Serious Mental Illness and Dementia

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Perspective. . . .

“How far you go in life depends on your being tender with the young, compassionate with the aged, sympathetic with the striving, and tolerant of the weak and strong. Because someday in your life you will have been all of these.”

George Washington Carver
DIFFERENTIAL DIAGNOSIS OF DEMENTIA

Vascular dementias
- Multi-infarct dementia
- Binswanger’s disease

Other dementias
- Frontal lobe dementia
- Creutzfeldt-Jakob disease
- Corticobasal degeneration
- Progressive supranuclear palsy
- Many others

Vascular dementias and AD

Lewy body dementias
- Parkinson’s disease
- Diffuse Lewy body disease
- Lewy body variant of AD

AD and Lewy body dementias

AD

5% 10% 65% 5% 7% 8%

Assessment of Dementia

Medical history
Neuropsychiatric examination
Mental status tests

<table>
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Dementia

Blood tests
Imaging

B12 or folate
Neurosyphilis
Thyroid
Organ failure
HIV

Multi-infarct
Hydrocephalus
Tumor
Subdural
MS

Alzheimer’s, Pick’s, FTD, Lewy
Body, Vascular, PD+dementia,
Progressive supranuclear palsy,
Corticobasal, Huntington’s,
Creutzfeldt-Jacob, more
How do we know it’s not Alzheimer’s?
How do we know it’s not Alzheimer’s?

- Hallucinations
- Step-wise Decline
- Behavior
- Tremor
- Misc.

Gradual onset
Progression
Memory loss
The Alzheimer’s Disease Epidemic

AD Prevalence by Age

- 65-74: 3%
- 75-84: 19%
- >85: 47%

US Population
> 85 years old (in millions)

- 1930: 0
- 1950: 0
- 1970: 0
- 1990: 0
- 2010: 0
- 2030: 0
- 2050: ~18

... ~5 million today... nearly 50% over age 85 have AD...
70 million baby boomers... ~$150 B annual costs today...
Pathology of Alzheimer's Disease

- Brain Atrophy
- Plaques
- Tangles
The Amyloid Hypothesis

Neuritic Plaque

Amyloid Precursor Protein

Aβ42

Neurofibrillary Tangles

γ-secretase

Presenilins

Aβ42

Amyloid Oligomers

Aβ42

ApoE

ApoJ

Amyloid Clearance
Tauopathies

- Neurofibrillary tangles in AD composed of aggregated tau protein
- Pick bodies and other abnormal inclusions in FTD also composed of aggregated tau
- AD brains also contain deposits of amyloid in plaques
What is Tau?

- Neurons transport material to and from the cell body and synapse through axons along microtubule ‘tracks’
- Tau protein binds to microtubules, stabilizes the tracks, and helps them function normally
Consequences of TAU abnormalities
Disease Mechanisms in Tauopathies

- Tau proteins stick together in ‘aggregates’
- Insoluble Tau accumulates and damage neurons
- Microtubules may not function properly
- Axonal transport may be disrupted

Biomarkers of Brain Aging

- **Serum/Blood:**
  - APOE
  - presenilin/APP mutations
  - TREM2

- **CSF:**
  - AB-42
  - Phosphorylated tau

- **Structural Imaging**
  - CT, MRI
  - PET-Amyloid/tau
  - DTI

- **Functional Imaging**
  - FDG-PET, fMRI

- **Other**
  - Sniff test
  - Risk factors
Poor recognition of early memory loss

- <10% of patients with mild dementia recognized by MD at the time of office visit
- 3.2% of MCI cases recognized
- Why???
  - Differences between normal age-associated memory lapses and clinically important MCI are subtle
  - Average length of office visit: 13-18 minutes
  - The most common screening test: 7-10 minutes

Callahan and Hendrie 1995; Valcour et al. 2000)
“Low-tech” approach to detect early symptoms of AD

- Requirements for widespread screening
  - Quick & easy
  - Cheap
  - Quick & easy!

- Mini-Cog (Borson et al. 2000)
  - Brief 3-item memory test
  - Clock drawing test
  - 3-5 min to perform
  - No special training
Draw A Clock Task

- Ask patient to draw a large circle (1 pt)
- Ask patient to place numbers on the face of the clock (1 pt)
- Ask patient to put hands on the clock to display ten minutes after eleven
  - One point for correct hand placement
  - One point for correct hand length
The Montreal Cognitive Assessment

- 30-question test
- Takes around 10 minutes to complete
- Published in 2005
- Assesses orientation, short-term memory, executive function, language abilities, and visuospatial ability
- Includes a clock drawing task and Trails B
- Scoring of the MoCA
  - Scores range from 0 to 30
  - 26 and higher generally considered normal
  - Normal controls had an average score of 27.4
  - 22.1 in people with mild cognitive impairment
  - 16.2 in people with Alzheimer’s disease
SLUMS

- Saint Louis University Mental Status Examination
- Designed to be more sensitive to MCI than the MMSE
- 11 items
- Measures orientation, short-term memory, calculations, naming of animals, clock drawing, and recognition of geometric figures
- Scores range from 0 to 30
  - 27-30 considered normal
  - 21-26 suggests Mild Neurocognitive Disorder
  - 0-20 indicates dementia
SLUMS

- SLUMS and the MMSE compared in 705 male veterans 60 and older
- Both tools detected dementia
- Only the SLUMS recognized patients with MCI
- Took an average of seven minutes to administer
- Test is free
Folstein Mini-Mental State Exam

- Takes approximately 10 minutes to administer
- Examines areas including
  - **Orientation** (person, place, and time)
  - **Attention** (spelling “World” backwards or counting by 3’s)
  - **Memory** (recalling 3 items)
  - **Language** (naming two objects, following a command, writing and reading a sentence)
  - **Visuomotor Functioning** (copying a design)

Score ranges from 0-30 points
Neurodegenerative Disease: Complex Traits with Common Environmental and Genetic Factors

Genes

Alzheimer’s Disease

Environment

Risk or Protective Factors
- Head trauma
- Depression
- Hypertension
- Cholesterol
- Homocysteine
- B12, folate
- Education
- Exercise
- Mediterranean Diet
- NSAIDS
- Statins
- Red Wine
Alzheimer’s Disease Treatments

**Symptomatic**
- Cholinesterase inhibitors (Aricept, Razadyne, Exelon)
- Memantine (Namenda)

**Failed**
- NSAIDS
- Estrogen
- Statins
- Vitamin B Supplements
- Flurizan
- Gingko Biloba
- …..and many more

**Neuroprotective?**
Importance of MCI Recognition

- ~10 - 15% annual conversion rate of MCI to dementia
- ~1-2% annual conversion rate in cognitively normal individuals
- Identification of MCI allows early intervention
- Identification of MCI necessary for research to develop better treatments and prevention of AD and other dementias
Biomarkers Change Long before the disease is detected

- Amyloid deposition begins 17 years before the disease is expressed
- Hippocampal Atrophy begins at least 4 years before the disease is expressed

- Australian Imaging Biomarker and Lifestyle Study (villemagne, Lancet Neurology 2013:12:357-67.)
Early Detection and Prediction of AD: PET and MRI

Preclinical Stages

“Healthy”

Mild Cognitive Impairment

Alzheimer Disease

Cognition

Preclinical Stages

Mild Dementia

Moderate Dementia

Severe Dementia

Age

50 55 60 65 70 75 80 85 90
Early Detection and Prediction of AD: PET Imaging of Aβ in the Alzheimer Disease Neuroimaging Initiative

Mormino et al., Brain, 2009
Preclinical Evidence of Alzheimer’s Disease in Asymptomatic Individuals with ApoE4

Reiman et al., NEJM 334:752, 1996
Emerging Therapeutics in AD

- **Anti-amyloid agents**
  - Immunotherapy (vaccines, immunizations) (Phase II)
  - Secretase inhibitors and modulators (Phase III)
  - Fibrillization inhibitors (Phase III)
  - Statins (Phase IV)

- **Neuroprotective compounds (examples)**
  - Antioxidants (curcumin - proof of concept)
  - Nerve growth factor-like (Phase III)
  - NMDA receptor blockers
  - Tau-related agents

- **Symptomatic agents**
  - Transmitter-based (cholinergic and non-cholinergic)
How do we improve cognitive reserve?

- Life exposures
  - Family Environment
  - Education
  - Occupation
  - Leisure
- Physical/vascular factors
  - Exercise
- Direct effect of life experiences
  - Stress
  - Work experiences
Educational Level

Strong association with risk of any Dementia

- **Kungsholmen Project**
  - 1810 ss over 75 yo
  - Subjects with <8 years education were 2.6 times more likely to get AD

- **Nurses Health Study**
  - 19,319 nurses >70
  - The higher the attainment, the better the test performance

- **Nun Study**
The Nun Study

- 700 School Sisters of Notre Dame are participating
- Current ages are from 75 to 106 years old
- Information is available from their early teen years to the time of death, including autopsy in those participants who have died
Exercise Protects the Brain

Effect of Physical Activity on Cognitive Function in Older Adults at Risk for Alzheimer Disease
A Randomized Trial

Context Many observational studies have shown that physical activity reduces the risk of cognitive decline; however, evidence from randomized trials is lacking.

Objective To determine whether physical activity reduces the rate of cognitive decline among older adults at risk.

Design and Setting Randomized controlled trial of a 24-week physical activity intervention conducted between 2004 and 2007 in metropolitan Perth, Western Australia. Assessors of cognitive function were blinded to group membership.

Participants We recruited volunteers who reported memory problems but did not meet criteria for dementia. Three hundred eleven individuals aged 50 years or older were screened for eligibility, 89 were not eligible, and 52 refused to participate. A total of 170 participants were randomized and 138 participants completed the 18-month assessment.

Intervention Participants were randomly allocated to an education and usual care group or to a 24-week home-based program of physical activity.

Results In an intent-to-treat analysis, participants in the intervention group improved 0.26 points (95% confidence interval, −0.89 to 0.54) and those in the usual care group deteriorated 1.04 points (95% confidence interval, 0.32 to 1.82) on the ADAS-Cog at the end of the intervention. The absolute difference of the outcome measure between the intervention and control groups was −1.3 points (95% confidence interval, −2.38 to −0.22) at the end of the intervention. At 18 months, participants in the intervention group improved 0.73 points (95% confidence interval, −1.27 to 0.03) on the ADAS-Cog, and those in the usual care group improved 0.04 points (95% confidence interval, −0.46 to 0.88). Word list delayed recall and Clinical Dementia Rating sum of boxes improved modestly as well, whereas word list total immediate recall, digit symbol coding, verbal fluency, Beck depression score, and Medical Outcomes 36-Item Short-Form physical and mental component summaries did not change significantly.

Conclusions In this study of adults with subjective memory impairment, a 6-month program of physical activity provided a modest improvement in cognition over an 18-month follow-up period.
Physical Activity

- Metaanalysis of 18 longitudinal studies of adults >55 yo
- Greater activity associated with greater cognitive improvement
- Combination exercise (aerobic+stretching) > aerobics alone
- *Sessions less than 30 minutes did nothing*
Cognitive and Leisure Activity

Bronx Aging Study (1980-83)

- 469 ss age 75-85
- Activities associated with lower risk of dementia included...
  - Playing board games
  - Playing a musical instrument
  - Reading
  - Dancing
Prevalence of AD (per 1000 cases)

Cholesterol Lowering Drugs & Risk of AD

2-4 x lower risk of AD with statins

Lovastatin Pravastatin (Mevacor) (Pravachol)

4,180 2,326

captopril furosemide β-blockers (Capoten) (Lasix)

4,616 15,106 10,395

Wolozin et al., Arch Neurol 2000
DIFFERENTIAL DIAGNOSIS OF DEMENTIA

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Vascular dementias and AD

Other dementias
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Lewy body dementias
- Parkinson’s disease
- Diffuse Lewy body disease
- Lewy body variant of AD

AD and Lewy body dementias

AD

5% 10% 65% 5% 7% 8%

Focus on...

Frontotemporal Dementia
Lewy Body Dementia
Frontotemporal dementia...

- Prevalence ≈~10% of presenile dementias
- Onset 6-7th decade
- E4 allele overrepresented
Frontotemporal Dementia

- Associated with degeneration of frontal, temporal lobes
- Syndromes include…
  - Progressive subcortical gliosis
  - Non AD frontal lobe dementia
  - Primary progressive aphasia (Mesulam syndrome)
  - Semantic dementia
  - Pick’s Disease
Pick’s Disease and FTD - Are they the same thing?

- First clinical description by Arnold Pick in 1892
- Pathology described by Alzheimer in 1911
  - Pick bodies
  - Composed of Tau
- Classic cases of Pick’s disease are rare
- Similar clinical features to other types of FTD
Control

FTD

Temporal Lobe Atrophy

Frontal Lobe Atrophy
Frontotemporal Dementia

Distinctive core features
- Decline in social interpersonal conduct
- Impaired regulation of personal conduct
- Emotional blunting
- Loss of insight
- Severe language disturbance
- No severe memory loss
- No spatial disorientation

Supportive features
- Decline in personal hygiene
- Mental rigidity
- Distractibility
- Hyperorality & dietary changes
- Stereotyped behavior
- Utilization behavior
- Earlier onset

Neary et al. (1998) Neurology 51:1546
Clinical Features

Personality changes usually precede GROSS dementia by several years.
Sometimes withdrawn and apathetic.
Sometime disinhibited, loss of judgement.
50% commit an antisocial act that can lead to arrest.
FTD-clinical features

Kluver-Bucy Syndrome:
- In animals, removal of anterior temporal lobes, bilateral amygdala
  - Hyperorality
  - Placidity
  - Sensory agnosia
  - Lose social behaviors

Loss of serotonin!
FTD- cognitive features

Economical language decline is usually the first feature
  – Verbal stereotypies
  – Word list generation impairments
  – Semantic anomia
  – Visuospatial skills relatively preserved

EEG:
  – Frontal sowing, or normal
Distinguishing FTD from AD

Many FTD patients may meet clinical criteria for Alzheimer’s disease

Severe focal atrophy may not be detectable early

Core features of FTD can occur in AD
  – Personality changes
  – Behavioral problems
  – Language difficulties

Clinical features most effective in distinguishing FTD from AD
  – Social conduct disorders
  – Hyperorality
  – Akinesia
  – Lack of severe amnesia
  – Lack of visual perceptual deficit

Rosen et al. (2002) Neurology 58:1608
Distinguishing FTD from SMI

FTD
- Personality changes
- Behavioral problems
- Language difficulties

SMI
- Hyperorality
- Akinesia
- Lack of severe amnesia
- Lack of visual perceptual deficit
Treatment of FTD

- No specific treatment
- Neurochemical changes not well defined
  - Possible reduction in frontal-temporal serotonin
  - No established benefit of cholinesterase inhibitors for cognitive symptoms
- Limited effectiveness of drugs against specific target symptoms

Symptomatic drug therapy

- SSRI antidepressants
  - Mood disturbances
  - Compulsions
  - Hyperorality
- Antiepileptics
  - Carbamazepine; Valproate
  - Agitation and aggression
- Atypical neuroleptics
  - Agitation and aggression
Treatment of FTD

**Behavioral approaches**
- Susceptible to environment
  - Control environmental triggers for problem behaviors
- Poor executive function
  - Provide structure
- Limited judgment & insight
  - Early cessation of driving
  - Limit financial dealings
  - Possible job changes

**Education-support**
- Potential for severe difficulty at early stages
- Socially inappropriate behaviors
- Loss of emotional responsiveness
- Severe communication problems
- Risk of agitation and aggression
  - Often younger patients
Lewy Body Dementia

First described in 1960’s

- Okasaki, et al 1961

# 2 cause of dementia

- Accounts for at least 10% of post-mortem samples
- 15% community-based dementias in London
- 36% US ADC referrals
Dementia with Lewy Bodies (DLB)

Core features of DLB
- Fluctuations
  - Periods of severe confusion of unresponsiveness
- Hallucinations
  - Complex, vivid visual hallucinations
- Parkinson’s-like symptoms
  - Initially may be mild
  - Tremor less frequent

Supportive features
- Frequent falls
- Syncope or transient loss of consciousness
- Neuroleptic sensitivity
- Systematized delusions
- Non-visual hallucinations

McKeith et al. (1996) Neurology 47:1113
Delirium
- Fluctuating confusion
- Attentional deficits
- Intermittent loss of consciousness

Psychiatric symptoms
- Visual hallucinations
  - Persistent, complex

Parkinsonian symptoms
- May precede dementia
- Rigid, akinetic parkinsonism
- Frequent falls

Memory complaints are first in 60-70%
Faster rate of decline than AD
death in 5-8 years
Minimal response to l-dopa
DLB: International Consensus Criteria

- Core symptoms:
  - Fluctuating confusion
  - Visual hallucinations
  - Spontaneous parkinsonism

- Two needed for probable DLB,
- 1 needed for possible DLB

- Specificity > 0.8
- Sensitivity ~ 0.22-0.8
- Attention, visuospatial skills more impaired than AD
- Recent memory may be well preserved early
Other Symptoms…

Sleep disturbance:
- REM sleep behavior disorder is common

Depression
- 33-50%
- No data on treatment for depression
DLB Similarities to AD and PD

- **Cognitive symptoms similar to AD**
  - Prominent memory loss
  - Executive dysfunction
  - Visuospatial impairments
  - Language impairments

- **Some atypical features**
  - Prominent attentional problems

- **Motor symptoms similar to PD**
  - Bradykinesia
  - Postural instability
  - Rigidity

- **Some atypical features**
  - Symmetrical
  - Less frequent tremor
  - Less responsive to dopaminergic therapy
What are Lewy bodies?

- Composed of multiple proteins
  - Cytoskeletal proteins
  - Protein degrading enzymes
  - Alpha-synuclein aggregates

- Mutations in alpha-synuclein responsible for rare cases of genetic PD
  - Normal function is unknown
  - Protein aggregation promoted by mutations
Neuropathology in DLB

- Distribution of Lewy bodies
  - Brainstem Lewy bodies
  - Degeneration of nigra
  - Dopamine deficiency
  - Diffuse cortical Lewy bodies

- Alzheimer’s-like pathology
  - Pathological overlap with AD
  - AD cases with Lewy bodies

- Combined neurochemical deficiencies
  - Acetylcholine
  - Dopamine
Treatment of DLB

- **Cholinergic deficits**
  - Loss of acetylcholine producing cells
  - Severe deficit
  - Possibly best responders to cholinesterase inhibitors

- **Dopaminergic deficits**
  - Loss of dopamine-producing cells
  - Variable response to dopamine replacement therapy

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Tacrine (Cognex)
Donepezil (Aricept)
Rivastigmine (Exelon)
Galantamine (Reminyl)
Treatment of DLB

**Cholinergic deficits**
- Loss of acetylcholine producing cells
- Severe deficit
- Possibly best responders to cholinesterase inhibitors

**Dopaminergic deficits**
- Loss of dopamine-producing cells
- Variable response to dopamine replacement therapy
Treatment: AchE Inhibitors

- Limited, open label trials show reductions in
  - Hallucinations
  - Delusions
  - Apathy
Schizophrenia in late life

- One year prevalence over age 65 is 0.6%
- 12% of schizophrenics were over 50 years old in 2004
  - Will double by 2024
- Economic costs associated with functional impairment are among the highest in late life
  - Cognition is the strongest predictor of function
  - 80% are in the community
Positive symptoms

**Schizophrenia**
- Delusions
  - Fixed, false, idiosyncratic
  - Not mood congruent
- Hallucinations
  - Most are auditory…can be visual/smell/taste/touch
- Disorganization
  - Speech or thought
- Catatonia

**Compared to Dementia**
- Delusions often ‘reality based’
- Visual hallucinations more common
- Responds to lower doses of antipsychotics..usually
- Disorganized later in disease
Longitudinal study of hallucinations in NYC

- 104 subjects followed 12-116 months
- 35% lived independently or with family
- Cross sectional results: 36% had hallucinations
  - 32% auditory
  - 13% visual
  - 9% olfactory
Auditory Hallucinations in NYC

- 73% clear
- 55% every day
- 56% were pleasant
- 61% good
- 58% command
- 56% obeys commands
Type and Identity of voices…

**Type:**
- 34% evaluative
- 34% directive
- 32% Mundane

**Identity:**
- 23% God
- 3% Devil
- 15% Relatives
Negative symptoms

- Social withdrawal (Autism)
- Difficulty with emotions (affect)
- Poor self care (ambivalence)
- Anhedonia (Affect)
Paranoid subtype

- Delusions of persecution, sometimes grandiose
- Attention difficulties
- Normal Intellect
- Behavioral problems include...
  - Anger
  - Withdrawal
  - Anxiety
Cognition in Schizophrenia

- Cognition declines after at least 2 years followup among institutionalized individuals
- After age 65, MMSE declines by 1 point per year
- Community dwelling schizophrenics show stability in cognitive measures compared to age matched controls.
  - Also, no decline in social functioning
Cognitive impairments in...

**Schizophrenia-impairments in:**
- Working memory
- Long term memory
- Attention
- *Processing speed*
- Executive function

**Dementia-impairments**
- Amnesia-recent memory
- Aphasia-language
- Apraxia
- Agnosia
So... how does SMI interact with dementia

- Badly
- Often, in facilities one diagnosis is neglected
  - It's usually Serious Mental Illness
- Dementia often makes psychotic symptoms less vivid, sometimes more 'reality based'
- Dementia mitigates the expression of schizophrenia, not the opposite
- In SNF’s, regulatory pressures often result in undermedicating
  - Mandatory attempts at dose reduction
Tyrant in the house?

"Thorazine" can control the agitated, belligerent mood and help the patient to live a composed and useful life.

When "Thorazine" is administered to the agitated mood, there is a marked decrease in its nerve-racking symptoms of hallucinations, delirium, insomnia, nervousness, violent protection, and "day and night" pacing or rocking.

On "Thorazine" therapy, the patient often forms a more regular routine and quieting holing and improvements in his general behavior. As the patient becomes more tranquil and cooperative, he is able to live a composed and useful life.

THORAZINE™

one of the fundamental drugs in medicine

Smith Kline & French Laboratories, Philadelphia

for prompt control of senile agitation

THORAZINE™

"Thorazine" can control the agitated, belligerent mood and help the patient to live a composed and useful life.

Smith Kline & French Laboratories
Overview of RCT Evidence for Drugs

- Pain medications
- Anticonvulsants
- Antidepressants
- Benzodiazepines
- Cholinesterase inhibitors
- Memantine
- Antipsychotics
Pain Medications

• Empiric pain management protocol in nursing home residents with agitation
  – Placebo-controlled 8 week RCT, n=352
  • Step 1: acetaminophen (68%)
  • Step 2: oral morphine (2%)
  • Step 3: buprenorphine patch (23%)
  • Step 4: pregabalin (7%)
  – Agitated symptoms improved at 8 weeks with treatment vs. placebo, and worsened in 4 week washout

Husebo et al, BMJ. 2011;343:d4065
Antidepressants

- **SSRIs**
  - 5 studies vs. placebo
  - 3 studies vs. typical antipsychotics
  - Possible small benefits on agitated symptoms

**Other Antidepressants**

- Trazodone
  - 2 studies = haloperidol, small N
  - 1 study = placebo

Seitz et al, Cochrane Reviews 2011;2;CD008191
Anticonvulsants

Divalproex

– 4 studies = placebo, poorly tolerated
– Cognitive decline and hippocampal damage?

Carbamazepine

– Mixed evidence
– Concerns of poor tolerability, drug interactions
  Lonergan and Luxenberg, Cochrane Reviews 2009;3;CD003945
  Tariot et al, Arch Gen Psychiatry 2011;68(8):853-61
  Fleisher et al, Neurology 2011;77(13):1263-71
Benzodiazepines/anxiolytics

Oxazepam, alprazolam, diphenhydramine, buspirone

- 3 studies = haloperidol
- No placebo controlled studies

trial design problems, cognitive impairment issues with most of these drugs
• Not recommended for scheduled use

Meeks and Jeste, Current Psychiatry
2008;7(6):50-65
Antipsychotic Choice

• Evidence supports modest symptom improvements with
  – Haloperidol (*Haldol®*)
  – Olanzapine (*Zyprexa®*)
  – Quetiapine (*Seroquel®*)
• less supportive evidence
  – Risperidone (*Risperdal®*)
  – Aripiprazole (*Abilify®*)
• Research does not support use of other antipsychotics in dementia
  *available as less expensive generic
Evidence for the Use of Antipsychotics for Behavioral Disturbances

**Modest efficacy in RCTs with some drugs**
- Risperidone for psychosis
- Aripiprazole and Risperidone for neuropsychiatric symptoms

Benefits less in those without psychosis, in nursing homes, and with severe cognitive impairment
- Haloperidol similar efficacy to atypicals
- 4 negative placebo controlled trials with quetiapine

Maglione et al. Off-label use of atypical antipsychotics: an update.
Evidence for the Use of Antipsychotics for Behavioral Disturbances

CATIE-AD

- Time to discontinuation was primary outcome
  - Olanzapine, Quetiapine, Risperidone no better than placebo
- Time to discontinuation due to lack of efficacy favored Olanzapine and Risperidone
- Time to discontinuation due to adverse effects favored placebo

AHRQ Summary of Efficacy: Atypical Antipsychotics
Aripiprazole Olanzapine Quetiapine Risperidone

Dementia-Overall ++ + + ++
Dementia-Psychosis + +/- +/- ++
Dementia-Agitation + ++ +/- ++

Legend:
++ = Moderate or high evidence of efficacy
+ = Low or very low evidence of efficacy
+/- = Mixed results

http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports
Potentially appropriate antipsychotic treatment targets

• Hallucinations

• Delusions (note: memory problems are often mistaken for delusions, e.g. thinks people are stealing lost items...or are they?)

• Aggressive behavior (especially physical)
Appropriate antipsychotic treatment targets

- If the symptom presents a danger to the patient or others
- Or, causes the patient to experience
  - Inconsolable or persistent distress
  - Significant decline in function
  - Substantial difficulty receiving needed care
Inappropriate antipsychotic treatment targets

- Wandering
  - Unsociability
  - Poor self-care
  - Restlessness
  - Impaired memory
  - Inattention or indifference to surroundings

- Verbal expressions or behaviors that do not represent a danger to the resident or others
  - Nervousness
  - Uncooperativeness
  - Fidgeting
  - Mild anxiety
Parkinson’s Disease / Lewy Body Dementia

– Tolerate antipsychotics poorly
– Reduce antiparkinson med doses for psychosis
– Cholinesterase inhibitors may reduce hallucinations
– Memantine may produce global improvements

Frontotemporal Dementia

– Preliminary data for trazodone and stimulants
– Mixed data on paroxetine
  • May worsen cognition

We can learn from antipsychotic RCT’s

- Rule out/ treat concomitant medical illness
- Simplify medications
- Give attention to subjects
- ‘Passively educate’ staff
Antipsychotic discontinuation studies

The few placebo-controlled studies of antipsychotic discontinuation show mixed results and some recent studies showed little difference on drug versus placebo.

The largest study that discontinued AD patients from different antipsychotics showed greater worsening on placebo by 12 months in patients with greater baseline psychopathology.

Pilot Study of haloperidol discontinuation in AD

44 AD patients with psychosis or agitation received open haloperidol treatment for 20 weeks

- 22 responders were randomized, double-blind, to continue haloperidol or switch to placebo for 24 weeks
  - 40% relapsed on haloperidol, 80% relapsed on placebo

Antipsychotic Discontinuation in Alzheimer’s Disease: ADAD trial

Identification of target symptoms in AD patients with psychosis or agitation/aggression
• Initial systematic open treatment with risperidone
• Responders at 16 weeks were randomized
• Two clinically relevant time-points (16 and 32 weeks after randomization) for discontinuation
ADAD trial: Key Inclusion/Exclusion criteria

- Age 50-95 years
- Probable AD
- MMSE 5-26 outpatients, 2-26 nursing home patients
- Excluded stroke, TIA, uncontrolled atrial fibrillation
- Presence of either psychosis (NPI ≥ 4 on delusions or hallucinations) or behavioral dyscontrol (NPI ≥ 4 on agitation/aggression)
Phase A open label risperidone treatment

Reduction in NPI core ($t=17.2$, $p < .0001$), target symptoms ($t=22.4$, $p < .0001$)

- Average 0.7 point increase in EPS (Simpson-Angus Scale, $t=2.64$, $p=0.009$), no change in AIMS
- Somatic symptoms improved (TESS, $t=6.1$, $p < .0001$)
- MMSE decreased half a point on average ($t=2.7$, $p=0.007$) and ADAS-cog did not change
Relapse in first 16 weeks after randomization

Last observation carried forward for all subjects except:
(1) Death was counted as relapse;
(2) Patients counted as relapsed if they were at imminent risk of relapse before dropout based on review of records by a psychiatrist independent of the study (n=2 on placebo and n=1 on risperidone)

Time to relapse and risk of relapse favored risperidone over placebo

Relapse rates
60% (24/40) relapsed on placebo, 32.9% (23/70) relapsed on Risperidone (Chisq=7.40, p=0.004)
Relapse in final 16 weeks after randomization

Both time to relapse and risk of relapse favored risperidone over Placebo

Relapse rates
48% (13/27) relapsed on placebo
15% (2/13) relapsed on risperidone
Chisq=4.33, p=0.017
Non-antipsychotic Management of Difficult Behaviors in dementia and chronic severe mental illness
For every patient we should assess...

- Environment
- Patient
- Medical issues
What we really need is an effective...

Behavioral Management Team
“I lift, you grab. ... Was that concept just a little too complex, Carl?”
Approach to Agitation, Psychosis in the elderly

- Medical issues --delirium should be first concern
  - Treatable cause of psychosis
  - Important cause of morbidity, mortality
- Prior psychiatric diagnosis associated with psychosis
  - Depression, Dementia complicated by delusions
- Psychosocial influences
  - Premorbid personality, inappropriate environment
Caregiver Education in the Nursing Home

Intervention

- *Ongoing education is critical...it will have to go beyond the minimal requirements*

Patient Response

- Improved social interactions
- Decreased agitation during care
- Improved function (social)

Caregiver Response

- Improved interactive behaviors
- Change in caregiver burden
BPSD Clusters

‘Aggression’
- Aggressive resistance
- Physical aggression
- Verbal aggression

‘Psychomotor agitation’
- Walking aimlessly
- Pacing
- Trailing
- Restlessness
- Repetitive actions
- Dressing/undressing
- Sleep disturbance

‘Depression’
- Sad
- Tearful
- Hopeless
- Low self esteem
- Anxiety

‘Apathy’
- Withdrawn
- Lack of interest
- Amotivation

‘Psychosis’
- Hallucinations
- Delusions
- Misidentifications

Adapted from McShane R. Int Psychogeriatr 2000
Psychosis/Delusions in Dementia

Delusional thought content (eg, paranoia) is common (studies suggest 34% to 50% incidence)

Common delusions, many of which are written off
- Marital infidelity
- Patients, staff are trying to hurt me
- Staff, family members are impersonators
- People are stealing my things
- My house is not my home
- Strangers living in my home
- Misidentification of people
- People on TV are real

At the heart of all behavioral interventions are simple concepts

- Take the entire context into account
- Simplify Everything, break it down
- Realize that management is often counter-intuitive
- Realize the patient is lost
Nonpharmacologic Management of Behavioral Disturbances

- Distraction
  - Tolerance
  - Speak slowly, low pitched voice
  - 1-step commands

- Exercise
  - Assure adequate lighting
  - Music..the right kind
  - Time orientation
  - Routine
  - Slow pace
Before Intervening…

- Review, treat medical, psychiatric conditions
- Possible causes…**Delirium**!
  - UTI
  - Medications
  - Delirium, dehydration, infection,
  - Pain
  - “simple” adjustment to change

- Identify Target symptoms
- Evaluate context
Interpersonal Interventions

- Repetition
- Redirection
  - Distraction
- Reassurance
  The mindset of most demented patients is to be *lost*.
- Group activities
Environmental Modifications 1

- Provide visual cues
- Reasonable level of stimulation
- Assess Mirrors, TV, overhead paging
- Assure proper lighting
- Locks, alarm systems
Environmental correlates of agitation

- 53 special care units
- 3723 observations of patient behaviors

Factors associated with agitation
  - Low light
  - Low “home likeness”
  - Low cleanliness
  - Low staff treatment quality

Environment is independent of staff, treatment issues

Sloan, 1998
Environmental Modification 2

- Wandering paths
- Visual barriers
  - Doorknobs
  - Window panels in doors
  - Door screens
  - Tape patterns on floors
- Routine activities routinely
Wanderers

- The activity is the treatment
- Need safe wandering space
- Appropriate level of stimulation
  - Adequate staff-patient interactions
  - Reduce extraneous noise

- Environment adjustments to reduce elopements
Intervening with severe disruptive vocalizers

- At 2 months follow-up, 50-66% were better
- Helpful interventions (6 month follow-up):
  - Food, drink, tobacco 11.7%
  - Verbal interaction 11.1%
  - Family visit 8.3%
  - Comfort measures 7.8%
  - Companionship 6.7%

All medications combined accounted for 10.6% helpful interventions

Sloane, 1999
The Daughterectomy

- She’s on a mom induced guilt trip
- She’s after something
- She just can’t slip out..
- Must have the long goodbye
Physical Aggression

- Identify triggers
- Staff feedback
  - In basic ADL’s
- Redirect, reassure
- Control affect
- Staff training
Personal Care Tasks

- Divide tasks into small steps
- Demonstrate the task
- Have patience
- Reassure, provide positive feedback
Summary: Behavioral Interventions

- Identify target behaviors
- Involve patient, caregiver, and environment
- Accommodate
- Be creative
DAMNED if you do
DAMNED if you don't