Update on Medications to treat Dementia Disorders

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Dementia

- Major Types
  - Alzheimer Disease
  - Lewy Body Dementia
  - Frontotemporal Dementia
- Postmortem autopsy often shows mixed brain abnormalities
- Others
  - Vascular Dementia
    - Cerebrovascular disease
  - Neurocognitive Impairment
    - Brain injury
    - Medications: sedative-hypnotics, anxiolytics
    - Parkinson disease, Huntington disease

Risk Factors

- Non-modifiable:
  - Genetics, family history
  - Down Syndrome
  - Older Age
  - History of Traumatic Brain Injury
- Modifiable
  - Diabetes
  - Mid-life Obesity
  - High cholesterol
  - Smoking
  - Depression
  - Physical inactivity

Screening

- Early warning signs:
  - Challenges in planning or solving problems
  - Changes in mood and personality
  - Confusion with time/place
  - Decreased poor judgement
  - New problems in speaking/writing
  - Misplacing things and losing ability to retrace steps
  - Trouble understanding visual images and spatial relationships
  - Withdrawal from work or social activities

Preventable Forms of Dementia

- D: Drugs (any drug with anticholinergic activity)
- E: Emotional distress (Depression)
- M: Metabolic (hypothyroid)
- E: Eyes and Ears declining
- N: Normal pressure hydrocephalus
- T: Tumor or other space-occupying lesion
- I: Infection (UTI, syphilis, AIDS)
- A: Anemia (vitamin B12 or folate deficiency)

Drugs to Avoid in Dementia

- Drugs with anticholinergic effects
  - Older antihistamines
    - Ex. Diphenhydramine (Benadryl, Tylenol PM)
  - Drugs for overactive bladder
    - Ex. Oxybutynin
  - Tricyclic antidepressants
    - Ex. Amitriptyline
  - Muscle relaxants
    - Ex. Cyclobenzaprine (Flexeril)

Benzodiazepines linked to increased AD risk

British Medical Journal, 9/9/14

- Case-controlled study of 9,000 in France
  - 43-51% increased risk if used BZs within previous 5 years
  - Even stronger risk if used BZs for 6 months or longer
- Review of Canadian insurance database: 7184 matched, 6 years
  - Showed a significantly increased risk; even after adjusting for anxiety, depression, and insomnia
  - Increased with dose and extended half-life
- Reinforces use for short-term only (not to exceed 3 months), lower doses, and dedicated monitoring of cognitive function

Benzodiazepines

- Generally avoid
  - reserve for acute crisis (agitation, alcohol withdrawal, or severe anxiety)
- Elderly prone to benzodiazepine-associated confusion, cognitive impairment, delirium, paradoxical excitation, and night wandering
- Benzodiazepines are among the medications that pose the greatest fall risk in the elderly, especially at high doses
- Associated with increased mortality
- In general, start with one-third to one-half the recommended adult dose
- Work with pharmacist to schedule taper

Dextromethorphan 20 mg/ quinidine 10 mg (*Nuedexta*)®

- Labeled indication is pseudobulbar affect
- Dextromethorphan blocks NMDA receptors and quinidine boosts dextromethorphan levels
- May modestly improve agitation in one in six patients over 10 weeks at a dose of 30/10 mg twice daily [Evidence level B; lower-quality RCT]
- Dose: one capsule daily for seven days, increased to one capsule every 12 hours
- Many drug interactions due to inhibition of CYP2D6 by quinidine and metabolism of quinidine via CYP3A4, and potential for serotonin syndrome with dextromethorphan (e.g., if used with SSRI or tricyclic)
- Serious adverse effects include falls and QT prolongation
- Costs about $750/month

Screening

- **Medication Therapy Management with Pharmacist**
- **Medicare: Annual Wellness Visit**
  - **Eligible if Medicare B for at least 12 months**
  - **Emphasizes preventive care – Includes assessments for vision, hearing, cognition, and other important indicators of health**
  - **Covered once annually**
    - Assessment tools: Baseline and yearly

    https://www.alz.org/media/Documents/alzheimers-well-visit-algorithm.pdf
      - General Practitioner Assessment of Cognition
        - Administer to Patient: 5 minutes
      - Mini-Cognitive Assessment Instrument
        - Administer to Patient: 2-4 minutes
        - Validated for primary care, dementia
      - Memory Impairment Screen
        - Administer to Patient: 4 minutes
        - Specific to Alzheimer Disease
- American Academy of Neurology guidelines
  - **Structural neuroimaging with CT or MRI to clarify diagnosis**

Over-the-Counter Supplement Interventions to Prevent Cognitive Decline, Mild Cognitive Impairment, and Clinical Alzheimer-Type Dementia: A Systematic Review.

Annals of Internal Medicine January 2018

- **Purpose:** Summarized the evidence on efficacy and harms of OTC supplements to prevent or delay cognitive decline
- **Study Selection:** 38 trials of at least 6 months duration that enrolled adults without dementia and compared cognitive outcomes with an OTC supplement vs placebo or active controls
- **Data Synthesis:** Few studies examined effects on clinical AD dementia or MCI, and those that did suggested no benefit
  - Daily folic acid plus vitamin B_{12} was associated with improvements in performance on some memory tests that were statistically significant but of questionable clinical significance.
  - Moderate-strength evidence showed that vitamin E had no benefit
  - Evidence about effects of omega 3 fatty acids, soy, ginkgo biloba, folic acid alone or with other vitamins or multi-ingredient supplements did not reduce risk for cognitive decline.
- **Conclusion: Evidence is insufficient to recommend any OTC**

Physical Activity Interventions in Preventing Cognitive Decline and Alzheimer-Type Dementia: A Systematic Review

Annals of Internal Medicine January 2018

- **Purpose:** Assess physical activity interventions in slowing cognitive decline and delaying onset of dementia
- **Study Selection:** Trials 6 months or longer, enrolled adults without clinically diagnosed cognitive impairments, and compared cognitive and dementia outcomes
- **Data Synthesis:** 32 eligible trials compared a physical activity intervention with an inactive control
  - Evidence was insufficient to draw conclusions of aerobic training, resistance training, or tai chi for improving cognition
  - Evidence regarding effects on dementia prevention was insufficient for all physical activity interventions
  - Low-strength evidence showed that **physical activity, diet, and cognitive training** improved several cognitive outcomes
- **Conclusion: A multidomain intervention showed a delay in cognitive decline (low-strength evidence)**

Dementia Prevention, Intervention, and Care Livingston, et al. *The Lancet*. July, 2017

- **Advances in technology:**
  - **Diagnosis and assessment**
    - Computerized neuropsychological assessments and video-conferenced examinations
    - Detecting progression: wearable sensors to detect changes in gait or activities of daily living
    - Virtual reality: assessment of activities of daily living, such as meal preparation
  - **Monitoring**
    - Sensors/cameras to detect falls, heat, gas, satellite tracking devices,
    - Physiological sensors/smart garments: pulse, blood pressure, oxygen saturation, blood glucose, sleep

Dementia Prevention, Intervention, and Care Livingston, et al. *The Lancet*. July, 2017

- **Assistive technology**
  - Cognitive aids: reminder systems, medication management; activities of daily living prompting
  - Activities of daily living assistance: robots to help with eating, washing, and mobility
  - Safety: electrical outlet shut-off devices, hands-free taps, and water temperature sensors
  - Combination: robot to assist with care and monitor physiological or environmental changes and send information to caregiver
- **Therapeutic technology**
  - Communication: support reminiscence-based communication between people with dementia, caregivers, or chat groups
  - Companionship: robotic animals
  - Activity: technology to deliver music, messages, images, and video tailored to an individual's interests

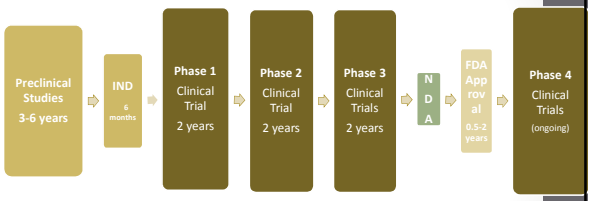
Clinical Trial Research Consortium – NIH, December 2017

- Created infrastructure with expert leadership to streamline implementation of trials
- Developing innovative trial design methods, outcomes and analysis strategies
- Maintaining trial site quality standards during and between trials
- Developing and implementing cutting-edge participant recruitment and retention strategies, especially in diverse populations
- Using a centralized Institutional Review Board
- Developing and running capture systems for data
- Securing centralized tissue banking for specimens
- Providing centralized imaging, biostatistics, bioinformatics and data management and analysis support
- Facilitating and managing public-private partnerships
- 35 sites in 24 states and District of Columbia
- **2018: 5600+ Research articles published in Journals**

Statistical vs. Clinical Significance[6]

- Controversial
- ADAS-cog scale
  - Change of ≥4 points defined as clinically significant improvement in many studies
- MMSE
  - Change of ≥3 points defined as clinically important in many studies
- Some patients may receive considerable benefit, while others receive no benefit at all

FDA Approval Process



Clinical evaluation of anti-dementia drugs[5]

- Guidelines set by FDA in 1990
- Treatment must show benefit based on both a cognitive assessment and clinician's global impression
- No requirements for trial size or duration
- All current drugs were approved based on these guidelines, but now recognized as purely symptomatic agents

Since then, over 170 failed drug trials for AD

- Disease-modifying therapies
  - Therapies to reduce amyloid plaque burden
    - Alteration of β-amyloid metabolism
    - Prevention of β-amyloid aggregation
    - Promotion of β-amyloid clearance from the central nervous system

Phase II Study halted at 3 doses (of 6 planned)

- due to meningoencephalitis and no differences noted in cognition

Treatment Management

Patient-related

- Age
- Lifestyle
- Employment status
- Co-morbidities
- Cognitive/psychiatric profile
- Caregiver status

Treatment- related

- Non-Pharmacologic Interventions
  - Education
  - Support
  - Exercise
  - Nutrition
- Medications
  - Efficacy
  - Side Effect Profile
  - Timing

Depression

- Depression may affect 25% of Alzheimer's patients.
  - Associated with wandering, agitation, and aggression
- Evidence of antidepressant benefit for depression is conflicting due to study differences, but are relatively well-tolerated compared to antipsychotics
- **Sertraline** has the most data and may also improve behavior and functioning, and reduce caregiver stress. Consider starting with sertraline 25 mg daily, increasing by 25 mg each week to a max daily dose of 150 mg
- **Citalopram** is effective for agitation and reducing caregiver distress, but can cause QT prolongation and worsen cognition [Evidence level B; lower-quality RCT]. Citalopram may also be as effective as risperidone for behavioral and psychotic symptoms.
- **Trazodone** may improve agitation, irritability, and depression; however, concern for sedation, falls, hypotension

- Anxiety: SSRI, SNRI, trazodone
- Agitation: citalopram, trazodone
- Irritability: trazodone
- Psychosis: citalopram
  Diabetic neuropathy: venlafaxine, duloxetine

Antipsychotics, atypical

- Benefits are small, at best
- Consider risks: cardiovascular events (e.g., stroke), metabolic effects (weight gain, diabetes, dyslipidemia), pneumonia, pulmonary embolism, movement disorders, anticholinergic effects, orthostatic hypotension, sedation, fatigue, cognitive decline, QT prolongation, and death.
- There is one more death for every 50 to 100 dementia patients on an atypical antipsychotic over 8 to 12 weeks
- Use one-third to one-half the usual starting dose, or the smallest strength available (but consider risk titrate to the lowest effective dose) and limit to a four-week trial
- If there is no clinically significant response or side effects, taper by no more than 50% every two weeks and discontinue
- If response is good, continue use but attempt to taper and discontinue within four months. Monitor for recurrence at least monthly during the taper and for at least four months after discontinuation.

Decisions about tapering should be made with input from the patient (if possible), decision-maker, and others who interact with the patient Set expectations that many patients can be tapered successfully

In long-term care facilities in the U.S., unless contraindicated, a taper **must** be attempted twice in the first year, in two separate quarters, with at least a month between attempts. After the first year, n attempt must be made annually, unless contraindicated.

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- Aripiprazole, risperidone, and olanzapine have the best evidence of efficacy
- Risperidone:
  - for aggression and psychosis in severe Alzheimer's dementia
  - starting oral dose of 0.25 mg twice daily, increased by 0.25 mg/day every two to four day
  - Optimum dose for most patients is 0.5 mg twice daily (max 1 mg twice daily)
- Olanzapine:
  - Initial: 2.5 mg at bedtimel. Max 10 mg/day, usually divided twice daily
  - U.S. Centers for Medicare & Medicaid Services suggests a max of 5 mg/day n nursing home residents
- Aripiprazole dose: initial 2 mg/day, up to Max 10 mg once daily
- Reserve haloperidol for emergency situations such as acute delirium
- Reserve long-acting injectables for patients with a concomitant chronic psychotic disorder

Pimavansrin (Nuplazid)®

- FDA-approved for treatment of hallucinations and delusions in PD
  - However, most patients in clinical trials did not have dementia
  - Second line therapy
- BBW warning: increased mortality in elderly patients with dementia-related psychosis as with other antipsychotics
- Seems to work by blocking 5-HT2A and 5-HT2C receptors, not dopamine receptors
  - Pimavanserin improves SAPS-PD score by 37%, vs 14% for placebo
  - The risk of a serious adverse effect or death may be 2.38 times higher with pimavanserin vs placebo (95% CI 1.00 to 5.73, p=0.05), with almost 10% of pimavanserin patients experiencing a serious adverse effect or death
  - Dose is 34 mg (two 17 mg tablets) once daily.
    - The dose is 17 mg once daily with strong CYP3A4 inhibitors
  - Pimavanserin can prolong the QT interval. Avoid QT-prolonging drugs
  - Very expensive (about $2,000/month)

Current FDA-Approved Drugs for Dementia

- Cholinesterase Inhibitors
  - Donepezil (Aricept)
  - Rivastigmine (Exelon)
  - Galantamine (Razadyne)
- Memantine (Namenda)

Cholinesterase Inhibitors Mechanism of Action

- Acetylcholine is a major neurotransmitter in the brain
- Cognitive symptoms in Alzheimer disease are thought to be due to degeneration of cholinergic neurons
- Cholinesterase inhibitors inhibit the breakdown of acetylcholine by acetylcholinesterase in the synaptic cleft
  - Results in **increased acetylcholine** available for synaptic transmission

Cholinesterase Inhibitors Common Adverse Effects

- Mild to moderate gastrointestinal symptoms
  - Nausea
  - Vomiting
  - Diarrhea
  - Abdominal pain
  - Anorexia
- Gradual dose titration can improve tolerability

Cholinesterase Inhibitors Adverse Effects

- Generally dose-related
  - Dizziness
  - Headache
  - Urinary incontinence
  - Syncope
  - Decreased heart rate
  - Muscle weakness
  - Salivation
  - Sweating
- Gradual dose titration can improve tolerability

Donepezil (Aricept)

- Dosage forms
  - Tablet: 5mg, 10mg, 23mg
  - Orally disintegrating tablet: 5mg, 10mg
- Mild-to-Moderate Alzheimer
  - 5mg once daily at bedtime
  - May increase to 10mg after 4-6 weeks
- Moderate-to-Severe Alzheimer
  - Initial: 5 mg daily at bedtime
  - May increase to 10 mg once daily after 4-6 weeks
  - May increase further to 23 mg daily after ≥3 months
- Off-Label: Parkinson, Lewy body, Vascular, TBI
  - 5-10mg daily at bedtime

Donepezil (Aricept) in Severe Alzheimer Disease

- Randomized controlled trials showed significantly improved cognitive function in severe Alzheimer disease
- 23 mg dose vs. 10 mg dose
  - Little increased benefit with higher dose
  - Increased adverse effects with higher dose

Donepezil (Aricept) Efficacy

- 24 studies- mainly mild and moderate dementia
- Statistically significant improvement in ADAS-cog score in Alzheimer disease and vascular dementia
  - Average change in score did not reach clinical significance
- Statistically significant improvement in CIBIC-plus score for mild to moderate Alzheimer disease
  - Unclear if changes were clinically important
- Majority of trials <1 year

Rivastigmine (Exelon)

- AD: Mild-to-Moderate and Moderate-to-Severe
- PD: Mild-to-Moderate
- Dosage forms
  - Oral: Capsule and Solution
    - Initial dosing: 1.5mg twice daily with food
    - Dose can be increased by 3mg every 2 weeks
    - Max dose = 6mg twice daily
  - Transdermal: Patch
    - Initial dosing: 4.6mg daily, may titrate every 4 weeks to
    - Max dose 9.5mg or 13.3mg daily
    - If liver dysfunction, max dose is 4.6mg
  - Oral to patch conversion
    - Total daily dose of <6mg oral, switch to 4.6mg patch
    - Total daily dose of 6-12mg oral, switch to 9.5mg patch
- If dose missed for more than 3 days, restart with initial dosing.
- Off Label: LBD: 1.5mg twice daily, titrate every 2 weeks up to 6mg twice daily

Rivastigmine (Exelon) Properties

- Reversibly inhibits both acetylcholinesterase and butyrylcholinsterase
  - Clinical relevance is uncertain
- Transdermal patch
  - Associated with ~3 times less GI adverse effects than oral rivastigmine

Rivastigmine (Exelon) Efficacy

- 9 studies
- Statistically significant improvement in ADAS-cog
- Statistically and clinically significant benefit using the CIBIC-plus
- No significant improvement in behavior or quality of life
- Duration of trials <7 months

Galantamine (Razadyne)

- AD: Mild-to-Moderate
- Dosage forms
  - Oral: tablet and solution
    - Initiate: 4mg twice daily with food
    - Every 4 weeks, may be increased by 8mg daily
    - Max dose is 12mg twice daily
  - Extended-release (ER) capsule
    - Initiate at 8mg once daily with breakfast
    - Every 4 weeks, may be increased by 8mg daily
    - Max dose is 24mg daily
- Off-label: Severe AD, PD, LBD
- Kidney or Liver dysfunctions:
  - Moderate: max dose is 16mg daily
  - Severe: use is not recommended

Galantamine (Razadyne) Efficacy

- 10 studies
- Pooled data showed statistically significant benefit using ADAS-cog
  - No clinically significant benefit
- Statistically significant improvement using CIBIC-plus
- Duration of trials <1 year

Memantine (Namenda)

- Mechanism of action
  - N-methyl-D-aspartate (NMDA) antagonist
  - Prevents the excitotoxic effects of glutamate in the brain by blocking NMDA receptors
- FDA-labeled indication: Moderate to severe AD
- Dosage Forms:
  - Tablet: 5mg, 10mg
    - Initial 5mg daily
    - Each week, increase by 5mg daily to a target dose of 20mg daily
    - Doses > 5mg daily should be given in 2 divided doses
  - Long-acting capsules:
    - Initial 7mg daily
    - Each week, increase by 7 mg daily to a target dose of 28 mg daily
- Off-label: Mild-to-Moderate Vascular Dementia
  - Initial: 5mg daily, increase weekly to 10mg twice daily

Memantine (Namenda) Efficacy

- Cochrane review in 2006 found no benefit in mild Alzheimer disease
- Pooled data showed statistically significant benefit in moderate to severe Alzheimer disease using the SIB scale
- Statistically significant change on the CIBIC-plus scale with 20 mg dose
- Overall improvement not clinically significant

Memantine (Namenda)

- Usually well tolerated
- Most common adverse effects
  - Dizziness (7%)
  - Headache (6%)
  - Confusion (6%)
  - Constipation (5%)
  - Hypertension (4%)
  - Drowsiness (3%)
  - Hallucinations (3%)

Mild Cognitive Impairment

- Individuals with mild cognitive impairment (MCI) are at increased risk for developing Alzheimer disease
- Evidence does not support the use of cholinesterase inhibitors in MCI
- Some sources recommend a trial of donepezil if memory symptoms are especially difficult for the patient

Clinical Recommendations

- Decision to initiate therapy with a cholinesterase inhibitor or memantine should be individualized
- Choice of pharmacologic agents should be based on tolerability, adverse effect profile, ease of use, and cost
  - Insufficient evidence to recommend one cholinesterase inhibitor over another

In Practice

- Donepezil (Aricept) is used most often
  - Once daily dosing
  - Greatest number of studies
  - Generic
- Rivastigmine (Exelon) Patch
  - Can sometimes be used if patient is unable to tolerate oral cholinesterase inhibitors despite gradual dose titration
- Memantine (Namenda)
  - Better tolerated than cholinesterase inhibitors

Discontinuation of Therapy

- May cause cognitive and behavioral decline
  - Monitor patient closely for changes
  - Symptoms may not be fully reversible
- General indications for discontinuation
  - No detectable benefit after 3-6 months
  - Nonadherence to the medication
  - Patient or caregiver chooses to stop therapy
  - Progression to a stage of disease where there is no significant benefit from continued therapy
- Weigh benefits and risks

Potentially Inappropriate Meds

- Question Drug Prescribing in Advanced Dementia
  - More than half of nursing home residents with advanced dementia use meds of "questionable" benefit.
  - Choosing Wisely campaign initiative of the American Board of Internal Medicine Foundation
- Long-term care pharmacy database: 5406 patients
  - 53.9% received at least 1 drug of questionable benefit
    - cholesterase inhibitors 36.4% and memantine 25.2%
      - Minimal dementia benefit, but increased risk for syncope, hip fracture, arrhythmia, and urinary retention
    - Statins
      - Increased risk of memory loss and confusion
- Parsons C. Polypharmacy and inappropriate medication use in patients with dementia: an underresearched problem. *Therapeutic Advances in Drug Safety*. 2017;8(1):31-46. doi:10.1177/2042098616670798.

Conflicting Results with Marijuana

- Studied in vitro: Extremely low levels of delta-9-tetrahydrocannabinol (THC)
  - decreased production of amyloid beta (Aβ), inhibits its aggregation in cell cultures, and may enhance mitochondrial function.
  - Patients with extracellular Aβ and amyloid plaque in early stages may benefit
- Concerns remain about memory impairment with THC, but is usually seen only at "abuse" concentrations
- Multiple brain regions show low perfusion on SPECT in marijuana users. The most predictive region distinguishing marijuana users from healthy controls, the hippocampus, is a key target of Alzheimer's disease pathology. This study raises the possibility of deleterious brain effects of marijuana use.
- Translation to patients with minor cognitive impairment or AD will require further studies

In the Pipeline:

BACE 1 Inhibitor

- 2202 patients with MCI due to AD or mild AD
- Provides potent and sustained inhibition of BACE1 and produced prolonged suppression of plasma and CSF A peptides in healthy subjects and patients with mild to moderate Alzheimer's disease.
- Several have been studied, but AZD3293 is the only BACE1 inhibitor to have demonstrated prolonged suppression of plasma concentration.
- No safety and tolerability concerns were identified up to the highest single or multiple doses studied.
- Two Phase III studies of AZD3293 (AMARANTH, NCT02245737; and DAYBREAK-ALZ, NCT02783573) are now ongoing
- Phase III: completion by 2021

Bryostatin

- protein kinase C epsilon (PKCε) activator: works through synaptic growth factors, as well as anti-amyloid and anti-tangle signaling pathways in the brain to induce growth of mature synapses in the brain and prevent neuronal death.
- Bryostatin-1 is the first PKCε modulator to be tested in a Phase 2 clinical study for patients suffering from advanced AD
- Exploratory Phase 2 study in 150 patients
- Two doses of bryostatin (20µg and 40µg) were compared with controls to assess safety and preliminary efficacy after 12 weeks of treatment.
- Now planning a confirmatory study in advanced AD patients not taking memantine as background therapy to evaluate whether the improvements in those patients can be replicated.

Anti-AB monoclonal antibodies

- Aducanumab, EMERGE (phase 3, NCT02484547),
- ENGAGE (phase 3, NCT02477800)
- It preferentially binds to an aggregated protein that is not normally accessible in the Aβ monomer to reduce the number of amyloid plaques present in the brain
- It is thought that by reducing the amyloid plaques may slow neurodegeneration and reduce disease progression
- 1700 patients with MCI due to AD or mild AD CDR
- 18 month trials (completion by 2022)
- Compared with a placebo, in slowing cognitive and functional impairment in people with early-stage Alzheimer's disease.
- Participants receive monthly infusions. Two doses of will be tested

Phase II results to be presented at Alzheimer's Association International Conference 7/25/18

- BAN2401 is a humanized monoclonal antibody
- BAN2401 selectively binds to neutralize and eliminate soluble, toxic Aβ aggregates that are thought to contribute to the neurodegenerative process in Alzheimer's disease
- May have the potential to have an effect on disease pathology and to slow down the progression of the disease
- 800 MCI due to AD or mild AD
- Phase II
- Completed in July

- Crenezumab, CREAD (phase 3, NCT02670083)
- Anti-Aβ monoclonal antibody
- 750 MCI/ prodromal AD or mild AD
- 2 years (completion by 2021)

Methylene blue

- Chemical name: leuco-methylthioninium bis(hydromethanesulphonate - a dye used in research and for the treatment of malaria
- LMTM is intended to reduce the formation of tau protein tangles in the brain
- **LMTM in clinical trials** TauRx has completed two Phase 3 clinical trials
  - The first Phase 3 trial (NCT01689246) included 891 participants with mild to moderate Alzheimer's disease at 115 centers in 16 countries.
    - Researchers found no significant difference in cognitive scores or ability to perform activities of daily life between the treatment and control groups.
    - But a subset of patients who were not taking other treatment for Alzheimer's disease, a benefit was seen. The low dose of 4 mg twice a day, which had been used as the control, appeared to benefit patients who were taking it as their only treatment (monotherapy)
  - TauRx's second Phase 3 trial (NCT01689233 seemed to confirm the findings
- Next step would be to conduct randomized controlled studies of LMTM in Alzheimer's patients in which the 4 mg twice daily dose would be compared with placebo in monotherapy participants
- February 2019

Carvediol

(ended 2016, no results published)

- Carvedilol phosphate is a non-selective α/β-adrenergic receptor antagonist and vasodilator
- Widely prescribed to treat high blood pressure and other cardiovascular problems, and is available as an extended-release capsule
- Side effects include slowness of movement, dizziness, fatigue, headache, and nausea
- The rationale for evaluating it in Alzheimer's disease grew out of several lines of research suggesting that neurovascular dysfunction contributes to age-related dementia, that antihypertensive treatment in incident Alzheimer's may slow further cognitive decline, and that carvedilol improves synaptic transmission and amyloid-related and cognitive outcomes in mouse models of Alzheimer's disease (Dunn and Nelson, 2014; Rosenberg et al., 2008; Wang et al., 2011).
- Meta-analysis of the epidemiological literature has shown hypertension in mid-life—but not in late life—to increase risk for dementia

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Clinical Trials[2-4]

- Phase 1
  - Small group (20-100) healthy volunteers
  - Frequent and serious adverse effects
  - Safe dosage range
  - Absorption, distribution, metabolism, excretion, duration of action
- Phase 2
  - Larger group (100-500) who have the disease being studied
  - Preliminary efficacy
  - Safety continues to be evaluated
  - Short-term

Clinical Trials[2-4]

- Phase 3
  - Large randomized placebo-controlled trials
  - 1,000-5,000 patient volunteers
  - Safety and efficacy in:
    - Different populations
    - Different dosages
    - Combination with different drugs
- New Drug Application (NDA) filed with FDA
- Phase 4
  - Post-marketing surveillance
  - General use by medical practitioners
  - Safety and efficacy with long term use

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- idalopirdine, a selective 5-hydroxytryptamine-6 receptor antagonist, improve cognitive change in patients with mild to moderate Alzheimer disease when added to cholinesterase inhibitors?
- **Findings** In 3 randomized clinical trials that included a total of 2525 patients with Alzheimer disease treated with cholinesterase inhibitors, the added use of idalopirdine compared with placebo did not decrease cognitive loss over 24 weeks.

2018

- BACE1 inhibitor trials, thus far persistently negative, should not be dismissed; they contain an important message. While they are being interpreted by some as a verdict on the validity of the amyloid cascade hypothesis, such a judgment appears to be premature; the ACH remains the more versatile putative theory when compared with alternative interpretations of Alzheimer's disease. In the framework of the "second component" model for Aβ overproduction in SAD, the lessons from the trials can be formulated as follows: (a)-Familial Alzheimer's disease and sporadic Alzheimer's disease should be considered two distinctly different diseases as far as the mechanisms of beta amyloid generation are concerned. (b)-Human trials of BACE1 inhibitors should be conducted separately, with discrete familial AD and sporadic AD cohorts.

Phase III trials restarted in 2017 with larger doses

- two trials of bapineuzumab in mild-to-moderate Alzheimer's disease, and in the same issue, Doody et al.[2] report on two trials of solanezumab for this condition. The negative results of these phase 3 trials may be interpreted in two ways: either treatment was too late in the course of the disease or amyloid-beta (Aβ) alone is the wrong target for an effective treatment of Alzheimer's disease. The first interpretation may be clarified when the results of ongoing treatment trials involving persons with preclinical Alzheimer's disease are available. These trials include the Dominantly Inherited Alzheimer Network Trial (DIAN-TU; ClinicalTrials.gov number, NCT01760005), Alzheimer's Prevention Initiative (API; NCT01998841), and the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease study (A4 Study; NCT02008357). The second interpretation has not yet been tested. Several tau-related vaccines are in advanced preclinical stages and will soon enter clinical trials. Since the pathologic process of Alzheimer's disease is characterized by the accumulation of both amyloid plaques and neurofibrillary tangles,[3] it is reasonable to assume that a treatment strategy focusing on both targets may be more beneficial than a strategy focusing only on amyloid-related imaging inflammation (ARIA) are a concern

- Azeliragon, STEADFAST (phase 3, NCT02080364)
- RAGE inhibitor, inflammation modulator
- In April 2018, VtV announced that STEADFAST had failed to meet its co-primary endpoint (April 2018 news). The trial was set to run until June 2019 but was terminated in June 2018. A two-year, open-label extension study to evaluate continued safety parameters and progression slopes, had been projected to enroll 640 STEADFAST completers and run through 2020; however, in June 2018, with 298 people enrolled, it was terminated as well.