Terms used interchangeably

NCBS = noncognitive behavioral symptoms of dementia

BPSD = behavioral and psychological symptoms of dementia

NPS = neuropsychiatric symptoms of dementia
Management of NCBS
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*

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

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 sx & 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)
Seminal events with 1\textsuperscript{st} 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 behavior
- 45% have at least 4 disruptive behaviors

- Behaviors are a chronic feature, but different symptoms emerge as the illness progresses
- Mood sx, psychomotor agitation are most persistent
NCBS: Range and Peak Prevalence During AD Progression

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

The Progression of AD

Adapted from Feldman H, Gracon S. In: Clinical Diagnosis and Management of Alzheimer’s Disease. 1996:239-253
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 glutamate)
## Common Noncognitive Behavioral Sxs

<table>
<thead>
<tr>
<th>Changes In</th>
<th>Timing</th>
<th>Frequency</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mood</strong></td>
<td>Especially Early</td>
<td>Frequent</td>
<td>• Depression</td>
</tr>
<tr>
<td></td>
<td>Early</td>
<td></td>
<td>• Anxiety</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Mania</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Apathy</td>
</tr>
<tr>
<td><strong>Thinking+Perception</strong></td>
<td>Early and Late</td>
<td>Frequent</td>
<td>• Suicidal ideation</td>
</tr>
<tr>
<td></td>
<td>Late</td>
<td></td>
<td>• Delusions, suspiciousness</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Hallucinations</td>
</tr>
<tr>
<td><strong>Activity</strong></td>
<td>Early and Late</td>
<td>Frequent</td>
<td>• Agitation, verbal, physical</td>
</tr>
<tr>
<td></td>
<td>Late</td>
<td></td>
<td>• Aggression</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Disordered eating behavior</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Disordered sleep/activity cycle</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Sexually, socially inappropriate behav</td>
</tr>
</tbody>
</table>
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
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;
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?
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
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)

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)

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\(^3\)

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

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.”
Choosing from among the riches?
An Updated Position in 2016

THE AMERICAN PSYCHIATRIC ASSOCIATION

PRACTICE GUIDELINE
ON THE
Use of Antipsychotics to Treat Agitation or Psychosis in Patients With Dementia
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

APD vs PLA GLOBAL SCORE in Dementia

<table>
<thead>
<tr>
<th>Study ID</th>
<th>SMD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td></td>
</tr>
<tr>
<td>Breder, 2004/Mintzer, 2007, 2.5, 10mg</td>
<td>0.16 (-0.05, 0.37)</td>
</tr>
<tr>
<td>DeDeyn, 2003, 10mg mean</td>
<td>0.06 (-0.21, 0.34)</td>
</tr>
<tr>
<td>Streim, 2004/Streim, 2008, 8.6mg mean</td>
<td>0.36 (0.11, 0.61)</td>
</tr>
<tr>
<td>Subtotal (I-squared = 22.1%, p = 0.277)</td>
<td>0.20 (0.04, 0.35)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td></td>
</tr>
<tr>
<td>DeDeyn, 2004, 1, 2, 5, 5, 7.5mg</td>
<td>0.14 (-0.05, 0.34)</td>
</tr>
<tr>
<td>DeBerdt, 2005, 5.2mg mean</td>
<td>-0.02 (-0.27, 0.23)</td>
</tr>
<tr>
<td>Schneider, 2006/Sultzer, 2008, 5.5mg mean</td>
<td>0.15 (-0.11, 0.40)</td>
</tr>
<tr>
<td>Street, 2000, 5, 10, 15mg</td>
<td>0.30 (-0.03, 0.63)</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.485)</td>
<td>0.12 (0.00, 0.25)</td>
</tr>
<tr>
<td>Quetiapine</td>
<td></td>
</tr>
<tr>
<td>Schneider, 2006/Sultzer, 2008, 56.5mg mean</td>
<td>0.15 (-0.11, 0.42)</td>
</tr>
<tr>
<td>Tariot, 2006, 96.9mg median</td>
<td>0.22 (-0.07, 0.52)</td>
</tr>
<tr>
<td>Zhong, 2004/Zhong, 2007, 100, 120, 200mg</td>
<td>0.04 (-0.21, 0.28)</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.610)</td>
<td>0.13 (-0.03, 0.28)</td>
</tr>
<tr>
<td>Risperidone</td>
<td></td>
</tr>
<tr>
<td>Brodaty, 2003/Brodaty, 2005, 0.95mg mean</td>
<td>0.46 (0.23, 0.69)</td>
</tr>
<tr>
<td>DeBerdt, 2005, 1mg mean</td>
<td>-0.13 (-0.38, 0.12)</td>
</tr>
<tr>
<td>Dedeyn, 1999, 1.1mg mean</td>
<td>0.12 (-0.14, 0.38)</td>
</tr>
<tr>
<td>Katz, 1999, 12mg</td>
<td>0.32 (0.11, 0.53)</td>
</tr>
<tr>
<td>Mintzer, 2006, 1.03mg mean</td>
<td>-0.01 (-0.21, 0.18)</td>
</tr>
<tr>
<td>Schneider, 2006/Sultzer, 2008, 1mg mean</td>
<td>0.40 (0.13, 0.68)</td>
</tr>
<tr>
<td>Subtotal (I-squared = 74.6%, p = 0.001)</td>
<td>0.19 (0.00, 0.38)</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

Atipriprazole effect size 0.20
Olanzapine effect size 0.12
Questiapine effect size 0.13
Risperidone effect size 0.19

### AGITATION score

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect Size</th>
<th>Dose Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>0.30</td>
<td>2.5-10 mg/d</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>0.19</td>
<td>1-15 mg dose range</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>0.05</td>
<td>25-600 mg dose range</td>
</tr>
<tr>
<td>Risperidone</td>
<td>0.22</td>
<td>0.5-2.5 mg dose range</td>
</tr>
</tbody>
</table>

---

**Figure 6. Dementia placebo comparisons—agitation**

- 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

---

### PSYCHOSIS score in Dementia

**Figure 5. Dementia placebo comparisons—psychosis**

- **Aripiprazole effect size 0.20**
- **Olanzapine effect size 0.12**
- **Quetiapine effect size 0.13**
- **Risperidone effect size 0.19**

Do APD Increase 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

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

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**\(^4\)

---

The Suspected Chain of Events

Off label use

MetS

CVA

Other APD effects
What should the prudent clinician do to optimize treatment effectiveness and patient safety?
Use DICE to Assess NCBS and Suggest Nonpharmacologic Treatments

Describe → Investigate

Evaluate ← Create

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**

- 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

When Medications Are Required

APD alternatives (off-label like APD) include:

- Cognitive enhancers
- Antidepressants
- Analgesics
- Anticonvulsants
- Anxiolytics
- Cannabinoids
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."
Dang!... Now where was I going?

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

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

- Another antipsychotic may be safer?
  - ziprasidone, aripiprazole may have advantages but insufficient literature in older patients

- 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

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

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 (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)

Rate the SEVERITY of the symptom (how it affects the patient):
- 0 = No
- 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)

DELUSSIONS
1. Does the patient believe that others are stealing from him or her, or planning to harm him or her in some way?

HALLUCINATIONS
2. Does the patient act as if he or she hears voices?
   Does he or she talk to people who are not there?

AGITATION OR AGGRESSION
3. Is the patient stubborn and resistive to help from others?

DEPRESSION OR DYSPHORIA
4. Does the patient act as if he or she is sad or in low spirits? Does he or she cry?

ANXIETY
5. Does the patient become upset when separated from you? Does he or she have any other signs of nervousness, such as shortened breath, sighing, being unable to relax, or feeling excessively tense?

ELATION OR EUPHORIA
6. Does the patient appear to feel too good or not excessively happy?

APATHY OR INDIFFERENCE
7. Does the patient seem less interested in his or her usual activities and in the activities and plans of others?
## NPI-Q neuropsychiatric inventory

### SUBJECT ID

<table>
<thead>
<tr>
<th>VISIT NO</th>
</tr>
</thead>
</table>

### 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?

- 

### IRRITABILITY OR LABILITY

9. Is the patient impatient and cranky? Does he or she have difficulty coping with delays or waiting for planned activities?

- 

### MOTOR DISTURBANCE

10. Does the patient engage in repetitive activities, such as pacing around the house, handing buttons, wrapping strings, or doing other things repeatedly?

- 

### NIGHTTIME BEHAVIORS

11. Does the patient awaken you during the night, rise too early in the morning, or take excessive naps during the day?

- 

### APPETITE AND EATING

12. Has the patient lost or gained weight, or had a change in the food he or she liked?

- 

---

<table>
<thead>
<tr>
<th>DISINHIBITION</th>
<th>IRRITABILITY OR LABILITY</th>
<th>MOTOR DISTURBANCE</th>
<th>NIGHTTIME BEHAVIORS</th>
<th>APPETITE AND EATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.3</td>
<td>9.3</td>
<td>10.3</td>
<td>11.3</td>
<td>12.3</td>
</tr>
<tr>
<td>8.2</td>
<td>9.2</td>
<td>10.2</td>
<td>11.2</td>
<td>12.2</td>
</tr>
<tr>
<td>8.1</td>
<td>9.1</td>
<td>10.1</td>
<td>11.1</td>
<td>12.1</td>
</tr>
</tbody>
</table>
# Suggested Antipsychotic Drug Screening/Monitoring

<table>
<thead>
<tr>
<th>Suggested Timeframe and Screening</th>
<th>Baseline</th>
<th>4 Weeks</th>
<th>8 Weeks</th>
<th>12 Weeks</th>
<th>Quarterly</th>
<th>Annually</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal/Family History</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Weight (BMI)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Fasting Plasma Glucose</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Fasting Lipid Profile</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

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 with 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
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?

Joan 90yo MWF: PDx 2 yr, POTS, PE, AFIB, OSA, Npathy, MCI? (FAMILY) presented 1/2017 for depression, VH (bugs) delusional – (duplicative residence, impositors), 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. Don’t want to feel hopeless, don’t want Ses”
PE/MSE: PHQ 15/27 moca 21/30 attentional, construction, stm deficits

• Tx: exelon patch titration, disc w caregiver @vigilance, PT
• 4/17: VH and delusions resolved fxn 30% better 5/17: engaged 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

Describe ➔ Investigate

Evaluate ← Create
Caregiver describes problematic behavior

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

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

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

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?)

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*
Antipsychotic Drug withdrawal

Psychotic relapse in 1/3 with severe baseline auditory hallucinations stabilized on Risperidone, if 30% NPI improvement\(^1\)\(^2\) 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
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

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

### Alzheimer’s Decline: From Adult to Infant

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

Source: Dr. Barry Relsberg, Clinical Director of the Geriatric Study and Treatment Program at NYU Medical Center
### Abnormal Involuntary Mvmt Scale to assess Development of Tardive Dyskinesia

<table>
<thead>
<tr>
<th>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.</th>
<th>RATER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Facial and oral movements</strong></td>
<td>Name: __________________________</td>
</tr>
<tr>
<td>1. Muscles of facial expression eg, movements of forehead, eyebrows, periorbital area, cheeks, including frowning, blinking, smiling, grimacing</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>2. Lips and perioral area eg, puckering, pouting, smacking</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>3. Jaw eg, biting, clenching, chewing, mouth opening, lateral movement</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>4. Tongue Rate only increases in movement both in and out of mouth. NOT inability to sustain movement. Darting in and out of mouth.</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td><strong>Extremity movements</strong></td>
<td></td>
</tr>
<tr>
<td>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).</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>6. Lower (legs, knees, ankles, toes) eg, lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td><strong>Trunk movements</strong></td>
<td></td>
</tr>
<tr>
<td>7. Neck, shoulders, hips eg, rocking, twisting, squirming, pelvic gyrations</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td><strong>Global judgments</strong></td>
<td></td>
</tr>
<tr>
<td>8. Severity of abnormal movements overall</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>9. Incapacitation due to abnormal movements</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>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</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td><strong>Dental status</strong></td>
<td></td>
</tr>
<tr>
<td>11. Current problems with teeth and/or dentures?</td>
<td>No Yes</td>
</tr>
<tr>
<td>12. Are dentures usually worn?</td>
<td>No Yes</td>
</tr>
<tr>
<td>13. Edentia?</td>
<td>No Yes</td>
</tr>
<tr>
<td>14. Do movements disappear in sleep?</td>
<td>No Yes</td>
</tr>
</tbody>
</table>
NCBS/BPSD treatment algorithm

1. Confirm NCBS/BPSD = the presence of the behavioral and psychological symptoms of dementia (hx, differential of sx)

2. Assess MNCD/Dementia Severity (MOCA, ADAS - Cog, SIB, FAST)

   - Mild to Moderate MNCD --> Treat with AChEIs*
   - Moderate to Severe MNCD --> Treat with AChEIs* + memantine

   ALSO Initiate NONPHARMACOLOGIC psychological/behavioral Treatments
   Education of Caregiver and staff of Residential Care Facility + Cognitive Stimulation for Patient

3. Define Symptoms
   - Depressed/Anxious
   - Hypomanic/Manic
   - Psychotic
   - Agitation/Agression

4. Initiate RX Treatment (Obtain Informed Consent)
   - SSRI** antidepressants
   - Anticonvulsants Atypical Antipsychotic
   - Atypical Antipsychotics SGAs
   - SSRI Antidepressants Anticonvulsants Trazadone

5. If monotherapy fails and sx persist, use a judicious COMBINATION of meds (e.g., AChEI + Antidepressants + mood stabilizers or antipsychotics)

6. Reinforce psychological/behavioral techniques
   Lowest possible medication doses
   ASSESS Weekly: efficacy and side effects of medications
   CONTROL RF: modifiable cerebrovascular and cardiovascular risk factors (Atrial fibrillation/Diabetes/Hyperlipidemia/Hypertension)
   AFTER STABLE - Monthly taper attempts and a 4 months initiate taper

**SSRI (Selective Serotonin Reuptake inhibitors)  *AChEIS (Acetylcholinesterase inhibitors)
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

**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
**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

**Set realistic goals:** In most studies, 30-50% reduction in behavior is the gold standard
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

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

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

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

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

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

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

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