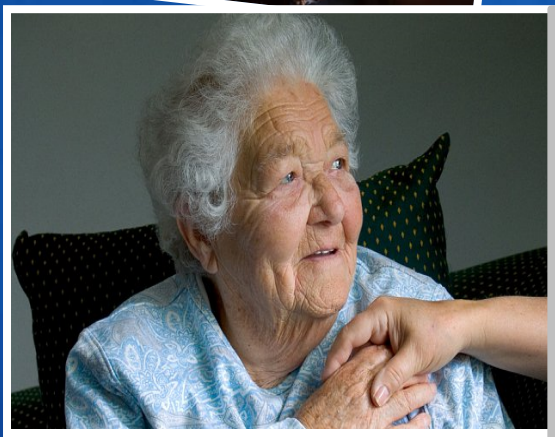
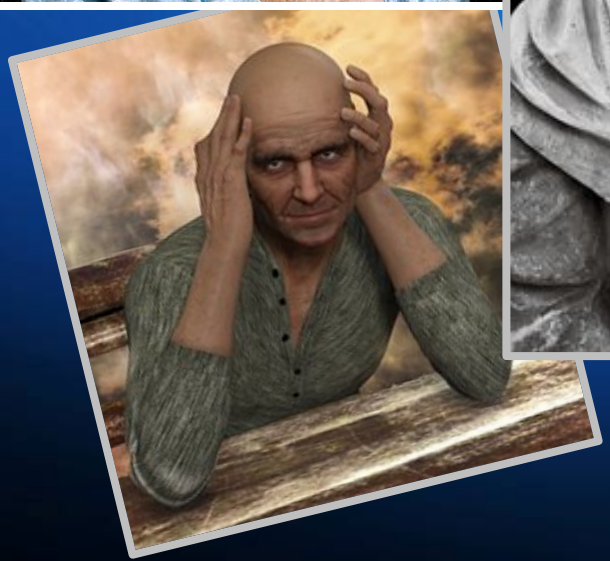
Dementia in Distress 2018





Managing the Noncognitive Behavioral Symptoms of Dementia

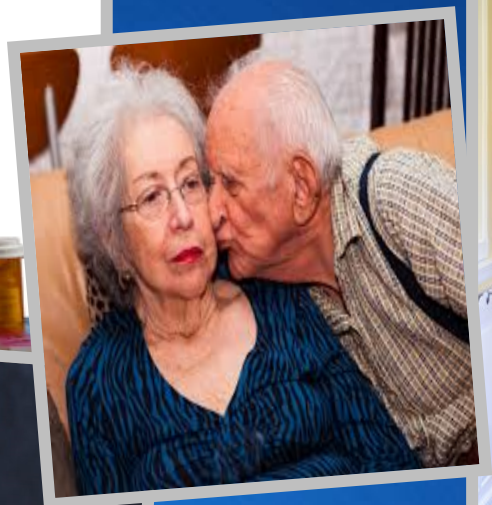
Terms used interchangeably

NCBS = noncognitive behavioral symptoms of dementia

BPSD = behavioral and psychological symptoms of dementia

NPS = neuropsychiatric symptoms of dementia

Management of NCBS



Disclosures

- I have no conflicts of interest to disclose
- No medication is indicated for **NCBS/BPSD/NPS**
- The off-label use of medications will be discussed

- quinidine/dextromethorphan (Nudexta) indicated for pseudobulbar affect, pimavanserin (Nuplaizid) indicated for Parkinson's disease psychosis

DSM5 definition of dementia "Major Neurocognitive Disorder "

A. Evidence of significant **cognitive decline** in 1 or more cognitive domains based on

1. Concern
2. Objective evidence

B. Cognitive deficits interfere with **independence**

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.

Importance of NCBS/BPSD/NPS

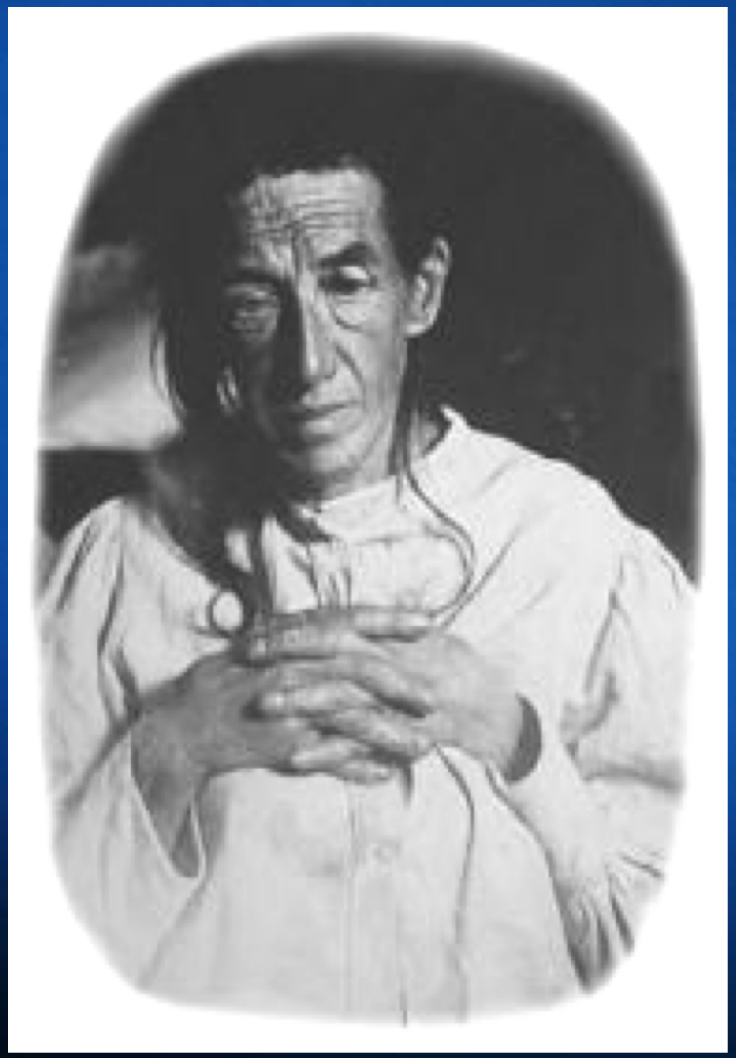
- **Prevalent**: **>95%** of people with dementia/**MND*** will experience NCBS over 5 years
- NCBS are associated with significant **morbidity**,
- high numbers portend rapid functional decline[1,2]
- **No medication is FDA approved for NCBS**
- **No established standard exists for the management of NCBS**

*** MND= Major Neurocognitive Disorder**

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.

The Importance of Behaviors

was recognized even in Alzheimer's Index Patient



- Pathological jealousy
- Paranoid delusions
- Auditory hallucinations
- Screams for many hours in a horrible voice
- Agitated, non-cooperative
- Plaques and tangles on autopsy

Management of NCBS in 2018

- **Noncognitive Behavioral Symptoms (NCBS)**
  - Definitions, context
  - The impact of NCBS/BPSD
- **Management of NCBS in 2018**
  - **Nonpharmacologic strategies**
  - **Somatic treatments and strategies:**
    - **Which medication strategies are used by prudent practitioners?**
    - **Indications for APD (antipsychotic drug) use**
      evidence? dangers? guidelines ? what's new?
- **Evolving Management of NCBS:**
  - An algorithm, a plan, a partnership

"To play it safe, I still take one aspirin every other day."

Definitions:

Major Neurocognitive Disorder, MND "dementia " consists of 2 domains : **Cognitive** and **Noncognitive**

Noncognitive Behavioral Symptoms (NCBS) =
Behavioral & Psychological Symptoms in Dementia (BPSD) =
Neuropsychiatric Symptoms (NPS) =

- **NCBS or BPSD :** ***"A heterogeneous range of : psychological reactions, psychiatric sxs & behaviors that impair the care of the patient in a given environment AND may be unsafe or disruptive***

(adapted from Barucha et al, CNS Spectrum, Nov 2002)

Impact and Burden of NCBS/BPSD

- Seminal events with 1st identification of dementia and referral to a specialist
- indicate rapid progression, worse prognosis +outcomes
- Harbinger of ADMISSION to assisted living facility, nursing home or hospital, **premature institutionalization**
- Cause caregiver stress, burnout, burden

(esp paranoia, aggression and sleep -wake disturbances)

- Disproportionately drives cost of care $300 billion/year- US (direct+ indirect costs)

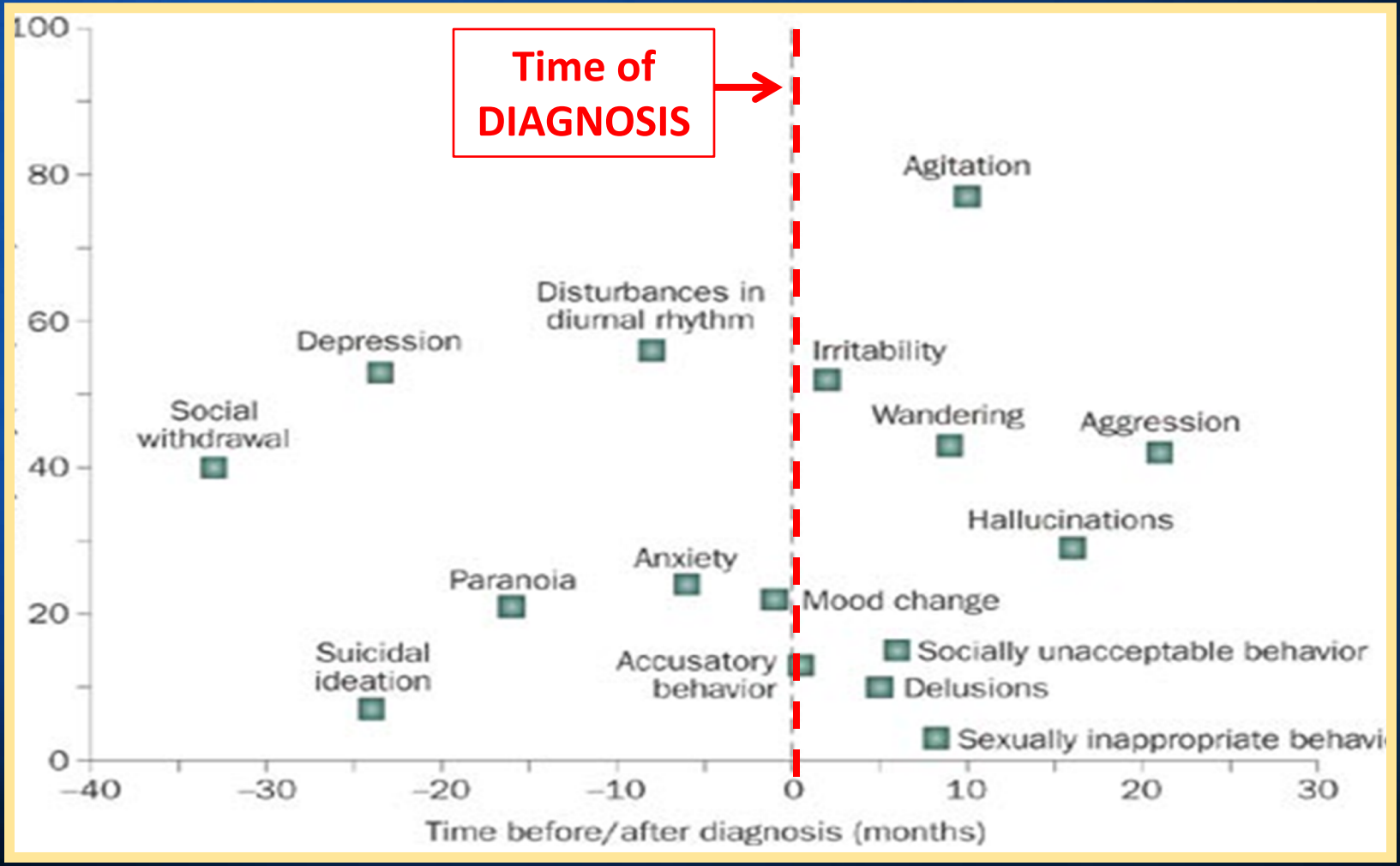
Prevalence of NCBS/BPSD

- ***Community***
  - 65% have at least 1 disruptive behavior
  - 40% have at least 3 disruptive behaviors

- ***Nursing Homes***
  - 90% have at least 1 disruptive behaviors
  - 45% have at least 4 disruptive behaviors

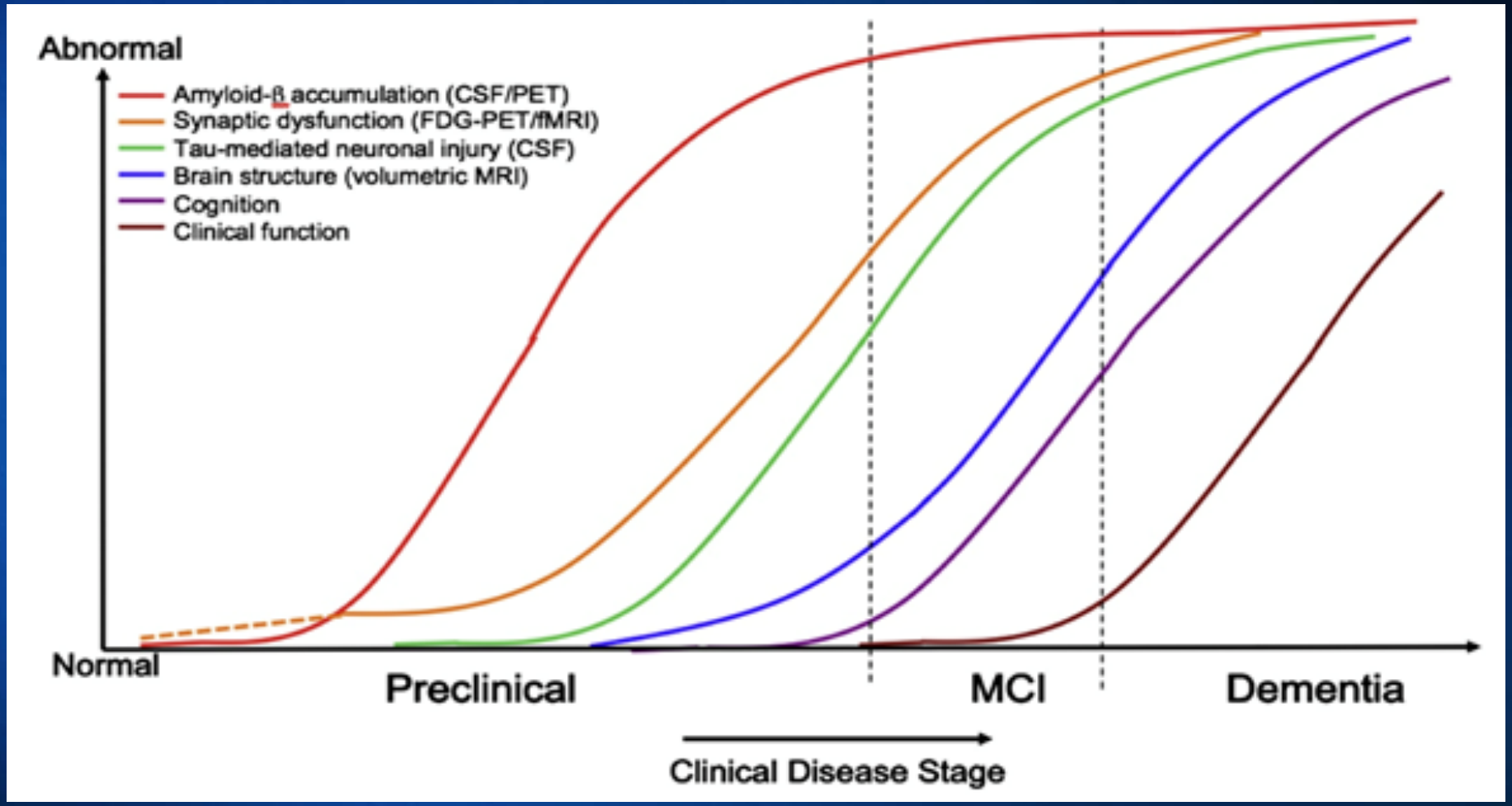
- Behaviors are a chronic feature, but different symptoms emerge as the illness progresses
- **Mood sxs, psychomotor agitation are** most persistent

NCBS: Range and Peak Prevalence During AD Progression



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

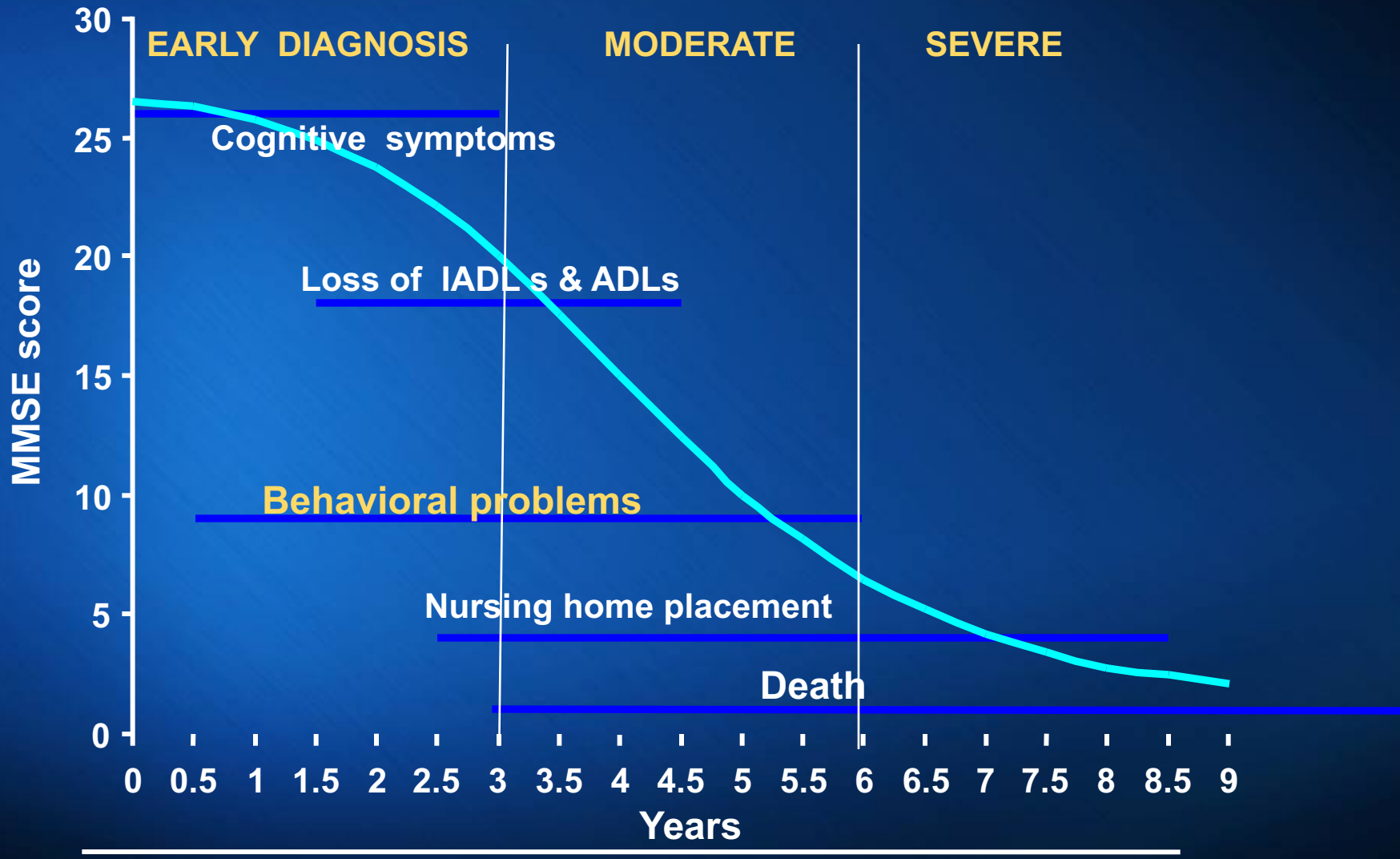
Preclinical Alzheimer's Disease



Accumulation of Aβ oligomers → plaques may precede cognitive dysfunction by 10 years or longer

Jack CR, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, et al. Hypothetical model of dynamic

The Progression of AD



Adapted from Feldman H, Gracon S. In: *Clinical Diagnosis and Management of Alzheimer's Disease.* 1996:239-253.

Stress + Cognitive Deficits → Disruptive Behaviors

Behavioral episodes reflect stresses that exceed a patient's coping skills (in a system at a given point in time):

- **Unmet physical/ medical/psychological needs (Adverse med effects, untreated medical issues 40%[1])**
- **Anxiety, depression, grief**
- **Environmental and caregiver triggers**

Even the seasons form a great circle in their changing, and always come back again to where they were. The life of a man is a circle from childhood to childhood, and so it is in everything where power moves…. Black Elk 1863-1950

what causes NCBS ?

Contributing factors:

- *patient-specific factors* *medical, psychiatric, neurobiologic*
- *environmental factors*
- *caregiver factors*

Patient Neurobiologic factors : circuit degeneration

3 subcortical circuits prefrontal (motivated behavior)
orbitofrontal (inhibitory, conforming)
dorsolateral (executive fxn: plan, org)

5 cortico-cortical circuits (involve common neurotransmitters MAOs, serotonin, norepinephrine, dopamine, and glutatmate)

Common Noncognitive Behavioral Sxs

Changes In	Timing	Frequency	Examples
Mood	Especially Early	Frequent	• Depression • Anxiety • Mania • Apathy
Thinking+ Perception	Early and Late	Frequent	• Suicidal ideation • Delusions, suspiciousness • Hallucinations
Activity	Early and Late	Frequent	• Agitation, verbal, physical • Aggression • Disordered eating behavior • Disordered sleep/activity cycle • Sexually, socially inappropriate behav

BPSD symptom clusters *NEUROIMAGING + BIOMARKERS?*

- *ANXIETY- worry, shadowing, clinging, perseverative*
- *DEPRESSION tearful, hopeless, suicidal*
- *APATHY – disinterest , withdrawal*
- *PSYCHOSIS – hallucinations, delusions (varied) duplicative residence or imposter, suspicious*
- *AGGRESSION –physical*
- *AGITATION- verbal + physical (pacing, hoarding, wandering negativism, refusing meds, showers)*
- *MOTOR- pacing, rummaging, dressing, undressing, leaving*
- *NIGHTTIME- disturbed sleep behaviors /circadian rhythms*
- *EATING – decreased or refusal, compulsive eating*
- *DISINHIBITION- social, sexual*

Antipsychotic Use in Dementia

- Use of Antipsychotic Drugs (APD) for treatment of people with dementia/agitation is discouraged
  - APD are off-label in US for agitation in dementia.
  - FDA requires boxed warning of risks
  - In Europe, only risperidone is licensed for ≤6 wks for treatment of agitation with severe aggression nonresponsive to other treatments.[1]
- Yet…in 2012:
  - 16% of people with dementia were receiving APD, many for ≥ 6 months.[2]
  - In Taiwan, SGA prescribing increased from 17 to 22%[3]

1. Corbett et al. BMJ 2014;349:g6420doi: 10/1136/bmj.g6420;
2. Barnes et al. Br J Psychiatry 2012;201:221-6.
3. Chiu et al. Int Clin Psychopharmacol 2017;32:262-70.

How Effective/Safe Are APD for Treatment of Agitation/Dementia?

- Clinical effect of APD for agitation is limited
- APD increase overall mortality
- In younger patients, they are linked with MetS

So...

- Why does their use for agitation continue?
- Can they help?
- If so, how can they be used safely?

Focus of this Presentation

- APD for Behavioral symptoms in Dementia (NCBS/BPSD) how effective, how dangerous?
- Why are they used?
- What is their relationship with metabolic syndrome and CVA?
- *How does a prudent clinician optimize* treatment efficacy and patient safety in this era of black box warnings and new guidelines?

History of why APD are still used : CVAE Warnings - 2003

- 1998: Janssen explored a dementia indication for Risperdal and promoted it to providers
- 2001: Janssen (and others) sponsored a few thousand CME "Senior Care Seminars" re BPSD
- 2003:
  - FDA requests Janssen to modify Risperdal label: "significantly higher incidence of cerebrovascular adverse events in patients treated with risperidone"
  - FDA requests Janssen to send letter to doctors warning of CVAE risk in elderly dementia patients

justice.gov/sites/default/files/opa/legacy/2013/11/04/us-complaint-pa.pdf

April 2005 – The Plot Thickens

FDA Boxed Warning for APDs notes: "increased risk of death compared to placebo"

- In 17 RCTs:
  - 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 or infections (heart failure, sudden death) or (pneumonia)
  - Study groups included: aripiprazole (3), olanzapine (5), risperidone (7), quetiapine (2), ziprasidone (1), haloperidol (2);
  - Warning was extended to clozapine, 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.

CATIE - AD Results - Further Data about Limited Benefits, Significant Risks

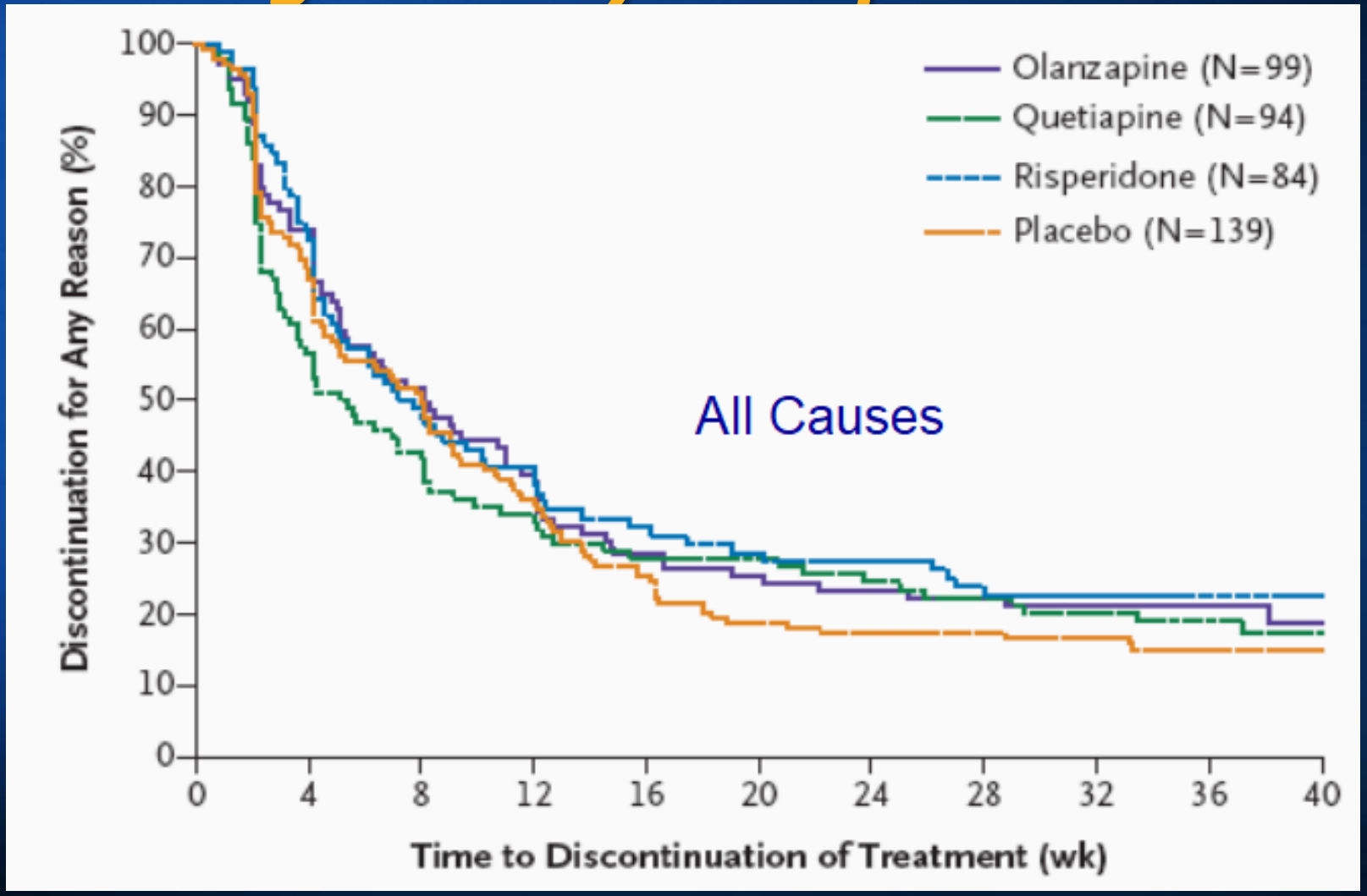
- Multi-center, double-blind, randomized, placebo-controlled 36 week flexible dosing study in 421 AD outpatients with agitation and/or psychosis

- 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.

Discontinuation of Treatment According to Study Group



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

CATIE - AD: CONCLUSIONS

- All cause discontinuation: study drugs /APDs = placebo
  - EPS a common reason for drug discontinuation
  - Efficacy in treating behavioral problems:
    olanzapine = risperidone > quetiapine and placebo

- Adverse events : APD > placebo:
  (EPS, sedation, confusion, increased body weight,
  but not CVA or falls or worsened cognition)

- No large clinical benefit of treatment with APD vs PBO
  (atypical antipsychotic medications as compared to placebo)

Schneider LS et al. NEJM 2006;355:1525-38; Zheng et al. Am J Psychiatry 2009;166:583-590.

Atypical Antipsychotics (SGAs) Additional Safety Issues In Elders

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

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

Are Typical Antipsychotics (FGAs) A Better Alternative? No!

- Temporary increased interest related to concerns about atypicals
- Efficacy appears similar; side effects differ
  - EPS including TD
  - Sedation, hypotension, weight gain, anticholinergic, Ses
  - Mortality rate with typicals appears no lower, possibly higher than with atypicals[1,2]

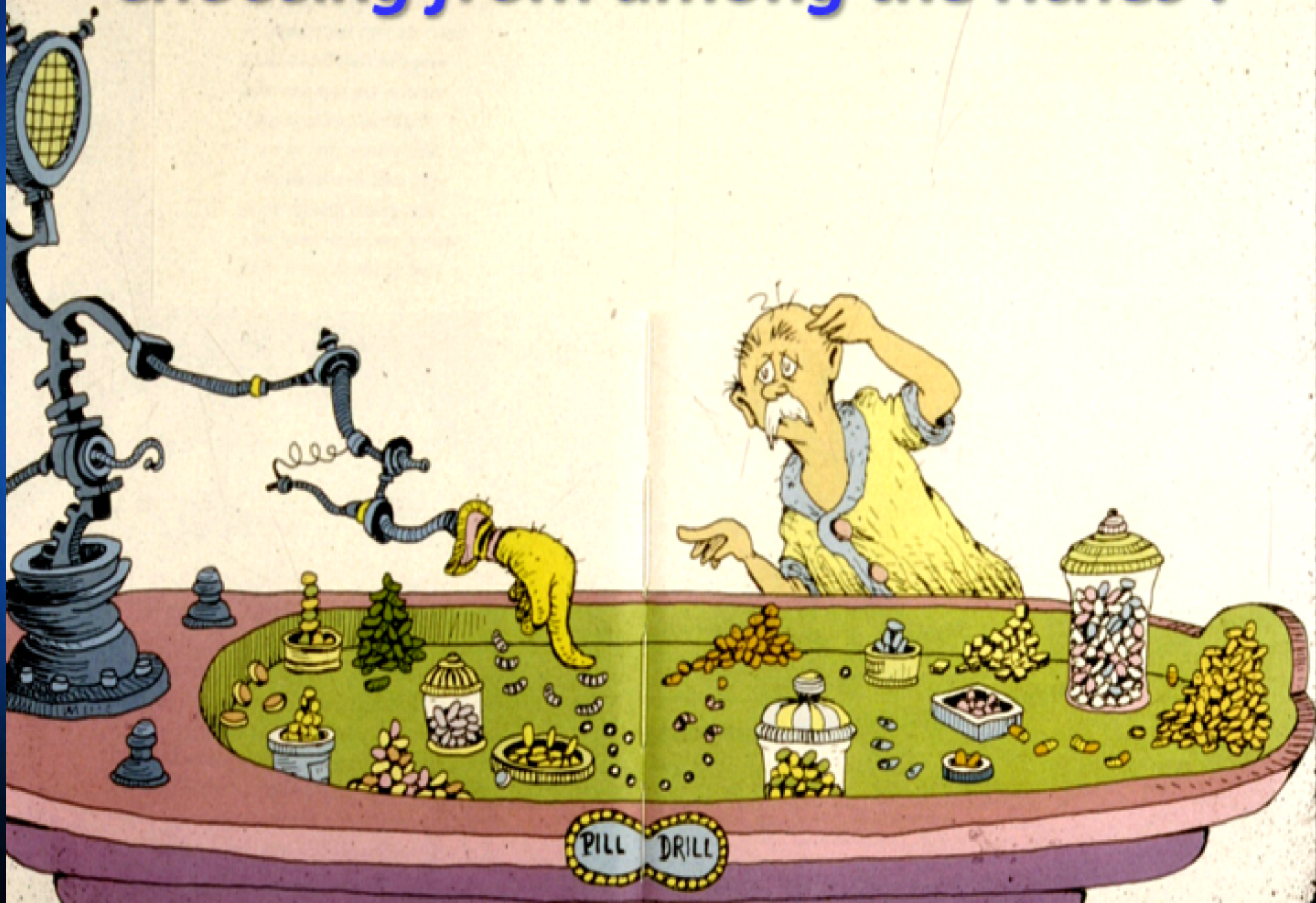
1. Wang et al. N Engl J Med. 2005;353:2335-2341;
2. Ray et al. NEJM 2009; 360:225-35

APA Practice Guideline For Treatment Of Patients With Alzheimer's Disease & Other Dementias (2nd Ed.) Took A Pragmatic Position in 2007

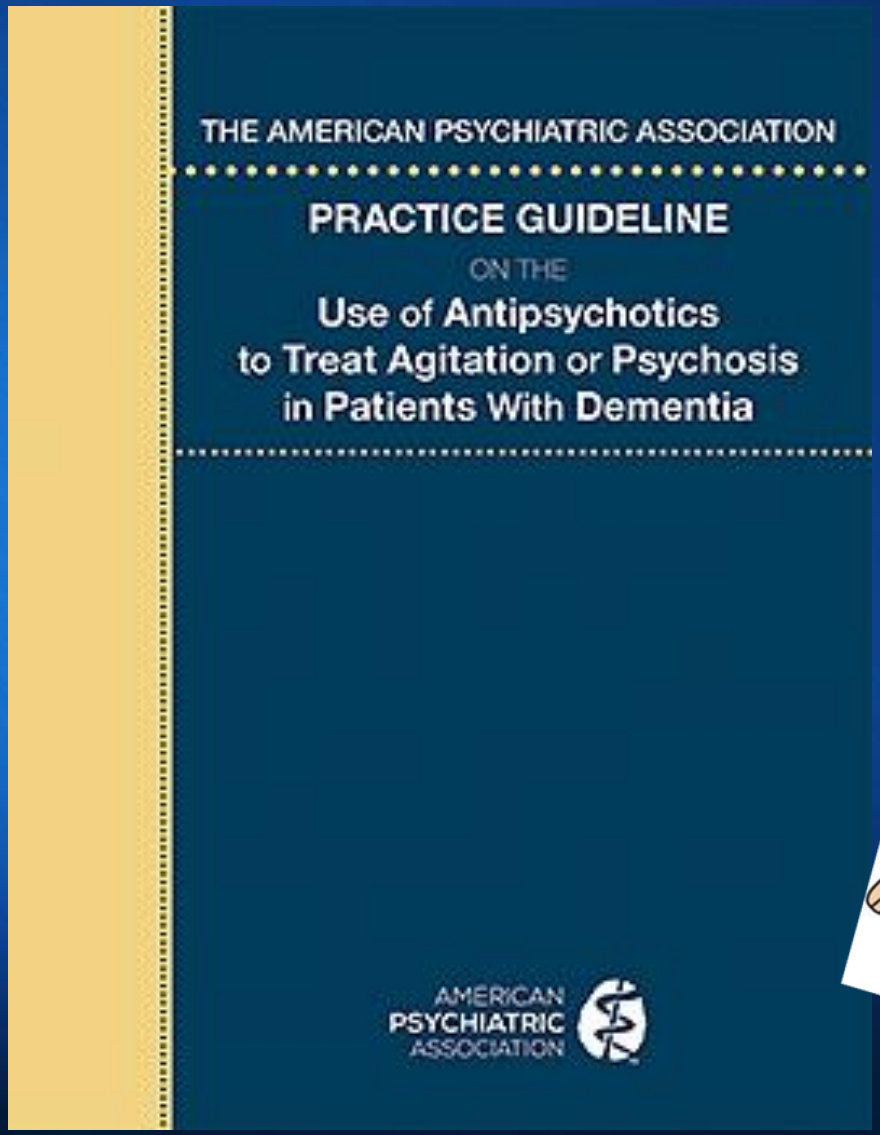
"Antipsychotics are the primary pharmacological treatment available for psychotic symptoms in dementia…considerable evidence from randomized, double-blind, placebo-controlled trials and meta-analyses for the efficacy of both first-generation and second-generation agents although this benefit is often modest…risks and benefits of these medications must be reassessed on an ongoing basis."

Rabins et al. Am J Psychiatry 2007;164(10 Suppl)

Choosing from among the riches ?



An Updated Position in 2016



APA Guidelines

- Statement 5: “Nonemergency antipsychotic medication should only be used for the treatment of agitation or psychosis in patients with dementia when **symptoms are severe, are dangerous, and/or cause significant distress to the patient.”**
- Statement 6: Review response to nonpharmacological interventions before initiating APD therapy
- Statement 7: Assess and discuss risks before initiating nonemergency APD treatment
- Statement 8: Initiate APD at a low dose,
- use minimum effective dose

APA 2016: The American Psychiatric Association Practice Guideline on the Use of Antipsychotics to Treat Agitation or Psychosis in Patients with Dementia.

APA Guidelines - More Directive

- Statement 9: Review use if clinically significant side effect develops
- Statement 10: Taper /withdraw after 4 weeks in absence of response
- Statement 12: Taper and withdraw after 4 months in responder unless symptoms recurred with prior tapers
- Statement 13: With tapering, assess symptoms monthly during taper and for 4 months after discontinuation

APA 2016: The American Psychiatric Association Practice Guideline on the Use of Antipsychotics to Treat Agitation or Psychosis in Patients with Dementia.

Experts Did Not Rule Out Use of APD:

"Which of the following antipsychotics would you refuse to prescribe to a patient with dementia because of potential adverse effects?"

86% responded "NONE"

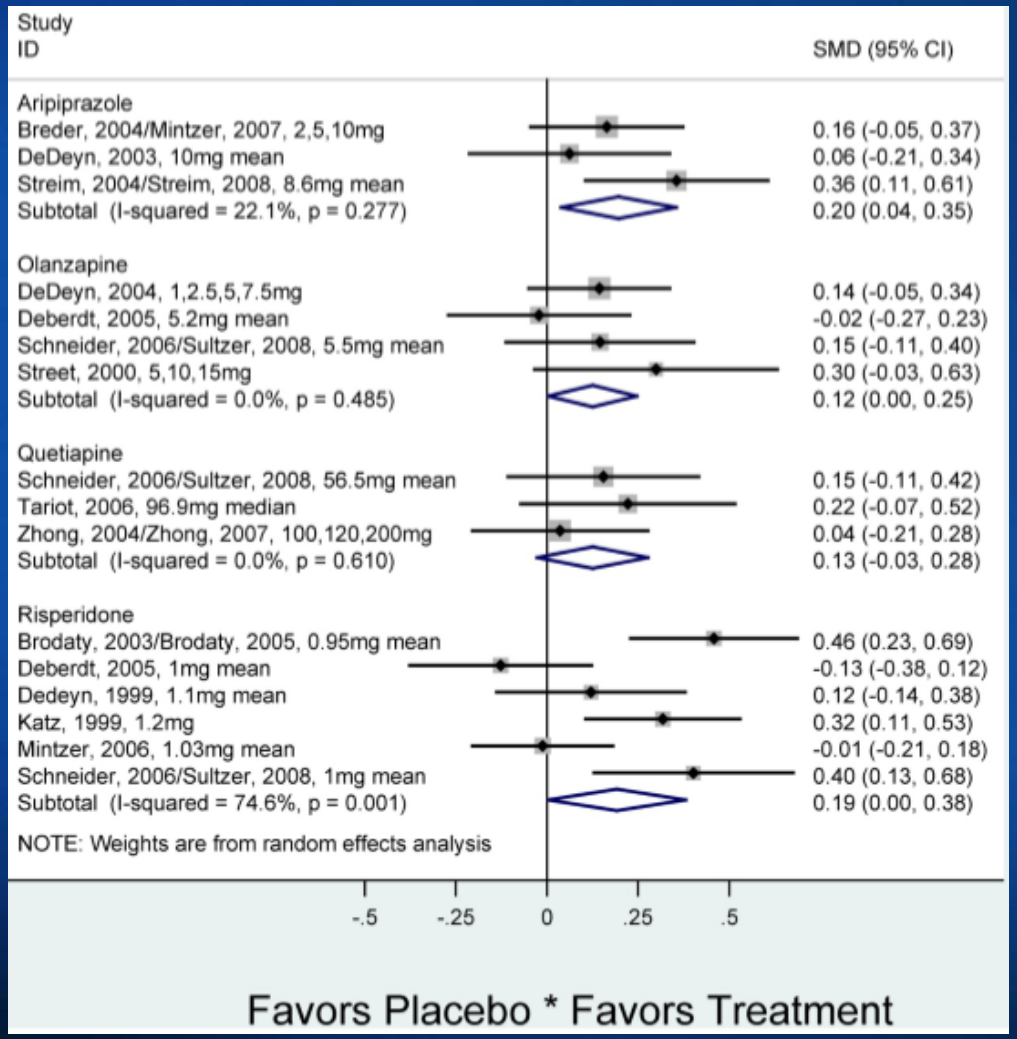
APA 2016: The American Psychiatric Association Practice Guideline on the Use of Antipsychotics to Treat Agitation or Psychosis in Patients with Dementia. P 208.

Evidence Base for APA Guidelines

- APA Guideline is largely based on data from AHRQ review of APD placebo controlled trials
- Conclusion of AHRQ review: Aripiprazole, olanzapine, risperidone exceed placebo (with small effect sizes) in treatment for behavioral symptoms of dementia including aggression, agitation, psychosis
- Risks: Multiple adverse events are increased with antipsychotic use

Maglione et al M, Ruelaz Maher A, Hu J, et al. Review No. 43.
Rockville MD, Agency for Healthcare Research and Quality, September 2011.
www.effectivehealthcare.ahrq.gov/reports/final.cfm

APD vs PLA GLOBAL SCORE in Dementia



Aripiprazole effect size 0.20

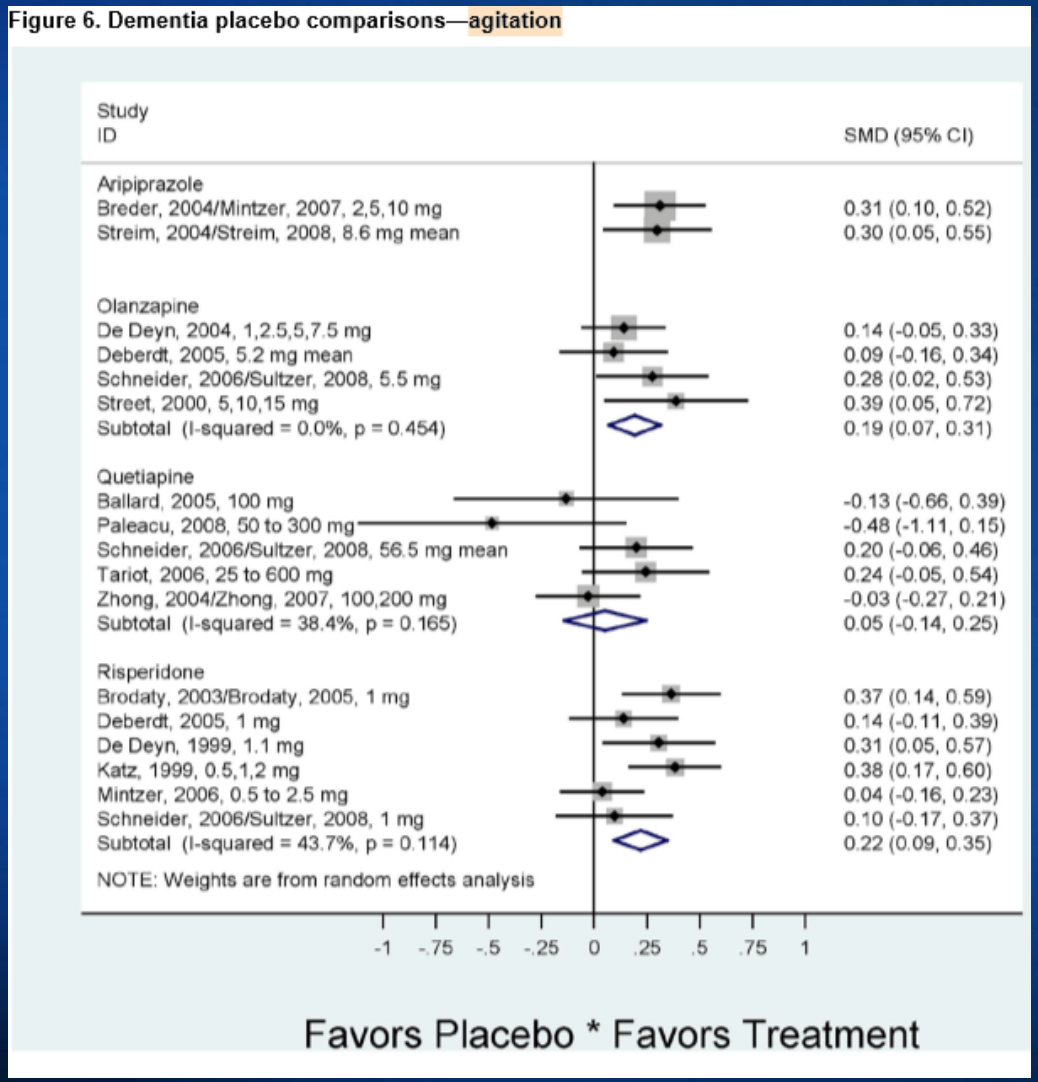
Olanzapine effect size 0.12

Questiapine effect size 0.13

Risperidone effect size 0.19

Maglione et al M, Ruelaz Maher A, Hu J, et al. Review No. 43.
Rockville MD, Agency for Healthcare Research and Quality, September 2011.
www.effectivehealthcare.ahrq.gov/reports/final.cfm

APD vs PLA for AGITATION score in DEMENTIA



Aripiprazole effect size 0.30 for 2.5-10 mg/d

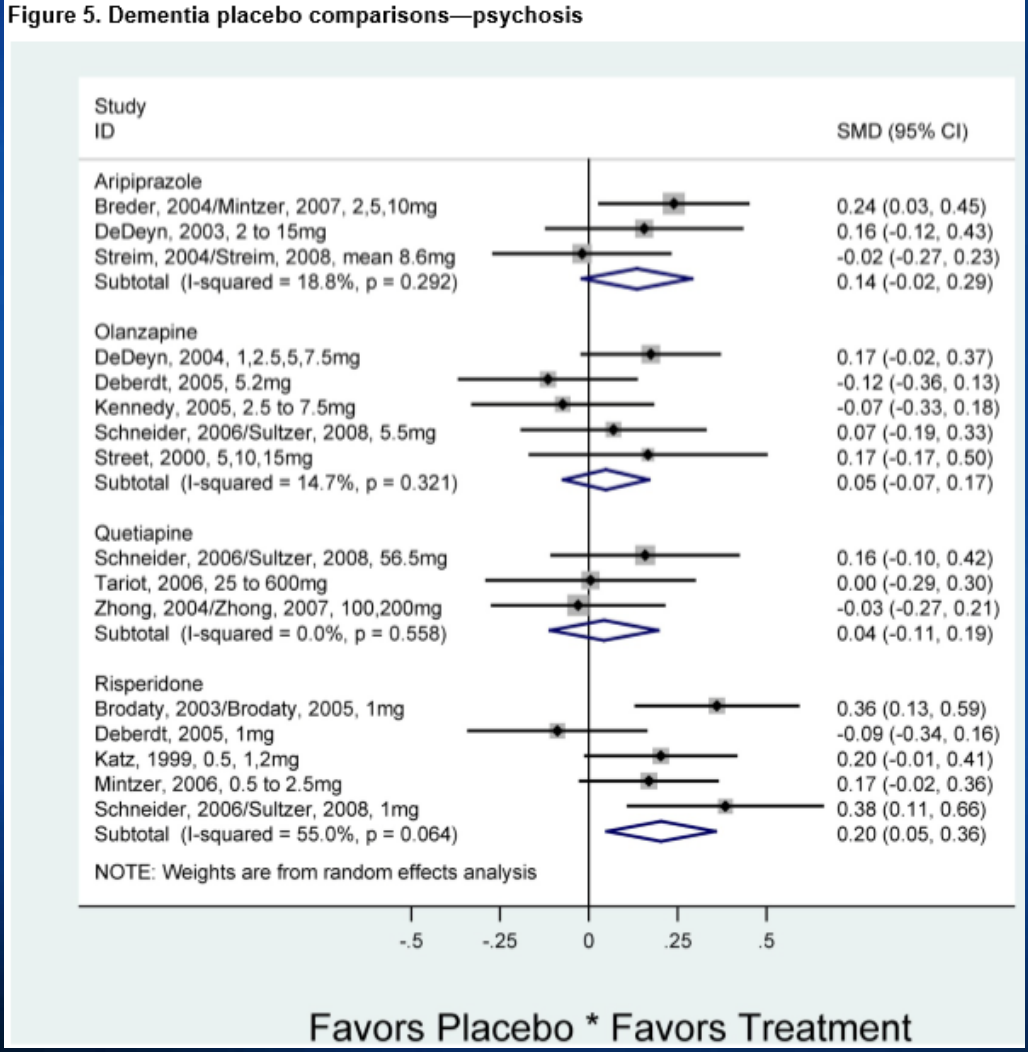
Olanzapine effect size 0.19 1-15 mg dose range

Quetiapine effect size 0.05 25-600 mg dose range

Risperidone effect size 0.22 0.5-2.5 mg dose range

Maglione et al M, Ruelaz Maher A, Hu J, et al. Review No. 43. Rockville MD, Agency for Healthcare Research and Quality, September 2011. www.effectivehealthcare.ahrq.gov/reports/final.cfm

APD vs PLA PSYCHOSIS score in Dementia



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www.effectivehealthcare.ahrq.gov/reports/final.cfm

Do APD Increase CVA?

Do Antipsychotics Increase The Risk for CVA?

- Based on systematic review of cohort and controlled trials:[1]
  - Higher rate of CVAs is associated with APD treatment of elderly but absolute increase in risk is small, CVAs were rare
  - FGA not safer than SGA
  - Risk increased by older age, cognitive impairment, vascular dementia, concurrent anticoagulants, atrial fibrillation, hypertension, history of prior CVA
  - Estimated NNH over 1 year = 28.6

- **Risk is in first month of use (OR 1.17 to 12.4)[2]**

1. Sachetti et al. Drug Safety 2010;33:273-88;
2. Imfeld et al. Neurology 2013;81:910-9.

Why?

- Thrombosis
  - Similar to increased DVT risk with APD
  - Sedation, obesity
  - Hyperleptinemia, increased coagulability
  - Postural hypotension, arrhythmias
- Inflammatory cytokines (IL-6)
- Other disease risk factors
  - Elevated homocysteine
  - Changes in phospholipid metabolism

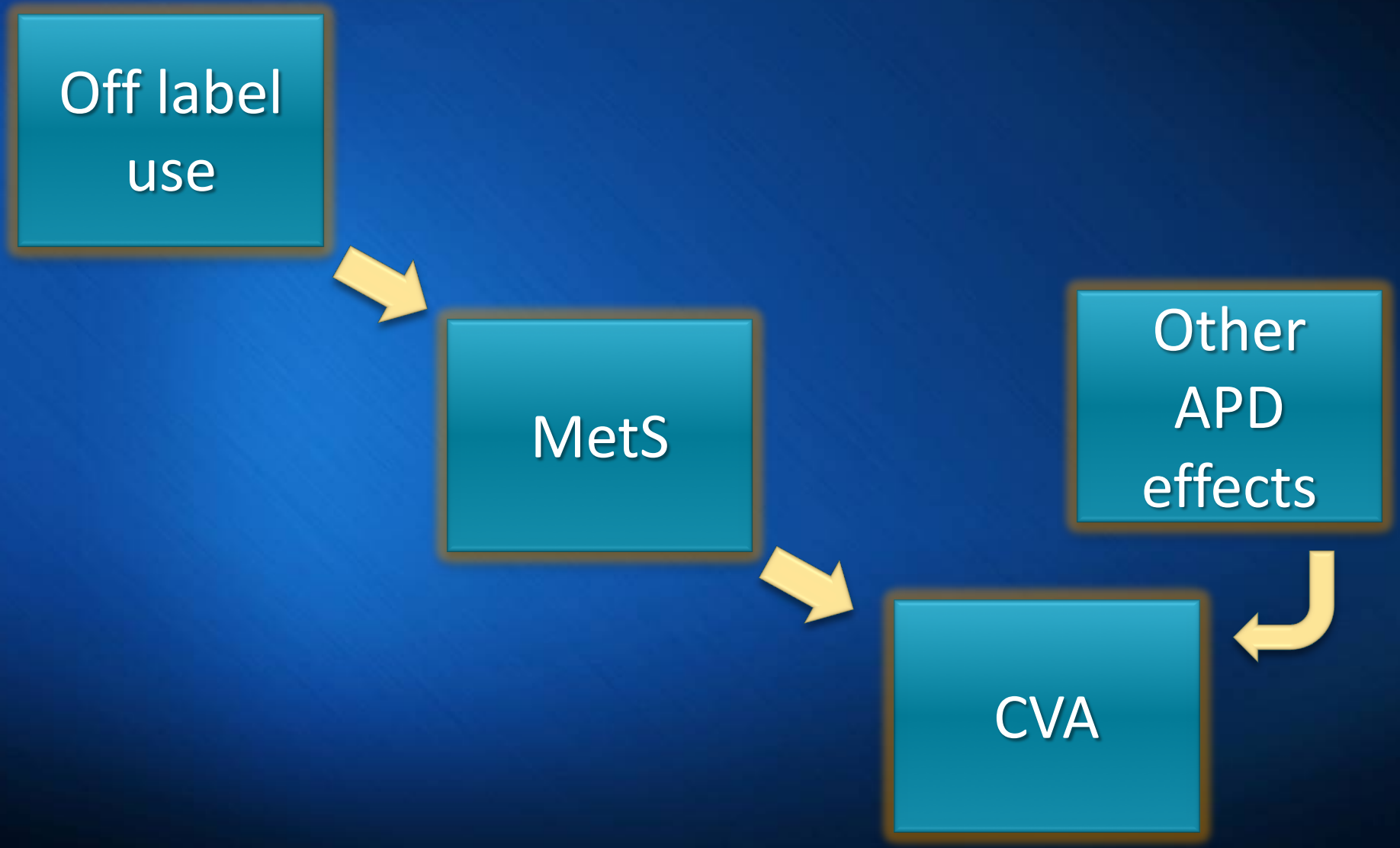
1. Sachetti et al. Drug Safety 2010;33:273-88

In Some Trials, APD Increased the Risk for MetS Syndrome in Elderly with Dementia

- 90 day observation: 29,203 nursing home residents with dementia linked first generation APD with new DM onset.[1]
- 2.2 year follow up of 44,121 elders (42% dementia) newly treated with FGA or SGA linked treatment with increased hyperglycemia, FGA and SGA. OR for SGA **2.86**[2]
- **1 year follow up of mixed adults >40 years old, treated with aripiprazole, olanzapine, quetiapine, or risperidone[3] showed:**
  - **New MetS in 36.5%**
- **In other trials – metabolic effects of APD in geriatrics were balanced by improvements in metabolic #s: MetS may be more diverse or complicated in elderly…more data needed** [4]

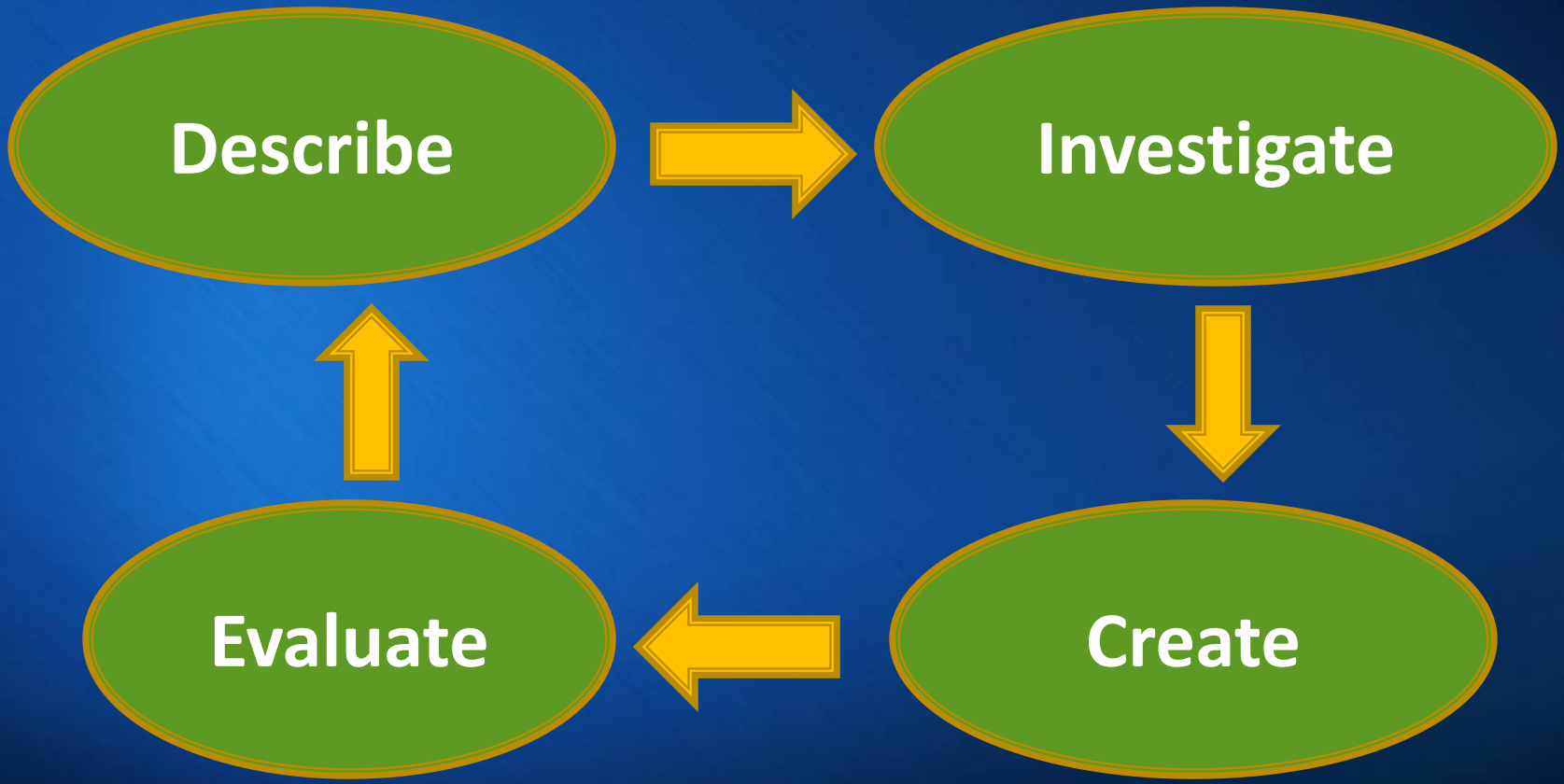
1. Jalbert et al. Am J Geriatr Pharmacother 2011;9:153-63 ;
2. Lipscombe et al. Am J Geriatr Psychiatry 2011;19:1026-33;
3. Jin et al. J Clin Psychiatry 2013;74:10-8.
4. Gurevitz et al. Consult Pharm 2004;19:809-12;

The Suspected Chain of Events



What should the prudent clinician do to optimize treatment effectiveness and patient safety?

Use DICE to Assess NCBS and Suggest Nonpharmacologic Treatments



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

Try Person-Centered Approach First

- **Adopt** the patient's perspective
  - What are they experiencing?
  - How does it look/feel from their perspective?

- Embrace the patient's reality /**validate** their experience, flgs
  - What they are experiencing is real to them
  - You can "join them" in their reality without accepting their point of view, yet still not contradict/argue

Accepting the pt's reality calms, communicates helpfulness

An alternative to confronting, arguing, reorienting

USE NONPHARMACOLOGIC STRATEGIES first

targets : patient, environment, caregiver

effect size = 0.40 [1]

- Validation, reassurance
- Distract, leave the room
- Simulated presence therapy (spouse, child or sib)
- **Decrease Stimuli** : Snoezelen Room
- Engage in a pleasant physical activity :
- Music Therapy, Pet Therapy
- Light Therapy, Aromatherapy
- Acupuncture, Hand Massage
- Cognitive training and rehabilitation (PST)

Assess Other Factors Affecting Drug Safety/Effectiveness

- Placebo response
- Gender
- Age
- Genetics
- Pain
- Diet
- Smoking
- Alcohol
- Caffeine
- Exercise
- Disease
- Drugs
- Herbs
- Personality
- Social Support
- Adherence

1. Ballard et al. Lancet Neurol 2009;8:151-7.
2. Weiden PJ. J Clin Psychiatry 2007;68[suppl 4]:34-9

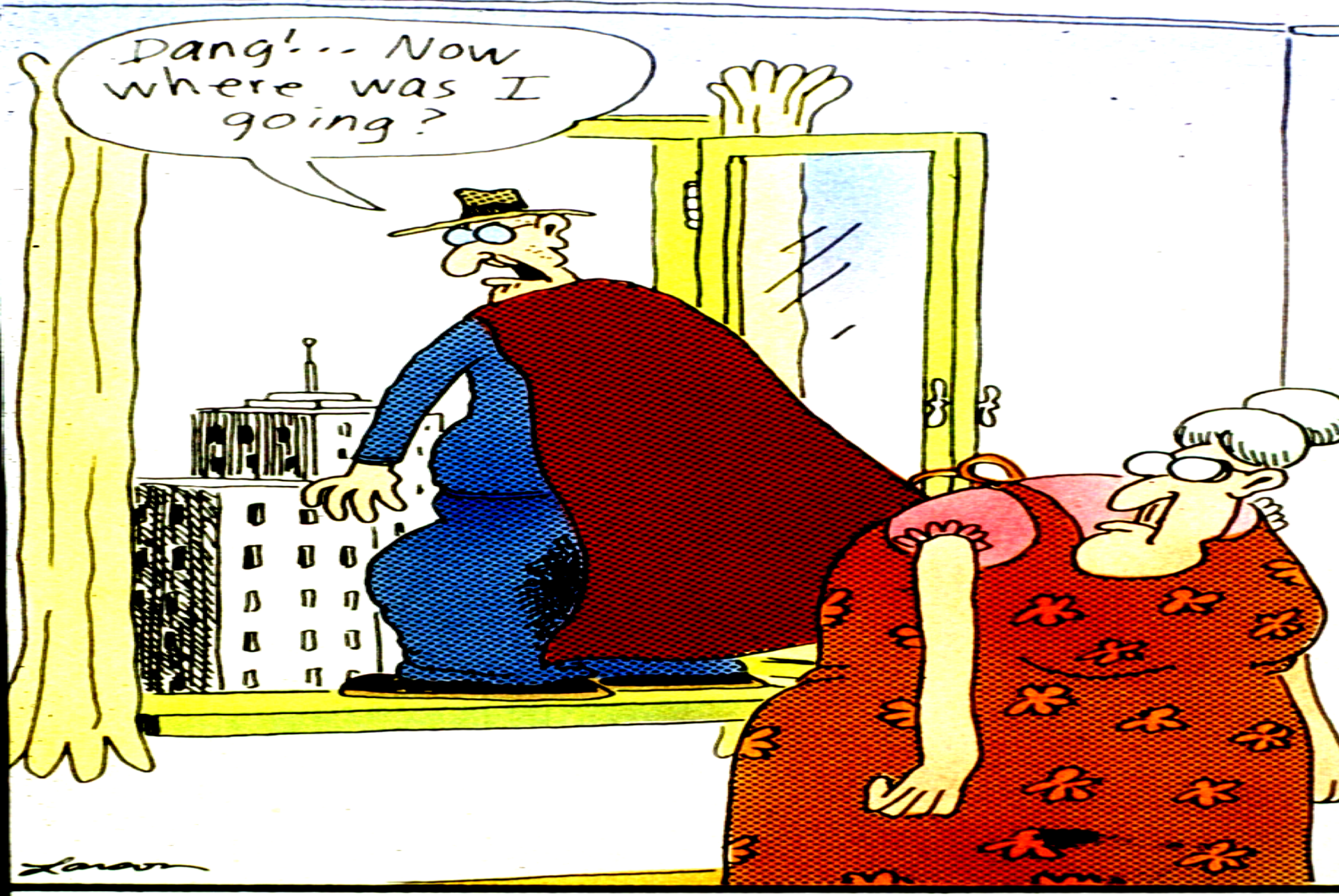
When Medications Are Required

- APD alternatives (off-label like APD) include:
  - Cognitive enhancers
  - Antidepressants
  - Analgesics
  - Anticonvulsants
  - Anxiolytics
  - Cannabinoids

Alzheimers Dementia : optimizing

- Early diagnosis (relief!)
- Early treatment: ACHEIs
- Maintenance treatment: ACHEI + Memantine
- Maximize nonpharmacologic strategies
- Thoughtful, measured “pulsed” treatment for severe NCBS
- Remove anticholinergics, benzodiazepines, toxins, safety threats
- Incorporate lifestyle changes (dietary , exercise, supplements
- Focused education and support for caregiver + patient dyad
- multidisciplinary+ palliative +focused on quality of life

"Frank, I want you to try antidepressants."



Superman in his later years

Optimal Dosages

- Olanzapine 2.5 – 10 mg/d
- Risperidone effectiveness at 1 mg/d, 2 mg/d
- Aripiprazole: 2-10mg/d; 2 mg/d may be too low
- Brexipiprazole :0.5mg-2mg/d
- Quetiapine - 12.5 mg-200mg/d

  Is a higher dose more effective??
- Ziprasidone : 10mg IM very helpful (***my experience***)
- Lurasidone : 20mg/d - 80mg/d ?
- Clozapine :6.25 mg- 200mg/day

Katz et al. 1999; Street et al 2000; DeDeyn et al 2004; Breder et al. 2004; Mintzer et al. 2007; Ahong et al. 2007

Practical Suggestions for APD Use:

- Consider etiology of dementia –treat as if this was your mom (avoid treating LBD with APD)
- Reserve nonemergency APD use for severe, dangerous, or significantly distressing symptoms
- Assess R/B, discuss with patient or surrogate decision maker with input from others
- Start at low dose, titrate and allow agent to reach pharmacokinetic steady state, (use minimum effective dose
- Monitor adverse effects, Document rationale, response, discussion
- Discontinue as soon as appropriate
  - After 4 weeks if no response
  - At 4 months for responders unless prior tapering led to symptom recurrence

1. Ballard et al. Lancet Neurol 2009;8:151-7.
2. Weiden PJ. J Clin Psychiatry 2007;68[suppl 4]:34-9

Practical Suggestions for APD Use

- Assess symptoms at least monthly during taper and for at least 4 months after d/c
  - In 70% of patients, no worsening of symptoms occurred after APD withdrawal [1]
- Another antipsychotic may be safer?
  - ziprasidone, aripiprazole may have advantages but insufficient literature in older patients[2]
- In absence of delirium, haloperidol is not first line nonemergency antipsychotic of choice.
- Long acting injectable APDs not recommended tx unless used for co-occurring chronic psychotic disorder
- Obtain EKG to determine QTc before titrating dose

1. Ballard et al. Lancet Neurol 2009;8:151-7.
2. Weiden PJ. J Clin Psychiatry 2007;68[suppl 4]:34-9

APD Documentation

- Behavioral + environmental interventions trialed (DICE)
- TARGET SYMPTOMS for APD and MND w Behav Disturbanc
- GOALS of TREATMENT (measure NPI: decrease # aggressive episodes by 50%)
- Alternative medications trialed (ACHEIs,SSRIs, ACD)
- EDUCATION /CONSENT process with patient/family
- SET EXPECTATIONS with TEAM:
  - coordinate, monitor w involved clinicians, staff, family
  - timeframe for assessment of ASE/results (~4.5 x t 1/2)
  - magnitude of improvement possible ~30% -50%
- Re-assess benefits/side effects at titration intervals , document plan, document rationale for changes
- Lowest doses necessary, shortest duration
- Taper at 1 mo or 4 mos, document presence,absence of sxs

NPI Q

Study Name or Acronym: _____

9 6

NEUROPSYCHIATRIC INVENTORY QUESTIONNAIRE (NPI-Q)

4 0

SUBJECT ID | | | | | | | |

VISIT NO | | | |

DATA SOURCE | | | | |

SITE NO | | | |

VISIT DATE | | | MM | | DD | | | | YYYY

Please ask the following questions based upon changes.
Indicate "yes" only if the symptom has been present in the past month; otherwise, indicate "no".

	Present in the PAST MONTH: 0 = No 1 = 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 (the caregiver) experience because of the 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)
DELUSIONS			
1. Does the patient believe that others are stealing from him or her, or planning to harm him or her in some way?	1.1	1.2	1.3
HALLUCINATIONS			
2. Does the patient act as if he or she hears voices? Does he or she talk to people who are not there?	2.1	2.2	2.3
AGITATION OR AGGRESSION			
3. Is the patient stubborn and resistive to help from others?	3.1	3.2	3.3
DEPRESSION OR DYSPHORIA			
4. Does the patient act as if he or she is sad or in low spirits? Does he or she cry?	4.1	4.2	4.3
ANXIETY			
5. 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?	5.1	5.2	5.3
ELATION OR EUPHORIA			
6. Does the patient appear to feel too good or act excessively happy?	6.1	6.2	6.3
APATHY OR INDIFFERENCE			
7. Does the patient seem less interested in his or her usual activities and in the activities and plans of others?	7.1	7.2	7.3

NPI Q neuropsychiatric inventory

PD-DOC

Study Name or Acronym: _____

NEUROPSYCHIATRIC INVENTORY QUESTIONNAIRE (NPI-Q)

9 6 4 0

SUBJECT ID | | | | | | | | VISIT NO | | | |

	Present in the PAST MONTH: 0 = No 1 = 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 (the caregiver) experience because of the 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)
DISINHIBITION			
8. 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?	8.1 ☐	8.2 ☐	8.3 ☐
IRRITABILITY OR LABILITY			
9. Is the patient impatient and cranky? Does he or she have difficulty coping with delays or waiting for planned activities?	9.1 ☐	9.2 ☐	9.3 ☐
MOTOR DISTURBANCE			
10. Does the patient engage in repetitive activities, such as pacing around the house, handling buttons, wrapping string, or doing other things repeatedly?	10.1 ☐	10.2 ☐	10.3 ☐
NIGHTTIME BEHAVIORS			
11. Does the patient awaken you during the night, rise too early in the morning, or take excessive naps during the day?	11.1 ☐	11.2 ☐	11.3 ☐
APPETITE AND EATING			
12. Has the patient lost or gained weight, or had a change in the food he or she likes?	12.1 ☐	12.2 ☐	12.3 ☐

Suggested Antipsychotic Drug Screening/Monitoring

Suggested Timeframe and Screening	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

Evolving Pharmacologic Treatment Principles for NCBS/ BPSD

- **Use of medications reserved for symptoms that persist after non-pharmacological treatments have failed**
- **Choice of medication influenced by the urgency of the situation, and guided by trial and error**
- **Behaviors may be classified as *emergent* or *non-emergent*.**
- ***Emergent behaviors* may need to be treated with IM formulations or medications including antipsychotics, these may require inpatient psychiatric treatment**

Evolving Pharmacologic Treatment Principles for NCBS/ BPSD

- Cognitive and noncognitive target symptoms associated w various neurotransmitter deficiencies
- **NONPHARMACOLOGIC STRATEGIES** are first line tx
- A **combination of medications** will be used to treat **NCBS/BPSD/NPS** target symptoms
- **Acetylcholinesterase inhibitors (ACHEIs) are useful for behavioral symptoms**
- **Antidepressants** are first line therapy for anxiety, dysphoria, helpful adjuncts for aggression, agitation
- ? Atypical antipsychotics may be necessary for **dangerousness** , adjuncts in treatment of refractory psychosis

PHARMACOLOGIC TREATMENTS for "Non-Emergency" Distress, Agitation

- Start treatment with a cholinesterase inhibitor
  - Add memantine if the patient is moderate to severely demented
  - If agitation persists, try an SSRI antidepressant.
  - If the SSRI antidepressant is unhelpful, trial SNRI –esp mirtazapine, consider gabapentin
  - If all the monotherapy trials fail, then use a combination therapy.
- ***Avoid benzodiazepines!***
- ***?Avoid Antipsychotics Drugs***

Algorithm for Treating Emergent "Urgent" Escalating Agitation

- Emergent behaviors may need to be treated with antipsychotics (po or IM) +/- adjuncts

- Offer Risperidone: 0.25 mg-1.0 mg dose (liquid?)
- Or Ziprasidone 20 mg po or 10 mg IM dose
- Or Aripiprazole 2.0-5.0 mg dose
- Or Olanzapine 2.5 mg-5 mg dose

reassess: If symptoms < 50% improved, repeat dose in 30-60min

May need 1-2 repeats before the patient calms down

+ Benzodiazepines for rescue or adjunctive use ? (not w Olanzapine)

- **may require inpatient psychiatric treatment?**

Modified from Tampi RR, et al. Clinical Geriatrics. 2011;19(6):31-40

Joan 90yo MWF : PDx 2 yr, POTS, PE, AFIB,OSA, Npathy, MCI? (FAMILY)

presented 1/2017 for depression, VH (bugs) delusional – (duplicative residence, imposters), confusion

MEDS Sinemet, azilect, failed donepezil and memantine

"life not worth living, mem probs, attention and concentration poor, confused, disappointed, cant problem solve or know what's going on. Dont want to feel hopeless, don't want Ses"

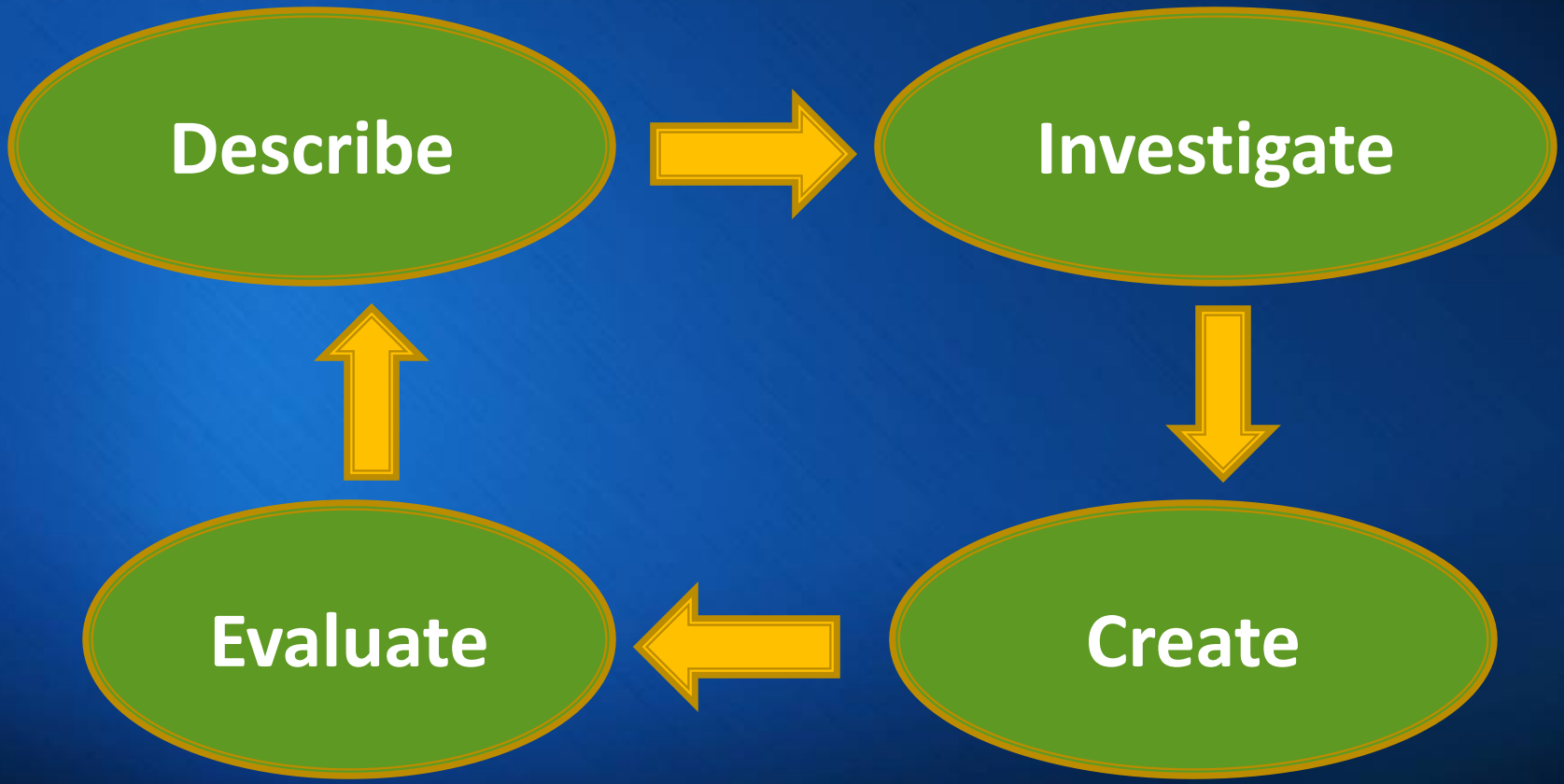
PE/MSE: PHQ 15/27 moca 21/30 attentional, construction, st deficits

- Tx: exelon patch titration, disc w caregiver @vigilance, PT
- 4/17: VH and delusions resolved fxn 30% better 5/17: engage w reality, cg, ex, planning SB. no depression
- 6/17, pneumonia /rehab 7/17 Avenidas- cptr class, ?Provigil
- 7/17 8/17 planned party for grandson, ex w caregivers reading, obtaining tickets to theater/music

Joan Dementia with anxiety, psychosis

- 10/17: anxiety@ abandonment suspiciousness @caregivers –reassurance, ↓modafinil (no benefit
- 3/2018 :UTI, hospzn
- 5/2018 : good energy, anxiety worried abt husband- sleeping apart, disc marital issues, "VH of strings"
- 7/2108: worried about dying ; Zoloft added 12.5mg titrated to 25 mg/d
- 10/2018: MOCA 19 calm, good mood, talking abt Stanford musicians, joking, started palliative care, open to discussion, still has "strings" and manipulates them

Use DICE to Assess NCBS and Suggest Nonpharmacologic Treatments



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 Factors/perspective**
  - Medication side effects
  - ?Untreated Pain, itching
  - 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, tone
- **Environment :** Social, cultural, physical

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

Create

- Strategize behavioral interventions
- **EDUCATE** Provide caregiver education +support
- Enhance communication with the patient
- Respond to physical problems
- **ADD STRUCTURE /ROUTINE**

Create meaningful activities for the patient

Simplify tasks

- **SIMPLIFY ENVIRONMENT**

Ensure the environment is safe

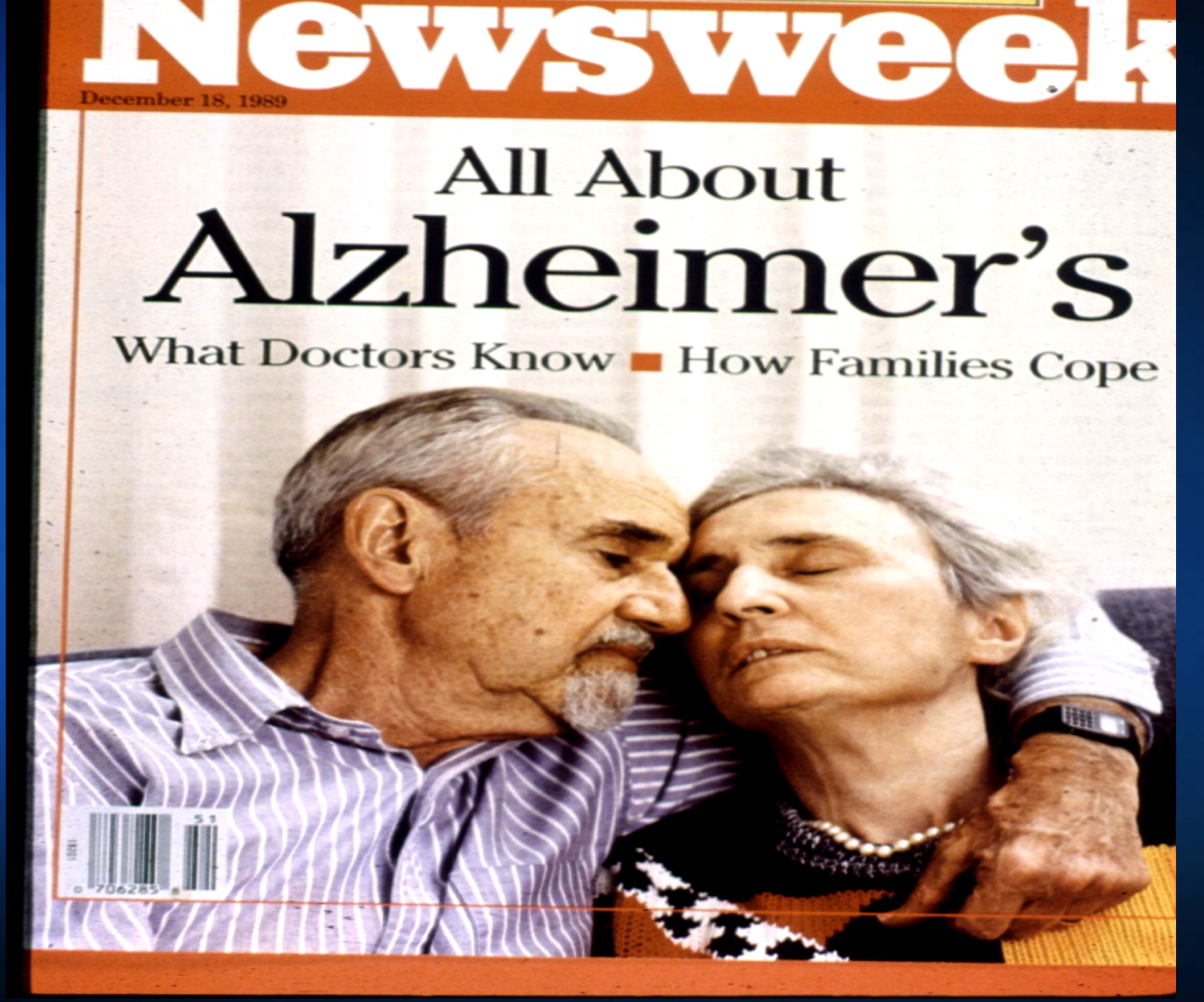
Decrease /increase stimulation in the environment

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

Evaluate

- **Which interventions did the caregiver implement?**
- **Have there been any unintended consequences or "side effects" from the intervention(s)?**
- **If the caregiver did not implement the interventions, why?**
- **What changes in the environment have been made?**
- **MEASURE: Have the intervention(s) been effective for the problem behavior(s)? (30-50% reduction in incidents?)**

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


Newsweek
December 18, 1989
All About
Alzheimer's
What Doctors Know ■ How Families Cope

THANK YOU !!!

Questions??

grace.nadolny@gmail.com

...a note of thanks to my patients and families and to colleagues Drs Ayati and Ellison

Behavioral Intervention Examples

- Caregiver education (Fast, Reisberg Scales)
- Distraction and redirection
- Activity/exercise
- Prosthetic (habilitative) environment
- Simulated presence/Reminiscence
- Music therapy – individualized
- Aromatherapy / massage

*Interventions must not exceed patient's **capacity***
to learn + remember

Antpsychotic Drug withdrawal

- Psychotic relapse in 1/3 with severe baseline auditory hallucinations stabilized on Risperidone, if 30% NPI improvement [12]

  level 1 +2 evidence

- Discontinuation syndromes: chol rebound, dyskinesia

APD switch guidelines :Humber NHS guidelines (NHS 2012 Mar PDF)

Taper Gradual 4 wks (NICE 2014 Sep PDF)

1 NEJM2012
2 Am J of Psych 2017 April

NCBS APPENDIX

Behaviors

According to Dr. Barry Relsberg's theory, an adult with Alzheimer's disease goes through a reversal of normal human development, from adulthood to infancy.

Stages of Normal Development

Approximate Age	Abilities Acquired
1. Older adult	Normal for age
2. Mature adult	Normal abilities
3. Young adult	Can perform complex job
4. 7 years - adolesence	Can handle simple banking
5. 5-7 years	Selects clothes properly
6. a. 5 years	Puts on clothes properly
b. 4 years	Can take shower
c. 4 years	Goes to toilet unaided
d. 36-54 months	Achieves urinary control
e. 24-36 months	Achieves bowel control
7. a. 15 months	Can say 5 or 6 words
b. 12 months	Can speak a word
c. 12 months	Can walk
d. 6-9 months	Can sit up
e. 8-16 weeks	Can smile

Alzheimer's Decline: From Adult to Infant

Alzheimer Stage	Loss of Ability in Adults
1. Normal adult	No cognitive decline
2. Normal elderly adult	Mild forgetfulness
3. Borderline Alzheimer's	Can't perform complex job
4. Early Alzheimer's	Cannot handle finances
5. Moderate Alzheimer's	Can't select clothes
6. a. Severe Alzheimer's	Can't put on clothes
b. Severe Alzheimer's	Can't adjust shower
c. Severe Alzheimer's	Unable to use toilet unaided
d. Severe Alzheimer's	Loses urinary control
e. Severe Alzheimer's	Loses fecal control
7. a. Late Alzheimer's	Speaks fewer than 5 or 6 words
b. Late Alzheimer's	Speaks only one word
c. Late Alzheimer's	Can't walk
d. Late Alzheimer's	Can't sit up
e. La[illegible]heimer's	Can't smile

Chart by Robert Pasternak

Source: Dr. Barry Relsberg, Clinical Director of the Geriatric Study and Treatment Program at NYU Medical Center

APD use: AIMS assess q 4 mos?

Abnormal Involuntary Mvmt Scale to assess Development of Tardive Dyskinesia

KEY: 0 = None
1 = Minimal, may be extreme normal
2 = Mild
3 = Moderate
4 = Severe

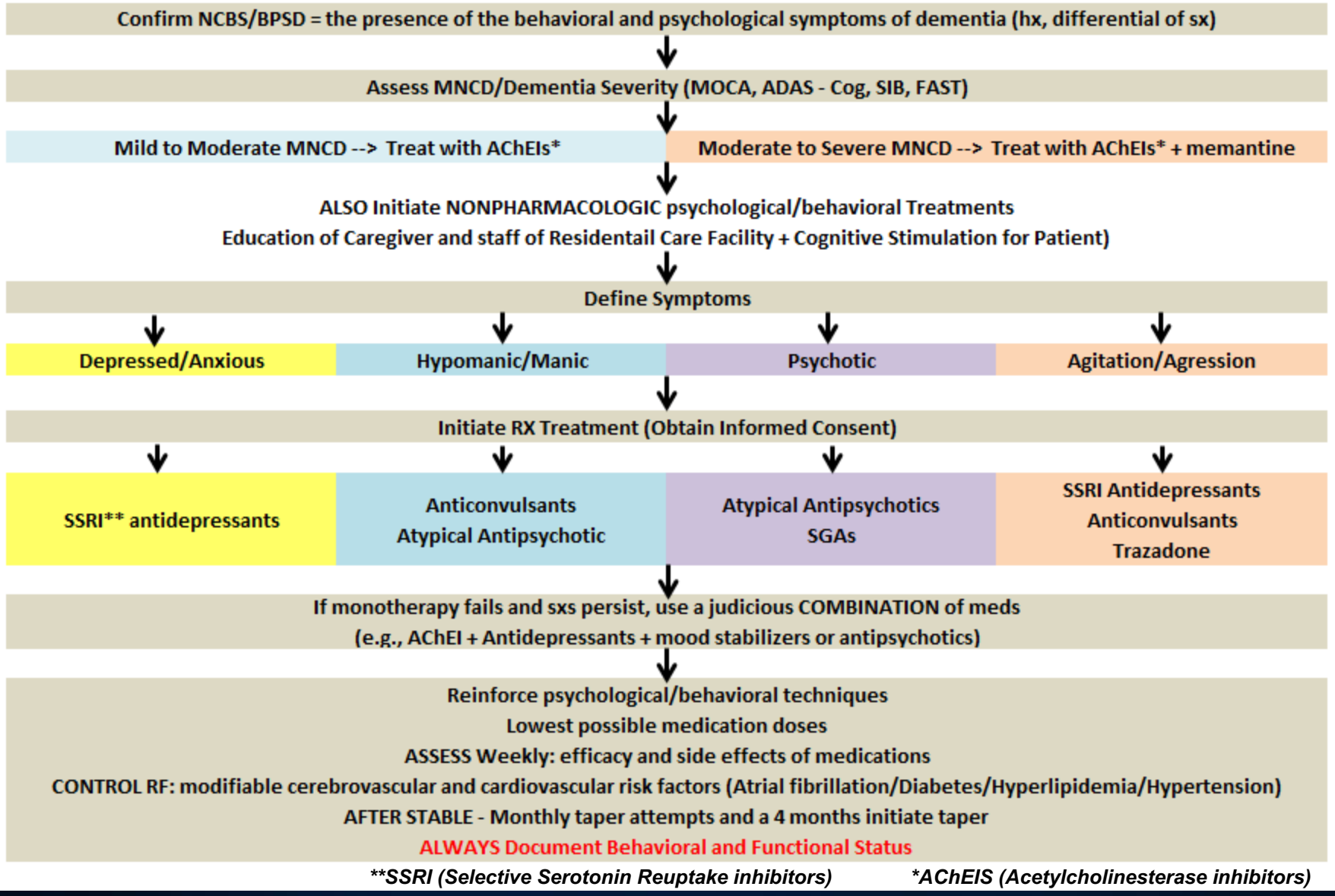
NAME: _____

DATE: _____

Prescribing practitioner: _____

MOVEMENT RATINGS: Rate highest severity observed. Rate movements that occur upon activation one less than those observed spontaneously. Circle movement as well as code number that applies.		RATER Date
Facial and oral movements	1. **Muscles of facial expression** eg, movements of forehead, eyebrows, periorbital area, cheeks, including frowning, blinking, smiling, grimacing	0 1 2 3 4
	2. **Lips and perioral area** eg, puckering, pouting, smacking	0 1 2 3 4
	3. **Jaw** eg, biting, clenching, chewing, mouth opening, lateral movement	0 1 2 3 4
	4. **Tongue** Rate only increases in movement both in and out of mouth. NOT inability to sustain movement. Darting in and out of mouth.	0 1 2 3 4
Extremity movements	5. **Upper (arms, wrists, hands, fingers)** Include choreic movements (ie, rapid, objectively purposeless, irregular, spontaneous) athetoid movements (ie, slow, irregular, complex, serpentine). DO NOT INCLUDE TREMOR (ie, repetitive, regular, rhythmic).	0 1 2 3 4
	6. **Lower (legs, knees, ankles, toes)** eg, lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot	0 1 2 3 4
Trunk movements	7. **Neck, shoulders, hips** eg, rocking, twisting, squirming, pelvic gyrations	0 1 2 3 4
Global judgments	8. **Severity** of abnormal movements overall	0 1 2 3 4
	9. **Incapacitation due to abnormal movements**	0 1 2 3 4
	10. **Patient's awareness of abnormal movements** Rate only patient's report - No awareness 0 - Aware, no distress 1 - Aware, mild distress 2 - Aware, moderate distress 3 - Aware, severe distress 4	0 1 2 3 4
Dental status	11. **Current problems with teeth and/or dentures?**	No Yes
	12. **Are dentures usually worn?**	No Yes
	13. **Edentia?**	No Yes
	14. **Do movements disappear in sleep?**	No Yes

NCBS/BPSD treatment algorithm



Modified from Tampi RR, et al. Clinical Geriatrics. 2011;19(6):31-40.

Assessment

Obtain History

(Medical, Psychiatric, Medications, Pre-morbid personality, Cognition, Functions)

↓

Complete a Physical Examination

(Rule out underlying medical or neurological disorders)

↓

Order Investigations

(Blood tests, Urine examination, Vitamin B 12 & Folate levels, VDRL, Neuroimaging)

↓

Complete standardized rating scales and/or neuropsychological testing

↓

Medical/Neurological disorders → Treat underlying disorder(s)

↓

Drug effect → DEPRESCRIBE Remove offending drug(s)

↓

Confirm BPSD

Tampi RR, et al. Clinical Geriatrics. 2011;19(5):41-46

Systematic Evaluation of BPSD

- 1st Conduct a Medical +Psychiatric Evaluation of patient!
  - Eliminate iatrogenic contributions to increased agitation (benzodiazepines, sympathomimetics)
  - ID + Treat pain or discomfort (from teeth, headache, back)
  - Treat hypoxia

- Next – Evaluate the Caregiver + Environment
  - Allow adequate wandering space/valid restraints
  - Consistent, predictable, non-threatening environment
  - Caregiver : Individualized approach to each patient (switch if necessary)
  - Caregiver Structure daily activities

A Systematic Evaluation of BPSD

Psychopharmacologic Approach

- **ID Target symptoms and the goals of treatment:**

(decrease episodes of agitated aggressive episodes of yelling profanities, pushing or grabbing at others and threatening others by 50% from 10 /week to <5/week)

- Count target behaviors at baseline + regular intervals
- Use non - pharmacologic strategies first
- Select a drug based on medical history and symptoms (**psychobehavioral metaphor**
- Set realistic goals: In most studies, 30-50% reduction in behavior is the gold standard

A Systematic Evaluation of BPSD

- *Psychopharmacologic Approach*
  - Titrate slowly: low dose, allow time to equilibrate to steady state concentration (~4.5 half lives) before titrating higher
  - **Monitor efficacy/Deprescribe:**
  - Document rationale for any change in medications
  - Wait: drug environment interventions take 2-4 weeks

Gradually decrease psychotropics with the goal to discontinue them based on results: within 1 or 4 months (if antipsychotics),

~8 -12 months if other psychotropics (my opinion)

Optimizing AD
First Steps

- Educate family/Caregiver
  - AD Dementia in general
    - Cognition, function, behaviors (changes heterogeneous dynamic, fluctuating, lower reserve, non-linear).
    - Use Reisberg Scales FAST/GDS)
  - Dementia Stage and Care Expectations
    - Avoid expectation-reality mismatch &miscommunication: the “progression /regression” model of aging & dementia
    - Learning a “new language,” new approach to interact, communicate

Optimizing AD Strategies

- Remove deleterious medications/ Reduce stress /Remove ETOH
- Start and maintain combination treatment with ChEI/memantine - add-on; try to maintain "the sweet spot"
- Treat comorbid conditions; promote quality sleep, life & health
- Promote restorative sleep (diagnose and treat sleep apnea)
- Promote NON PHARMACOLOGIC APPROACHES including general physical, social & mental activity and health (and good diet and exercise) and serenity
- Treat anxiety and depression not responsive to behavioral interventions and combination treatment with ChEI+memantine
- AVOID regular use of antipsychotics & benzodiazepines
- ? ADJUNCTIVE :ECASA 81, Vitamin E* (*except severe cardiovascular disease/ blood thinners, bleeding history/diathesis), Vitamin C, Vit B6/B12/folate

Adapted from Atri, A. Effective Pharmacological Management of Alzheimer's Disease. *Am J Managed Care*, 2011.

What is Metabolic Syndrome (MetS) and what is relationship of APD to MetS and CVA?

Focus On Metabolic Syndrome: A Mortality - Increasing Adverse Effect

- A syndrome, not a disease, with 6 components:
  - Abdominal obesity
  - Increased blood pressure
  - Atherogenic dyslipidemia
  - Insulin resistance +/- glucose intolerance
  - Proinflammatory state
  - Prothrombotic state

Grundy et al. Circulation 2004;109:433-8.

What is the Metabolic Syndrome?

- Metabolic Syndrome can be asymptomatic
- Mechanisms:
  - Reduced anti-inflammatory cytokines
  - Reduced adiponectin (hormone regulating glucose levels and fatty acid breakdown)
  - Insulin resistance central obesity
  - Can occur WITHOUT weight gain
  - Medical complications independent of weight gain

National Health and Nutrition Examination Survey III, 1988-1994

WHO Operational Criteria for Diagnosing Metabolic Syndrome

- Insulin resistance, identified by 1 of:
  - Type 2 diabetes
  - Impaired fasting glucose
  - Impaired glucose tolerance
  - Low glucose uptake (hyperinsulinemic euglycemic conditions)
- Plus 2 of:
  - HTN or antihypertensive medication
  - BMI > 30 kg/m2
  - TRIGLYCERIDES ≥ 150 mg/dL
  - HDL < 35
  - Urinary albumin excretion ≥ 30 mcg/min or albumin/creatinine ≥ 30 mg/g

http://whqlibdoc.who.int/hq/1999/WHO_NCD-NCS_99.2.pdf

In Some Observational Trials, APD Increase the Risk for MetS Syndrome in Elderly with Dementia

- Observational trials:
  - 90 day observation: 29,203 nursing home residents with dementia linked first generation APD with new DM onset.[1]
  - 2.2 year follow up of 44,121 elders (42% dementia) newly treated with FGA or SGA linked treatment with increased hyperglycemia, FGA and SGA. OR for SGA 2.86[2]
  - **1 year follow up of mixed adults >40 years old, treated with aripiprazole, olanzapine, quetiapine, or risperidone[3] showed:**
    - **New MetS in 36.5%**
    - **Aripiprazole > olanzapine (could reflect allocation bias)**
    - **More SAE with quetiapine than others**

1. Jalbert et al. Am J Geriatr Pharmacother 2011;9:153-63;
2. Lipscombe et al. Am J Geriatr Psychiatry 2011;19:1026-33;
3. Jin et al. J Clin Psychiatry 2013;74:10-8.

But Not In All Observational Trials…

- Review of 90 NH residents with dementia receiving SGA showed small average weight gain over study period.
  - N with significant weight gain = N with significant weight loss.[1]

- Retrospective chart review of 56 veterans ≥65 with dementia after initiation of atypical APD:[2]
  - 10% developed impaired fasting glucose (increase by 9.7 mg/dL from baseline to follow up)
  - Significant weight gain in 8.92% but overall, weight decreased by 1.3 kg during study period
  - Worsening lipids in 14.5% but lipid levels improved overall in study population

1. Gurevitz et al. Consult Pharm 2004;19:809-12;
2. Mathys et al. Consult Pharm 2009;24:201-9.

More Controlled Trials Are Needed

- Controlled trials:[1]
  - Risperidone: No difference in onset DM or prl in CATIE-AD
  - APD not associated with change in BP, glucose, triglycerides
  - Olz associated with decrease in HDL and increase in girth
- **Conclusion – Metabolic effects of APD may be more diverse or complicated in elderly…more data are needed**

1. Maglione et al M, Ruelaz Maher A, Hu J, et al. Review No. 43. Rockville MD, Agency for Healthcare Research and Quality, September 2011. www.effectivehealthcare.ahrq.gov/reports/final.cfm;

Metabolic Syndrome Increases Stroke Risk

- MetS important is a risk factor for CVA
- 16 studies metaanalyzed with 116,496 participants
- MetS pooled RR 1.7 for CVA
- Higher risk for women than men
- Higher risk for Ischemic than Hemorrhagic

Li et al. Metabolic syndrome and stroke: a meta-analysis of prospective cohort studies.
J Clin Neuroscience 2017;40:34-8.