Don’t you METFORget about me: Metformin use in Alzheimer’s Disease

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Learning Objectives

• Describe the key clinical characteristics of Alzheimer’s Disease (AD)
• Explain treatment goals and the available treatment options for AD
• Analyze available data on use of metformin for the prevention of AD
• Design a treatment regimen for a patient with AD

Required Reading


Suggested Reading

Background Information on Alzheimer’s Disease

• Definition
  o Dementia is a broad term for acquired cognitive defects that are “sufficient to interfere with social or occupational functioning”\(^1\).
  o Dementia can result from several central neurodegenerative and ischemic processes
  o Most common types of dementia
    ▪ Alzheimer’s Disease
    ▪ Vascular Dementia
    ▪ Lewy-Body Dementia
    ▪ Mixed Dementia
    ▪ See Appendix A for more information
  o Alzheimer’s Disease is the most common form of dementia and is an irreversible, progressive brain disease\(^2\).

• Epidemiology\(^2\)
  o AD is estimated to affect around 5.7 million Americans
  o Sixth leading cause of death among all adults and fifth among those ≥ 65 years old
  o Incidence of AD increases with age and doubles every 5 years beyond age 65

Figure 1: Projected Number of People with AD from 2010-2050

[Graph: Projected Number of People Aged 65 or Older With Alzheimer’s Disease, by Age Group, United States, 2010–2050]


• Etiology\(^3,4\)
  o Not entirely understood but thought to include genetic, environmental, and lifestyle factors
  o Genetically linked early onset AD accounts for less than 1% of cases
    ▪ Alterations of chromosomes 1, 14, or 21 have been noted
    ▪ Most common mutation is of chromosome 14 which produces a protein called presenilin 1
    ▪ Presenilin 2 is produced by chromosome 1
    ▪ These proteins are involved in amyloid precursor protein (produced by chromosome 21) processing
  o Genetic linking to late onset AD
    ▪ Apolipoprotein E (APOE) genotype
    ▪ Three major subtypes of alleles of APOE
      • *2, *3, *4
- APOE*4 associated with abnormalities in mitochondria, cytoskeletal dysfunction, and **low glucose usage**
- Risk of developing AD is 2-3 times higher in patients with one APOE*4 allele and 12 times higher with two APOE*4 alleles
- Important to note APOE*4 is not used for diagnosis and is not always present in individuals with AD
  - Environmental factors
    - Age
    - Decreased reserved capacity of the brain
      - Low education level
      - Reduced mental and physical activity levels
      - Reduced brain size
    - Down’s syndrome
    - Depression
    - Mild cognitive impairment
- Pathophysiology

Figure 2: Brain Regions


- **Key lesions** have been identified in patients with AD
  - Amyloid plaques and neurofibrillary tangles (NFT) found in the cortical areas and medial temporal lobes
  - Amyloid plaques
    - Generally observed **extracellularly**
    - Beta amyloid peptides produced from the processing of amyloid precursor proteins
    - Mechanism thought to be an imbalance between production and clearance of beta amyloid peptides that causes aggregation and accumulation
    - Neuronal damage seen with plaque structures
  - Neurofibrillary tangles (NFT)
    - Commonly found **intracellularly** in neurons in the hippocampus and cerebral cortex
    - Abnormally hyperphosphorylated tau proteins
    - Tau proteins normally provide structural support to microtubules
      - Extra phosphorylation leads to inability to effectively bind microtubules, microtubules collapse, cells cannot function and eventually die
    - Density of tangles correlates with severity of dementia
• Seen in other forms of dementia
  o Degeneration of neurons and synapses as well as cortical atrophy
  o Possible mechanisms that can lead to changes in the brain
    ▪ Beta amyloid aggregation and deposition leading to formation of plaques between neurons
    ▪ Hyperphosphorylation of tau protein leading to NFT formation inside neurons
    ▪ Synaptic failure and depletion of neurotransmitters
      • Acetylcholine (AcH)
        o Loss of cholinergic activity correlated with AD severity
        o Late stage AD has reduced cholinergic neurons and a loss of nicotinic receptors in hippocampus and cortex
        o Presynaptic nicotinic receptors control release of important neurotransmitters like AcH and others that are important in memory and mood
        o Therapeutic target
          ▪ Increase AcH to improve/minimize symptoms
      • Abnormalities in glutamate pathways of cortex and limbic structures
        o Excitotoxicity can contribute to AD
        o Blocking N-methyl-D-aspartate (NMDA) receptors can decrease activity of glutamate and possibly decrease cellular injury
    ▪ Mitochondrial dysfunction
    ▪ Oxidative stress
    ▪ Impaired insulin signaling in the brain
    ▪ Inflammatory processes
      o Thought to be an inflammatory response to amyloid deposition in attempt to clear plaques
      o Release of cytokines and chemokines are elevated in AD brains
    ▪ Loss of calcium regulation
  o Diabetes (DM can increase risk of dementia\textsuperscript{3,4}
    ▪ Effects of potentially toxic glucose metabolites on the brain and vasculature
    ▪ Disturbances in insulin-signaling pathways
      • Periphery and brain
    ▪ It is possible that insulin may also regulate the metabolism of beta amyloid and tau proteins
      o Pathogenesis of AD is still not clearly defined but is most likely a multi-modal mechanism
      o Common features of AD remain the same no matter what the cause

Figure 3: Normal neuron vs AD neuron

![Image from: https://whyfiles.org/117alzheimer/2.html](https://whyfiles.org/117alzheimer/2.html)
- Accumulation of NFTs and amyloid plaques
- Destruction of cholinergic pathways
- Dementia that slowly progresses until death

- Presentation\textsuperscript{3,4,5,7}

Table 1: Signs/Symptoms of AD

<table>
<thead>
<tr>
<th>Signs and Symptoms</th>
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</thead>
<tbody>
<tr>
<td>Memory loss – poor recall and misplacing things</td>
</tr>
<tr>
<td>Aphasia – speech changes</td>
</tr>
<tr>
<td>Apraxia – inability to coordinate facial/lip movements and trouble planning speech movements</td>
</tr>
<tr>
<td>Agnosia – inability to interpret sensations or recognize things</td>
</tr>
<tr>
<td>Disorientation – impaired perception of time and inability to recognize familiar faces</td>
</tr>
<tr>
<td>Impaired executive function</td>
</tr>
<tr>
<td>Inability to care for self</td>
</tr>
<tr>
<td>Depression/psychotic symptoms</td>
</tr>
<tr>
<td>Behavioral disturbances</td>
</tr>
</tbody>
</table>

- Diagnosis\textsuperscript{3,4,7}
  - Definitive diagnosis can only be confirmed by autopsy, but a clinical diagnosis is confirmed with the aid of the following
    - Imaging
      - Computerized tomography (CT)
      - Magnetic resonance imaging (MRI)
    - Labs
      - Rule out vitamin B12 and folate deficiencies
      - Rule out hypothyroidism
      - Complete blood count, electrolytes, and liver function tests
    - Patients exam and history should show
      - Cognitive decline from previously higher baseline
      - Cognitive decline has started to affect social or occupational functioning
    - Medication review and management to rule out medication causes
      - Cognitive impairment
        - Benzodiazepines, sedative hypnotics, anticholinergics, opioids, antipsychotics and anticonvulsants
      - Delirium
        - NSAIDs, histamine receptor, antagonists, digoxin, amiodarone, antihypertensives, and corticosteroids
  - Tools to monitor disease progression
    - See Appendix B for more information
    - Alzheimer’s Disease Assessment Scale-Cognition (ADAS-cog)
    - Mini-Mental Status Examination (MMSE)
    - Bushcke Selective Reminding Test (SRT)
    - Alzheimer’s Disease Cooperative Study Clinical Global Impression of change for Mild Cognitive Impairment (ADCS CGIC-MCI)
    - Wechsler Memory Scale Revised (WMS)
    - Neuropsychiatric Inventory Questionnaire (NPI-Q)
    - Digit Span (forward/backward)
- Clox Exam
- St. Louis University Mental Status Exam (SLUMS)
- Stages of AD as defined by mini-mental status examination (MMSE)\textsuperscript{3,5}

Table 2: MMSE Scores

<table>
<thead>
<tr>
<th>Stage</th>
<th>MMSE Scores</th>
<th>Signs/symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>26-18</td>
<td>- Difficulty remembering recent events</td>
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<tr>
<td></td>
<td></td>
<td>- Ability to manage finances, prepare food, and carry out other household activities</td>
</tr>
<tr>
<td>Moderate</td>
<td>17-10</td>
<td>- Requires assistance with activities of daily living</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Disoriented to time</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Recall of recent events is severely impaired</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Forgets details of past life, names of family and friends</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Fluctuation of functioning</td>
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<tr>
<td></td>
<td></td>
<td>- Generally, denies problems but can become suspicious or tearful</td>
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<tr>
<td></td>
<td></td>
<td>- Driving ability lost</td>
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<td></td>
<td></td>
<td>- Agitation, paranoia and delusions can occur</td>
</tr>
<tr>
<td>Severe</td>
<td>9-0</td>
<td>- Lost ability to speak, walk and feed self</td>
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<td></td>
<td></td>
<td>- Incontinence of urine and feces</td>
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<td></td>
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<td>- 24/7 care required</td>
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</tbody>
</table>

- Management\textsuperscript{3,4,8}
  - Presently no cure for AD exists
  - Goals of treatment are to treat symptoms of AD and preserve patients’ cognitive function for as long as possible\textsuperscript{8}
  - General treatment options
    - Mild to moderate disease
      - Donepezil
      - Rivastigmine
      - Galantamine
      - Titrate to recommended maintenance dose as tolerated
    - Moderate to severe disease
      - Donepezil
      - Consider adding memantine
      - Titrate to recommended dose
    - Consider memantine or cholinesterase inhibitor therapy alone
  - Non-Pharmacological
    - Behavioral interventions to aid in the following
      - Sleep disturbances, wandering, urinary incontinence, agitation, depression, anxiety, and aggression
Figure 4: Non-pharmacological options

- **Pharmacotherapy**
  - Choice of pharmacologic agent should be based on tolerability, adverse effect profile, ease of use, and cost of medication\(^1\)
  - Cholinesterase inhibitors
    - All show similar symptomatic improvement in cognitive, global, and functional outcomes for mild to moderate AD
    - Duration of benefit varies from 3-12 months
    - Do not abruptly discontinue these agents
      - Worsening cognition and behavior have been noted
  - Combination therapy
    - Generally, for moderate to severe AD
    - Adding different MOAs for improved symptom relief
    - Significantly better outcomes including slowed cognitive and functional decline vs monotherapy

<table>
<thead>
<tr>
<th>Table 3: Cholinesterase Inhibitors(^3,^8,^9)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medication</strong></td>
</tr>
<tr>
<td>MOA</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>C/I</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>ADEs</td>
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<td>------</td>
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<tr>
<td>Initial Dose</td>
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<tr>
<td>Usual Range</td>
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<td></td>
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<tr>
<td>Adjustments</td>
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<tr>
<td>Monitoring</td>
</tr>
<tr>
<td>Additional</td>
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<td></td>
</tr>
</tbody>
</table>

**Table 4: Antiglutamatergic Medications**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Memantine (Namenda)</th>
<th>Memantine ER (Namenda XR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOA</td>
<td>NMDA-antagonist which in turn blocks glutamatergic neurotransmission Mitigates excitotoxic neurotoxicity and provides neuroprotection Prevents glutamatergic overstimulation at NMDA receptors</td>
<td></td>
</tr>
<tr>
<td>C/I</td>
<td>Hypersensitivity to memantine or any component of its formulation</td>
<td></td>
</tr>
<tr>
<td>ADEs</td>
<td>Headache, constipation, confusion, and dizziness Nausea/vomiting/diarrhea</td>
<td></td>
</tr>
<tr>
<td>Initial Dose</td>
<td>5mg daily</td>
<td>ER: 7mg daily</td>
</tr>
<tr>
<td>Usual Range</td>
<td>10mg BID</td>
<td>ER: 28mg daily</td>
</tr>
<tr>
<td>Adjustments</td>
<td>Severe renal impairment: target dose of 5mg BID or 14mg daily ER cap</td>
<td></td>
</tr>
<tr>
<td>Monitoring</td>
<td>Cognitive function, functional outcomes such as activities of daily living, periodic ophthalmic exam</td>
<td></td>
</tr>
<tr>
<td>Additional</td>
<td>Indicated for moderate to severe AD Alone or in combination with cholinesterase inhibitors Long half-life around 60-80 hours</td>
<td></td>
</tr>
</tbody>
</table>
Neuropsychiatric symptom management\(^3,4,7\)

- **Antipsychotics**\(^9\)
  - Not FDA approved for neuropsychiatric symptoms in patients with AD
  - Modest treatment benefit and increased potential for significant harm
    - Consider individual risk/benefit
    - Patients with severe symptoms that have not responded to other measures and should not be used beyond 12 weeks
  - **Adverse effects**
    - Somnolence, extrapyramidal symptoms, abnormal gait, worsening cognition, and cerebrovascular events
  - **Black box warning for increased risk of death in patients with AD**\(^8\)

- **Antidepressants**\(^7\)
  - Selective serotonin reuptake inhibitors (SSRIs) are used most often in patients with AD
  - Citalopram, Escitalopram, and Sertraline are well tolerated in this patient population and most often utilized
  - Avoid tricyclic antidepressants (TCAs) because of their anticholinergic activity and potential to worsen AD
  - Low dose trazodone has been used to treat insomnia in patients with AD

### Table 5: Adapted from Table 2 in the American Geriatric Society Guidelines\(^8\)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Medication</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agitation in psychosis</td>
<td>Aripiprazole, Olanzapine, Quetiapine, Risperidone</td>
<td>2.5-12.5mg daily, 2.5-10mg daily, 12.5-100mg daily, 0.25-3mg daily</td>
</tr>
<tr>
<td>Agitation in depression</td>
<td>SSRIs, Citalopram, Sertraline</td>
<td>10-30mg daily, 25-200mg daily</td>
</tr>
<tr>
<td>Anxiety/mild-moderate irritability</td>
<td>Buspirone, Trazodone</td>
<td>15-60mg daily, 50-100mg daily</td>
</tr>
<tr>
<td>Agitation or aggression unresponsive to 1(^{st}) line</td>
<td>Carbamazepine, Divalproex, Olanzapine intramuscular (IM)</td>
<td>300-600mg daily, 500-1500mg daily, 2.5-5mg daily</td>
</tr>
<tr>
<td>Sexual aggression/impulse control symptoms in men</td>
<td>Second generation antipsychotic or divalproex, If no response: conjugated equine estrogens OR Medroxyprogesterone IM</td>
<td>see above, 0.625-1.25mg daily, 100mg q week</td>
</tr>
</tbody>
</table>

**Insulin resistance in Alzheimer’s disease**\(^3,10-12\)

- “Type 3 Diabetes” and insulin’s role in AD\(^10-12\)
  - Recently proposed that AD is an “insulin-resistant brain state” and it has also been referred to as “type 3 diabetes”
  - Insulin’s effect on beta amyloid and tau proteins
  - **Insulin has been noted to promote brain beta amyloid clearance**
  - **In rat models insulin has shown a biphasic effect on tau phosphorylation**
• Short-term administration showed rapid hyperphosphorylation while long-term administration resulted in decreased phosphorylation
  ▪ Insulin resistance in the brain is associated with increased levels of tau and amyloid beta proteins which are key lesions noted in AD patients
  ▪ Neurons in the brains of patients with type 2 diabetes could be more vulnerable to the toxic effects of amyloid beta proteins due to insulin resistance and deficiency
  ▪ Insulin resistance/deficiency could lead to increased production of amyloid beta plaques which could induce oxidative damage to mitochondria
  ○ Insulin resistance and low levels of insulin in the brain are associated with cognitive impairment and AD\textsuperscript{10-12}
    ▪ One mechanism that has been observed is amyloid beta oligomers binding to hippocampal neurons which then trigger the removal of dendritic insulin receptor substrates from plasma membranes
    ▪ Reductions in brain glucose metabolism have been associated with AD
    ▪ Deficits in insulin signaling, reduced sensitivity pertaining to leptin and neurotrophins, and therapeutic responsiveness to incretins have been noted in AD patients
    ▪ Decreased levels and sensitivity of insulin, insulin growth factor, and insulin receptors were noted in AD neuropathology
  ○ These concepts lead to the hypothesis that insulin or insulin sensitizers can be utilized in the prevention of progression of AD

Figure 5: Possible mechanism of antidiabetics in treatment of AD\textsuperscript{11}

• Metformin
  ○ Hypothesized MOA related to AD
    ▪ Insulin sensitizers can be utilized to modulate insulin resistance in the brain which may lead to development of AD
    ▪ Metformin activates AMP-activated protein kinase (AMPK) which enhances insulin signaling\textsuperscript{13}
      • AMPK also regulates tau phosphorylation and amyloid beta production
Table 6: Metformin

<table>
<thead>
<tr>
<th>Medication</th>
<th>Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOA</td>
<td>Decreases hepatic glucose production, decreases intestinal absorption of glucose and <strong>improves insulin sensitivity</strong></td>
</tr>
</tbody>
</table>
| C/I        | Severe renal dysfunction eGFR <30 mL/minute/1.73 m2  
             | Acute or chronic metabolic acidosis with or without coma  
             | Hypersensitivity to metformin or any component |
| ADEs       | Nausea, vomiting, diarrhea, flatulence  
             | Lactic acidosis  
             | B12 deficiency |
| Initial Dose | 500mg once daily  
               | SA: 500mg to 1g once daily |
| Usual Range | 2.5g daily in divided doses  
               | SA: 2000mg daily |
| Adjustments | eGFR 45-60 max 2g/day  
               | eGFR 30-45 preexisting: do not initiate; max 1g/day  
               | eGFR falls between 30-45 during therapy: dose reduce 50%; max 1g/day  
               | eGFR <30 use is contraindicated |
| Monitoring | Blood glucose, hemoglobin A1c, hemoglobin/hematocrit, red blood cells, renal function, vitamin B12, and folate |

Clinical Question and Evidence Review

**Clinical Question: Does metformin have a role in the management of Alzheimer’s Disease?**

- Literature Review\(^{11-13}\)

**Table 7: Epidemiologic studies\(^{14-18}\)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| Peila et al.   | The Honolulu-Asian Aging Study found that diabetes in old age is related to an increased risk of AD and AD pathology on autopsy  
                 | Notably in patients with APOE*4 allele                                                                                                                                                                   |
| Otta et al.    | Type 2 diabetes was noted to almost double the risk of dementia and AD                                                                                                                                 |
| Luchsinger et al. | Study evaluating vascular risk factors; diabetes and smoking were the strongest risk factors for developing AD                                                                                               |
| Xu et al.      | 1301 patients in Sweden aged 75 years and older found diabetes had no significant relationship with AD but did have a significant relationship with vascular dementia                                                |
| Cheng et al.   | Meta-analysis; the aggregate relative risk of AD for patients with diabetes was lower than relative risk for vascular dementia                                                                           |

- Recent studies
  - In recent studies evaluating antidiabetics for prevention of AD patients without APOE*4 responded better than those with APOE*4  
    - Suggests that patients with genetically linked AD may not benefit from therapies targeting insulin

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Table 8: Recent Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| Hsu et al.    | Study conducted in Taiwan found that type 2 diabetes increased risk for dementia more than two-fold  
Compared to untreated diabetics those treated with sulfonylureas experienced a reduction in hazard ratio and those treated with metformin had an even greater reduction in hazard ratio |
| Moore et al.  | Australian study reported an increased risk for cognitive impairment among type 2 diabetics following long-term treatment with metformin  
Adverse effects found were largely due to Vitamin B12 deficiencies  
Once corrected decreased risk for cognitive impairment was seen |
| Ng et al.     | Study in Singapore showed metformin provided neuroprotection in older adults with type 2 diabetes (T2DM)                                                                                                     |
| Gupta et al.  | Metformin influenced insulin resistance and reduced AD type changes of tau hyperphosphorylation and beta amyloid overproduction in a hyper-insulin induced cell line                                              |

- In depth literature Review

Table 9: Luchsinger et al.

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Purpose</td>
<td>• To obtain preliminary evidence of feasibility, safety, and efficacy of metformin for Alzheimer’s disease (AD) prevention among patients with amnestic mild cognitive impairment (AMCI)</td>
</tr>
<tr>
<td>Design</td>
<td>• Double-blind, placebo-controlled, randomized pilot trial, single site study</td>
</tr>
</tbody>
</table>
| Patient Population | • Inclusion:  
  o Age 55-90 years old with AMCI defined by Petersen criteria without treated diabetes (DM) and with BMI 25kg/m2 or higher  
  o Memory complaint expressed by participant and recognized by informant  
  • Exclusion:  
    o Individuals with dementia, current psychiatric disorders such as depression, bipolar or schizophrenia, individuals with uncontrolled hypertension, cancer within the last 5 years, use of cholinesterase inhibitors or memantine |
| Intervention | • Patients were randomized to metformin or placebo in a 1:1 ratio  
  • Randomization was stratified and blocked  
  • Metformin was administered as 500mg tablets and was titrated weekly from 500mg once daily to 1000mg BID  
  • Patients were maintained on the highest tolerated dose |
| Outcomes | • Primary outcome: changes from baseline to month 12 in total recall of Buschke Selective Reminding Test (SRT) and AD assessment scale-cognitive subscale (ADAS-cog)  
  • Secondary outcome: imaging outcomes such as change in relative glucose uptake (rCMRgl) in the posterior cingulate-precuneus in brain Fluorodeoxyglucose Positron Emission Tomography |
| Statistics | • Baseline characteristics between metformin and placebo group T-tests were used to compare means, and chi-squared to compare proportions  
  • Analysis of covariance (ANCOVA) was used to compare outcomes between treatment groups following intention to treat approach and adjusting for variable that were different at baseline |
Post-hoc analyses relating dose of metformin to outcomes with linear regression using placebo and persons who did not tolerate metformin as reference and stratified analyses by APOE*4, age, BMI, fasting insulin, and HbA1c

Statistical significance established at two-sided alpha of 0.05

Results

331 patients were screened in person, 87 met eligibility criteria and 7 declined randomization
80 were randomized; 40 in each arm
65 patients completed 12-month follow-up, 6 completed 9-month follow-up, and 9 had less than 9 months of follow-up
Only difference in baseline characteristics was lower ADAS-Cog score in metformin group; comparison of primary outcome is adjusted for this variable
Both SRT and ADAS-Cog scores improved in placebo and metformin groups
A statistically significant difference was noted for SRT with greater improvement noted in the metformin group
No differences noted between groups for secondary outcomes
Stratified analyses showed metformin achieved statistically significant improvements in SRT scores for patients that were ≤ 63.7 years old, those without APOE*4, those with HbA1c ≤ 6%, and those with insulin levels > 9 IU/dL

Table 1a: comparison in primary clinical outcomes

<table>
<thead>
<tr>
<th></th>
<th>Metformin</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAS-Cog</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>12.0 ± 4.0</td>
<td>14.6 ± 6.1</td>
<td>0.02</td>
</tr>
<tr>
<td>Last visit</td>
<td>12.1 ± 3.8</td>
<td>12.8 ± 6.2</td>
<td>0.52</td>
</tr>
<tr>
<td>Crude difference</td>
<td>0.0 ± 3.3</td>
<td>-1.98 ± 5.5</td>
<td>0.06</td>
</tr>
<tr>
<td>Adjusted difference</td>
<td>-0.5 ± 4.1</td>
<td>-1.4 ± 4.1</td>
<td>0.34</td>
</tr>
<tr>
<td>Total recall SRT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>34.2 ± 7.9</td>
<td>36.1 ± 9.5</td>
<td>0.32</td>
</tr>
<tr>
<td>Last visit</td>
<td>43.6 ± 9.1</td>
<td>41.5 ± 8.4</td>
<td>0.31</td>
</tr>
<tr>
<td>Crude difference</td>
<td>9.4 ± 8.5</td>
<td>5.7 ± 8.7</td>
<td>0.05</td>
</tr>
<tr>
<td>Adjusted difference</td>
<td>9.5 ± 6.1</td>
<td>5.4 ± 6.1</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Strengths

Baseline characteristics were well matched between groups and adjustments were made for the baseline ADAS-Cog score difference between groups
Double-blind, placebo-controlled, randomized trial
All results were reported even those prior to adjustments

Limitations

Small sample size; not powered to detect significant differences
Post-hoc analysis results could be due to chance rather than accurate analysis
Designed as a pilot study evaluating feasibility, safety and efficacy

Conclusions

Author: safe and feasible to conduct a randomized trial of metformin among persons with MCI
Preliminary evidence of efficacy for total recall SRT but not ADAS-Cog was seen and is most significant with higher doses of metformin, among younger patient, those without APOE*4, those with lower HbA1c, and those with higher baseline fasting insulin levels
There is still a need for larger controlled trials to determine metformin use in AD
Reviewer: Metformin use in patients who are not currently taking antidiabetic medications and who have MCI has demonstrated benefit on total SRT scores from baseline to 12 months
It is important to take caution in the value of this conclusion as this trial has many limitations
Additional trials are needed that have been accurately powered to detect statistical differences
Table 10: Koenig et al.


| Purpose | To determine the CNS effects of metformin in AD |
| Design | 16 week randomized, double-blinded, placebo-controlled, crossover pilot study |

| Patient Population | Inclusion:  
| | • Non-diabetic patients with mild cognitive impairment and early AD  
| | • Age 55-80, no known history of DM or pre-diabetes, diagnosis of MCI or early dementia due to AD, fasting blood glucose <110 or HbA1c <6  
| | Exclusion:  
| | • Subjects with concomitant depressive symptomatology, potential vascular etiology to their cognitive complaints, any CNS disease other than suspected AD, history of DM or pancreatic, liver, or renal disease, history of substance abuse or dependence within the past two years, current use of medications with known adverse CNS effects |

| Intervention | Patients were randomized in a 1:1 ratio to receive metformin 2000mg/day for 8 weeks followed by placebo for 8 weeks or vice versa  
| | Dose titration schedule: metformin 500mg or placebo daily for week 1, then daily divided doses increased by 500mg per week until max of 2000mg/d (1000mg twice daily) was reached  
| | For patients with GI intolerance max tolerated dose was allowed |

| Outcomes | Primary outcome: outcomes in this study were exploratory; safety, cerebrospinal fluid analyses, functional neuroimaging, and cognition were all evaluated during this study  
| | Goals: to demonstrate that a “nimble phenotyping trial design could be implemented in a clinical population with early AD, to determine whether metformin was safe, tolerated, and biologically-active in the CNS of individuals with AD, and to explore whether metformin exerted salutary effects on AD cognitive and biological markers |

| Statistics | Descriptive statistics were used to characterize and compare the treatment arms  
| | Differences across groups were tested using Fisher’s Exact Test or Wilcoxon Rank-sum with Wilcoxon signed-rank test used for pairwise comparisons  
| | P value < 0.05 was considered significant and p < 0.10 was considered a trend  
| | Alpha = 0.05 and power = 0.80 |

| Results | 20 subjects met eligibility criteria and were enrolled, and all completed the 16 week study  
| | 9 women and 11 men all being Caucasian participated; mean age 70, baseline demographic measures did not differ significantly between treatment groups  
| | Most common side effects were GI related, lactic acidosis and hypoglycemia  
| | Cerebrospinal fluid (CSF) was collected at week 0 and week 8; no significant change within individuals in CSF glucose or protein levels or in CSF amyloid beta, total tau, or phosphorylated tau levels across groups  
| | No statistically significant treatment effects were seen in any of the MRIs taken at week 0, 8, and 16 on regular analysis but on post-hoc analysis a significant increase in superior and middle orbitofrontal cerebral blood flow over 8 weeks of treatment with metformin but not placebo  
| | Statistically significant treatment effect of metformin was observed in ONE measure of executive functioning (Trails-B)  
| | Statistical trends favoring metformin for a measure of learning and memory and a measure of attention |

Table 1b: Change in Executive Functioning

<table>
<thead>
<tr>
<th>Measure</th>
<th>Regression Coefficient</th>
<th>df</th>
<th>F value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-19.8817</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sequence</td>
<td>16.7682</td>
<td>1,13</td>
<td>1.71</td>
<td>0.2143</td>
</tr>
<tr>
<td>Phase</td>
<td>-0.4488</td>
<td>1,13</td>
<td>0.00</td>
<td>0.9543</td>
</tr>
<tr>
<td>Drug</td>
<td>-18.2646</td>
<td>1,13</td>
<td>5.64</td>
<td>0.0337</td>
</tr>
</tbody>
</table>
Strengths
- Baseline characteristics between groups were well matched
- Study population was relevant to clinical practice in that they looked at patients without DM diagnosis but at high risk of developing AD

Limitations
- Small study population with multiple points of analysis
- Outcomes were not specifically defined
- Pilot study with short follow-up
- No washout period between cross over groups

Conclusions
- **Author:** Metformin penetrates the blood-brain barrier but did not exert a measurable effect on CSF in this study
- Improved executive functioning with metformin treatment was noted with trends suggesting improvement of learning, memory, and attentional abilities
- **Reviewer:** Some benefit was noted with metformin use in this population specifically learning, memory, and attention but with the small sample size and multiple limitations it is difficult to extrapolate this data to the general population
- Additional studies are warranted and should examine similar endpoints

Table 11: Shi et al

<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Purpose</strong></td>
</tr>
<tr>
<td><strong>Design</strong></td>
</tr>
</tbody>
</table>
| **Patient Population** | **Inclusion:**
- Veterans with T2DM who were ≥ 50 years old
- Index date: first date of DM diagnosis
**Exclusion:**
- ND before index date, mental disorder, drug abuse, alcohol abuse, cognitive impairment due to intracranial or head injury, subsequent effects of cerebrovascular disease, severe disease such as cancer, renal failure, or cirrhosis, pregnant |
| **Intervention** | Metformin exposure from index date to time of first clinical outcome (diagnosis of ND) |
| **Outcomes** | **Primary outcome:** first diagnosis of ND including dementia, Alzheimer’s disease (AD), Parkinson’s disease (PD), Huntington’s disease (HD) and mild cognitive impairment during the follow-up period
**Secondary outcome:** separately measured AD, PD, HD, dementia, and cognitive impairment |
| **Statistics** | Statistical differences between sub-cohorts of metformin use, never used metformin, and length of metformin exposure were compared by one-way analysis of variance for continuous variables and chi square test for categorical variables
- Controlled for age, gender, race, medical history and other oral antidiabetic medications
- Incidence rates for ND were given for entire sample size and for metformin exposure sub-cohorts with and without controlling for the above factors
- 95% confidence intervals (CI) were presented as well as two-tailed alpha level of 0.05 to determine statistical significance |
Results

- 6046 patients with a median follow-up of 5.2 years; mean age 63 years old, 97.62% male and 59.97% white
- 2993 never received metformin therapy, 932 received less than 1 yr, 566 received 1-2 years, 789 received 2-4 years, and 766 more than 4 years
- Metformin exposure cohort showed 11.48 ND cases per 1000 patients per year compared to 25.45 ND cases per 1000 patients per year in the group without metformin exposure
- Incidence rate of dementia was 8.46 cases per 1000 patients per year compared to 19.82 cases per 1000 patients per year with and without metformin respectively
- Cohorts of 2-4 years and ≥ 4 years of metformin exposure were both significantly associated with lower risk of ND
- Cohorts with metformin exposure >2 years had significantly lower risk of dementia compared with non-metformin treatment
- Less than 2 years of metformin exposure did not demonstrate potential benefit for any kind of ND
- Metformin exposure greater than 2 years was associated with significantly lower risk of developing ND, dementia, PD, or AD

Table 1c: Hazard Ratios

<table>
<thead>
<tr>
<th>Length of metformin exposure</th>
<th>≤1 year vs no</th>
<th>1-2 years vs no</th>
<th>2-4 years vs no</th>
<th>&gt;4 years vs no</th>
</tr>
</thead>
<tbody>
<tr>
<td>ND</td>
<td>aHR*</td>
<td>95% CI</td>
<td>aHR*</td>
<td>95% CI</td>
</tr>
<tr>
<td>0.88</td>
<td>0.64 to 1.21</td>
<td>0.80</td>
<td>0.60 to 1.33</td>
<td>0.62</td>
</tr>
<tr>
<td>Dementia</td>
<td>1.51</td>
<td>0.93 to 2.46</td>
<td>0.56</td>
<td>0.24 to 1.31</td>
</tr>
<tr>
<td>PD</td>
<td>2.19</td>
<td>0.86</td>
<td>0.88</td>
<td>0.33 to 2.21</td>
</tr>
<tr>
<td>Mild cognitive impairment†</td>
<td>0.86</td>
<td>0.19 to 3.81</td>
<td>1.50</td>
<td>0.36 to 6.19</td>
</tr>
</tbody>
</table>

*Non-metformin treatment cohort was the reference group for adjusted HR (aHR) estimation.
†Bad estimation due to small number of events.
AD, Alzheimer’s disease; ND, neurodegenerative disease; PD, Parkinson’s disease; PSW, propensity score weight.

Strengths

- Statistical analysis was controlled for cohort demographics, clinical characteristics and antidiabetic medications at baseline using propensity score weights
- Large population size
- Clinically relevant outcomes studied

Limitations

- Study arms were not matched for baseline characteristics or population size
- B12 levels were not monitored for the patient population
- Retrospective trial with confounders such as additional antidiabetic medications
- Difficult to extrapolate findings beyond this patient population, which was largely older, white, males

Conclusions

- **Author:** Long-term metformin therapy > 2 years was associated with lower incidence of ND and the subtype outcome of dementia among elderly veterans with T2DM. **Only** metformin use >4 years was associated with lower incidence of PD and AD.
- **Reviewer:** Although, benefit was noted with long-term metformin use for decreased incidence in ND in this trial, it is important to note that several statistical corrections had to be made to arrive at this conclusion. Additional trials are needed in which cohorts are well matched in size as well as baseline characteristics.
Information Summary

Table 12: Summary

<table>
<thead>
<tr>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Questions surrounding Alzheimer’s disease pathogenesis and targets for prevention as well as treatment still exist</td>
</tr>
<tr>
<td>• Patients with diabetes are at an increased risk for developing AD</td>
</tr>
<tr>
<td>• Insulin is known to play a role in development of AD</td>
</tr>
<tr>
<td>• Insulin resistance in the brain is associated with increases in tau and amyloid beta proteins which are key characteristics of AD</td>
</tr>
<tr>
<td>• Currently studies involving different antidiabetic medications for the use in AD are ongoing</td>
</tr>
<tr>
<td>• Still a need for additional randomized clinical trials evaluating the benefit of metformin use in Alzheimer’s disease</td>
</tr>
<tr>
<td>• Metformin has demonstrated conflicting evidence in the improvement of cognition and prevention of neurodegenerative disorders</td>
</tr>
<tr>
<td>• Current literature is limited by small population size and modest improvements of cognition</td>
</tr>
</tbody>
</table>

Presenter’s Recommendations

Table 6: Recommendations

Do NOT Recommend

- For routine use in the prevention of AD

Could Consider Recommending

- Patients with diagnosis of pre-diabetes or diabetes despite age
  - Patients with elevated BMI, FBG, or HbA1c without the diagnosis of diabetes
    - with MCI and additional risk factors
    - without APOE*4 allele
    - without contraindications to metformin
References


Appendix A: Most common dementia types

- **Lewy Body Dementia**
  - Problems with thinking, memory, movements, trembling, hallucinations, and REM sleep disturbances
  - Characterized by Lewy bodies which are abnormal alpha-synuclein protein fragments

- **Alzheimer’s Dementia**
  - Changes in mood, confusion, and memory loss
  - Key lesions are amyloid beta plaques and tau tangles

- **Vascular Dementia**
  - Lack of blood flow to the brain
  - Risk factors: HTN, stroke, smoking, DM, HLD, and obesity

- **Mixed Dementia**
  - Signs and symptoms of more than one type of dementia
## Appendix B: Mental status exams

<table>
<thead>
<tr>
<th>Exam</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SRT</strong></td>
<td>Designed to measure verbal learning and memory using a list-learning procedure over multiple trials. Involves reading the subject a list of 12 unrelated words and then asking them to recall immediately as many of these 12 words as possible. The process is repeated with the words the subject didn’t remember until all 12 words are remembered, or 12 trials have been completed.</td>
</tr>
<tr>
<td><strong>ADAS-cog</strong></td>
<td>Worsens by 5 points in 1 year for mild disease and 7-11 points in 1 year for moderate disease. 4-point change represents a clinically significant change. Used in clinical trials and most frequently used test to measure cognition (ADAS). Subscale that measures cognitive ability. Primarily measures language and memory and is more thorough than MMSE. Consists of 11 parts and takes approx. 30 min to admin.</td>
</tr>
<tr>
<td><strong>ADCS CGIC-MCI</strong></td>
<td>A means to assess global change in a mild cognitive impairment clinical trial by providing a semi-structured format to allow clinicians to gather necessary clinical information from both subject and informant to allow for an overall impression and clinical change.</td>
</tr>
<tr>
<td><strong>WMS revised</strong></td>
<td>Measures different memory functions in a person. Made up of seven subtests (spatial addition, symbol span, design memory, general cognitive screener, logical memory, verbal paired associates, and visual reproduction). 5 index scores reported for auditory memory, visual memory, visual working memory, immediate memory, and delayed memory.</td>
</tr>
<tr>
<td><strong>MMSE</strong></td>
<td>Untreated patients show average decline of 2-4 points per year. Successful treatment shows decline of less than 2 pts per year. 30-point questionnaire that is used extensively in research to measure cognitive impairment. Tests orientation, attention, memory, language and visual-spatial skills. Scores need to be adjusted for education level.</td>
</tr>
<tr>
<td><strong>NPI-Q</strong></td>
<td>Informant-based interview that assesses neuropsychiatric symptoms over the previous month. Doesn’t ask the patient but asks the patient’s care giver these questions.</td>
</tr>
<tr>
<td><strong>Digit span</strong></td>
<td>Most commonly used test to assess working memory capacity because digit-span task cannot be affected by factors such as semantics, frequency of appearance in daily life, complexity etc. Item recall backwards for a specific sequence of numbers. Measures working memory’s number storage capacity.</td>
</tr>
<tr>
<td><strong>CLOX</strong></td>
<td>Executive clock drawing task. Have the patient draw a clock with a specific time including clock hands and numbers then score it in the CLOX1 section. Evaluator draws a clock and asks patient to copy that drawing this is evaluated in CLOX2 section.</td>
</tr>
</tbody>
</table>