Dementia: Therapeutic Update

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Outline
- Dementia Overview and Need for Assessment in DD Population
- National Task Group Initiative
- DSQIID Pilot Project at State of Ohio Developmental Centers
- Dementia Treatment

Dementia

According to the DSM-IV-TR (2000), Dementia is characterized by multiple cognitive deficits, that include impairment in memory, and at least one of:
- Aphasia
- Apraxia
- Agnosia
- Disturbance in executive functioning

The Diagnostic Manual-Intellectual Disability (DM-ID, 2007) adds that Dementia involves:
- a clinically significant deficit in cognition that represents a significant change from a previous level of functioning. (emphasis added)

Dementias are a subset of a larger group of Neurodegenerative Diseases (ND), which also include Huntington’s Disease, Multiple Sclerosis, and motor neuron disorders.
- Multiple etiologies
- Variety of clinical manifestations
- Can be reversible depending on underlying pathology and course

Consider three individuals, all age 25, all with an IQ of 50, and accompanying social and adaptive dysfunction:
- Patient A: Has Down Syndrome
- Patient B: Had head injury at age 10
- Patient C: Had head injury at age 19
What is each person’s primary neuropsychiatric diagnosis?
Dementia
- Consider three individuals, all age 25, all with an IQ of 50, and accompanying social and adaptive dysfunction:
  - Patient A: Intellectual disability
  - Patient B: Intellectual disability
  - Patient C: Dementia

Dementia vs. Amentia
- This illustrates the conceptual distinction between these two forms of permanent cognitive disorders:
  - Early onset = Intellectual Disability = A-mentia
  - Later onset = De-mentia

Dementia vs. Amentia
- The differences between Amentia (ID) and Dementia are:
  - Age of onset
  - The fact that in ID, all subsequent development has taken place after the etiological incident or activity

Epidemiology of Dementia in Individuals with Intellectual Disability
- In persons with DS, prevalence of dementia doubles every 5 years between 45-60 (N=506)
  - Up to age 49: 8.9%
  - Age 50-54: 17.7%
  - Age 54-59: 32%
  - Above age 60: 25.6%
    - (lower % thought to be due to increased mortality in DS patients with dementia)
    - Coppus, et al., 2006

Epidemiology of Dementia in Individuals with Intellectual Disability
- 11.4% of 105 adults with ID > 65 (Patel et al. 1993)
- 21.6% of 134 adults with ID > 65 (Cooper 1997)
- 2.7% of adults in NY with ID (w/o DS) > 65 (Zigman et al 2004)
- 18.3% of 284 adults with ID (w/o DS) > 65 (Strydom et al. 2009)
- 16.8% of 506 adults with ID and DS > 45 (Coppus et al. 2006)

Pathophysiology of Dementia in Individuals with Intellectual Disability
- Hallmarks of AD pathology in DS:
  - Amyloid plaques (extracellular)
  - Neurofibrillary tangles (intracellular)
- Deposition of beta amyloid appears related to over-expression of the amyloid precursor protein (APP) gene, on the long arm of chromosome 21.
Pathophysiology of Dementia in Individuals with Intellectual Disability
- Oxidative stress (OS) (imbalance between production and removal of reactive oxygen species) is thought to be the bridge between DS and AD
- OS is thought to precede development of pathology of AD; amyloid deposition appears to be compensatory cellular response

Phenomenology of Dementia in Individuals with Intellectual Disability
- Symptoms in early stage AD in DS:
  - Forgetfulness
  - Confusion
  - Slowness in activity and speech
  - Difficulty with multi-stage direction
  - Sleep disturbance
  - Loss of skills, needs more prompts
  - Social withdrawal
  - Balance problems
  - New emotional/behavioral problems
  - Visual hallucinations
  - “Covering up” memory dysfunction
  - Personality change
  - (Dab et al., 2007a)

Pathology of Dementia in Individuals with Intellectual Disability
- Risk factors for developing AD in DS:
  - Increasing age
  - Lower pre-morbid level of function
  - Menopause, particularly early-onset
  - Higher frequency of APOE e4 allele

Need for Assessment
- Increased longevity of individuals with developmental disabilities (DD)
  - 173,000 over age 60 in 1995; to 332,900 by year 2025 (AAMR-IASSD Work-group, 1995)
- Dementia in ID
  - ID may hasten onset of Dementia by up to 15 years (Cooper & Holland, 2007)
  - Down’s Syndrome: earlier onset (brain changes at age 40; Mann, 1988) and higher rate of occurrence (about 55% ages 60-69; Prasher, 1995)
  - Alzheimer’s Type is 3 times more likely (Strydom et al., 2007)

Screening Instruments
- Neuropsychological assessments
  - Mini-Mental State Exam (MMSE)
    - Normed for general population
    - Existing cognitive deficits not considered
  - Down Syndrome Mental Status Exam
    - Floor effect for severe to profound ID (Tyrell et al., 1996)
  - Test for Severe Impairment
    - Designed for MMSE scores < 10 out of 30
    - 1/3 of questions require verbal response

Difficulty in Dementia diagnosis with Intellectual Disability (ID)
- Cloak of competence
- Acquiescence bias
- Diagnostic overshadowing
- Baseline exaggeration
- Intellectual distortion
- Lack of reliable and standardized criteria and diagnostic procedures
- Importance of early recognition/diagnosis
- About ½ that meet criteria go undiagnosed (Strydom et al., 2007)
Screening Instruments

- Observer-rated assessments more useful (Deb & Braganza, 2001)
  - Dementia Scale for Down’s Syndrome (DSDS; Gedye, 1995)
  - 60 items
  - Variable screening cut-off
  - Dementia Questionnaire for Persons with Mental Retardation (DMR; Evenhuis, 1992)
  - 50 items
  - Cut-off score varies by level of ID
  - No criteria for Profound ID established

Dementia Screening Questionnaire for Individuals with Intellectual Disabilities (DSQIID)

- Deb et al., 2007b
- Two-stage methodology
  - 1) Focus group/qualitative interviews
  - 2) Field testing and statistical analysis
- Valid and reliable
- Four-factor analysis
  - Memory/Confusion, feelings of insecurity, sleep problems, behavior problems

DSQIID

- Observer-rated questionnaire
  - Carer with knowledge of individual
  - Follow-up with same carer recommended by Deb
- Three parts
  - 1) Level of best ability
  - 2) 43 multiple-option questions on symptoms/behavior associated with Dementia
  - 3) 10 comparative questions
### DSQIID Scoring

- **Assesses change in cognitive function**
  - Multiple-option questions
    - “Always been the case” = 0
    - “Always, but worse” = 1
    - “New symptom” = 1
    - “Does not apply” = 0
  - Comparative questions
    - “Yes” = 1
    - “No” = 0

- **Deb et al., 2007b**
  - Recommended cut-off score of 20
  - 31 times more likely to have positive diagnosis of Dementia
  - Different cut-off for severe/profound ID?
  - Refer for further assessment

- **Follow-up**
  - Changes assessed from prior to onset of cognitive decline, not prior assessment
  - Serial use over time recommended
  - Scoring manual by DSQIID authors pending
DSQIID Pros/Cons

- **Pros**
  - Easy to administer and score (10-15 minutes)
  - Cut-off score constant, not variable
  - Helps staff to recognize signs and symptoms of Dementia

- **Cons**
  - False positives (e.g., psychosis, medical issues)
  - Symptoms manifested differently in early stages across levels of MR, DS
  - Different cut-off for severe-profound MR?

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What is the Value of Early identification?

- An early diagnosis may **slow the progression** of symptoms; early treatment can help maintain a person’s current level of functioning.
- An early and accurate diagnosis can also help to **identify reversible conditions** that may mimic dementia such as depression, medication side effects, substance abuse, vitamin deficiencies, dehydration, bladder infections or thyroid problems.
- An initial assessment can avoid the trauma of a diagnosis of dementia where it does not exist. It also prevents unnecessary and possibly harmful treatment resulting from misdiagnosis

Variety of Early Indicators

- Reduced work performance
- Difficulties with recent memory and new learning
- Changes in communication skills including impoverishment in language use compared with baseline
- Emotional lability, heightened irritability, apathy, “coarsened” social behavior

Pre-clinical signs of dementia

Neuropathological changes are likely to precede clinical signs of probable Alzheimer’s dementia by more than a decade

- If dementia can be identified earlier, there is the potential to proactively address signs and symptoms.
- Interventions, services or supports may be more effective if offered prior to significant cognitive and/or functional change.
- Greater opportunity to impact quality of life and quality of care

Benefits of Early Identification of Change

- Identifying the cause of decline can lead to proper, targeted care and affords a greater chance of benefiting from existing treatments
- Early diagnosis can help ease the anxiety that may accompany unexplainable changes in behavior
- Educating persons with dementia and their caregivers gives them time for advanced care planning
- The quality of life for both the person with dementia and the family can be maximized
- Earlier treatment may delay the progression of symptoms
What complicates early recognition of dementia?

- Dearth of standardized assessments for persons with IDD that confirm/disconfirm significant changes in cognition and adaptive functioning
- Debate about what constitutes significant change among persons with pre-existing memory and other cognitive impairments
- Diagnostic overshadowing...everything is attributed to IDD

I/DD may complicate early recognition

- Pre-existing cognitive impairment, behavioral disorders and poor emotional control may complicate recognizing the early signs of dementia
- Early cognitive and functional changes may be subtle or intermittent
- Pre-existing level of intellectual ability, sensory impairment, and health status may all impact upon cognitive and functional status

A few words about diagnosis...

- Proceed with caution
- Probable AD
- What about other types of dementia?
- May take time to confirm/disconfirm a diagnosis
- What is the value of a diagnosis in terms of services, treatment and supports
- MCI and the progression to dementia

A First Pass Screen

- The information collected from the NTG-EDSD can be shared with the consumer’s primary care physician and then a determination of need for further testing or a referral to a specialist can be made at that time.

Need for an administrative tool

- Clinicians report that individuals are not brought to attention until well advanced in the dementing process
- Need for an administrative tool that will help link individuals who exhibit change to relevant health care options
- Cognitive and functional status are not usually included in annual health screenings
- For those eligible, the NTG-EDSD could be used as part of the Annual Wellness Visit

Rationale for development of the NTG-EDSD

- Need to equip family and professional caregivers with a tool to capture information about changes in cognition and function
- Provide caregivers with a format to share important information with the consumer’s health care practitioner
- Tool trains caregivers to be better observers and reporters of relevant signs and symptoms of change
Piloting the NTG-EDSD

- Tool based on the DSQIID (Deb, 2007)
- Unlike the original instrument, the NTG does not purport that the NTG-EDSD should be used for the purpose of diagnosis or assessment
- Items from the Longitudinal Health Inventory have been added to provide information about chronic health conditions
- The NTG-EDSD can be downloaded from the AADMD website

On-line resources for screening


NTG-EDSD

- Early Detection Screen for Dementia
  - an instrument adapted from the Dementia Screening Questionnaire for Individuals with Intellectual Disabilities (Deb et al., 2007) and the Dementia Screening Tool (adapted by Philadelphia Coordinated Health Care Group from the DSQIID, 2010)
  - Down Syndrome begin age 40 then annually, non-DS begin when changes are noted
  - Piloted in 8 sites during the Fall of 2012

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Disclaimer Slide

- Approval for this project was obtained by the following:
  - Youngstown Developmental Center (YDC) Superintendent, Cindy Renner
  - Youngstown Developmental Center (YDC) Human Right Committee
  - Warrensville Developmental Center (WDC) Superintendent, Wendy DiGregorio

Youngstown Developmental Center (YDC)

- State of Ohio residential facility (ICF/MR) for individuals with DD
- Located in Mineral Ridge, OH (NE)
- September 2013 census = 96
- Level of ID
  - Mild: 7%
  - Moderate: 19%
  - Severe: 19%
  - Profound: 55%
YDC
- 83 of 96 residents (86%) have formal behavior support plan
- Individuals with Down’s Syndrome = 5

WDC
- 82 of 94 residents (87%) have formal behavior support plan
- Individuals with Down’s Syndrome = 2

Warrensville Developmental Center (WDC)
- State of Ohio residential facility (ICF/MR) for individuals with DD
- Located in Highland Hills, OH (NE)
- September 2013 census = 94
- Level of ID
  - Mild: 13%
  - Moderate: 42%
  - Severe: 18%
  - Profound: 27%

Resident Screenings
- YDC
  - No standardized assessment of Dementia in place prior to 2009
  - Total DSQIIDs administered: N=114
- WDC
  - No standardized assessment of Dementia in place prior to 2013
  - 4 Dementia diagnoses at screening
  - Total DSQIIDs administered: N=39
- Initial DSQIID screening to all residents age 50 and older (DS 40+)
- Additional assessment of younger individuals thought to have deteriorating cognitive skills

Initial Screening Results
- YDC Initial DSQIID administration: N=68
  - Scores ≥ 20 | N=5
    - Suspicion of Dementia | N=9
    - Formal Dementia diagnosis | N=4
- WDC Initial DSQIID administration: N=36
  - Scores ≥ 20 | N=1
    - Suspicion of Dementia | N=6
    - Formal Dementia diagnosis | N=4
Follow-up Protocol

- Individuals with scores ≥ 20 (or major increase in score upon follow-up) referred for further psychiatric/neurological evaluation
  - Differential diagnosis
  - Treatment implications
    - Medications
    - Behavioral interventions
    - Environmental modifications

- DSQIID currently offers no formal guidance for follow-up evaluation

- Recommendations from one of DSQIID developers (Dr. Deb)
  - Follow up with same professional/caregiver
  - Compare behavior/skills with prior functioning level (e.g., prior to onset of cognitive deficits), not previous assessment
  - Scoring manual/guidelines???

Follow-up Protocol

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<tr>
<th>Score</th>
<th>Follow-up</th>
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<tr>
<td>0</td>
<td>5 years</td>
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<tr>
<td>1 to 4</td>
<td>3 years</td>
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<td>5 to 11</td>
<td>1 year</td>
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<tr>
<td>12 to 19</td>
<td>6 months</td>
</tr>
<tr>
<td>20+</td>
<td>3 months</td>
</tr>
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</table>

*Or as needed based on clinical status

Follow-up Results

- DSQIID rescreens administered: N=49
- Individuals reassessed N=26
- Individuals scoring ≥ 20 N=7

- DSQIID "false positives"
  - 78 y.o. male with Bipolar Disorder
  - 47 y.o. male with Bipolar Disorder
  - 55 y.o. male with Severe OCD/drug side-effects
  - 56 y.o. male with Autism/OCD

- DSQIID not developed as a diagnostic tool or to follow progression of illness
- Same score ≠ same presentation
- Inter-rater reliability check
- Insight for caregivers, professionals, etc.
Dementia and ID: Diagnostic and Therapeutic Update

“Incidence of dementia in older people with intellectual disabilities are up to five times higher than older adults in the general population. Screening may be useful in this population given the high incident rates, particularly as more effective treatments become available.”

(Strydom et al., Incidence of dementia in older adults with intellectual disabilities, Research in Developmental Disabilities, 2013)

Dementia and ID: Diagnostic and Therapeutic Update

Theoretical Approaches:
- Accumulation of beta amyloid
- Hypo-cholinergic hypothesis
- Neuro-inflammation
- Calcium hypothesis
- Insulin resistance
- Peroxidation of lipids

Dementia and ID: Diagnostic and Therapeutic Update

Outline
- Theoretical approaches to treatment
- Prevention of dementia
- Treatments are both pharm and non-pharm
- Importance of early identification in treatment
- Treatment of dementia in neurotypical persons
- Treatment of dementia in persons with ID and DS
- Dementia treatments in non-demented persons with ID
- Treatment of dementia in persons with ID w/o DS
- Treatment of associated symptoms of dementia in persons with ID
- The future

Dementia and ID: Diagnostic and Therapeutic Update

Prevention:
- Can certain lifestyles or behaviors contribute to longevity and brain health?
- Certain regions in the world (blue zones) are associated with clusters of centenarians:
  - Sardinia Italy
  - Loma Linda California
  - Okinawa Japan
- What do they have in common? Inhabitants who:
  - Are physically active
  - Are socially engaged
  - Eat a diet high in Omega 3 Fatty Acids

Dementia and ID: Diagnostic and Therapeutic Update

Prevention Strategies:
- Exercise
- Mental Stimulation
- Diet
- Stress reduction
- Other

Living longer
Prevention Strategies:

Exercise
- Has the most evidence of efficacy
- Walking as little as 15 minutes per day reduces AD risk
- Routine exercise further reduces risk, and is associated with decreased AD biomarkers

Diet
- Obesity increases risk of AD
- Weight reduction decreases risk (bariatric surgery improves cognition)
- Mediterranean diets (high in Omega-3 FA) improve memory, and reduce risk for MCI.
- Fruits and vegetables (antioxidants) improve cognition
- Refined sugars and trans-fats impair cognition
- Moderate alcohol is good for brain health (may be effect of stress-reduction, or Resveratrol in red wine)

Stress reduction
- Stress is a known contributor to cognitive impairment
- Chronic stress increases risk for AD
- Stress hormones (glucocorticoids) impair neuronal plasticity and cause dendritic atrophy
- Meditation affects biomarkers of inflammation and telomerase activity

Others
- Avoid head trauma
- Avoid smoking
- Have a positive outlook
- Treat age-related disease vigorously (particularly in women)
- Obesity
- Hypertension
- Hypercholesterolemia
- Diabetes
- Atrial fibrillation
- Depression
- Get sufficient sleep

Treatment of AD in persons without ID
- FDA-approved for mild-moderate AD
  - Cognex® (tacrine), first approved Acetylcholine-esterase inhibitor
  - Aricept® (donepezil) 1996
  - Exelon® (rivastigmine) 1997; 2007
  - Razadyne® Reminyl (galantamine) 2001
- FDA-approved for moderate-severe AD
  - Aricept® (donepezil)
  - Namenda® (memantine), an N-methyl D-aspartate (NMDA) antagonist: (blocks toxic effects of excess glutamate) 2003
- (Can be given together)

NIH National Institute on Aging, Published July 2010; updated
Dementia and ID: Diagnostic and Therapeutic Update

**Pharmacological Treatment in Persons with DS and AD**

**Donepezil (Aricept)** 10 mg/day in DB PC, parallel group design, in 27 patients with DS and mild-mod AD

- Non-statistically significant reduction in primary outcome measure (Dementia Scale for MR), and secondary measures (SIB and ABS), relative to placebo
- 50% of donepezil patients had improved mean DMR scores, c/t 31% with placebo
- No life threatening AE
- SE of diarrhea, insomnia, fatigue and nausea
  - Sample size too small

**Dementia and ID: Diagnostic and Therapeutic Update**

**Pharmacological Treatment in Persons with DS and AD**

**Donepezil (Aricept)** 10 mg/day in DB PC, parallel group design, in 27 patients with DS and AD

- This group continued in open label treatment for 2 years. The treatment group showed significant reduction in deterioration of cognitive functions and adaptive behavior
  - (Prasher, Adams & Holder. Int J Ger Psych, 2005)

**Dementia and ID: Diagnostic and Therapeutic Update**

**Pharmacological Treatment in Persons with DS and AD**

**Rivastigmine** in 17 patients with DS and AD to 13 on placebo.

- Both groups deteriorated over 24 weeks
- Rate of decline less rivastigmine group


**Dementia and ID: Diagnostic and Therapeutic Update**

**Pharmacological Treatment in Persons with DS and AD**

**Two year** randomized DB PC trial of antioxidant supplementation (900 IU alpha-tocopherol, 200 mg ascorbic acid, 600 mg alpha-lipoic acid) in 53 DS and AD

- No improvement in cognitive function, nor stabilization of cognitive decline on any outcome measure, c/t placebo
- No serious AE
  - (Lott et al., Am J Med Genet 2011)

**Dementia and ID: Diagnostic and Therapeutic Update**

**Pharmacological Treatment in Persons with DS w/o AD**

- Rivistigmine transdermal patches in treatment of dementia in AD in adults with DS—pilot study

  - (Prasher et al., Int J Ger Psych 2013)
Dementia and ID: Diagnostic and Therapeutic Update

Pharmacological Treatment in Persons with DS w/o AD

Similar study in younger patients:

DBPC study of 129 DS adolescents age 10-17:

Donepezil “failed to demonstrate benefit vs. placebo” over 10 weeks

(Kishnani et al., Am J Med Genet C: Semin Med Genet)

Dementia and ID: Diagnostic and Therapeutic Update

Pharmacological Rx in Persons with ID and DS (w/o diagnosed AD)

DBPC study: 21 DS adult women with severe cognitive impairment were given donepezil 3 mg per day, or placebo for 24 weeks. Those taking donepezil did better than those on placebo on the International Classification of Functioning, Disability, and Health scaling system. ICF scores improved, and w/o AE

(Kondoh et al., Int J Psych Med)

References:

Boada et al., Translational Psych 2012
Kishnani et al., Am J Med Genet 2009
Kishnani et al., Am J Med Genet 2010
Kondoh et al., Int J Psych Med 2011
Lott et al., Am J Med Genet 2011
Prasher et al., Int J Ger Psych 2013
Prasher, Fung, & Adams. Int J Ger Psych, 2005
Prasher, Huxley, & Haque. Int J Ger Psych; 2002
Small GW: Brain health and Alzheimer’s prevention. Lecture 11; APA Annual Meeting, May 2013
Strydom et al., Incidence of dementia in older adults with intellectual disabilities. Research in...
Dementia and ID:
Diagnostic and Therapeutic Update

- Review: Alzheimer’s Medications May Not Benefit Patients With MCI.

  MedPage Today (9/17, Boyles) reports that four medications often prescribed for Alzheimer’s “failed to improve cognition or function in patients with mild cognitive impairment (MCI) and were even associated with harms— including diarrhea, nausea and vomiting, according to a review published Sept. 16 in CMAJ. Included in the review were “eight randomized trials that compared donepezil (Aricept), galantamine (Razadyne), rivastigmine (Exelon), or memantine (Namenda) with placebo.” Notably, there were “no significant improvements in cognition were seen with the cognitive enhancing drug, as measured by the Mini-Mental State Examination (three trials of donepezil, mean difference (MD) 0.14, 95% CI: -0.22 to 0.50) and the Alzheimer’s Disease Assessment Scale cognition subscale (three trials, standardized MD -0.07, 95% CI -0.16 0.01), and use of these medications appeared to have no long-term affect on how people functioned.”

Discussion

- Questions/Comments?
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