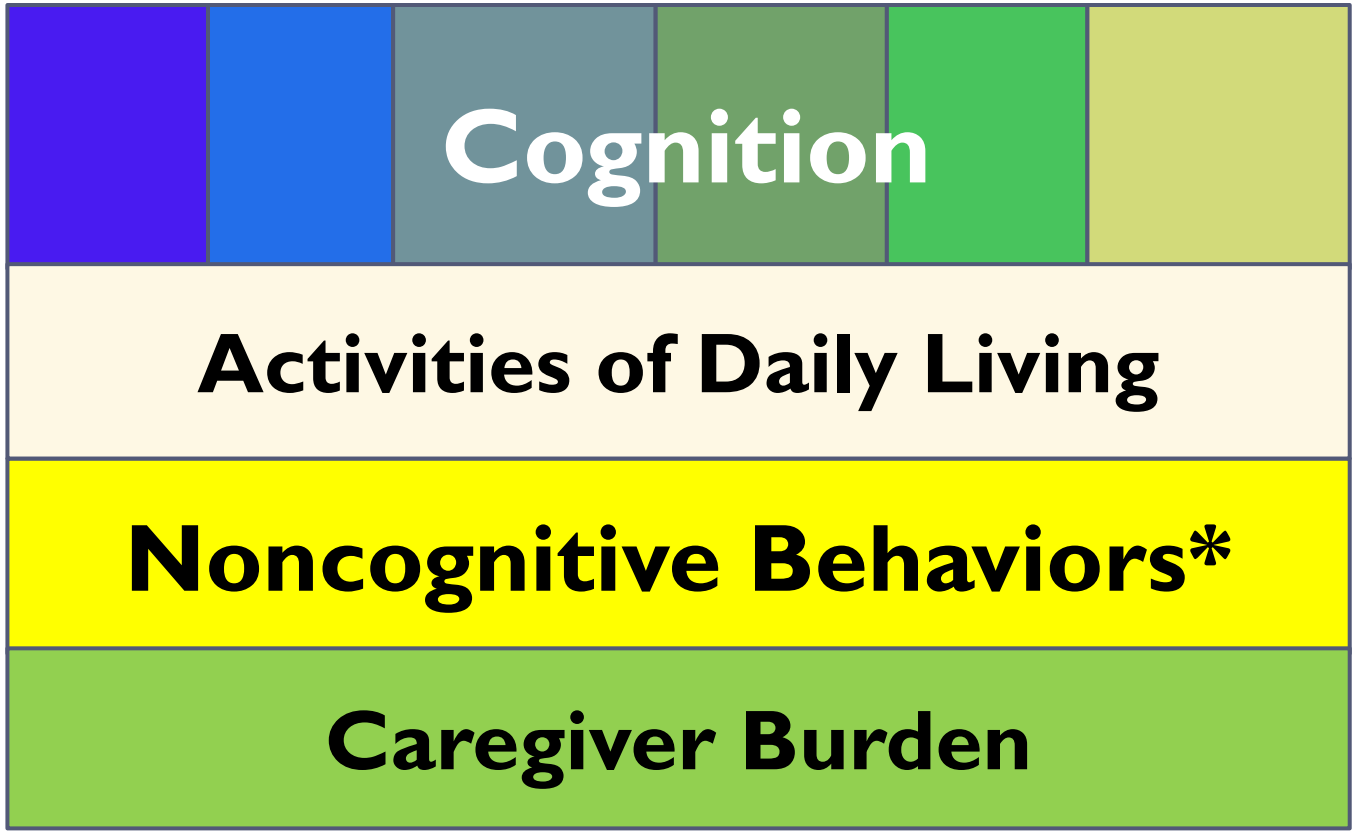
Memantine: Characteristics

	Available in oral tablets, oral solution, immediate and extended release
Starting dose	5 mg/d IR, 7 mg/d XR
Maximum recommended dose	10 mg bid IR, 28 mg/d XR
$T_{1/2}$ (hours)	60-80
Plasma protein binding	45%
CYP450 substrate of	NA
CYP450 inhibitor of	NA
Excretion	Renal
Cost	High

How Helpful? / How Harmful?

- Both med classes: Modest benefits in multiple domains
- Cholinesterase inhibitors:
  - Common: GI symptoms, insomnia, vivid dreams, fatigue, increased urination, cramps
  - Uncommon: syncope, bradycardia, confusion, depression, agitation
  - Caution with liver/gastric disease, COPD, bradycardia, sick sinus, inadequate supervision
- Memantine
  - More common: headache, constipation
  - Uncommon: confusion
  - Agitation can occur early, but is infrequent

And Yet Other Aspects of MNDs Are As Important As Cognition



*behaviors in demented individuals not attributable to other medical or psychiatric cause

The Caregiver's Map of Dementia

Importance of NCBS

- More than 90% of people with MND will experience NCBS
- NCBS are associated with significant morbidity, more rapid functional decline[1,2]
- **No medication is FDA approved for NCBS**
- **There is no established standard for the management of NCBS**

1. Lyketsos CG et al. Am J Psychiatry 2000;157:708-714.
2. Tractenberg RE et al. J Neuropsychiatry Clin Neurosci 2002; 14:11-18.

Even Alzheimer's Index Patient Showed Severe Behavioral Symptoms

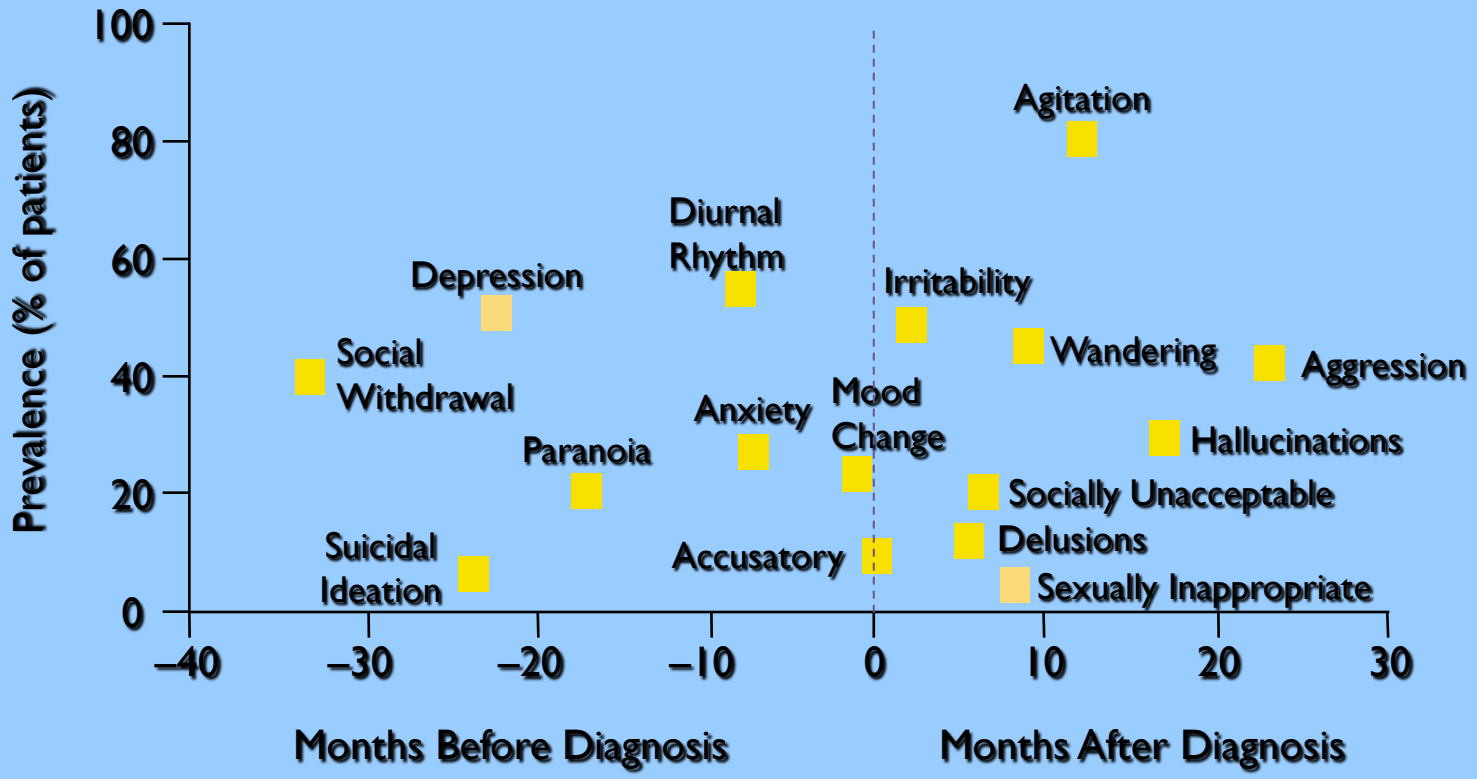
The NCBS of Alzheimer's index patient, Auguste D:

- *Pathological jealousy*
- *Paranoid delusions*
- *Auditory hallucinations*
- *Screams for many hours in a horrible voice*
- *Agitated, noncooperative*

Common Noncognitive Behavioral Symptoms

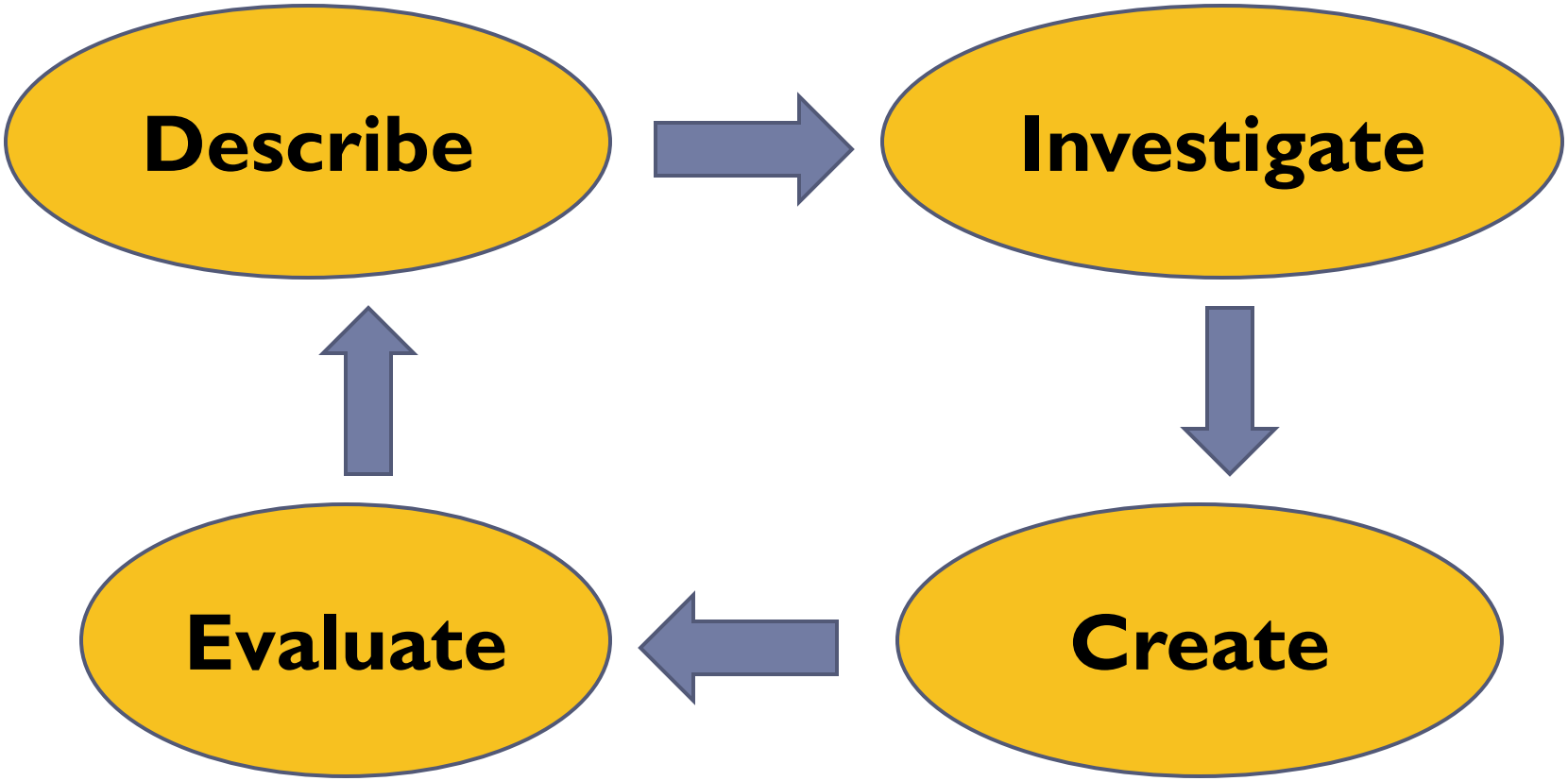
Changes in:	Timing	Frequency	Examples
Mood	Early	Frequent	Anxiety Depression Mania
Thinking	Early Later	Frequent	Suicidal ideation Delusions Hallucinations
Activity	Early and Late	Frequent	Apathy Agitation/Aggression Wandering Disordered eating behavior Sexual inappropriate behavior Sleep/activity cycle disruption

NCBS: Range and Peak Prevalence During AD Progression



- from Jost BC, Grossberg GT. *J Am Geriatr Soc.* 1996;44:1078-1081.

DICE: A Systematic Nonpharmacologic Approach to NCBS



Kales et al. JAGS 2014;62:762-9.

Describe

- Caregiver **describes problematic behavior**
- Context (who, what, when and where)
- Social and physical environment
- Patient perspective
- Degree of distress to patient and caregiver

Kales et al. JAGS 2014;62:762-9.

Investigate

- Patient
  - Medication side effects
  - Pain
  - Functional limitations
  - Medical conditions
  - Psychiatric comorbidity
  - Severity of cognitive impairment, executive dysfunction
  - Poor sleep hygiene
  - Sensory changes
  - Fear, sense of loss of control, boredom
- Caregiver effects/expectations
- Social and physical environment
- Cultural factors

Kales et al. JAGS 2014;62:762-9.

Create

- Respond to physical problems
- Strategize behavioral interventions
- Providing caregiver education and support
- Enhancing communication with the patient
- Creating meaningful activities for the patient
- Simplifying tasks
- Ensuring the environment is safe
- Increasing or decreasing stimulation in the environment

Kales et al. JAGS 2014;62:762-9.

Behavioral Intervention Examples

- Caregiver education
- Prosthetic (habilitative) environment
- Distraction and redirection
- Activity/exercise
- Simulated presence/Reminiscence
- Individualized music therapy
- Aromatherapy / massage

Treatment must not exceed patient's capacity to learn/remember

Evaluate

- Has the intervention(s) been effective for the problem behavior?
- Have there been any unintended consequences or "side effects" from the intervention(s)?
- Which interventions did the caregiver implement?
- If the caregiver did not implement the interventions, why?
- What changes in the environment have been made?

Kales et al. JAGS 2014;62:762-9.

Clinical Vignettes

- Psychosis
- Agitation/Aggression
- Apathy
- Depression
- Sexualized Inappropriate Behavior
- Sleep Disturbance

All vignettes are composite descriptions in order to protect individual identities.

Vignette 1: Psychosis

- Mr. A, 78 years old with Lewy Body Dementia, has appeared intermittently psychotic and at times his delusions precipitate agitated, aggressive, or wandering behavior. Symptoms threaten his continued residence at home, where his frail wife cares for him.

- In addition to behavioral interventions, what medication might be helpful?

Medications: Atypical Antipsychotics Modest Effects, Significant Drawbacks

Syndromes	Usual Agents	Evidence Says	Suggested Use
Psychosis Agitation Aggression	Risperidone	Modest benefit	Begin with 0.25 mg/d Increase up to 2 mg/d
	Olanzapine	Modest benefit	Begin with 2.5 mg/d Increase up to 15 mg/d
	Quetiapine	Questionable	Begin with 12.5 mg/d Increase up to 200 mg/d
	Aripiprazole	Questionable	Begin with 2 mg/d Increase up to 10 mg/d
	Clozapine	Questionable	Begin with 6.25 mg/d Increase up to 300 mg/d

CATIE-AD Results

- Multi-center, double-blind, randomized, placebo-controlled 36 week flexible dosing study in 421 AD outpatients with agitation and/or psychosis.
- Assessed effectiveness and safety of:
  - Olanzapine (5.5 mg/d)
  - Risperidone (1 mg/d)
  - Quetiapine (~50 mg/d)
  - Placebo
- Primary outcomes:
  - All-cause treatment discontinuation
  - CGIC responder rates

Schneider LS et al. NEJM 2006;355:1525-38.

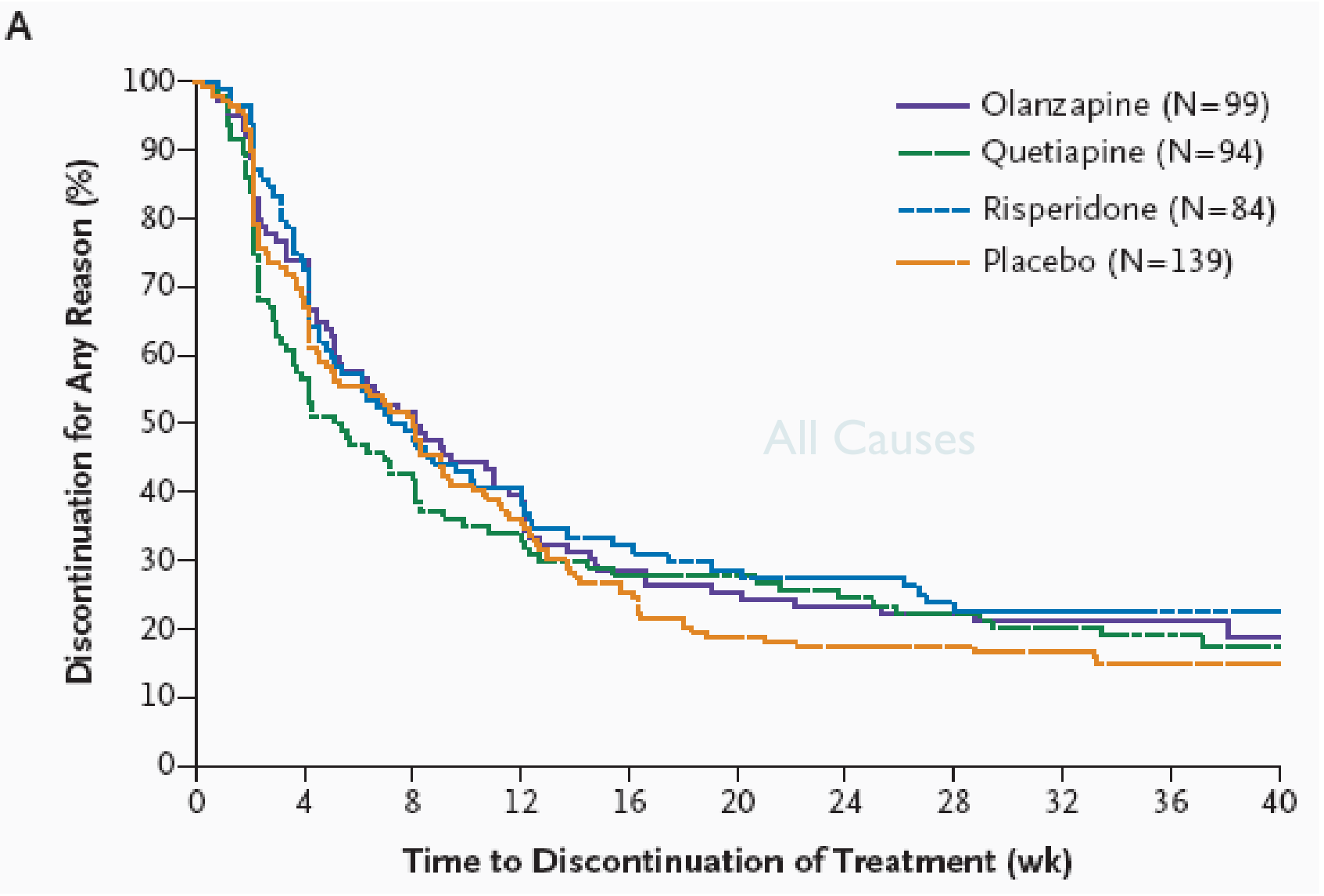


Figure 2. Discontinuation of Treatment in Phase 1 According to Study Group.

Schneider LS et al. NEJM 2006;355:1525-38.

CATIE-AD: CONCLUSIONS

- All cause discontinuation: drugs = placebo
- EPS a common reason for drug discontinuation
- Olanzapine & risperidone equally effective in treating behavioral problems and superior to quetiapine and placebo, *but only in patients who did not develop EPS*
- "No large clinical benefit of treatment with atypical antipsychotic medications as compared with placebo"

Schneider LS et al. NEJM 2006;355:1525-38.

What Harm Can It Do?

- Somnolence, orthostatic hypotension, gait disturbance[1]
- Extrapyramidal symptoms including tardive dyskinesia[1]
- ADA warning for risk of diabetes with all atypical antipsychotics[2]
- FDA warning of increased CVAEs and increased mortality in elderly patients with dementia[3,4]

1. McDonald WM. J Clin Psychiatry. 2000;61(suppl 13):3-11; 2. American Diabetes Association, et al. Diabetes Care. 2004;27:596-601; 3. Wang et al. N Engl J Med. 2005;353:2335-2341; 4. Schneider et al. JAMA. 2005;294:1934-1943.

Class-Associated Severe AE And Mortality Concerns

- FDA Boxed Warning (April 11, 2005) notes "increased risk of death compared with placebo"
  - In 17 PCTs, Deaths among 3611 drug treated patients were 4.5%, Deaths among 1766 placebo treated patients were 2.6% (OR = 1.6)
  - Causes of death - Most were heart related (heart failure, sudden death) or infections (pneumonia)
  - Studies included: aripiprazole (3), olanzapine (5), risperidone (7), quetiapine (2), ziprasidone (1), haloperidol (2); and warning was extended to clozapine and Symbyax (olanzapine/fluoxetine) and later to typical antipsychotics as well (based on additional case-controlled studies)

US Food and Drug Advisory. http://www.fda.gov/cder/drug/advisory/antipsychotics.htm. Accessed March 7, 2007.

Antipsychotics: Clinical Recommendations

- Document use of behavioral and environmental interventions
- Document antipsychotic's target symptoms
- Educate health care representative about benefits, risks
- Coordinate care with that of other involved clinicians
- Establish time frame for assessment of results
- Frequently assess (and document) benefits and AEs
- Use lowest doses necessary for the shortest time period
- **Evidence suggests typicals are as dangerous as the atypicals**

Suggested Screening/Monitoring

	Baseline	4 Weeks	8 Weeks	12 Weeks	Quarterly	Annually
Personal/Family History	X					X
Weight (BMI)	X	X	X	X	X	
Waist circumference	X					X
Blood Pressure	X			X		X
Fasting plasma glucose	X			X		X
Fasting lipid profile	X			X		

ADA, APA, AACE, NAASO Diabetes Care 2004;27:596-601

AND…Discontinuation May Be An Option

Table 2. Differences in Change in Behavioral Symptoms Between Placebo (N = 36) and Neuroleptic (N = 46) Groups of Patients With Dementia Enrolled in a 3-Month Discontinuation Trial: Statistical Evaluation

	Mean ± SD Change			
Variable	Placebo	Neuroleptic	z Value[a]	p Value
Behavioral factors				
NPI total score	–1.3 ± 9.4	0.2 ± 12.0	0.73	.46
Agitation	–1.0 ± 5.1	–1.0 ± 5.3	0.14	.89
Mood	–1.1 ± 7.7	–0.62 ± 8.1	0.19	.85
Psychosis	–0.5 ± 3.2	–0.9 ± 3.5	0.83	.41
Quality of life				
Well-being	–0.18 ± 1.72	0.35 ± 2.41	0.77	.44

[a]Mann-Whitney U test.
Abbreviation: NPI = Neuropsychiatric Inventory.

Ballard et al. J Clin Psychiatry. 2004;65:114-9

Medications: Typical Antipsychotics

Syndromes	Usual Agents	Evidence Says	Suggested Use
Psychosis Agitation Aggression	Haloperidol (PO or IM)	No better than atypicals –EPS including TD, sedation, weight, anticholinergic, hypotension; Less metabolic syndrome; no less mortality	0.5 to 2 mg/d can be used for acute sedation
	Perphenazine		Not recommended
	Trifluoperazine		

1. Wang et al. N Engl J Med. 2005;353:2335-41; 2. Ray et al. NEJM 2009;360:225-35.

Medicolegal Considerations

- A patient with decisional capacity can consent to antipsychotic treatment.
- With GUARDIANSHIP:
  - Patient or guardian **cannot** give consent
  - Court order (Rogers Guardianship) is required
- With an ACTIVATED HEALTH CARE PROXY:
  - Patient can assent if HCP agrees
  - Patient's refusal may imply valid wish to revoke HCP, requiring Rogers Guardianship.
- Massachusetts State Budget amendment, 2014, increases restriction of antipsychotics in LTCFs:

2014 Massachusetts State Budget:

- …(b) The department shall establish a schedule of psychotropic medications that shall not be administered to a resident by a facility without informed written consent. (c) Prior to administering psychotropic medication listed on the schedule created under subsection (b), a facility shall obtain the informed written consent of the resident, the resident's health care proxy or the resident's guardian. Informed written consent shall be obtained on a form approved by the department, which shall include, at a minimum, the following information: (i) the purpose for administering the listed psychotropic drug; (ii) the prescribed dosage; and (iii) any known effect or side effect of the psychotropic medication. The written consent form shall be kept in the resident's medical record.

Vignette 2: Agitation/Aggression

- The children of a 90 year old woman with moderate to severe AD ask for help. Mother's nursing home says behavior is intolerable. She aggressively resists personal care – including changing of her Depends. She injured herself during a fall when she tried to bite her caregiver. She wanders anxiously day and night, seeking an exit. She is intrusive and frightening to other residents.

- Besides behavioral interventions, what medications might be of help?

Agitation

"Inappropriate verbal, vocal or motor activity that is not judged by an outside observer to be an obvious outcome of the needs or confusion of the individual."

--Jiska Cohen-Mansfield, Ph.D.

- Aggression and psychosis are often comorbid
- Aggression is a safety issue in Long Term Care Facilities[1]
  - 5% of nursing home residents are physically aggressive each year
  - 60-94% of these are cognitively impaired
  - More than 1000 of MA's 110,000 nursing home residents are attacked by other residents each year

1. Alzheimer's Association: Aggressive behavior among long term care residents. A study prepared for the Governor's Task Force on Alzheimer's Disease and Related Senile Dementias [Indiana]. June 30, 2002.

Memantine for Agitation

- Pooled analysis, three 6-month RCTs in moderately severe to severe AD subjects[1] with agitation/aggression or psychosis showed:
  - 60% with NPI agitation/aggression, delusions, or hallucinations at baseline
  - More Memantine NPI responders at 12 and 24 weeks
  - More Memantine agitation/aggression responders
  - NNT for NPI at 24 weeks = 7, few adv. Event failures
- Possible synergistic benefit in combination with donepezil (cognition, ADLs, agitation, lability, eating behavior)[2]

1. Wilcock et al. J Clin Psychiatry 2008;69:341-8; 2. Tariot PN, Farlow MR, Grossberg GT, et al. JAMA. 2004;291:317-24

Medications: Antidepressants A Safer Alternative for Agitation?

Syndromes	Usual Agents	Evidence Says	Suggested Use
Agitation Aggression Psychosis Anxiety Depression Apathy	**Citalopram**	As good as antipsychotics – modestly beneficial[1-3]	5 mg/d up to 20 mg/d, but higher doses are discouraged by FDA in elderly
	Escitalopram	Not tested in treatment of agitation, aggression, psychosis in dementia but may have value as alternatives	5 mg/d up to 20 mg/d
	Sertraline		25 mg/d up to 200 mg/d
	Fluoxetine		Not well defined
	Paroxetine		Not well defined

1. Pollock BG. Am J Psychiatry. 2002;159:460-465; 2. Pollack BG, et al. Am J Geriatric Psychiatry. 2007; 15:942-952; 3. Porsteinsson et al. JAMA 2014;311:682-91.

What Harm Can This Do?

- SRIs
  - QTc prolongation (citalopram)
  - Agitation, Insomnia
  - Hyponatremia
  - Loss of appetite
  - Sedation
  - EPS
  - Bruising/bleeding
  - Syncope

Medications: Anticonvulsants Supported by Only Limited Evidence

Syndromes	Specific Agents	Evidence Says	Suggested Use
Agitation Aggression Mania	Carbamazepine	Modest benefit[1,2], limited data base	Start 100 mg/d, increase up to 300 mg/d
	Divalproex	Poor evidential support for use except possibly in secondary mania	Typical range used is 500 to 1250 mg/d (blood level 50 to 100 mcg/ml)
	Lamotrigine	Lacking evidence	
	Gabapentin		
	Topiramate		
	Oxcarbazepine		

1. Tariot et al. Am J Psychiatry. 1998;155:54-61; 2 . Olin et al. Am J Geriatr Psychiatry. 2001;9:400-405.

What Harm Can This Do?

- Carbamazepine: SJS, arrhythmia, syncope, hepatotoxicity, agranulocytosis, thrombocytopenia, drug interactions, hyponatremia, nausea, constipation
- Divalproex: somnolence, thrombocytopenia, weight gain, tremor, hepatotoxicity, pancreatitis (rare), drug interactions
- Gabapentin: dizziness, sedation, ataxia, nasuea, agitation, diarrhea, constipation, weight gain, SJS, renal failure, depression

Medications: Others

Specific Agents	Use	Evidence Says	Suggested Use
Prazosin[1]	Agitation	Small positive evidence base	1 mg/d, can increase up to 6 mg/d
Dronabinol [2]		Small positive evidence base	2.5 mg/d Can increase to 10 mg/d
Paracetamol[3]		One positive RTC	
Opioids[4]		Support for use based on hypothesized presence of pain (comfort care level)	Long-acting oxycodone 10 mg q 12 h or long-acting morphine 20 mg q d
Cyproterone[5]	Sexualized behavior, aggression	Small supportive evidence base (not first line)	50 mg bid
ECT[6]		Small positive evidence base	

1.Wang et al. Am J Geriatric Psychiatry 2009;17:744-51; 2. Walther et al: Psychopharmacology 2006;185: 524–528; 3. Husebo et al. BMJ 2011;343:d4065; 4. Manfredi et al: Int J Geriatric Psychiatry 2003;18:700-5.; 5. Bolea-Alamanac et al. J Psychopharmacol. 2011;25:141-5; 6. Grant and Mohan. ECT 2001;17:205-9.

What Harm Can This Do?

- Prazosin: Headache, drowsiness, tiredness, weakness, blurred vision, nausea, vomiting, diarrhea, constipation
- Dronabinol: drowsiness, dizziness, hypotension, hallucinations, dysphoria, headaches, palpitations
- Cyproterone: fatigue, dizziness, headache, nausea, flushing, leg pain, palpitations, chest pain, and others
- ECT: risk of anesthesia, temporary increase in confusion and memory difficulty

Medications: Anxiolytics
Rarely Helpful / Significant Risks

Syndromes	Specific Agents	Evidence Says	Suggested Use
Agitation Aggression	**Lorazepam**	Sometimes useful for acute agitation[1]	0.5 to 1 mg po or IM
	Clonazepam	Possible modest benefit for some patients with significant potential adverse effects[2]	0.5 mg hs to 0.5 mg bid, but generally not recommended
	Alprazolam	Some support but problematic in practice[3]	0.25 to 0.5 mg qd to bid, but generally not recommended
	Buspirone	Inconsistent support for use, but adverse effects are minimal[4,5]	15 to 90 mg/d in divided doses

1. Meehan et al: Neuropsychopharm 2002:26:494-504; 2. Calkin et al. Int J Geriatr Psychiatry. 1997;12:745-9; 3. Christensen and Benfield. J Am Geriatr Soc. 1998;46:620-5; 4. Tiller et al. Lancet 1988;2(8609): 5. Cooper JP. Psychiatry Neurosci. 2003;28:469.

What Harm Can This Do?

- Benzodiazepines are controversial because of:
  - Sedation
  - Falls/fractures
  - Disinhibition/worse agitation
  - Impaired cognition
  - Dependance/tolerance/withdrawal
  - Minimal efficacy data
- Buspirone: mild side effects
  - Headache, nausea, rarely may increase agitation

Vignette 3: Apathy

- The husband of an 84 year old woman with moderate AD complains that his wife must be depressed. She no longer manages household chores or seems interested in doing anything. She was formerly an enthusiastic companion, but now seems content to watch TV and neglect other activities.

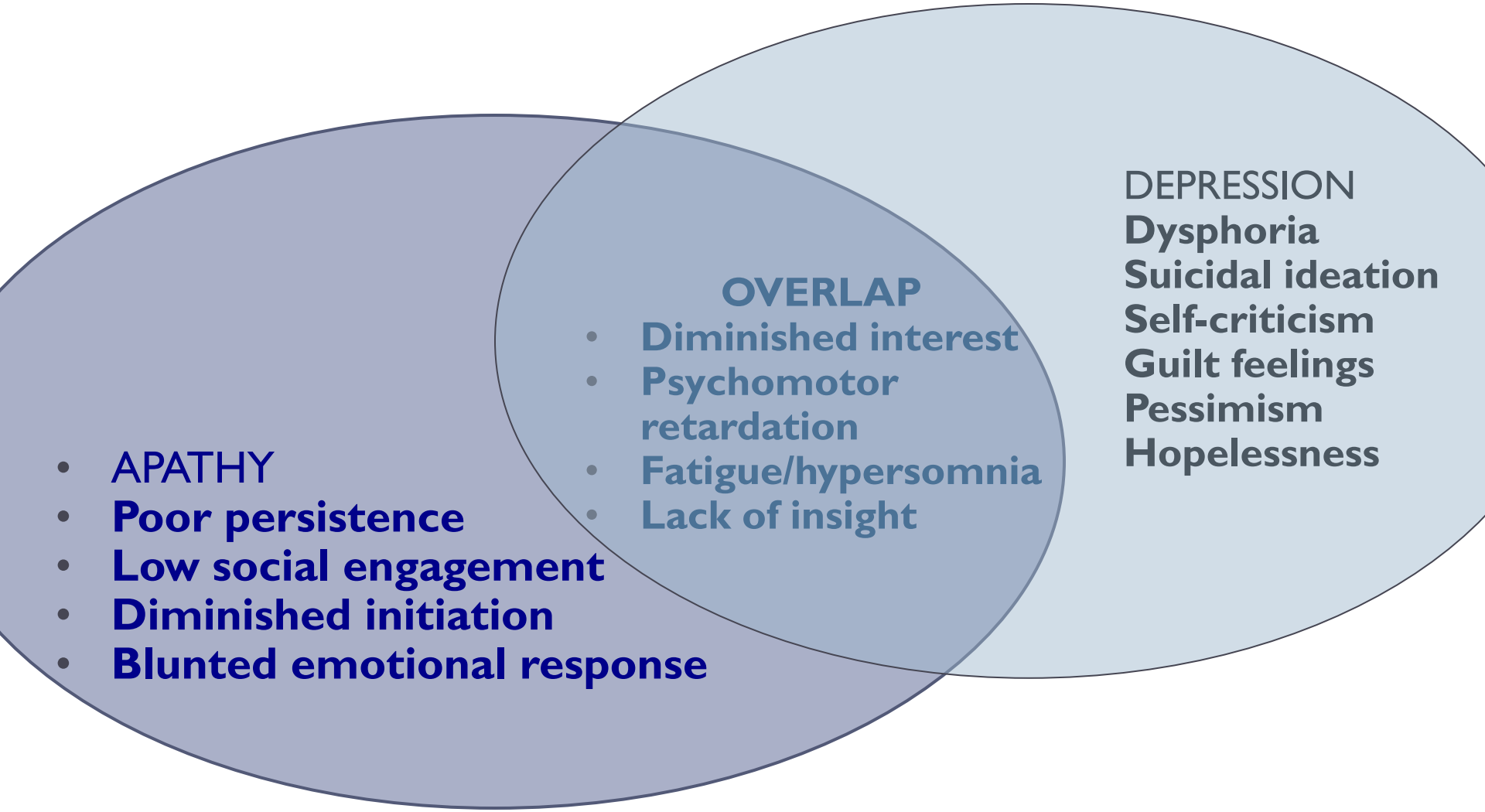
- What might help?

Definition of Apathy[1]

- Loss of initiative and motivation
- Decreased social engagement
- Emotional indifference
- Often associated with:
  - Limited insight
  - Low interest
  - Blunted emotional response
  - Poor persistence
  - Impaired ADLs
- In AD: up to 92% of severely impaired[2]

1. Padala et al. J Neuropsychiatry Clin Neurosci. 2007;19:81-3 2007;
2. Landes et al. J Am Geriatr Soc. 2001;49:1700-7.

Distinguishing Apathy from Depression[1]



Landes et al. J Am Geriatr Soc. 2001;49:1700-7

Treatment of Apathy in Dementia

- Behavioral treatments
  - Maintain meaningful activities
  - Encourage preexisting interests
  - Structured music and art therapy program better than "free activities"
  - Schedule pleasant activities at energy nadirs

Landes et al. J Am Geriatr Soc. 2001;49:1700-7;
Galynker et al. J Neuropsychiatry Clin Neurosci. 1997;9:231-9.

Treatment of Apathy in Dementia

- Potential pharmacologic treatments
  - Consider
    - Cholinesterase inhibitors +
    - Memantine +/-
    - **Methylphenidate ++**
    - **Antidepressants: Bupropion +,** SSRIs +/-
    - Antipsychotics -, Anticonvulsants -
  - Avoid overmedication
  - Take drug interactions into account

Landes et al. J Am Geriatr Soc. 2001;49:1700-7;
Galynker et al. J Neuropsychiatry Clin Neurosci. 1997;9:231-9.
Rosenberg et al. J Clin Psychiatry 2013;74:810-6 (ADMET trial).

Medications: Stimulants
Can Increase Agitation / Can Help Apathy

Syndromes	Specific Agents	Evidence Says	Suggested Use
Apathy Depression	Methylphenidate	Modest benefit in apathy	5 mg/d up to 10 mg bid with monitoring
	Amphetamine	Evidence is lacking	Not recommended
	Modafinil		

Medications: Antidepressants

Syndromes	Usual Agents	Evidence Says	Suggested Use
Apathy	Bupropion	May benefit apathy	Start at 75 mg/d Increase in usual adult dose range with caution

Landes et al. J Am Geriatr Soc. 2001;49:1700-7;
Galynker et al. J Neuropsychiatry Clin Neurosci. 1997;9:231-9.
Rosenberg et al. J Clin Psychiatry 2013;74:810-6 (ADMET trial).

What Harm Can This Do?

- Stimulants
  - Agitation
  - Insomnia
  - Psychosis
  - Anxiety
  - Elevated BP
- Bupropion
  - Seizure, agitation, anxiety, insomnia, loss of appetite,
  - Elevated HR, BP

Vignette 4: Depression

- A woman expresses alarm at her 87 year old husband's suicidal comments: "I'm a husk. I shouldn't be alive". Her husband has probable Vascular Dementia. She wants to know how to help him feel better and optimize enjoyment of his life despite his cognitive impairment.

- What might help?

Depression in Alzheimer's Disease

- Prevalence of clinically significant depression in AD: 30-50% (half or more is minor)
- Rate in Vascular Dementia may be higher
- Not solely determined by
  - awareness of dementia
  - severity of cognitive impairment
- Proposed mechanisms
  - Noradrenergic cell loss in locus ceruleus
  - Serotonergic cell loss in dorsal raphe nuclei

Lyketsos and Olin. Biol Psychiatry 2002;52:243-52.

Provisional Criteria: Depression in AD

- 3 or more of following in 2 week period
  - Depressed mood
  - Decreased positive affect/pleasure in usual activities/contacts
  - Social isolation or withdrawal
  - Disruption in appetite
  - Disruption in sleep
  - Psychomotor changes
  - Irritability
  - Fatigue/loss of energy
  - Worthlessness, hopelessnesss, guilt
  - Thoughts of death, SI or behavior

- Meets criteria for DAT
- Distress or disruption
- Not delirium, drug, medication, or better accounted for by other conditions

Olin et al. Am J Geriatr Psychiatry. 2002 Mar-Apr;10:125-8.

Also Note "Masked" Depression in Demented Patients

- Likelihood that depression is present is increased in the presence of:
  - Delusions[1]
  - Verbal/physical aggressive behaviors[2]
  - Suicidal or self-destructive behaviors
  - Disruptive vocalizations[3]
  - Weight loss[4]

1. Bassiony et al. Int J Geriatr Psychiatry. 2002;17:549-56;; 2. Menon et al. Int J Geriatr Psychiatry. 2001;16:139-46; 3. Dwyer and Byrne. Int Psychogeriatr. 2000 ;12:463-7; 4. Morley and Kraenzle. J Am Geriatr Soc. 1994 Jun;42:583-5

DIADS

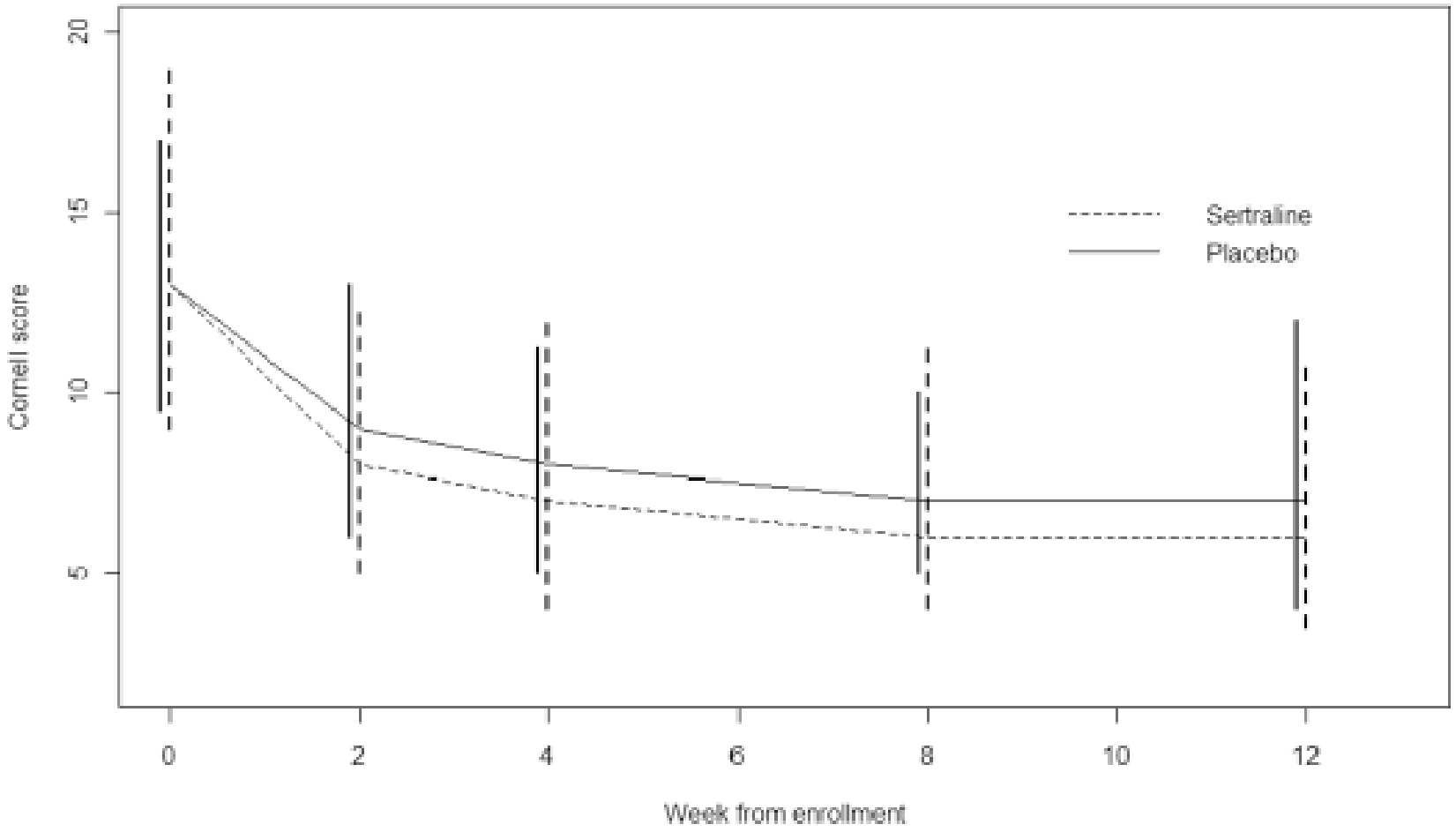


Figure 2.
CSDD medians* at each visit by treatment group. Error bars represent the range between the first and third quartiles.

Rosenberg et al. Am J Geriatr Psychiatry 2010;18:136-45.

Treatment of Depression in Dementia

- Non-Pharmacologic: Address dependency fears, self-esteem; Avoid frustration; Schedule pleasant events, including Music Therapy and other interventions.
- Antidepressant trials: Inconsistent conclusions
  - Positive: moclobemide, clomipramine, citalopram, sertraline
  - Negative: imipramine, fluoxetine, venlafaxine, sertraline, mirtazapine
  - ECT effective in retrospective study
  - Little support for antidepressant effect of stimulants
  - No evidence supporting the use of cognitive enhancers or antipsychotics in treating depressive symptoms

1. Nyth et al. Acta Psychiatr Scand. 1992 ;86(2):138-45; 2. Lyketsos et al. Am J Psychiatry. 2000; 157:1686-9; 3. Petracca et al. J Neuropsychiatry Clin Neurosci. 1996;8:270-5 ;4. Roth et al. Br J Psychiatry. 1996;168:149-57; 5. Rao and Lyketsos Int J Geriatr Psychiatry. 2000 ;15:729-35

Medications: Antidepressants
Depression in AD Response Less Certain

Syndromes	Usual Agents	Evidence Says	Suggested Use
Depression Agitation Aggression Psychosis Anxiety Apathy	Citalopram	As good as antipsychotics – modestly beneficial[1-3]	5 mg/d up to 20 mg/d, but higher doses are discouraged by FDA in elderly
	Escitalopram	May be similar to escitalopram	5 mg/d up to 20 mg/d
	Sertraline	Not better than placebo for depression	25 mg/d up to 200 mg/d
	Fluoxetine	Evidence lacking	Not well defined
	Paroxetine	Evidence lacking	Not well defined
	Bupropion	May benefit apathy	Start at 75 mg/d Increase in usual adult dose range with caution

1. Pollock BG. Am J Psychiatry. 2002;159:460-465; 2. Pollack BG, et al. Am J Geriatric Psychiatry. 2007; 15:942-952; 3. Porsteinsson et al. JAMA 2014;311:682-91.

Antidepressants for Depressed, Demented Patients: What's A Clinician To Do?

- Differential diagnosis
- Assess severity and "masked" depression
- Consider psychosocial interventions
- Choose a medication and target symptoms
- Monitor improvement and adverse effects
- Modify approach based on outcome
- Consider discontinuation

Vignette 5: Sexual Inappropriate Behavior

- A 78 year old man with moderate FTLD is in danger of being rejected from his Assisted Living Facility. He makes inappropriate sexual comments to staff, touches other residents, and masturbates in public areas.

- What might help?

Inappropriate Sexual Behaviors

- Prevalence: 7 - 25% of demented patients
- More frequent in:
  - Males
  - Long term care settings
  - Greater cognitive impairment severity
- Consequences:
  - Embarrassment
  - Confinement/isolation
  - Disruption of structured living environments
  - Trauma
  - STDs
  - Liability and regulatory issues for care setting

Nonpharmacologic Caregiver Interventions

- Psychoeducation for caregivers
  - Supportive counseling of spouse
  - Reframe sexual expression as drive for closeness/ comfort/ reassurance
  - Clarification of misinterpreted social cues
- Staff attitudes
  - Rigid attitudes may mistake acceptable sexual expression for inappropriate behavior
  - Suitable sex education program for staff may improve patient care

Nonpharmacologic Patient Interventions

- Don't ignore, but avoid confrontation
- Explanation to extent possible
- Distraction and redirection
- Environmental modifications
  - Single rooms for patients
  - Avoid inappropriate external cues like overstimulating television or radio programs.
  - Modified clothing, e.g. trousers that open in the back or lack zippers
  - Provide adequate social activity, keep hands busy

Pharmacologic Treatments

- No double-blind placebo controlled trials.
- Minimal studies of antipsychotics, anticonvulsants
- Use medications only when other methods fail and in combination with non-pharmacologic treatments.
  - Reduce or discontinue medications that can contribute to these behaviors.
  - Avoid potentially disinhibiting bzd's
  - Start low and go slow with therapeutic medication

Medications for Treatment of Inappropriate Sexual Behavior in Dementia Anecdotally Supported – Use With Caution

Medication	Typical Dose	N	Common Side Effects
Paroxetine, Citalopram	20 mg/d	1	GI sx, asthenia, sweating, tremors, dizziness, anxiety, headache, sedation
Clomipramine	150-200 mg/d	2	Sedation, GI sx, weight changes, anxiety, tremors, sweating
Quetiapine	25 mg/d	1	Sedation, orthostatic hypotension, headache, dizziness, constipation
Trazodone	150-500 mg/d	4	Sedation, orthostatic hypotension, dizziness, headache, GI sx, priapism
Gabapentin	300 mg tid	1	Somnolence, fatigue, dizziness, ataxia, peripheral edema, depression, weight gain, tremor
Cimetidine	600-1600 mg/d	10	GI disturbance, confusion, LFT increases, rash, blood dyscrasias
Pindolol	40 mg/d	1	Bradycardia, CHF, hypotension, lightheadedness, depression, nausea, vomiting

Modified from Black et al.J Geriatr Psychiatr Neurol 2005;18:155-62; Alikhalil et al. Int Urol Nephrol 2003;35:299-302

Medications for Treatment of Inappropriate Sexual Behavior in Dementia

Medication	Typical Dose	N	Common Side Effects
Antipsychotics Cholinesterase inhibitors or memantine			Not shown efficacious for this symptom
MPA	100-300 mg/d IM q 2 wk	6	Weight changes, abdominal pain, dizziness, nausea, depression, insomnia, pelvic/breast pain, edema
Diethylstilbestrol	1 mg/d	1	As above
Estrogen	0.625 mg/d	39	As above
Leuprolide acetate	7.5 mg/month IM	1	As above

Modified from Black et al.J Geriatr Psychiatr Neurol 2005;18:155-62; Alikhalil et al. Int Urol Nephrol 2003;35:299-302

Vignette 6: Sleep Disturbance

- An 86 year old man has been caring for his 84 year old wife with moderate to severe AD. Her insomnia is increasing, and she wanders around the house at night. He fears she'll fall or wander out of the house.

- What might help?

Sleep Disturbances In AD

- Sleep disturbances affect majority of Alzheimer's disease patients
  - Half of outpatients, more with severe dementia
  - Sleep disorder can worsen cognitive and behavioral functioning
- Typical sleep disturbances:
  - Awakenings – increased and extended
  - Decreased SWS and REM
  - Up to 40% of time in bed can be awake
  - Sleepiness and napping is common in day
  - Day-night disturbances, sun-downing
  - RLS and nightmares in FTD, LBD, PDD
  - RBD in FTD, AD, VaD

Swearer et al. 2002, in Qizilbash N, et al. Evidence-Based Dementia Practice. 2002;
McCurry et al. Sleep Medicine Reviews 2000;4:603-28. Pistacchi et al. Neuro Sci July 18, 2014, epub ahead of print.

Multifactorial Etiology Of Sleep Disturbances

- Neurodegenerative disorder effects on circadian rhythm
- Medication effects
- Environmental conditions including boredom with daytime napping
- Comorbid disorder
  - Medical illness including pain
  - Sleep disorder
  - Mood or anxiety disorder

Swearer et al. 2002, in Qizilbash N, et al. Evidence-Based Dementia Practice. 2002; McCurry et al. Sleep Medicine Reviews 2000;4:603-28.

Behavioral Treatment Of Sleep Disturbances

- Differential diagnosis required
- Caregiver education re hygiene
- Attention to sleeping environment
- Therapeutic use of activity schedule:
  - Target activities during nap time
  - Schedule pleasant, engaging events
- Efficacy of bright light therapy not clear

Swearer et al. 2002, in Qizilbash N, et al. Evidence-Based Dementia Practice. 2002;
McCurry et al. Sleep Medicine Reviews 2000;4:603-28.

Pharmacotherapy of Sleep Disturbances

- Lack of long-term trials
- Cholinesterase inhibitors can affect sleep adversely.
- Antipsychotics may worsen circadian rest-activity disturbances.
- Antidepressants: Consider trazodone, avoid anticholinergic drugs
- Anticonvulsants: further study needed
- Benzodiazepines' side effects create potential hazard; avoid short-term agents especially
- Zolpidem 10 mg hs improved duration of sleep[1] and decreased nighttime wandering[2] but can be hazardous.

1. Shaw et al. J Int Med Res. 1992;20:150-61
2. Shelton and Hocking Ann Pharmacother. 1997;31:319-227

Medications: Hypnotics
Use With Caution / Monitor Safety

Syndromes	Specific Agents	Evidence Says	Suggested Use
Insomnia	Trazodone	Mixed, but not consistent support for insomnia/agitation[1,2]	25 to 250 mg/d, use divided doses in higher range
	Zolpidem	Possible benefit claimed in elderly psychiatric inpatients[3] , limited case reports in demented patients[4]	5 to 10 mg at hs (lower doses now recommended)
	Mirtazapine	Anecdotal support in AD with depression+insomnia[5]	
	Not recommended: Diphenhydramine and other antihistamines, melatonin, ramelteon		

1. Teri et al. Neurology. 2000;55:1271-8. 2. Sultzer et al. *J Am Geriatr Soc.* 2001; 3. Shaw et al. J Int Med Res. 1992;20:150-61. 4. Shelton and Hocking Ann Pharmacother. 1997;31:319-227; 5. Raji and Brady. Ann Pharmacother. 2001 Sep;35(9):1024-7.

What Harm Can This Do?

- Trazodone: sedation, hypotension, priapism
- Zolpidem:
  - Sedation
  - Falls/fractures
  - Disinhibition/worse agitation
  - Impaired cognition
  - Dependance/tolerance/withdrawal
  - “sleep driving”

Complying With Institutional Psychotropic Monitoring Guidelines

CMS' State Operations Manual Guides Nursing Home Surveys

- Citation for use of "Unnecessary Drugs" (F-329), includes:
  - Excessive dose, includes duplicate therapy
  - For excessive duration
  - Without adequate monitoring
  - Without adequate indications for use
  - In presence of adverse consequences- dose should be decreased or discontinued
  - Any combination of the reasons above

F329 - Unnecessary Meds

- Antipsychotics
  - …**not** indicated for wandering, poor self care, restlessness, impaired memory, fidgeting, nervousness, uncooperativeness, verbal expressions, insomnia, mild anxiety, inattention or indifference to surroundings, behaviors that do not represent a danger to others
  - [only for] Danger to self or others, symptoms due to mania or psychosis, acute emergencies of 7 days or less.

F329 – Antipsychotic GDR

- Residents who use antipsychotic drugs receive gradual dose reductions (GDR), and behavioral interventions, unless clinically contraindicated, in an effort to discontinue these drugs
  - Within 1st year after admission on antipsychotic or after initiation
  - GDR in 2 separate quarters, with at least one month between attempts
  - After 1st year, GDR annually
  - GDR is clinically contraindicated if:

    MD documents clinical rationale for use and worsening after GDR attempts (2 in last year or 1 within facility) – or specific approved diagnosis.

Summary: What Is "Best Practice" for Treatment of NCBS in AD?

- Behavioral analysis and nonpharmacologic treatment when possible
- Consider full range of medications
- Choose medication based on symptoms, side effects, drug interactions, patient factors.
- Monitor response and adverse effects, aiming for lowest effective dose and shortest duration needed.
- Comply with regulatory guidelines for use.

Useful References

- Kaplan M, Hoffman SB: Behaviors in Dementia. Best Practices for Successful Management. Health Professions Press, Inc. Baltimore, MD, 1998.
- Kales et al. Management of neuropsychiatric symptoms of dementia in clinical settings: Recommendations from a multidiscipinary expert panel. JAGS 2014;62:762-9.
- Herrmann et al. Pharmacological recommendations for the symptomatic treatment of dementia: the Canadian Consensus Conference on the diagnosis and treatment of dementia 2012. Alzheimer's Research & Therapy 2013;5(Suppl 1):S5-17.
- O'Brien et al. Clinical practice with anti-dementia-drugs: a revised (second) consensus statement from the British Association for Psychopharmacology. J Psychopharm 2011;25:997-1019.
- Burns et al. Optimising treatment and care for people with behavioral and psychological symptoms of dementia. Alzheimer's Society, July 2011.

QUESTIONS AND DISCUSSION