Dementia – New Aspects & Treatments

Sevil Yasar, MD, PhD
Johns Hopkins School of Medicine
Division of Geriatric Medicine & Gerontology
2/2/2019
Disclosure

• Nothing to disclose
Objectives

• Imaging in AD – new imaging tools.
• Pharmacological treatments for AD – symptomatic and disease modifying medications.
• Prevention strategies.
Imaging of AD – New imaging tools
Neuroimaging

• Structural imaging (AAN guidelines recommends imaging as part of evaluation)
  – CT
  – MRI

• Functional imaging
  – PET-FDG: evaluates subtle metabolic changes; AD: sensitivity 92%, specificity 63%; only used for questionable cases. → Reimbursed by Medicare to differentiate between MCI vs. AD, AD vs. FTD
New neuroimaging technologies

• Amyloid imaging
  – Pittsburgh compound-B (PiB-C11): Patients with AD demonstrate high concentrations of PiB when compared to normal controls. → Very short half-life 20 min thus mainly used for research.
  – Florbetapir-F18: Approved by FDA for clinical use (2011). → Sensitivity for the detection of moderate to high β-amyloid neuritic plaques was 92%, specificity was 95%. → Half-life 110 min.
  – Use only after extensive clinical evaluation!
    • Appropriate use: Atypical presentation, early onset (< 65y).
    • Inappropriate use: Typical presentation; onset > 65y, asymptomatic; for determining severity; for legal purposes.
– Currently not covered by Medicare, however it sponsored a study (IDEAS) across US in 18,000 people to explore possible benefit of covering Aβ imaging.

• Aim 1 was to see the impact on management → preliminary data: there was 31% change in medical therapy, 37% change in patient management.

• Aim 2 was to see the impact on ED visits → preliminary data: 18% reduction in ED visits and 11% reduction in hospitalizations.

(Data presented at AAIC 2017, London)
Pharmacological treatments for AD
Pharmacological treatment - Symptomatic medications

- Symptomatic medications:
  - Cognitive Symptoms (cholinergic and glutaminergic system) → currently 5 approved by FDA.
Current Medication - Recommendations

• American Academy of Neurology (2003):
  – Cholinesterase inhibitors should be **considered** in patients with mild to moderate AD, although studies suggest a small average degree of benefit.

• American College of Physicians, American Academy of Family Physicians (2008):
  – Clinicians should base the **decision** to initiate a trial of therapy with a cholinesterase inhibitor or memantine on individualized assessment. *(Grade: weak recommendation, moderate-quality evidence.)*
  – The decision to initiate therapy should be based on evaluation of benefits and risks associated with an individual patient.
Current – Symptomatic medications

– All AchE-I (donepezil, rivastigmine, galantamine) have shown greater efficacy than placebo in separate, randomized, double-blind, placebo controlled clinical trials, but no clinical trials which directly compare these drugs.

– 1 observational study, to evaluate cognitive function over 6 months period, who were treated or not treated with AchE-I:
  • N = 147 (40 donepezil, 30 rivastigmine, 32 galantamine, 45 nothing), selected from a memory clinic between 1991-1996.
  • Results: Treatment with any of the AchE-I significantly delayed global cognitive decline for at least 6 months, there was NO difference between the different groups.

How effective are these drugs - Cognition?

<table>
<thead>
<tr>
<th>Study</th>
<th>Cholinesterase inhibitor</th>
<th>ChEIs responders</th>
<th>Placebos responders</th>
<th>Total subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rogers,11 1998a</td>
<td>Donepezil</td>
<td>107/305</td>
<td>27/150</td>
<td>455</td>
</tr>
<tr>
<td>Rogers,10 1998b</td>
<td>Donepezil</td>
<td>76/298</td>
<td>17/152</td>
<td>450</td>
</tr>
<tr>
<td>Burns,12 1999</td>
<td>Donepezil</td>
<td>125/544</td>
<td>38/274</td>
<td>818</td>
</tr>
<tr>
<td>Rösler,18 1999</td>
<td>Rivastigmine</td>
<td>149/467</td>
<td>44/220</td>
<td>687</td>
</tr>
<tr>
<td>Raskind,20 2000</td>
<td>Galantamine</td>
<td>64/357</td>
<td>27/196</td>
<td>553</td>
</tr>
<tr>
<td>Wilcock,21 2000</td>
<td>Galantamine</td>
<td>84/414</td>
<td>33/203</td>
<td>617</td>
</tr>
<tr>
<td>Rockwood,24 2001</td>
<td>Galantamine</td>
<td>61/240</td>
<td>24/123</td>
<td>363</td>
</tr>
<tr>
<td>Wilkinson,23 2001</td>
<td>Galantamine</td>
<td>59/179</td>
<td>23/83</td>
<td>262</td>
</tr>
</tbody>
</table>

Responders Donepezil 22-35% vs. Placebo 11-18%
Responders Rivastigmine 30% vs. Placebo 20%
Responders Galantamine 25-33% vs. Placebo 16-28%

How effective are these drugs - Function?

Comments

• Problems with these studies:
  – All funded by drug companies.
  – Small and short (no information on: institutionalizations, death).
  – How do these numbers translate into daily life.
  – Pharmacogenetics – “responders” (10-20%) vs “non-responders” (80-90%).
  – How long are they effective if effective?

• Growing literature about long term effect (3 large epidemiological studies):
  – Increased risk bradycardia, pacemaker placement.
  – Increased risk falls, hip fracture.
More questions in clinic?

• Which should I use first?
• Which should I use when the first one fails?
• How long should I try?
• How long are these medications effective?
• Can I give combination of these medications?
• When should I stop?
• Should I taper?
Pharmacological treatment – Disease modifying medications

• Disease-Modifying Medications:
  – Currently none available !!!
Pharmacological treatment – Disease modifying medications

• Focus on AD...as we know it

Photo from sage.buckinstitute.org, credit Dr. Dale Bredeson
Amyloid cascade (simplified)

Pharmacological treatment – Disease modifying medications

• Disease-Modifying Medications:
  – Aβ
    • Inhibit production.
    • Inhibit aggregation.
    • Active and passive vaccinations against amyloid β (Aβ) vaccines.
    • Inhibit neurotoxicity.
Disease modifying medications – Inhibiting production

• BACE inhibitor (inhibits beta secretase): Verubecestat

• Phase III trial N=1958 patients with mild/moderate AD randomized to placebo, 12mg and 40 mg for 78 weeks.

Egan et al; NEJM 378, 2018
Cognition

Figure 2. Mean Change from Baseline in the ADAS-cog and ADCS-ADL Scores over 78 Weeks (Part 1 of the Trial).

Egan et al; NEJM 378, 2018

Function
Figure 2. Mean Change from Baseline in the ADAS-cog and ADCS-ADL Scores over 78 Weeks (Part 1 of the Trial).
Disease modifying medications – Inhibiting production

• Semagacestat: γ secretase inhibitor
• Phase III trial: N=1537 patients randomized to placebo, 100mg or 140mg
• Early termination after 76 weeks:
  – No difference in cognition.
  – High dose had greater functional decline.
  – Adverse events: weight loss, skin cancer, infections.
Disease modifying medications – Inhibiting production

- Semagacestat: γ secretase inhibitor
- Phase III trial: N=1537 patients randomized to placebo, 100mg or 140mg
- Early termination after 76 weeks:
  - No difference in cognition.
  - High dose had greater functional decline.
  - Adverse events: weight loss, skin cancer, infections.
Disease modifying medications – Inhibiting aggregation

• Tramiprosate: Binds soluble Aβ, inhibits neurotoxic aggregates.

• Phase III trial: N=1052 patients randomized to placebo, 100mg or 150mg twice daily.

• After 78 weeks:
  – No significant effect on cognition or clinical dementia rating.
  – Less hippocampal volume loss.
Pharmacological treatment – Inhibiting aggregation

• Tramiprosate: Binds soluble Aβ, inhibits neurotoxic aggregates.

• Phase III trial: N=1052 patients randomized to placebo, 100mg or 150mg twice daily.

• After 78 weeks:
  – No significant effect on cognition or clinical dementia rating.
  – Less hippocampal volume loss.
Disease modifying treatment – Monoclonal antibody

- Recent clinical trials (iv monoclonal antibodies against amyloid):
  - **Bapineuzumab** (Pfizer):
    - N=2204 (N=1090 were ApoE4 allele carriers, N=1114 non-carriers), primary outcome ADAScog and DAD.
    - iv administration of monoclonal antibodies against Aβ.
    - Phase III trial, **mild-to-moderate AD**, > 18 months → CSF showed increased Aβ, imaging studies showed decreased Aβ load in brain → but no effect on progression of AD (Phase III trial, 2012).

Salloway et al; NEJM, 2014
Figure 1. Primary Outcome.
Panel A shows the estimated mean change from baseline to week 78 in scores on the 11-item cognitive subscale of the Alzheimer’s Disease Assessment Scale (ADAS-cog11, with scores ranging from 0 to 70 and higher scores indicating greater impairment), and Panel B the estimated mean change from baseline to week 78 in the Disability Assessment for Dementia (DAD, with scores ranging from 0 to 180 and higher scores indicating less impairment) among APOE e4 carriers and noncarriers, according to study regimen. The P values that are shown are unadjusted. Bapi denotes bapineuzumab.
Figure 1. Primary Outcome.

Panel A shows the estimated mean change from baseline to week 78 in scores on the 11-item cognitive subscale of the Alzheimer’s Disease Assessment Scale (ADAS-cog11, with scores ranging from 0 to 70 and higher scores indicating greater impairment), and Panel B the estimated mean change from baseline to week 78 in the Disability Assessment for Dementia (DAD, with scores ranging from 0 to 100 and higher scores indicating less impairment) among APOE e4 carriers and noncarriers, according to study regimen. The P values that are shown are unadjusted. Bapi denotes bapineuzumab.
Disease modifying treatment – 
Monoclonal antibody
– Solanezumab (Elli Lilly) (2 separate RCT):
  • EXPEDITION1 N=1012 & EXPEDITION2 N=1040, primary outcome ADAScog and ADCS-ADL
  • iv administration of monoclonal antibodies against Aβ.
  • Phase III trial, mild-to-moderate-to-severe AD, >18 months.

Doody et al; NEJM, 2014
Mild and Moderate AD

Cognition

Function

Mild AD

Doody et al; NEJM, 2014
Disease modifying treatment – Monoclonal antibody

– Solanezumab (Elli Lilly):
  • EXPEDITION3 N=2129, primary outcome ADAScog and ADCS-ADL
  • iv administration of monoclonal antibodies against Aβ.
  • Phase III trial, mild-to-moderate-to-severe AD, >18 months.

Honig et al; NEJM, 2018
Disease modifying treatment – Monoclonal antibody

– **Gantenerumab (Roche):**
  - Press release: December 2014 – the phase III trial for pre-clinical was discontinued.
  - However, there is a phase III trial for mild-to-moderate AD in progress.

– **Aducanumab (Biogen):**
  - Presented first results of Phase I trial (N=166) in 2015 → showed decrease in amyloid AND slowing of cognitive decline in participants with MCI or mild AD.
  - Moved directly to phase III trial.
.. amyloid reduction

...stable cognitive function.
.. amyloid reduction

...stable cognitive function.

BAN 2401 (Biogen and Esai)

- Presented results at Alzheimer’s Association meeting (AAIC – Chicago, 2018)
- Phase II trial.
- 20-30% less decline in cognition.
  
  (no publication)
Thoughts

• RCT failure – why:
  – Too late?
  – Poor diagnosis?
  – Wrong target or drug?

• Testing amyloid cascade hypothesis – removing amyloid:
  – So far failed.....why?
Dementia ≠ AD ≠ Amyloid

The 90+ Study (pathology)

Prevalence of Amyloid Positivity on PET According to Age for the Different Dementia Diagnostic Groups

Kawas et al; Neurology, 2015

Ossenkoppelle et al; JAMA, 2015
Vascular disregulation in AD
(Itturia-Madina, Nature, 2016)
Tau vs. amyloid

- Tau: microtubule associated protein found in neurons (axons).
- Longitudinal study of 107 cognitively normal older adults with CSF studies at baseline showed that $\text{A}\beta$ effects on cognition and clinical dementia rating were only significant in the presence of elevated phosphorylated tau.
Disease modifying medications – Tau aggregation inhibitor

(LMTM = Leuco-methylthioninium bis(hydromethanesulfonate))

- Phase III trial in 891 patients with mild to moderate AD.
- 2 doses (oral twice daily) or control for 15 months
- Primary analysis did not show differences in cognitive or functional decline when used as add-on therapy to other dementia medication.
- Unclear why there may have been benefit as monotherapy.
- Trial in mild AD results coming.

Gauthier et al, Lancet, 2016
Disease modifying medications –
Tau aggregation inhibitor

(LMTM = Leuco-methylthioninium bis(hydromethanesulfonate)

- Phase III trial in 891 patients with mild to moderate AD.
- 2 doses (oral twice daily) or control for 15 months
- Primary analysis did not show differences in cognitive or functional decline when used as add-on therapy
- Unclear why there may have been benefit as monotherapy
- Trial in mild AD results coming:

Gauthier et al, Lancet, 2016
Disease modifying treatment – Intranasal insulin

- Intranasal Insulin:
  - Insulin processing is altered in brain cells of people with AD and is associated with increased Aβ formation → replacing insulin could decrease Aβ formation.
  - Phase II trial N=40 with mild-to-moderate AD (N=40) and MCI (N=64) → N=30 placebo, N=34 20IU and N=38 40IU intranasal insulin > 4m.
  - Primary outcome was memory and secondary outcome was functional status.
  - A subset of participants underwent lumbar puncture (N=23) and PET (N=40) before and after treatment.

Craft et al, Arch Neurol, 2012
Disease modifying treatment – Intranasal insulin

**eTable 2. Mean baseline and month 4 CSF Aβ42, tau, and tau/Aβ42 ratios with (standard errors) for placebo and combined insulin-treated groups.**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=8)</th>
<th>Insulin (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aβ42 (pg/ml)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>257.85 (35.17)</td>
<td>184.72 (25.65)</td>
</tr>
<tr>
<td>Month 4</td>
<td>247.13 (34.13)</td>
<td>175.03 (24.89)</td>
</tr>
<tr>
<td><strong>tau</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>152.45 (32.58)</td>
<td>133.41 (23.76)</td>
</tr>
<tr>
<td>Month 4</td>
<td>154.61 (31.40)</td>
<td>131.21 (22.90)</td>
</tr>
<tr>
<td><strong>tau/Aβ42 ratio</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.81 (.21)</td>
<td>0.83 (.16)</td>
</tr>
<tr>
<td>Month 4</td>
<td>0.81 (.22)</td>
<td>0.87 (.16)</td>
</tr>
</tbody>
</table>

Craft et al, Arch Neurol, 2012
Beyond tau and/or amyloid

Prevention Strategies
**Lifetime approach**: lifetime exposure to
- Diseases
- Lifestyle
- **35% of dementia risk is modifiable!!!**
Multi-target approach

RISK FACTORS
- Alcohol misuse
- Hypertension
- Dyslipidemia
- Obesity
- Unhealthy diet
- Smoking
- Diabetes
- Vascular insults
- Neuronal damage

APOE, Other genes

PROTECTIVE FACTORS
- Physical activity
- Education
- Cognitive and social activity
- Brain reserve

Transition
- Adult life
- Mid-life
- Late-life

DEMENTIA

Courtesy of Alzheimer’s Research and Prevention Foundation
www.alzheimersprevention.org
Diet

- Mediterranean Diet (MeDi)
  - Rich in fish, vegetables, fruits, cereals, unsaturated fatty acids – beneficial effect through decreasing cardiovascular risk factors – PREDIMED trial of ~7400 with participants high cardiovascular risk for stroke, heart attack assigned to 3 arms:
    - MeDi enriched with virgin oil 1L/week (1 gallon/month!)
    - MeDi enriched with nuts >3 servings/week (walnuts, almonds, hazelnut)
    - Low fat diet and education (control arm)
Cont’d

– Study had to be stopped earlier because the 2 MeDi arms did much better in reducing death, stroke, heart attack (Estruch et al., NEJM, 2013).

– Sub-study of 334 participants aged ~61 years who had cognitive tests at baseline and after ~4 year follow-up (Valls-Pedret et al., JAMA Int Med, 2015):
Figure 2. Changes in Cognitive Function Measured With Composites by Intervention Group

Valls-Pedret et al., JAMA Int Med, 2015
Multi-target approach

• **FINGER trial**
  – Double-blind RCT of people with high cardiovascular risk factors undergoing general health education (N=591) or multimodal intervention (N=631) over 2-year period.
  – Multimodal intervention:
    • diet 3 individual and 9 group session;
    • exercise (1-3 per week muscle strength and 2-5 aerobic exercise);
    • cognitive training (10 group session, individual home online sessions);
    • vascular risk factor monitoring (by nurse or MD, BP, weight - no medications prescribed).
  – Primary outcome – change in cognition over 2 years.

Ngaandu et al; Lancet, 2015
• Also significant change in:
  – Physical activity.
  – Dietary habits.
  – Weight.
  – No information on lipid and glucose levels, BP, death, new vascular events (heart attack or stroke).
Cont’d

• Alzheimer’s Association is funding **US POINTER** study (US study to PrOtect through lifestyle INTERvention to Reduce risk):
  – Double-blind RCT of people with normal cognition but high risk for cognitive decline/dementia who will be undergoing general health education or multimodal intervention over 2-year period. (recruitment starts 2018 N=2500 participants with history of hypertension, elevated blood sugar, history of cardiovascular) events.
  – Multimodal intervention:
    • Diet
    • Exercise
    • Cognitive training
    • Vascular risk factor monitoring
  – Primary outcome – change in cognition over 2 years.
SPRINT and SPRINT-MIND study (2018 – presented at AAIC meeting 2018)

• The Systolic Blood Pressure Intervention Trial (SPRINT) – to test hypothesis whether intensive BP control to SBP < 120 would reduce cardiovascular outcome when compared to standard goal SBP < 140 mmHg
  \[ N=9361, \text{median f/u 3.26 year, study was stopped due to significantly lower all-cause, cardiovascular mortality (~30%), even in older people (>75 y)} \] – however more adverse outcomes in intensive group.

The SPRINT research Group, NEJM, 2015
Cont’d

• SPRINT Memory and Cognition IN Decreased Hypertension (MIND) - to test hypothesis whether intensive BP control to SBP < 120 would reduce incident mild cognitive impairment (MCI) and/or dementia in sub-sample of 2800 participants when compared to standard goal SBP < 140 mmHg → preliminary results showed significantly reduced MCI incidence of 19% (while non-significant 17% decrease in dementia risk). → Subset also had MRI and intensive treatment group had significantly less new WML.

• (short f/u, no information on mediation, amyloid? tau?)
## Table 2. Incidence of Probable Dementia and Mild Cognitive Impairment by Treatment Group

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Treatment Group</th>
<th>No. With Outcome/Person-Years</th>
<th>Cases per 1000 Person-Years</th>
<th>No. With Outcome/Person-Years</th>
<th>Cases per 1000 Person-Years</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable dementia</td>
<td>Intensive</td>
<td>149/20 569</td>
<td>7.2</td>
<td>176/20 378</td>
<td>8.6</td>
<td>0.83 (0.67-1.04)</td>
<td>.10</td>
</tr>
<tr>
<td>MILD COGNITIVE IMPAIRMENT&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Standard</td>
<td>287/19 690</td>
<td>14.6</td>
<td>353/19 281</td>
<td>18.3</td>
<td>0.81 (0.69-0.95)</td>
<td>.007</td>
</tr>
<tr>
<td>Composite of mild cognitive impairment or probable dementia</td>
<td>Intensive</td>
<td>402/19 873</td>
<td>20.2</td>
<td>469/19 488</td>
<td>24.1</td>
<td>0.85 (0.74-0.97)</td>
<td>.01</td>
</tr>
</tbody>
</table>

<sup>a</sup>Intensive treatment group vs standard treatment group based on Cox proportional hazards regression.

<sup>b</sup>Participants adjudicated as having probable dementia at the first follow-up visit (year 2) do not contribute to the analyses of mild cognitive impairment.
Summary

- We still do not completely understand AD, but there is a lot of new information out there....
  - Disease begins at least 15-20y before symptoms.
  - Aβ is hallmark for AD (especially early onset AD), but brain autopsies show a very different picture – multiple pathologies present.
  - Both Aβ and tau is needed for clinical progression in AD.
  - New imaging technologies can help with early diagnosis and follow progression or treatment.
  - New medications, truly disease modifying medications, on the horizon.
  - Multi-targeted approach needed!
Thank you!

• Questions?