Latest Developments in Neuroscience Drug Therapy

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Objectives

• Describe new medications and/or new safety concerns for the following therapeutic areas:
  – Epilepsy
  – Multiple sclerosis
  – Stroke
  – Alzheimer’s disease
Epilepsy

- New medications
  - Lacosamide
  - Ezogabine/retigabine
  - Clobazam
  - Perampanel
  - Brivaracetam
Lacosamide

- Mechanism of action
  - Enhances slow sodium channel inactivation
  - Binds to the collapsin-response mediator protein 2 (CRMP-2)
    - May help prevent rearrangement of neuronal connections
    - May protect neurons from excitotoxicity and apoptosis
Physiology of Voltage-Gated Sodium Channels

Regulation of sodium channel long-term availability

Resting state

Resting membrane potential

Inactivated state-slow (within sec and beyond)

Inactivated state-fast (within msec)

Repolarization

Depolarization

Classical AEDs

Local anesthetics

Open state

LACOSAMIDE

msec=milliseconds; \( \text{Na}^+ = \text{sodium} \); sec=seconds

Adapted from Beyreuther, et al.

Lacosamide

• Pharmacokinetics
  – Low protein binding (<15%)
  – Metabolized by CYP2C19
  – Half-life 13 hours

• Adverse effects
  – Common – sedation, dizziness, nausea, ataxia, nystagmus
  – Rare – PR interval prolongation
  – Euphoria, especially at 800 mg dose
Ezogabine/Retigabine

- Opens voltage-gated potassium channels
- Enhances the outgoing, M-type potassium current
  - Repolarizes the membrane back towards resting potential and suppressing repetitive firing
- May also augment GABA-mediated currents
- Indicated for adjunctive treatment of partial-onset seizures
Ezogabine/Retigabine

• Pharmacokinetics
  – Excreted renally
  – Carbamazepine and phenytoin decrease ezogabine

• Adverse effects
  – Somnolence, dizziness, tremor
  – Confusion (9%), hallucinations (2%), psychosis (1%)
  – Urinary retention 2%
  – QT interval prolongation
Ezogabine/Retigabine

• FDA warning 4/26/13
• Pigment changes in the retina
• Blue skin discoloration
  – Lips, nail beds, face legs, sclera, conjunctiva
  – Average of 4 years of treatment
• Recommendation: baseline and periodic eye exams with visual acuity testing and dilated fundus photography
Ezogabine/Retigabine
Clobazam

• Mechanism of action – benzodiazepine; activates GABA receptor

• Adjunctive treatment of Lennox-Gastaut seizures for patients ≥ 2 years

• Pharmacokinetics
  – \( V_d = 100 \text{ L} \)
  – Active metabolite N-desmethylclobazam
  – Metabolized by CYP2C19; decrease dose in poor metabolizers
  – \( t_{1/2} = 36-42 \text{ hours} \) (metabolite 71-82 hours)
Clobazam

• **Drug-drug interactions**
  - Weak CYP3A4 inducer – hormonal contraceptives
  - CYP2D5 inhibitor
  - CYP2C19 inhibitors may increase clobazam (fluconazole, fluvoxamine, ticlopidine, omeprazole)

• **Development of tolerance**
Clobazam

- Adverse effects – sedation
  - Rare – Stevens-Johnson syndrome and toxic epidermal necrolysis
- Controlled substance
- Dosing
  - If 5 mg/day, can give as one dose; if >5 mg/day, should divide twice daily

<table>
<thead>
<tr>
<th></th>
<th>≤30 kg</th>
<th>&gt;30 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>5 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>Day 7</td>
<td>10 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td>Day 14</td>
<td>20 mg</td>
<td>40 mg</td>
</tr>
</tbody>
</table>
Perampanel

- **Mechanism of action**
  - Non-competitive AMPA glutamate receptor antagonist
    - Anti-seizure effects should still be maintained even when glutamate concentrations are high

- **Pharmacokinetics**
  - 95% protein bound to albumin and α1-acid glycoprotein
  - Metabolized by CYP3A4 and CYP3A5
  - Half-life = 105 hours

- **Interactions**
  - Decreases levonorgestrel
Perampanel

• Controlled substance – awaiting DEA classification

• Adverse effects
  – Dizziness
  – Gait disturbance/falls
  – Somnolence
  – Weight gain
  – Psychiatric and behavioral effects (aggression, hostility, irritability, anger, homicidal ideation) can occur with or without psychiatric history (2-20%)
Brivaracetam

• Phase III; results 2013
• Mechanism of action
  – Synaptic vesicle protein 2A ligand
  – Inhibits voltage-dependent sodium channels
• Efficacy
  – Likely similar to levetiracetam
  – Broad spectrum for generalized and focal seizures
Brivaracetam

• Pharmacokinetics
  – Linear
  – Low protein-binding; $V_d=0.6 \text{ L/kg}$
  – Renally eliminated; $t_{1/2}=8 \text{ hours}$

• Drug-drug interaction
  – Increased concentrations of 10,11-epoxide of carbamazepine
Multiple Sclerosis

• Disease modifying therapy
  – Fingolimod
  – Teriflunomide
  – Dimethyl fumarate

• Symptomatic therapy
  – Dalfampridine
  – Dextromethorphan/quinidine
Fingolimod

- Sphingosine-1-phosphate (S1P) receptor modulator
- S1P activates the S1P receptor 1
- High levels of S1P1 are seen when lymphocytes are in the lymph nodes and they are low when lymphocytes are in the bloodstream
- Fingolimod causes the lymphocytes to stay in the lymph nodes and so is immunosuppressive and anti-inflammatory
Fingolimod

• **Pharmacokinetics**
  – Steady-state concentrations within 1-2 months
  – Metabolized by CYP4F2 (major) and CYP2D6, 2E1, 3A4, and 4F12 (minor)
  – Half-life 6-9 days, effects for 1-2 months

• **Common adverse effects**
  – Headache
  – Liver enzyme elevations
  – Cough
  – Diarrhea
Fingolimod

- Serious adverse effects
  - Bradycardia; mean decrease 13 bpm; returns to baseline within one month of starting treatment
    - 1\textsuperscript{st} degree AV block 0.1%; 2\textsuperscript{nd} degree AV block 0.1%
  - Infection - 20-30% reduction of peripheral lymphocytes
    - Should not be used in conjunction with other immune modulating medicines
  - Macular edema (0.4%); risk increased with uveitis (20%) or diabetes
  - Dyspnea (5%); decreased FEV1
Fingolimod

• Pre-treatment
  – In patients with no history of chickenpox or vaccination against varicella zoster, should do antibody test and vaccinate, if negative. Do not start therapy for a month after vaccine
  – Ophthalmologic evaluation; repeat 3-4 months later
  – CBC
  – In patients on antiarrhythmic, beta blocker, or calcium channel blocker, get ECG, if one not performed in the past 6 months
Fingolimod

• Interactions
  – Class Ia or III antiarrhythmics – AV block
  – Ketoconazole – increase fingolimod levels
  – Vaccines
    • Less effect during/2 months after treatment
    • Do not use live attenuated vaccines
  – Antineoplastic, immunosuppressive, immunomodulating therapies
  – Beta blockers, diltiazem – bradycardia
  – WBC won’t be accurate
Fingolimod

• Dosing
  – 0.5 mg PO QAM
  – Observe for 6 hours after first dose for bradycardia

• Should not become pregnant for 2 months after stopping treatment
Teriflunomide

• Prevents lymphocyte activation

• Pharmacokinetics
  – Long half-life (8-19 days); takes about 3 mo to steady state; takes ave. 8 mo to eliminate (serum conc. less than 0.02 mcg/mL) and may take 2 years
  – Accelerated elimination procedures
    • Cholestyramine 8 g Q8H x 11 days
    • Activated charcoal powder 50 g Q12H x 11 days
Teriflunomide

- **Adverse effects**
  - Hepatotoxicity; avoid in pts with liver disease or with ALT >2 times ULN
  - Diarrhea, nausea
  - Alopecia, rash
  - Neutropenia, lymphopenia
  - TB infections reported; negative skin test required at baseline
  - Live virus vaccinations should not be administered
Teriflunomide

- Teratogenic; pregnancy category X
  - Negative pregnancy test at baseline
  - Adequate contraception for males and females
  - If pregnancy desired (male or female), discontinue, accelerated elimination procedures, 2 serum concentrations less than 0.02 mcg/mL taken 14 days apart
Dimethyl Fumarate

- **Mechanism of action**
  - Activates Nuclear factor-like 2 (antioxidative pathway) to protect glial cells
  - Shifts cytokine production from $T_h1$ to $T_h2$ pattern (IL-4 and IL-5)
  - May reduce chemokine or adhesion molecule production

- **Pharmacokinetics**
  - Hydrolysis to active metabolite, monomethyl fumarate
  - $V_d = 53-73$ L
  - Metabolized through the tricarboxylic acid cycle
  - Eliminated by exhaling $CO_2$
  - $t_{1/2} = 1$ hour
Dimethyl Fumarate

- No drug-drug interactions identified
- Adverse effects
  - Lymphocytes decrease by 30% over first year, then stabilize
    - No increase in infections in trials
  - Flushing in 40%, only 3% discontinued; giving with food may help; improves over time
  - Abdominal discomfort 30-40%
Dimethyl Fumarate

• Dosing
  – 120 mg twice daily x 7 days, then 240 mg twice daily
  – Do not crush or chew; sustained release

• Monitoring
  – Baseline – CBC within 6 months
Dalfampridine Extended-release

- 4-aminopyridine, fampridine
- FDA indication – improves walking in MS patients as demonstrated by an increase in walking speed
- Prolongs repolarization of action potential; enhances ability to travel through demyelinated regions
Dalfampridine Extended-release

• Early studies showed no difference in disability scale scores

• Later studies focused on timed 25-foot walks
  – Average increases in walking speed was statistically different in dalfampridine patients compared to placebo patients
    • Only 35% of patients responded and speed improved by 25%

• Pharmacokinetics
  – Renal elimination
    • Contraindicated if CrCl ≤ 50 mL/min
Dalfampridine Extended-release

- Adverse effects
  - Seizures
    - Contraindicated in patients with history of seizures
    - Risk increased with increased dose and with immediate-release
  - Urinary tract infections
  - Insomnia
  - Dizziness
  - Headache
  - Nausea
Dalfampridine Extended-release

• Dosage form
  – Sustained-release tablet

• Dose
  – 10 mg BID
Dextromethorphan/Quinidine

- Indicated for pseudobulbar affect – pathological laughing and crying
- Mechanism of action unknown
- Quinidine inhibits dextromethorphan metabolism though CYP2D6
Dextromethorphan/Quinidine

• **Pharmacokinetics**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dextromethorphan</th>
<th>Quinidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{\text{max}}$</td>
<td>3-4 hours</td>
<td>1-2 hours</td>
</tr>
<tr>
<td>$f_u$</td>
<td>0.3-0.4</td>
<td>0.11-0.2</td>
</tr>
<tr>
<td>$T_{1/2}$</td>
<td>13 hours</td>
<td>7 hours</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Extensively metabolized via CYP enzymes into multiple metabolites, one of which is active</td>
<td>Hepatic</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>Eliminated renally</td>
<td>Moderated by pH dependent reabsorption: at pH &lt; 7, 20% is found in urine unchanged. In pH &gt; 7, 5%</td>
</tr>
</tbody>
</table>

• **Dose**
  - 20 mg dextromethorphan/10 mg quinidine
  - 1 capsule daily x 7 days, then 1 capsule twice daily
Dextromethorphan/Quinidine

• Adverse effects
  – Contraindicated with QT disorders, atrioventricular block

• Drug-drug interactions
  – Inhibits CYP2D6
    • Particular caution with thioridazine and pimozide because of QT interval increase
  – Serotonin syndrome – contraindicated with monoamine oxidase inhibitors
Stroke

• Stroke prevention in atrial fibrillation
  – Dabigatran
  – Rivaroxaban
  – Apixaban

• Antiplatelet therapy
  – Cilostazol
  – Clopidogrel vs. aspirin/extended-release dipyridamole study results
Dabigatran

- Direct thrombin inhibitor
- Dose 150 mg twice daily
  - Reduce dose in renal dysfunction
- Don’t open capsule – increases bioavailability by 75%
- Monitoring not needed

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke (%/yrs)</td>
<td>1.11</td>
<td>1.69**</td>
</tr>
<tr>
<td>Major bleeds (%/yr)</td>
<td>3.11</td>
<td>3.36</td>
</tr>
</tbody>
</table>

**0<0.001
Dabigatran

- 3/29/11 – Product must be kept in original packaging due to breakdown with moisture contact; retains potency for 60 days after opening
- 12/7/11 – FDA conducting a safety review of post-marketing reports of serious bleeding events; update 11/2/12 no increased risk compared to warfarin
- 12/19/12 – FDA should not be used to prevent events in patients with mechanical heart valves
Rivaroxaban

- Factor Xa inhibitor
Rivaroxaban

- Dose 20 mg daily with evening meal
  - Food increases bioavailability
  - Reduce dose in renal dysfunction
- Metabolized by CYP3A4/5, CYP2J2, P-gp, ABCG2
  - Avoid use with combined P-gp and strong CYP3A4 inhibitors (ketoconazole, itraconazole, ritonavir, and conivaptan)
  - Avoid use with combined P-gp and strong CYP3A4 inducers (carbamazepine, phenytoin, rifampin, St. John’s wort)
  - Additional cautions with renal insufficiency
Rivaroxaban

- **ROCKET AF***
  - 14,264 patients with AF + prior stroke/TIA/systemic embolism OR + 2 RF (age ≥ 75, HTN, CHF, DM)
  - Demonstrated non-inferiority to warfarin

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban (per 100 pt-yrs)</th>
<th>Warfarin (per 100 pt-yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite endpoint**</td>
<td>2.1</td>
<td>2.4</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.0</td>
<td>2.2</td>
</tr>
<tr>
<td>Non-CNS systemic embolism</td>
<td>0.2</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation

**stroke or non-CNS systemic embolism
Rivaroxaban

• **Bleeding risks**

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<th>Warfarin (per 100 pt-yrs)</th>
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<tbody>
<tr>
<td>Major bleeding</td>
<td>3.6</td>
<td>3.5</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>0.2</td>
<td>0.5</td>
</tr>
<tr>
<td>Bleeding resulting in ≥ 2units blood</td>
<td>1.7</td>
<td>1.3</td>
</tr>
<tr>
<td>GI bleeding</td>
<td>2.0</td>
<td>1.2</td>
</tr>
</tbody>
</table>
Apixaban

• Direct, competitive factor Xa inhibitor
• Metabolized by CYP3A4
• AVERROES* trial (n=5599)
  – Unsuitable for warfarin
  – Apixaban 5 mg twice daily or 2.5 mg twice daily with ≥2 of the following: age ≥ 80; weight ≤ 60 kg; SrCr ≥ 1.5 mg/dL
  – Aspirin 81 mg, 162 mg, 243 mg, or 324 mg

*AVERROES=Apixaban Versus Acetylsalicylic Acid to Prevent Strokes in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment
## Apixaban

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Apixaban</th>
<th>Aspirin</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or systemic embolism</td>
<td>1.6%/year</td>
<td>3.7%/year</td>
<td>0.45 (0.32-0.62)</td>
</tr>
<tr>
<td>Disabling or fatal stroke</td>
<td>1%/year</td>
<td>2.3%/year</td>
<td>0.43 (0.28-0.65)</td>
</tr>
<tr>
<td>Stroke, systemic embolism, MI, death from vascular cause, major bleeding</td>
<td>5.3%/year</td>
<td>7.2%/year</td>
<td>0.74 (0.6-0.9)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1.4%/year</td>
<td>1.2%/year</td>
<td>1.13 (0.74-1.75)</td>
</tr>
</tbody>
</table>

- Without prior stroke or TIA and with CHADS$_2$ score of 0 or 1, apixaban was the same as aspirin

Apixaban

• ARISTOTLE* trial (n=18,201)
  – Atrial fibrillation + 1 additional stroke risk factor
  – Apixaban 5 mg twice daily or 2.5 mg twice daily with ≥2 of the following: age ≥ 80; weight ≤ 60 kg; SrCr ≥ 1.5 mg/dL
  – Warfarin INR 2-3

*ARISTOTLE=Apixaban for Reduction In STroke and Other ThromboemboLic Events
## Apixaban

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Apixaban (%)</th>
<th>Warfarin (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or systemic embolization</td>
<td>1.27%</td>
<td>1.60%</td>
<td>0.79 (0.66-0.95)</td>
</tr>
<tr>
<td>Death</td>
<td>3.52%</td>
<td>3.94%</td>
<td>0.89 (0.8-0.99)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2.13%</td>
<td>3.09%</td>
<td>0.69 (0.6-0.8)</td>
</tr>
</tbody>
</table>

- Not currently approved in the US for this use
- Should not be used if CrCl < 25 mL/min

Cilostazol

- Inhibits cyclic AMP (adenosine monophosphate) phosphodiesterase III–induced platelet aggregation
- Dose: 100 mg orally two times/day on an empty stomach
- Metabolized extensively by CYP3A4 and CYP2C19
Cilostazol

- Adverse effects: Headache, palpitation, diarrhea, and dizziness; rarely, thrombocytopenia or agranulocytosis
- Contraindicated in patients with congestive heart failure
- Monitoring: complete blood cell count with differential every 2 weeks for 3 months; periodically thereafter
PRoFESS Results

No difference between groups for recurrent stroke. Increased intracranial hemorrhage in asa/erdp group.

PRoFESS=Prevention Regimen for Effectively Avoiding Second Strokes
Haiku

For stroke prevention
Use an antiplatelet drug
Treat hypertension

Alzheimer’s Disease

• More than 200 agents in clinical trials for Alzheimer’s disease

• Many focus on amyloid
  – Decrease β-amyloid production
  – Decrease formation of oligomer β-amyloid
  – Increase β-amyloid clearance
  – Change downstream effect of β-amyloid
β-amyloid Production

APP-amyloid precursor protein; sAPP-soluble amyloid precursor protein; AICD – amyloid precursor protein intracellular domain

Soluble β-amyloid Oligomers

- These forms are more likely to be responsible for neurodegeneration and synaptic malfunction in AD
- Promote disturbances in glutamatergic neurotransmission and increase tau phosphorylation

Therapeutic Options

Decrease β-amyloid Production
- Semagacestat
- Tarenflurbil
- Avagacestat
- LY2811376
- Imatinib
- Statins
- Resveratrol

Decrease Oligomer Formation
- Tramiprosate
- ELND005
- PBT2

Increase β-amyloid Clearance
- Vaccines
- IVIG
- Monoclonal antibodies
  - Bapineuzumab
  - Solanezumab
  - Gantenerumab

Secretase Inhibitors

- Prevent the final cleavage of C99 to Abeta\textsubscript{40-42}
Semagacestat (LY450139)

- Two trials halted
- Compared to placebo, patients receiving semagacestat for 75 weeks were worse in cognition and ADLs and were at higher risk of skin cancer
- Possibly because of inhibition of the processing of an unknown substrate of γ-secretase or due to the accumulation of a neurotoxic precursor of β-amyloid

http://newsroom.lilly.com/releasedetail.cfm?releaseid=499794
Statins

• Elevated cholesterol may increase risk of Alzheimer’s disease
  – Increase β- or γ-secretase activity
  – Decrease the flux of APP through the non-amyloidogenic α-secretase pathway
  – Affect non-amyloid factors (local inflammation or tau metabolism)

• Trials of atorvastatin and simvastatin demonstrated no effect

Resveratrol

- Promotes the α-secretase cleavage of amyloid precursor protein
- Enhances clearance of amyloid beta-peptides
- Antioxidant
- Activates sirtuins to mimic effects of calorie restriction
- Phase 3: 12-month, placebo-controlled, double-blind study of mild-moderate (MMSE=12-26) AD

Oligomer β-amyloid Formation Inhibition or Destabilization

- Oligomers are formed by dimerisation or trimerisation of β-amyloid monomers
- Process mediated by metal ions
  - Zn$^{2+}$ assists in formation of β-amyloid fibrils and plaques
  - Cu$^{2+}$ assists in formation of soluble oligomers

Tramiprosate (Homotaurine, 3APS)

- Prevents β-amyloid conformational changes for oligomer and fibril production
- GABA<sub>A</sub> receptor activation
- Mild-moderate (MMSE=16-26), double-blind, placebo-controlled, phase 3 study
  - No statistical difference; may have been underpowered because of less-than-expected decline in placebo group
  - Differences on some subscales involving memory, language, and praxis skills
- Marketed as a neutraceutical Vivimind<sup>®</sup>
- BLU8499, prodrug of tramiprosate, is in Phase 2 trials

ELND005 (AZD-103, Scyllo-inositol)

- Prevents β-amyloid aggregation
- Small phase 2 study of 250 mg, 1000 mg, or 2000 mg vs. placebo showed no differences for cognitive function of 250 mg vs. placebo
- 1000 mg and 2000 mg doses had excess infections and deaths
- Attempting to determine correct dosage for future studies

PBT2

• Metal-protein attenuating compound
  – Inhibit Zn\(^{2+}\)- and Cu\(^{2+}\)-facilitated formation of β-amyloid oligomers
• Phase 2 study of 74 patients with mild (MMSE=20-26) AD with 50 mg, 250 mg, or placebo
• Non-significant changes in ADAS-cog and MMSE in the 250 mg group
• Significant improvement in category fluency and trails B tests of the neuropsychological test battery

Increase Clearance of β-amyloid by the Immune System

- Active immunization to generate an immune response to β-amyloid
- Passive immunization with anti-β-amyloid antibodies

Vaccines

• Early trial of a 6-dose vaccination schedule with aggregated human β-amyloid (AN1792) was halted because of increased meningoencephalitis in vaccinated patients (18/300; 6%)
  – Possibly due to a change in formulation
• Current strategies use smaller peptides and are currently in phase 1 or 2 studies
  – ACC-001 and QS-21
  – Affitope AD01
  – UB 311

IVIG

- Contains natural antibodies against β-amyloid
- AD patients may have reduced antibody concentrations
- Very small phase 2 and epidemiological studies show some promise
- Phase 3 study underway with 360 patients comparing 0.2 g/kg q2weeks and 0.4 g/kg q4 weeks

Bapineuzumab

- 234 patients with mild-moderate (MMSE=16-26) AD
- 0.15, 0.5, 1, or 2 mg/kg or placebo every 13 weeks
- No differences in efficacy
- Cerebral edema in 9.7% of bapineuzumab group (higher doses and APOE ε4 carriers)
  - Possibly due to antibody binding to vascular amyloid

Solanezumab (LY2052430)

- Humanized anti-β-amyloid peptide immunoglobulin G-1 monoclonal antibody
- 2 double-blind, placebo-controlled, phase 3 trials in 2052 mild-moderate AD patients
  - Placebo
  - 400 mg Q4 weeks for 80 weeks
- Secondary pooled analysis of both trials showed 34% reduction in ADAS-cog (p=0.001) and non-significant reduction in ADCS-ADL changes (p=0.057) in mild (MMSE=20-26) AD

Gantenerumab (RO4909832)

- Fully human, anti-\(\beta\)-amyloid monoclonal antibody
- Phase 2 PET scan study of 18 mild AD patients
  - 60 mg, 200 mg, placebo
  - 2 patients with cerebral edema
- Phase 3 study underway with MMSE \(\geq\) 24

Mean Amyloid Change from Baseline Compared to Placebo

Conclusions

• Many new and exciting developments in the area of neurology therapeutics
• With new mechanisms, often new adverse effects are seen