Death by PowerPoint

Slow and painful.

seen on 9GAG.COM

wodywentpro, ifunny.mobi
Alzheimer’s Disease

- First described by Alois Alzheimer, a German neuropathologist, in 1907
- Observed in a 51-year-old female patient with memory loss, disorientation, and hallucinations
- Postmortem studies characterized senile plaques and neurofibrillary tangles (NFTs) in the cerebral cortex
  - Senile plaques: Extracellular accumulation of insoluble fragments of beta-amyloid (Aβ₁-₄₂)
  - NFTs: Intracellular accumulation of hyperphosphorylated tau strands
Update on Dementia Risk
Assessing Impact

Impact is rising...

Change in Cause of Death: 2000 to 2014

ALZHEIMER'S DISEASE IS THE 6TH LEADING CAUSE OF DEATH IN THE UNITED STATES

Since 2000, deaths from heart disease have decreased by 14%
while deaths from Alzheimer’s disease have increased by 89%

1 IN 3 seniors dies with Alzheimer’s or another dementia

IT KILLS MORE THAN breast cancer and prostate cancer COMBINED

Alz Assoc, 2017—Facts and Figures
Prevalence of Dementia Will Increase Worldwide

Dementia is an acquired syndrome of decline in memory and other cognitive domains sufficient to affect daily function.

AD is the most common dementia and refers to a neurodegenerative brain disorder, regardless of clinical status, that results from continuous process of synaptic and neuronal deterioration.
CLINICAL CRITERIA FOR MILD COGNITIVE IMPAIRMENT

1. Cognitive (usually memory) Complaint – Preferably Corroborated by an Informant
2. Cognitive (usually memory) Impairment for Age and Education
3. Essentially Normal General Cognitive Function
4. Largely Preserved Activities of Daily Living
5. Not Demented
Not only is my short-term memory homble, but so is my short-term memory.
In - Office Evaluation

- A. History
- B. General exam
- C. Neuro exam
- D. Formal cognitive assessment tool
  1. MMSE
  2. MoCA
Differential Diagnosis

- Vascular: vascular dementia
- Inflammatory: CNS vasculitis, autoimmune
- Toxic: medication, psychoactive and endocrine
- Metabolic: hypothyroid, DM, hypercalcemia
- Infectious: fungal, TB, meningitis
- Nutritional: B12 deficiency
- Degenerative: AD, FTD, etc.
- Epileptic: nonconvulsive complex partial status
- Trauma: dementia pugilistica (CTE)
- Psychiatric: conversion disorder
- Neoplastic: meningeal carcinomatous, paraneoplastic, etc
- Normal Pressure Hydrocephalus
Common Causes of Dementia

- Alzheimer’s Disease
  - Amnestic multidomain dementia syndrome
  - Posterior Cortical Atrophy/visual variant
  - Logopenic Aphasic Variant
- Dementia with Lewy Bodies
- Vascular Cognitive Impairment
- Frontotemporal Lobar Degeneration
  - Progressive Nonfluent/Agrammatic Aphasia
  - Semantic Dementia
  - Frontotemporal Dementia Behavioral Variant
  - ALS Dementia
- Mixed
- Chronic Traumatic Encephalopathy
Vascular and AD overlap: Autopsy evidence

- Between 55-80% of AD patients have coincident vascular changes in the brain (Bangen et al., *Alzheimers & Dementia* 2015; Toledo et al., *Brain* 2013)

- Multiple studies have found less AD neuropathological changes (plaques, tangles) in patients with vascular changes for an equivalent level of cognitive impairment

Modified from Toledo et al, *Brain* 2013
(VP: Vascular Pathology; AD: Alzheimer’s Disease)
Frontotemporal dementia

- Behavioral variant (50%)
- Language variants (50%)
  - Primary Progressive Aphasia
    - Semantic variant
    - Nonfluent/agrammatic variant
Three PPA Variants

- **Non-fluent/agrammatic variant (nvfPPA)**
  - Effortful speech, agrammatism, motor speech deficits
  - Pathology: FTLD-Tau > FTLD-TDP

- **Semantic variant (svPPA)**
  - Fluent, grammatically correct speech with loss of word and object meaning
  - Pathology: FTLD-TDP

- **Logopenic variant (lvPPA)**
  - Hesitant speech with word finding difficulty, poor repetition

Gorno-Tempini et al. Ann Neurol 2004
Gorno-Tempini et al. Neurology 2011
Overview

Nomenclature – The “One Year Rule”

- Dementia
  - Parkinsonism
- Dementia
  - Parkinsonism
- Dementia
  - Parkinsonism
  - Dementia
  - Parkinsonism/PD
- Parkinsonism/PD
  - Dementia

1 year

DLB

PDD
Clinical Features DLB

- Cognitive
  - Dementia
  - Fluctuations
- Neuropsychiatric
  - Visual hallucinations
  - Delusions
  - Depression
  - Anxiety
- Motor
  - Parkinsonism
- Sensory
  - Anosmia
  - Color vision changes
- Sleep
  - REM Behavioral Disorder
  - Hypersomnolence
  - Insomnia
- Autonomic
  - Orthostatic hypotension
  - Urinary incontinence
  - Constipation
  - Erectile dysfunction
CHRONIC TRAUMATIC ENCEPHALOPATHY

General Criteria: All 5 criteria must be met

1) Hx of multiple impacts to the head based upon
   - Types of injuries:
     • mTBI or concussions, minimum of 4
     • Moderate/severe traumatic brain injury
     • “subconcussive” trauma
   - Source of exposures
     • Involvement of “high exposure” contact sports for minimum of 6 years, including at least 2 at college level or higher
     • Military Service
     • History of any other significant exposure to repetitive hits to the head
     • For moderate/severe traumatic brain injury, any activity resulting in the injury
General Criteria: *All 5 criteria must be met* (cont.)

2) No other neurological disorder present that likely accounts for all clinical features
3) Clinical features must be present for a minimum of 12 months
4) At least 1 Core Clinical Features must be present and considered a change from baseline
5) At least 2 Supportive Features must be present
**Core Clinical Features: At least 1 must be met**

1) *Cognitive*. Difficulties in cognition as reported by either self or informant, by history, or clinician’s report of decline and substantiated by impairment on standardized tests

2) *Behavioral*. Emotionally explosive, physically and/or verbally violent

3) *Mood*. Feeling overly sad, depressed, and/or hopeless
**Supportive Features: At least 2 must be present**

1) **Impulsivity**
2) **Anxiety**
3) **Apathy**
4) **Paranoia**
5) **Suicidality**
6) **Headache**
7) **Motor Signs.** Dysarthria, dysgraphia, bradykinesia, tremor, rigidity, gait disturbance, falls, and/or other features of parkinsonism

8) **Documented Decline.** Progressive decline in function and/or a progression in symptoms and/or signs, for a minimum of one year

9) **Delayed Onset.** Delayed onset of clinical features after significant head impact exposure, usually at least 2 years and in many cases several years after the period of maximal exposure
CHRONIC TRAUMATIC ENCEPHALOPATHY

Diagnostic Subtypes

1) Behavioral/Mood Variant (younger, mean 35 yrs)
2) Cognitive Variant (older, mean 59 yrs)
3) Mixed Variant
4) Dementia (criteria below)
   a) Progressive course of Cognitive Core Features, with or without Behavioral and/or Mood Core Features
   b) Cognitive impairment (or cognitive impairment exacerbated by behavioral and/or mood) severe enough to interfere with the ability to function independently at work or in usual activities, including hobbies, and instrumental activities of daily living
Summary – CTE

- Caused by multiple impacts to the head
- Characterized by perivascular accumulation of tau in neurons, astrocytes, & cell processes at the depths of the cortical sulci in an irregular pattern.
- Two main syndromes (also mixed & dementia):
  - Behavioral/Mood Variant (younger, m=35 yrs)
  - Cognitive Variant (older, m=59 yrs)
- Commonly initial features include:
  - Impairment in memory, executive func, attention, visuospatial, & language.
  - Depression, hopelessness, explosivity, out of control, violent
Causes of RPD
Hospitalized Patients

Causes of RPD vary with patient population
CJD is the most common diagnosis in inpatients.

Day and Tang-Wai, 2014—Neurodegen Dis Mgmt
Causes of RPD vary with patient population

CJD is the most common diagnosis in inpatients. Neurodegenerative diseases predominate in older outpatients.

Day et al. 2017—AAN Abstract #3524
Where to Begin?
Ask the Right Questions

Begin at the beginning (History & Physical)
1. Are you sure this is a rapidly progressive dementia?

The number one cause of rapidly progressive dementia is...
...an incomplete history.

- Dementia often has an insidious onset; caregivers/family members may misinterpret early symptoms and signs.
- The first “major” incident (e.g., getting lost, leaving pot on stove) may be interpreted as the first symptom.
Where to Begin?
Ask the Right Questions

Begin at the beginning (History & Physical)
1. Are you sure this is a rapidly progressive dementia?
2. Consider the demographics.
3. Clarify timing of symptom onset and progression.
   - Period of Evolution
     - Days to weeks → autoimmune diseases
     - Weeks to months → CJD
     - Months to years → neurodegenerative diseases
   - Pattern of progression
     - Steady progression → CJD/ neurodegenerative diseases
     - Fluctuations → autoimmune diseases

Where to Begin?
Ask the Right Questions

Begin at the beginning (History & Physical)
1. Are you sure this is a rapidly progressive dementia?
2. Consider the demographics.
3. Clarify timing of symptom onset and progression.
4. Search for associated symptoms and signs.
   - Stimulus sensitive myoclonus → CJD
   - Cortical localizing signs → CJD/ neurodegenerative diseases
   - Movement disorders → all causes
   - Seizures → autoimmune diseases
   - Underlying malignancy → autoimmune diseases
NMDAR Antibody Encephalitis - 1

- **Disease of the young** — 95% <45 years-old; 37% < 18 years-old

- **Characteristic Clinical Syndrome**
  - Prodrome (HA, fever, N/V, URI-like)
  - Acute neuropsychiatric symptoms
  - Amnesia, language dysfunction
  - Seizures
  - Abnormal movements
  - Subset with coma and autonomic dysfunction
Anti-LGI1 encephalitis
Clinical syndrome and long-term follow-up

Sonderen, et. al. Neurology, October 2016

B

Disease severity

Immune therapy
Seizure decrease
Cognitive improvement

Hyponatremia (65%)
T2 hyperintensity limbic system (74%)
Normal CSF (75%)
No tumor (89%)

Residual symptoms
Persistent amnesia for disease

Disease progression
Recovery

FBDS
Focal seizures
Insomnia
Memory deficits
Behavioral changes
Sleep disorder
PNS symptoms
To Evaluate Further, ...

- Paraneoplastic panel
- Antibodies
  - NMDAR
  - VGKC

A. Lab tests
B. Conventional imaging
C. Neuropsychological testing

**TABLE 3**
LABORATORY EVALUATION OF PATIENTS WITH DEMENTIA

<table>
<thead>
<tr>
<th>ROUTINE</th>
<th>OPTIONAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry group</td>
<td>Sedimentation rate</td>
</tr>
<tr>
<td>Complete blood count</td>
<td>Chest x-ray</td>
</tr>
<tr>
<td>Vitamin B₁₂ level*</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>Thyroid function studies*</td>
<td>Urinalysis</td>
</tr>
<tr>
<td>Syphilis serology</td>
<td>Drug levels</td>
</tr>
<tr>
<td>CT/MRI*</td>
<td>HIV testing</td>
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<tr>
<td></td>
<td>Lyme serology</td>
</tr>
<tr>
<td></td>
<td>24-urine for heavy metal</td>
</tr>
<tr>
<td></td>
<td>Electroencephalogram</td>
</tr>
<tr>
<td></td>
<td>Cerebrospinal fluid</td>
</tr>
<tr>
<td></td>
<td>PET/SPECT</td>
</tr>
</tbody>
</table>

*Suggested by the American Academy of Neurology.®

**Biomarkers in RPD**
Specific Biomarkers

**Biomarkers of CJD**
1. MRI: restricted diffusion & FLAIR changes
2. CSF: Total Tau, 14-3-3, neuron specific enolase
3. Real-time Quaking-Induced Conversion (RTQuIC) assay

<table>
<thead>
<tr>
<th>CJD Diagnosis</th>
<th>MRI</th>
<th>CSF Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DWI &amp; FLAIR</td>
<td>Total Tau</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>91</td>
<td>64</td>
</tr>
<tr>
<td>Specificity</td>
<td>94</td>
<td>95</td>
</tr>
</tbody>
</table>

Total tau, 14-3-3 and RT-QuIC are currently available via the National Prion Disease Pathology and Surveillance Center (Case Western Reserve).

Foutz et al. 2017—Ann Neurol
To Evaluate Further, ...

- A. Lab tests
- B. Conventional imaging
- C. Neuropsychological testing
- D. Genetic testing?
- E. Functional Imaging (PET)?
CHRONIC TRAUMATIC ENCEPHALOPATHY

Potential Biomarkers

1) *Cavum Septum Pellucidum.* Or cavum vergae, or fenestrations based on neuroimaging study
2) *Normal Beta Amyloid CSF Levels*
3) *Elevated CSF p-tau/tau Ratio*
4) *Negative Amyloid Imaging*
5) *Cortical atrophy* beyond expected for age as seen on MRI (or CT), and in particular, frontal, thalamic, hippocampal, and/or amygdalar atrophy
6) *Positive Tau Imaging (experimental).* PET paired helical filament tau imaging suggestive of abnormal tau deposition
7) *Cortical Thinning (experimental).* Based on MRI measurement
Biomarkers in RPD
Specific Biomarkers

Biomarkers of CJD

1. MRI: restricted diffusion & FLAIR changes

<table>
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<th>CJD Diagnosis</th>
<th>MRI</th>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>91</td>
</tr>
<tr>
<td>Specificity</td>
<td>94</td>
</tr>
</tbody>
</table>

Within deep gray structures and the cortical ribbon

Young et al. 2005—AJNR
NMDAR Antibody Encephalitis - 2

- **CSF** – Pleocytosis, OCBs; but can be normal
- **MRI** – usually normal or nonspecific
- **EEG** – slowing or epileptiform activity

- **Serology** – CSF or serum IgG NMDAR antibodies that target the GluN1 (NR1) subunit
  - 10% of pts will have +CSF serologies when serum is negative – send CSF when high index of suspicion

- **Ovarian teratoma** (which has a component of neuronal tissue that can express NMDAR) in ~50% in women aged 12-45 – vaginal ultrasound and pelvic MRI

- **Immunosuppression is favorable** – OR 2.7 for better outcomes with aggressive treatment in largest series to date of 577 pts (Titulaer, Lancet Neuro, 2013)
VGKC-antibody complex associated Limbic Encephalitis (LE)

- Later years
- Subacute onset
- Amnesia, Seizures, Hyponatremia
- +/-
  - Psychiatric features
  - Dysautonomia
  - Sleep
- ~10% cancer-associated
  (~90% of cases are autoimmune)
- Usually normal CSF or mild pleocytosis
- MRI with temporal lobe hyperintensities but can be normal
- (30% cases with normal CSF + MRI)

To Evaluate Further, ...

- A. Lab tests
- B. Conventional imaging
- C. Neuropsychological testing
- D. Genetic testing?
- E. Functional Imaging (PET)?

- Normal vs MCI vs dementia
- Domains involved
- Type of PPA
- Dementia patterns

![Neuropsychological Features](chart.png)

**Typical DLB Profile**

**Impaired on:**
- Memory measures
- BNT and/or Cat Flu

**Impaired on:**
- TMT, WAIS-DS
- WAIS-BD, -PC
- Rey-O CFT

Fenneman et al. Neurology 1899
To Evaluate Further, ...

A. Lab tests
B. Conventional imaging
C. Neuropsychological testing
D. Genetic testing?
E. Functional Imaging (PET)?
Risk factors for AD

- **Age**
  - Risk doubles every 5 years from 65-85
  - If could delay onset by 5 yrs = 50% reduction in cases

- **Family History**
  - 3-4 x baseline risk if an affected first degree relative
  - 38% by age 85

- **Genes**
  - If multiple family members affected before age 60
  - Consider mutations of PS1, PS2, APP
    - If present, risk approaches
  - Accounts for about 5% of all AD
  - Genetic counseling
  - About 40% in this group will have an identifiable mutation
Dementia

- APOE (Distribution and clearance of Aβ?, synaptic plasticity?)
  - Homozygous for E4
    - 85% chance of AD by age 85
    - 5-10 x baseline risk
  - Heterozygous for E4
    - 45-50% chance of AD by age 85
    - 2-4 x baseline risk
  - No E4
    - 5-15% chance of AD by age 85
- E2 appears protective
- Not specific for AD
- E2 (7%), E3 (79%), E4 (14%)
Summary

- The risk of AD increases with age, but younger onset is more likely to have a genetic basis.
- Autosomal dominant mutations should be suspected in the right setting; genetic counseling and testing should be offered.
- All other forms of possible inheritance are not clinically recommended at this time, but that may change if an effective therapy is discovered.
- AD specifically, and dementia generally, is usually a polygenic entity, as well as a pathologically heterogeneous disorder, especially in older patients.
To Evaluate Further, ...

- A. Lab tests
- B. Conventional imaging
- C. Neuropsychological testing
- D. Genetic testing?
  - E. Functional Imaging?
    - FDG-PET
    - Amyloid-PET
    - Tau-PET
    - SPECT (β-CIT)
Functional Imaging

- Position Emission Tomography (PET)
  - Labeled glucose
  - Metabolism decreases in areas specific for AD
  - Characteristic pattern can be present early in AD
  - Adds marginally to existing diagnostic criteria - more sensitive than specific
  - Can be helpful for distinguishing AD from other dementias
    - Different dementias have different patterns
    - Only approved neuro use is for distinguishing AD from Frontotemporal dementia
Human Amyloid Imaging Using Pittsburgh Compound-B

Appearance in expected gray matter areas
Absence in areas where there is no amyloid

Very little labeling
Absence of labeling in gray matter

Increases in fibrillar amyloid deposition in \textit{PSEN1 E280A} mutation carriers from the world’s largest ADAD kindred

adapted from Fleisher et al, Lancet Neurol 2012
<table>
<thead>
<tr>
<th>Dementias with amyloid deposition</th>
<th>Dementias without amyloid deposition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>Frontotemporal dementias</td>
</tr>
<tr>
<td>Lewy-body dementia</td>
<td>Cortico-basal degeneration</td>
</tr>
<tr>
<td>Some prion disorders</td>
<td>Progressive supranuclear palsy</td>
</tr>
<tr>
<td>Amyloid angiopathy</td>
<td>Vascular dementia without amyloid angiopathy</td>
</tr>
</tbody>
</table>

Figure 10. In vivo imaging of β-amyloid (Aβ) burden in aging and dementia. Representative distribution volume ratio (DVR) PET transaxial images (top) and sagittal images (bottom) of a 73-year-old healthy control (HC) subject (Mini-Mental State Examination {MMSE} = 30), a 78-year-old patient with dementia with Lewy bodies (DLB) (MMSE = 19), an 82-year-old patient with Alzheimer disease (AD; MMSE = 22), and an 80-year-old patient with frontotemporal dementia (FTD; MMSE = 25). DVR PET images show clear differences when comparing HC or FTD subjects with DLB or AD patients, with nonspecific Pittsburgh Compound B (PIB) binding in white matter in the HC and FTD subjects compared with PIB binding in the frontal, temporal, and posterior cingulate/precuneus cortex of the AD and DLB patients. From [24], with permission.
TAAU IMAGING

- $[^{11}\text{C}]\text{PBB3}$ preferentially interacts with high-affinity for components formed by tau assemblies.
Amyloid and Tau PET in Cognitively Normal and Symptomatic AD

Healthy A-Beta
Healthy Tau
Alzheimer’s A-Beta
Alzheimer’s Tau

Brier et al. Science Translational Medicine, 2016
Neuroimaging Features
DLB: Multimodal Brain Imaging Findings

Images courtesy:
Cliff Jack, Jr., MD
Kejal Kantarci, MD
Val Lowe, MD

Walker et al, The Lancet 2015
Amyloid PET imaging can be used to predict conversion from normal cognition to MCI/dementia.

CSF ratio of total-tau (t-tau) or phosphorylated-tau (p-tau) to β-amyloid can predict conversion from normal cognition to MCI/dementia.

APOE genotype predictive of finding abnormal amyloid PET scan in cognitively normal individuals.

p-tau/t-tau ratio may be helpful for diagnosis of CTE.

The various imaging/CSF studies can be used to more accurately diagnose dementia types (will be clinically useful when we have more specific treatments).
"You need strong medicine to relieve your stress. I'm prescribing a puppy."
MILD COGNITIVE IMPAIRMENT

- PHYSICAL ACTIVITY
- COGNITIVE ACTIVITY
- SOCIAL ACTIVITY
- CARDIOVASCULAR RISK FACTORS
- DIET

### Table 1: Clinical Trials in aMCI

<table>
<thead>
<tr>
<th>Agent</th>
<th>N</th>
<th>Duration</th>
<th>Endpoint</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td>269</td>
<td>24 weeks</td>
<td>Symptoms</td>
<td>Negative</td>
</tr>
<tr>
<td>Donepezil</td>
<td>821</td>
<td>48 weeks</td>
<td>Symptoms</td>
<td>Partially Positive</td>
</tr>
<tr>
<td>Donepezil/Vitamin E</td>
<td>769</td>
<td>3 years</td>
<td>AD</td>
<td>Partially Positive</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>1200</td>
<td>2-3 years</td>
<td>AD</td>
<td>Negative</td>
</tr>
<tr>
<td>Galantamine</td>
<td>995</td>
<td>2 years</td>
<td>CDR 1</td>
<td>Negative</td>
</tr>
<tr>
<td>Galantamine</td>
<td>1062</td>
<td>2 years</td>
<td>CDR 1</td>
<td>Negative</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>1018</td>
<td>3-4 years</td>
<td>AD</td>
<td>Negative</td>
</tr>
</tbody>
</table>

aMCI=amnestic MCI; AD=Alzheimer disease; CDR=Clinical Dementia Rating
Approved Drugs for AD Dementia in the USA

Drug
- Donepezil (Aricept)
- Rivastigmine (Exelon)
- Galantamine (Razadyne)
- Memantine (Namenda)

Mechanism of Action
- Cholinesterase Inhibitor
- Cholinesterase Inhibitor
- Cholinesterase Inhibitor
- Glutamate Modulator

As of September 2017, no other drugs near approval
Practical Issues in the Use of Cholinesterase Inhibitors

- When to start treatment with cholinesterase inhibitors?
  - When dementia is diagnosed

- What are contraindications?
  - Gastritis, chronic diarrhea, urinary urgency
  - Second degree AV block
Practical Issues in the use of Cholinesterase Inhibitors

- Who to treat?
  - Clinically diagnosed Alzheimer dementia
  - Dementia with Lewy Bodies
  - Consider treating when cerebrovascular disease dementia is diagnosed
  - Unlikely to be of value in bvFTD or non-AD PPA’s
  - Unlikely to be of value in MCI
  - Unlikely to be of value in severe dementia
Practical Issues in the use of Cholinesterase Inhibitors

- How to adjust dosing
  - Use standard doses of:
    - Donepezil 10 mg daily
    - Galantamine 24 – 32 mg daily
    - Rivastigmine 6 – 12 mg orally or 9.4 mg transdermal
  - Higher doses are commonly associated with gastrointestinal side effects
  - No compelling evidence that higher doses have greater efficacy

- Consider switching drugs when
  - Toxicity occurs that could be idiosyncratic and might not be class-specific
Practical Issues in the use of Memantine

- Who to treat?
  - Moderately severe AD dementia
- When to start treatment?
  - After starting a cholinesterase inhibitor
- Contraindications
  - None really
- How to adjust dose
  - Use standard dose
- When to stop?
  - Same as cholinesterase inhibitors
Practical Issues in the use of Cholinesterase Inhibitors

- When to stop cholinesterase Inhibitors?
  - When patients reach a stage of severe dementia where delay of symptom progression is no longer of value to them.
The Future of Therapeutics in AD

- Promising leads but still lacking a definitive therapy that alters the natural history, economics and outlook of the disease
- Many questions remain about best targets
Management of DLB and PDD Pharmacologic Options

- **Acetylcholinesterase inhibitors**
  - Donepezil *
  - Rivastigmine *
  - Galantamine *
- **Glutamate antagonist**
  - Memantine *
- **Atypical Neuroleptics**
  - Quetiapine **
  - Olanzapine **
  - Clozapine **
- **Antidepressants**
  - Sertraline
  - Citalopram
  - Venlafaxine

- **Dopaminergics**
  - Levodopa **
  - Pramipexole
  - Ropinirole
- **Sedative/hypnotics**
  - Clonazepam **
  - Melatonin **
- **Psychostimulants/Wake-promoting agents**
  - Methylphenidate
  - Armodafinil **

* Efficacy demonstrated in large RCT
** Efficacy suggested in small RCT
Treatment in FTD

- **SSRI**
  - Loss of dorsal raphe 5HT neurons
  - Low 5HT found on autopsy/CSF/PET
  - May underlie irritability, depression, compulsions

- **Avoid cholinesterase inhibitors, memantine**
  - Cholinesterase inhibitors: mixed effects on cognition, may worsen behavior
  - Memantine: no effect on behavior, may worsen cognition
APP Processing

![Diagram showing APP processing]

**APP**

- **α-secretase**
  - α-sAPP
  - CTFβ

- **β-secretase**
  - β-sAPP
  - CTFβ

- **γ-secretase**
  - Aβ sequence
  - Aβ
  - CTFγ

**genes involved**: PSEN1, PSEN2
## Selected Drug Candidates in Development For Treating Alzheimer’s Disease

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Company</th>
<th>Mechanism</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimebon (latrepirdine)</td>
<td>Pfizer/Medivation</td>
<td>Anti-beta amyloid</td>
<td>3</td>
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<tr>
<td>Bapineuzumab</td>
<td>Elan/Johnson &amp; Johnson</td>
<td>Anti-beta amyloid monoclonal antibody</td>
<td>3</td>
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<tr>
<td>Semagacestat (LY450139)</td>
<td>Eli Lilly</td>
<td>Gamma-secretase inhibitor</td>
<td>3</td>
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<tr>
<td>Solanezumab (LY2062430)</td>
<td>Eli Lilly</td>
<td>Anti-beta amyloid monoclonal antibody</td>
<td>3</td>
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<tr>
<td>Gammaglobulin IV</td>
<td>Baxter</td>
<td>Passive immunization</td>
<td>3</td>
</tr>
<tr>
<td>CERE-110</td>
<td>Ceregene Inc.</td>
<td>Gene therapy to deliver the nerve growth factor gene</td>
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<td>ACC-001</td>
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<td>R3487</td>
<td>Roche</td>
<td>Nicotinic alpha-7 partial agonist</td>
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</table>
Update on Dementia Treatment
Symptomatic AD Dementia

Can we treat AD dementia early to limit progression?

The PRIME Study: Aducanumab

165 patients with prodromal or mild AD and randomized to one of four groups.
- Each received monthly IV infusions for 1 year.

Dose-dependent reduction in cerebral amyloid binding was observed in treated patients.

There was a trend towards improvement in clinical outcomes (the study was not powered to detect this).

Sevigny et al 2016—Nature
Current prevention studies

- A4: sporadic asymptomatic persons aged 65-85 with elevated amyloid (solanezumab)
- DIAN-TU: dominantly inherited AD mutation carriers who are asymptomatic or very mildly asymptomatic (solanezumab or gantenerumab)
- API Colombia: family members of a PS1 mutation (E280A) kindred who are asymptomatic; 5 year study (crenezumab)
- CAP: asymptomatic APOE e4 homozygotes (active immunization CAD106 or BACE inhibitor)
- TOMMORROW: in asymptomatic persons with at risk TOMM40 allele; 5 year duration (pioglitazone)
## NPS in Major Neurocognitive Disorders

### Symptom Frequency (Percentage)

<table>
<thead>
<tr>
<th>Symptom Scale</th>
<th>MCI (N=61)</th>
<th>AD (N=45)</th>
<th>FTD (N=40)</th>
<th>LBD (N=41)</th>
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<tbody>
<tr>
<td>Delusions</td>
<td>9 (15.0)</td>
<td>10 (21.7)</td>
<td>10 (25.0)</td>
<td>17 (41.5)</td>
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<tr>
<td>Hallucinations</td>
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<td>Appetite/Eating</td>
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<td>23 (57.5)</td>
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NPS are core features of bvFTD and DLB.
# NPS in Major Neurocognitive Disorders

## Moderate-Severe Frequency (Percentage)

<table>
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<tr>
<th>Symptom/Scale</th>
<th>MCI (N=61)</th>
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<tr>
<td>Delusions</td>
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<tr>
<td>Hallucinations</td>
<td>0 (0.0%)</td>
<td>5 (10.9%)</td>
<td>2 (5.0%)</td>
<td>13 (31.7%)</td>
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<tr>
<td>Agitation/Aggression</td>
<td>7 (11.7%)</td>
<td>14 (30.4%)</td>
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<td>14 (34.1%)</td>
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<tr>
<td>Elation/Euphoria</td>
<td>3 (5.0%)</td>
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<td>Disinhibition</td>
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NPS in bvFTD and DLB = sig. patient morbidity
NPS in Major Neurocognitive Disorders

Caregiver Impact

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NPS in bvFTD and DLB = sig. CG distress
General Principles of Behavioral Management

- Try behavioral modification techniques
- Avoid anticholinergic medications
- Avoid benzodiazepines
- Eliminate hazardous environments
- Provide adequate supervision
- Correct sensory deprivation
- Control over-stimulation
- Educate caregivers
Things to Consider with Sudden Changes in Behavior

- Check for infection and dehydration
- Evaluate for changes in medical conditions
- Watch for adverse medication effects: Stop or adjust any new medication added
- Assist with pain management
- In hospital setting: get a sitter to reassure, calm, redirect
- Try behavioral modification techniques
- Environmental modification for reactive aggression
- **Endeavor to avoid hospital admission**
General Principles of Behavior Pharmacotherapy

- Behavioral drug use in dementia is off-label
- Treat specific underlying behaviors
- Patients may have several behaviors that are best treated with different medications
- Individualize
- Polypharmacy is typical
- Use very low doses: 1/2 to 1/3 dose
- Review ongoing need
Treatment of Depression in Dementia

- **SSRIs**: effective and good tolerability
  - Paroxetine and Fluvoxamine: slightly more sedating
  - Fluoxetine: more energizing
  - Sertraline and (Es)citalopram: in between

- **SNRIs**: Very few specific studies in dementia; may have beneficial side effects
Preferred Approaches for Depression in Dementia

- **First line preferred treatments**
  - Sertraline *, Citalopram *, Escitalopram
  - Paroxetine *, Fluvoxamine *, Fluoxetine *

- **Second line preferred treatments**
  - Venlafaxine, Bupropion, Mirtazapine
  - Trazodone *
  - Lamotrigine
  - Clomipramine*, Nortryptiline

- **AVOID**: tertiary tricyclic anti-depressants

*positive double blind studies
Anxiety

- Worry, nervousness, phobias, fear of being left alone and somatic complaints
- Godot syndrome: anxiety regarding upcoming events
- Common early in dementia
- Can lead to irritability and aggression
Preferred Approaches for Anxiety in Dementia

- **First line preferred treatments**
  - SSRI’s *, Trazodone

- **Second line preferred treatments**
  - Valproate *
  - Gabapentin/Lamotrigine
  - Buspirone
  - Donepezil *, Galantamine *, Rivastigmine

- **AVOID: Benzodiazepines**

*positive double blind studies
Behavior Modification Techniques

- Non-verbal Communication
  - Always smile
  - Use an open posture
  - Positive gestures
    - Nod yes
    - Wave hello
    - Shrug shoulders
    - Pat on the back
  - Hand them objects they like for distraction
Disinhibition / Intrusiveness

- Caused by impulsivity and poor judgement
- Often leads to intrusiveness
- Not typically severe in AD
- Very common in frontal lobe dementias
Treatment of Mood Lability, Disinhibition, Intrusiveness, Euphoria and Mania in Dementia

- **Dextromethorphan/quinidine**: Pseudobulbar affect
- **Anticonvulsants**: Good mood stabilizing properties but studies are lacking in dementia; Divalproex 250 to 1000 in divided doses and sprinkle formulation easy to give
- **SSRIs**: Studies show help with lability, social dysdecorum, disinhibition: watch for mania
- **Cholinesterase inhibitions**: Reduce disinhibition
- **Olanzapine**: Decreases disinhibition and euphoria
Preferred Approaches for Mood Liability, Disinhibition, Intrusiveness, Euphoria and Mania in Dementia

- **First line preferred treatments**
  - Valproate
  - Dextromethorphan/quinidine for PBA

- **Second line preferred treatments**
  - Citalopram *, SSRIs
  - Gabapentin, Lamotrigine, Carbamazepine other anticonvulsants
  - Galantamine *, Memantine *, Rivastigmine
  - Olanzapine * and other atypicals

*positive double blind studies
Behavior and Modification Techniques

- **Distraction and Redirection**
  - Verbal redirection
  - Object distraction
  - Food distraction
  - “Can you help me?”
Sleep Disturbances

- Diurnal rhythm disruption, repetitive wakenings, insomnia
- Disorientation and confusion in the evening or night (sundowning) often due to loss of sensory stimuli and fatigue; can lead to agitation and wandering
Treatment of Sleep Disturbances in Dementia

- Trazodone
  - Helpful for insomnia and sleep/wake cycle disturbances in doses from 50-150 mg qhs with minimal anticholinergic effects

- Zolpidem
  - In 2 AD patients showed less insomnia

- Gabapentin
  - Helped sleep in 20 AD subjects

- Melatonin
  - Mixed results in dementia but largest study showed no benefit
Preferred Approaches for Sleep Disturbances in Dementia

- **First line preferred treatments:**
  - Trazodone*
  - Zolpidem
  - Melatonin*

- **Second line preferred treatments:**
  - Mirtazepine, Nortryptiline if depressed
  - Quetiapine, Risperidone, Olanzapine if psychotic
  - Valproate if restless, intrusive or manic
  - Gabapentin

- **Avoid:** Barbiturates, benzodiazepines, hydroxyzine, diphenhydramine

*positive double blind studies
Behavior Modification Techniques for Sleep/Wake Cycle Disturbances

- Regular sleep habits
- Avoid naps
- Increase daytime activities
- Avoid late meals, caffeine, alcohol
Aberrant Motor Behaviors

- Wandering occurs in 3-26% of AD patients
- Psychomotor activity disturbances include:
  - Motor restlessness - hyperkinesis
  - Purposeless activities - pacing
  - Hoarding and hiding items - packing/unpacking
  - Dressing/undressing - hyperverbalness
  - Intrusive touching - pounding/tapping
  - Insistent verbal repetition - singing
Treatment of Aberrant Motor Behaviors in Dementia

- **Divalproex**
  - Reduces restlessness in dementia

- **Citalopram**
  - 20-40 mg daily decreased aberrant motor behaviors in open trial

- **Sertraline**
  - Trend toward reducing aberrant motor behaviors in DBPC study

- **Cholinesterase inhibitors**
  - Most will lessen “wanting to go” behaviors in AD

- **Risperidone, Quetiapine**
  - Helped with wandering and restlessness
Preferred Approaches for Aberrant Motor Behaviors in Dementia

- **First line preferred treatments**
  - Valproate*
  - Citalopram
  - Galantamine*, Rivastigmine, Memantine

- **Second line preferred treatments**
  - Sertraline, Paroxetine, Trazodone
  - Risperidone*, Quetiapine
  - Gabapentin

*positive double blind studies
Behavior Modification Techniques for Aberrant Motor Behaviors

- **Obsessive-Compulsive traits**
  - Provide activities (fold clothes, …)
  - Adequate supervision

- **Psychomotor activity disturbance**
  - Allow wandering in a safe, contained environment
  - Planned regular exercise, walking
Psychosis

- **Delusions** - fixed false beliefs
  - Theft
  - Jealousy
  - Phantom boarder
  - Spouse as imposter (Capgras)
  - House not home

- **Hallucinations** - spurious sensory experience
  - Visual, auditory, tactile, gustatory
  - Content (simple → complex)
  - Belief/insight
Phenomenology vs Etiology

- **Psychosis**
  - Idiopathic thought disorder?
  - Specific disease-related pathophysiology?
  - General medical condition (i.e. delirium)?
  - Iatrogenic (meds)?

- **Agitation**
  - Psychomotor dysregulation?
  - Altered sleep-wake cycle?
  - Pain or discomfort?
  - Response to perceived threat?
  - Search for trigger
DICE Approach to A/A
Kales et al., JAGS, 2014

- **Describe:** uncooperative? resisting help? aggressive (verbal /physical)? psychotic

- **Investigate:** social / environmental triggers; medical co-morbidities

- **Create:** behavior modification; environmental manipulation; pharmacologic intervention

- **Evaluate:** outcome; modified approach
# Antipsychotic Agents for BPSD

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Trial</th>
<th>n</th>
<th>Setting</th>
<th>Treatment Time, wk</th>
<th>Daily Dose, mg</th>
<th>Efficacy</th>
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<td>Risperidone</td>
<td>De Deyn et al, 22, 1999</td>
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<td>Katz et al, 33, 1999</td>
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<td>Suh et al, 34, 2004</td>
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<td>6</td>
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<td></td>
<td>Deberdt et al, 36, 2005</td>
<td>434</td>
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<td>De Deyn et al, 37, 2004</td>
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<td>Quetiapine</td>
<td>Tariot and Ismail, 38, 2002</td>
<td>378</td>
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<td>10</td>
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<td>Zhong et al, 39, 2004</td>
<td>333</td>
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<td>80</td>
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<td>26</td>
<td>50–100</td>
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+ indicates effective; − ineffective; −/+ partially effective; NH, nursing home; OPT, outpatients.
# Antipsychotic Agents for BPSD (cont.)

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<thead>
<tr>
<th>Antipsychotic</th>
<th>Trial</th>
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<th>Setting</th>
<th>Treatment Time, wk</th>
<th>Daily Dose, mg</th>
<th>Efficacy</th>
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<td>+</td>
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<td>De Deyn et al, 2005</td>
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<td>Risperidone/olanzapine vs promazine</td>
<td>Gareri et al, 2004</td>
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<td>Risperidone 1–2; olanzapine 5–10; promazine 50–100</td>
<td>Atypicals superior to promazine</td>
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<tr>
<td>Risperidone/olanzapine/quetiapine vs</td>
<td>Schneider et al, 2006</td>
<td>421</td>
<td>OPT</td>
<td>36</td>
<td>Risperidone 0.5 Olanzapine 2.5 Quetiapine 25</td>
<td>Risperidone and olanzapine superior to placebo and quetiapine; placebo superior to the 3 drugs for tolerability</td>
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## Atypical Antipsychotics

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<th>Dose</th>
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<th>Comment</th>
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<td>Risperidone</td>
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<td>--</td>
<td>++</td>
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<tr>
<td>Olanzapine</td>
<td>2.5-15 mg/d</td>
<td>+</td>
<td>+</td>
<td>wt. gain</td>
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<tr>
<td>Quetiapine</td>
<td>25-200 mg/d</td>
<td>++</td>
<td>+/-</td>
<td>QTc, (DLB)</td>
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<tr>
<td>Aripiprazole</td>
<td>2-15 mg/d</td>
<td>--</td>
<td>+/--</td>
<td></td>
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<tr>
<td>Clozapine</td>
<td>12.5-200 mg/d</td>
<td>++</td>
<td>+/-</td>
<td>monitoring</td>
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</tbody>
</table>
NPS in Frontotemporal Dementia

- **Cholinesterase inhibitors** - not effective, may worsen symptoms
- **Memantine** - demonstrated not to be helpful in DBPC study
- **Mood/anxiety/OCD sx** - SSRIs often helpful
- **Repetitive motor behaviors/agitation** - Trazodone 50-300 mg/day. (University of N. Carolina reports all of their FTD patients on combination of Sertraline and Trazodone)
- **Insomnia** - Melatonin 3-10 mg qhs
- **Hyperphagia** - Topamax?
Management of DLB and PDD
Pharmacologic Options

- **Acetylcholinesterase inhibitors**
  - Donepezil *
  - Rivastigmine *
  - Galantamine *

- **Glutamate antagonist**
  - Memantine *

- **Atypical Neuroleptics**
  - Quetiapine **
  - Olanzapine **
  - Clozapine **

- **Antidepressants**
  - Sertraline
  - Citalopram
  - Venlafaxine

- **Dopaminergics**
  - Levodopa **
  - Pramipexole
  - Ropinirole

- **Sedative/hypnotics**
  - Clonazepam **
  - Melatonin **

- **Psychostimulants/Wake-promoting agents**
  - Methylphenidate
  - Armodafinil **

* Efficacy demonstrated in large RCT
** Efficacy suggested in small RCT
Dextromethorphan / Quinidine (Nuedexta) (DM/Q)

- Combo Rx (Q increases bioavailability of DM)
- Approved for treating pseudobulbar affect (PBA)
- Phase 2 study for agitation in AD (DM 30/Q 10 BID) showed sig. reduction in NPI A/A scale relative to placebo
- Phase III 12-week DBPC studies using (d6)-dextromethorphan (reduces 1st pass hepatic metabolism allowing lower dose of Q) (AVP-786) are in progress (TRIAD-1 and TRIAD-2)
Pimavanserin (Nuplazid)

- 5-HT2A inverse agonist
- Phase 3 clinical trial showed efficacy and safety in PD psychosis and improved night-time sleep (34 mg/day) (Cummings et al, Lancet, 2014)
- Main side effects: peripheral edema, confusion, falls
- FDA approved for PD psychosis; AD agitation study underway
- Nelotanserin Phase 2 studies for visual hallucinations and RBD in DLB underway
"Mr. Osborne, may I be excused? My brain is full."
The history still matters.

Diagnostic tools for dementia are, and are continuing to, improve.

Research remains extremely active but has shifted to underlying causes of dementia rather than symptomatic treatments.

For mild cognitive impairment:
1. No expectation that ACHEI’s or memantine will be helpful.
2. Consider recommending physical, cognitive, social activity, cardiovascular risk factor modification, Mediterranean-like diet.

For Alzheimer disease:
1. Start ACHEI when dementia diagnosed.
2. Start memantine when dementia moderate.
THAT'S A LOT OF INFORMATION...

- **For FTLD:**
  1. Most will benefit from SSRIs
  2. Don’t use cholinesterase inhibitors and avoid memantine.
  3. Expect neuropsychiatric problems and expect polypharmacy may be necessary.

- **For Lewy body dementias (DLB and PDD):**
  1. Use cholinesterase inhibitors.
  2. Memantine may or may not be helpful.
  3. Expect neuropsychiatric problems and polypharmacy.

- **For neuropsychiatric symptoms of dementia:**
  1. Maximize use of behavioral techniques, which means educating caregivers.
  2. There are guidelines for pharmacological treatment although data can be thin. Use when benefits > risks.
  3. Research in this area of symptoms is increasing.
<table>
<thead>
<tr>
<th>CNS System</th>
<th>Clinical Manifestation</th>
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<tbody>
<tr>
<td>Personality</td>
<td>apathy, disinhibition</td>
</tr>
<tr>
<td>Mood-emotional</td>
<td>depression, euphoria, anxiety, irritability</td>
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<tr>
<td>Sensory-perceptual</td>
<td>hallucinations, delusions</td>
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<tr>
<td>Psychomotor</td>
<td>agitation, pacing, fidgetiness</td>
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<tr>
<td>Vegetative</td>
<td>sleep-wake cycle, appetitive</td>
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