Lithium and Dementia: A Memory ‘Fresh-Up’?

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Learning Objectives:

1. Review the pathophysiology and presentation of dementia, including its impact on society
2. Describe the diagnosis of dementia, cognitive function tests, and current treatment modalities
3. Discuss the current use of lithium and its possible mechanism of actions related to cognitive function
4. Analyze evidence for neuroprotection with lithium
5. Formulate a recommendation regarding appropriate candidates for neuroprotection with lithium
I. Introduction
   A. Broad term describing a range of symptoms
      1. Results from decline in cognitive function
      2. Not part of the normal aging process
      3. Impairs emotional control and/or ability to perform activities of daily living (ADLs)\textsuperscript{1,2}
   B. Now ‘major or mild neurocognitive disorders’ (NCD)\textsuperscript{3}
      1. Further delineated by causation
      2. Alzheimer’s disease (AD), Parkinson’s disease, Lewy body disease, human immunodeficiency virus (HIV) infection, frontotemporal lobar degeneration, or other conditions\textsuperscript{3}
   C. Modest or significant cognitive decline from previous level of performance in \( \geq 1 \) cognitive domains\textsuperscript{3}

<table>
<thead>
<tr>
<th>Domain</th>
<th>Description</th>
<th>Major criteria</th>
<th>Mild criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex attention</td>
<td>Sustained attention, divided attention, selective attention, processing speed</td>
<td>↑ difficulty with multiple stimuli; easily distracted; difficulty holding new information in mind</td>
<td>Normal tasks take longer; finds errors in routine tasks; work needs more double-checking</td>
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<tr>
<td>Executive function</td>
<td>Planning, decision making, working memory, responding to feedback/error correction, overriding habits/inhibition, mental flexibility</td>
<td>Abandons complex projects; must focus on 1 task at a time; must rely on others to plan instrumental ADLs (iADLs) or make decisions</td>
<td>↑ difficulty multitasking or resuming an interrupted task; extra effort (and ↑ fatigue) to organize, plan, make decisions</td>
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<tr>
<td>Learning &amp; memory</td>
<td>Immediate memory, recent memory [free or cued recall, recognition memory], very-long-term memory [semantic; autobiographical], implicit learning</td>
<td>Repeats self in conversation; cannot track short lists when shopping or plans for day; frequent reminders to reorient to task</td>
<td>Difficulty recalling recent events; ↑ reliance on lists or calendar; needs reminders to track book/movie characters; loses track of bills paid</td>
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<tr>
<td>Language</td>
<td>Expressive language [naming, word finding, fluency, grammar, syntax] and receptive language</td>
<td>Significant difficulty with expressive or receptive language; may not even recall names of close friends or family; decreased speech, echolalia</td>
<td>Noticeable word-finding difficulty; avoids specific names or terms; subtle grammatical errors</td>
</tr>
<tr>
<td>Perceptual-motor</td>
<td>Abilities subsumed under terms: visual perception, visuo-constructional, perceptual-motor, praxis, and gnosis</td>
<td>Significant difficulty with previously familiar activities or navigation; more confused at night or in lower light</td>
<td>More reliance on maps/others for directions; less precise in parking; ↑ effort for spatial tasks i.e. sewing</td>
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<tr>
<td>Social cognition</td>
<td>Recognition of emotions, theory of mind</td>
<td>Socially unacceptable behavior, i.e. dress or topics of conversation; disregard or unawareness of others’ reactions; disregard of safety; lack of insight into weather or social changes/cues</td>
<td>Subtle changes in behavior or attitude, i.e. ↓ ability to recognize social cues, ↓ empathy, ↑ extra- or introversion, ↓ inhibition</td>
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</table>

II. Epidemiology\textsuperscript{1-4}
   A. Dementia/major NCD prevalence estimated as 1-2% at age 65 years and up to 30% by 85 years\textsuperscript{3}
   B. Mild cognitive impairment (MCI) less well defined: 2-10% at age 65 and 5-25% by age 85\textsuperscript{3}
C. Other causes

1. Parkinson’s disease dementia (PDD): 50-80% of people with Parkinson’s disease
2. Mixed dementia
3. Creutzfeldt-Jakob disease
4. HIV infection
5. Traumatic brain injury (TBI)

III. Impact on Society

A. Prevalence and incidence

1. Estimated 5.3 million Americans with AD
   a. Of those, 5.1 million adults >65 years
      i. One in nine (11%) adults >65 years
      ii. Roughly one-third of adults 85 years and older
   b. Aging, Demographics and Memory Study (ADAMS): estimated 14% of adults >71 years have dementia
   c. Demographic differences
      i. Approximately 3.2 of the 5.1 million are women
      ii. African Americans: twice as likely as older whites to have AD/other dementias
      iii. Hispanics: 1-1.5 times as likely as older whites to have AD/other dementias

2. From 2015 to 2025, AD prevalence expected to increase at least 14% due to aging population
   a. In 2015: roughly every 67 seconds, someone in the US develops AD
   b. By 2050: projected to increase to one every 33 seconds

3. Past, present, future
   a. New cases
      i. In 2010: ~454,000 new cases
      ii. By 2030: projected 615,000 new cases (35% increase)
      iii. By 2050: projected 959,000 new cases (110% increase from 2010)
   b. Total cases of AD in those >65 years of age
      i. By 2025: may reach 7.1 million (40% increase from 2015)
      ii. By 2050: may reach 13.8 million, or as high as 16 million

B. Morbidity and mortality

1. Sixth leading cause of death in the US
2. Fifth leading cause of death in the US for age 65 and older
3. Dementia deemed the second largest contributor to death behind heart failure
4. From 2000 to 2013, deaths attributed to AD increased by 71%, while those attributed to heart disease decreased by 14%
5. Burden of disease, measured by daily adjusted life years (DALYs)
   a. From 1990 to 2010, AD rose from 25th to 12th most burdensome disease in the US
   b. In terms of years of life lost, AD rose from 32nd to 9th
   c. In terms of years lived with disability, AD rose from 17th to 12th

C. Caregiving

1. Care provided
   a. Assist with ADLs
b. Advocate for the care recipient to government agencies or service providers
c. Arrange and supervise paid caregivers

2. In 2014, caregivers of people with AD/other dementias provided ~18 billion hours unpaid care
   a. Nearly 22 hours of care per caregiver per week
   b. Valued at $12.17 per hour = $217.7 billion
   c. Nearly equal to costs of direct medical and long-term care for dementia

3. Impact on the caregiver
   a. Emotional well-being
   b. Financial strains
   c. Physical health
   d. Employment

D. Use and costs of health care, long-term care (LTC), and hospice
   1. Total payments in 2015 estimated at $226 billion for AD and other dementias
      a. Medicare and Medicaid expected to cover 68% ($153 billion)
      b. Out-of-pocket spending projected at $44 billion (19% of total payments)
   2. Average annual per person payment for health care and LTC, for Medicare beneficiaries age 65 and older, in 2014 dollars
      a. With AD and other dementias: $47,752
      b. Without AD and other dementias: $15,115
   3. Projected to increase to over $1 trillion in 2050 (in 2015 dollars)

IV. Pathophysiology and Presentation

<table>
<thead>
<tr>
<th>NCD</th>
<th>Pathophysiology</th>
<th>Characteristics</th>
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<tbody>
<tr>
<td>Alzheimer’s disease</td>
<td>• Amyloid plaques form from beta-amyloid protein deposits outside nerve cells</td>
<td>• Insidious onset, with gradual and progressive worsening of cognitive and behavioral symptoms</td>
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<tr>
<td></td>
<td>• Neurofibrillary tangles form from hyperphosphorylated tau protein inside cells</td>
<td>• Initially affects memory of recently learned information→ further ↓ memory and learning</td>
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<td>Vascular dementia</td>
<td>• Vascular changes from major stroke or multiple transient ischemic attacks (TIAs), infarcts or hypoperfusions</td>
<td>• Mood and emotional changes/instability</td>
</tr>
<tr>
<td>Dementia with Lewy Bodies</td>
<td>• Lewy bodies = abnormal aggregation (clumps) of protein α-synuclein, particularly in neurons of the cortex in people with dementia</td>
<td>• Confusion and alertness varying daily</td>
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<td></td>
<td></td>
<td>• Sleep disturbances and rapid eye movement (REM) sleep disorder, visual hallucinations</td>
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<td></td>
<td></td>
<td>• Parkinsonian movements (cognitive effects before or concurrent with movement sx’s)</td>
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<td></td>
<td></td>
<td>• Autonomic dysfunction</td>
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<tr>
<td>Frontotemporal dementia</td>
<td>• Progressive nerve cell loss in frontal and/or temporal lobes of the brain</td>
<td>• Most diagnosed in 40s to early 60s</td>
</tr>
<tr>
<td></td>
<td>o Behavior variant FTD (bvFTD)</td>
<td>• Early behavior and personality changes</td>
</tr>
<tr>
<td></td>
<td>o Primary progressive aphasia (PPA)</td>
<td>• Impaired language abilities (aphasia)</td>
</tr>
<tr>
<td></td>
<td>o Motor disturbances</td>
<td>• Motor (movement and muscle) disturbances may occur with or without behavior or language changes (i.e. Lou Gehrig’s Disease)</td>
</tr>
<tr>
<td>Parkinson’s Disease</td>
<td>• Lewy bodies (α-synuclein aggregates) in neurons of the substantia nigra</td>
<td>• Parkinson’s disease diagnosis ≥1 year prior</td>
</tr>
<tr>
<td>Dementia</td>
<td></td>
<td>(average ~10 years)</td>
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<tr>
<td>Mixed Dementia</td>
<td>• More than one type of dementia occur simultaneously</td>
<td>• Cognitive decline including changes in memory and judgment, delusions, visual hallucinations, and irritability and anxiety</td>
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<tr>
<td></td>
<td>• Most common: Alzheimer’s disease + vascular dementia</td>
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<td></td>
<td>• Often diagnosed with Alzheimer’s and then other diagnosis made at brain autopsy</td>
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</tbody>
</table>

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V. Reversible or Preventable Causes of Impairment⁶: **DEMENTIA-L**

A. Depression  
B. Excess alcohol use  
C. Medications (i.e. anticholinergic medications, corticosteroids)  
D. Electrolyte imbalances  
E. Normal pressure hydrocephalus tumor  
F. Thyroid dysfunction  
G. Infection – syphilis, AIDS  
H. Anemia – vitamin B12 or folate deficiency  
I. Liver disease

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### COGNITIVE FUNCTION TESTS, DIAGNOSTIC CRITERIA AND TREATMENT

#### I. Cognitive Function Tests and Diagnostic Criteria

<table>
<thead>
<tr>
<th>Table 3. Cognitive function tests⁸⁻¹⁴</th>
<th>Description</th>
<th>Scoring</th>
</tr>
</thead>
</table>
| **Mini Mental State Exam (MMSE)**  | ~10 minutes to administer, by MD  
• Areas of orientation, memory, attention and calculation, language and visual construction | 0-30 point scale (0 = worst)  
• ~23/24 = cognitive impairment  
• Normal: ≥27  
• Mild: 20-26  
• Severe: <10 |
| **The General Practitioner Assessment of Cognition (GP-COG)**  | Developed for primary care setting  
• <4 minutes for patient assessment, 2 minutes to interview caregiver  
• Short-term recall, time orientation, clock drawing, recall of recent news  
• Caregiver interview asks caregiver to assess patient now vs. 5-10 years ago | Patient exam: 0-9 point scale  
• 0-4: cognitive impairment  
• 5-8: more info required, proceed with step 2 (caregiver interview)  
• 9: no significant impairment  
• Caregiver interview: 0-6 point scale  
• 0-3: cognitive impairment |
| **Alzheimer's Disease Assessment Scale – Cognitive Section (ADAS-Cog)**  | Administered by MD or psychologist  
• Comprehensive cognitive test  
• Leading test for clinical (drug) trials | Scores 11 items, 0-70 point scale  
• ↑ score = ↑ cognitive impairment |
| **Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change (ADCS-CGIC)**  | Clinician’s assessment of change  
• Systematic way to assess clinically significant change in clinical trials | 7-point categorical scale assessing change from baseline in 15 areas  
• 1 = marked improvement to 7 = marked worsening |
| **St. Louis University Mental Status (SLUMS) Examination**  | Screens for cognitive deficits and identifies cognitive change over time  
• Accounts for level of education  
• 30 point scale |  
| **Neuropsychiatric Inventory (NPI)**  | Assesses behavioral changes that have appeared since illness onset  
• 12 domains; frequency rated 1-4 and severity rated 1-3 | Each domain score=freq x severity  
• Total score=sum of first 10 domains  
• 0-144 point scale  
• ↓ score = ↑ cognitive impairment |
| **Cambridge Cognitive Test (CAMCOG)**  | In: Cambridge Examination for Mental Disorders of the Elderly (CAMDEX)  
• Originally for primary degenerative dementia; advantage over some brief screening tests: covers a broader range of cognition in relatively short time | 67 items, 0-107 point scale  
• ↓ score = ↑ cognitive impairment  
• Detects mild cognitive deterioration  
• Cut-point 79/80 suggested to differentiate normal vs. demented  
• *Takes ~25 minutes |

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<table>
<thead>
<tr>
<th>Normal</th>
<th>High School</th>
<th>&lt; High School</th>
</tr>
</thead>
<tbody>
<tr>
<td>27-30</td>
<td>25-30</td>
<td></td>
</tr>
<tr>
<td>21-26</td>
<td>20-24</td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td>1-20</td>
<td>1-19</td>
</tr>
<tr>
<td>NCD</td>
<td>High School</td>
<td>&lt; High School</td>
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<tr>
<td></td>
<td>Normal</td>
<td>Mild</td>
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<td></td>
<td>Normal</td>
<td>Moderate</td>
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<tr>
<td></td>
<td>Normal</td>
<td>Severe</td>
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</tbody>
</table>

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Table 4. Diagnostic criteria for dementia/NCD$^{3,15,16}$

<table>
<thead>
<tr>
<th>DSM-IV-TR</th>
<th>Major NCD</th>
<th>DSM-5</th>
<th>Mild NCD</th>
<th>NINCDS-ADRDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Multiple cognitive impairments manifesting by both:</td>
<td>A. Evidence of significant cognitive decline from a previous level of performance in ≥1 cognitive domains based on:</td>
<td>A. Evidence of modest cognitive decline from a previous level of performance in ≥1 cognitive domains based on:</td>
<td>A. Moderate NCD</td>
<td>Dementia is diagnosed when there are cognitive or behavioral sx’s that:</td>
</tr>
<tr>
<td>1. Memory impairment</td>
<td>1. A concern of the individual, a knowledgeable informant, or clinician</td>
<td>1. A concern of the individual, a knowledgeable informant, or clinician</td>
<td>A. Interfere with ability to function at work or at usual activities; and</td>
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<tr>
<td>2. ≥1 of the following cognitive disturbances:</td>
<td>2. Substantial impairment in cognitive performance documented by standardized neuropsychological testing or another quantified clinical assessment</td>
<td>2. Modest impairment in cognitive performance documented by standardized neuropsychological testing or another quantified clinical assessment</td>
<td>B. Represent a decline from previous level of functioning and performing; and</td>
<td></td>
</tr>
<tr>
<td>a. Aphasia</td>
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<td></td>
<td>C. Are not explained by delirium or major psychiatric disorder; and</td>
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<tr>
<td>b. Apraxia</td>
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<td></td>
<td>D. Cognitive impairment is detected and diagnosed through a combination of (1) history-taking from patient + knowledgeable informant and (2) objective cognitive assessment (mental status exam or neuro-psychological testing)</td>
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<tr>
<td>c. Agnosia</td>
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<td></td>
<td>E. Cognitive or behavioral impairment involves ≥2 of the following domains:</td>
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<tr>
<td>d. Executive functioning</td>
<td></td>
<td></td>
<td>1. Impaired ability to acquire and remember new info</td>
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<tr>
<td>B. Cognitive deficits (A1, A2) cause significant impairment in social or occupational functioning and represent a significant decline from previous functioning</td>
<td>B. Cognitive deficits interfere with independence in iADLs</td>
<td>B. Cognitive deficits do not interfere with independence in iADLs</td>
<td>2. Impaired reasoning/handling of complex tasks, poor judgment</td>
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<tr>
<td>C. Gradual onset, continuing decline</td>
<td>C. Cognitive deficits do not occur exclusively in context of delirium</td>
<td>C. Cognitive deficits do not occur exclusively in context of delirium</td>
<td>3. Impaired visuospatial abilities</td>
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<tr>
<td>D. Cognitive deficits (A1, A2) are not due to the following:</td>
<td>D. Cognitive deficits are not better explained by another mental disorder</td>
<td>D. Cognitive deficits are not better explained by another mental disorder</td>
<td>4. Impaired language functions</td>
<td></td>
</tr>
<tr>
<td>1. Other CNS conditions</td>
<td>*Specify:</td>
<td></td>
<td>5. Changes in personality, behavior or comportment</td>
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<tr>
<td>2. Systemic conditions known to cause dementia (DEMENTA-L, above)</td>
<td>• Whether due to: Alzheimer’s disease, frontotemporal lobar degeneration, Lewy body disease, vascular disease, Parkinson’s disease, etc.</td>
<td></td>
<td>*Specify:</td>
<td></td>
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<tr>
<td>3. Substance-induced conditions</td>
<td>• With or without behavioral disturbances</td>
<td></td>
<td>1. Whether due to: Alzheimer’s disease, frontotemporal lobar degeneration, Lewy body disease, vascular disease, Parkinson’s disease, etc.</td>
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<tr>
<td>E. Deficits do not occur exclusively during the course of delirium</td>
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<td></td>
<td>2. With or without behavioral disturbances</td>
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<tr>
<td>F. Disturbance is not better accounted for by another Axis I disorder</td>
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<td></td>
<td>*Specify:</td>
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</table>

DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders, 4th ed., text rev.; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th ed.; NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association; iADLs = instrumental activities of daily living.
Table 5. DSM-5 diagnostic criteria for major or mild NCD due to AD

A. The criteria are met for major or mild neurocognitive disorder
B. There is insidious onset and gradual progression of impairment in ≥1 cognitive domains (for major NCD, at least two domains must be impaired)
C. Criteria are met for either probable or possible Alzheimer’s disease as follows:
   For major NCD: probable AD diagnosed if either of the following is present; otherwise, possible AD should be diagnosed
      1. Evidence of a causative AD genetic mutation from family history or genetic testing
      2. All three of the following are present:
         a. Clear evidence of decline in memory and learning and at least one other cognitive domain (based on history or serial neuropsychological testing)
         b. Steadily progressive, gradual decline in cognition, without extended plateaus
         c. No evidence of mixed etiology
   For mild NCD: probable AD diagnosed if there is evidence of a causative AD genetic mutation from either genetic testing or family history; possible AD is diagnosed if there is no evidence of a causative AD genetic mutation from either genetic testing or family history, and all three of the following are present:
      1. Clear evidence of decline in memory and learning
      2. Steadily progressive, gradual decline in cognition, without extended plateaus
      3. No evidence of mixed etiology
D. The disturbance is not better explained by cerebrovascular disease, another neurodegenerative disease, the effects of a substance, or another mental, neurological, or systemic disorder

II. Treatment
A. Current medications target symptoms of AD/dementia
B. New drugs in development target factors in the disease process
   1. Beta-amyloid (Aβ)
      a. Chief component of plaques
      b. Cleaved from amyloid precursor protein (APP) by beta-secretase and gamma-secretase
   2. Tau protein
      a. Chief component of tangles
      b. Goal: prevent phosphorylation and/or the collapsing and twisting of tau into tangles
   3. Inflammation
   4. Insulin resistance

Figure 2. Distinguishing treatment effects in AD
LITHIUM

I. Indications\textsuperscript{17,18}
A. FDA-approved: bipolar disorder
B. Off-label use: bipolar depression; augmentation of antidepressant in depression
C. For current uses, long-term: monitor to maintain serum lithium 0.6-1.2 mEq/L

II. Mechanism of Action\textsuperscript{17-20,22-28}
A. Mood disorders, thought to:
   1. Alter cation transport across nerve and muscle cell membranes
   2. Influence serotonin and/or norepinephrine reuptake
   3. Inhibit second messenger systems involving phosphatidylinositol cycle
B. May also provide neuroprotective effects
   1. Increase glutamate clearance
   2. Inhibit apoptotic glycogen synthase kinase activity
   3. Increase the levels of antiapoptotic protein Bcl-2
   4. Enhance the expression of neurotropic factors including brain-derived neurotrophic factor

III. Pharmacokinetics\textsuperscript{17,18}
A. Rapid and complete absorption
B. Not protein-bound, not metabolized
C. Half-life elimination 18-36 hours
D. Excreted unchanged primarily in the urine but also through sweat, saliva and feces
E. Roughly 80\% of filtered lithium reabsorbed in the proximal convoluted tubules

IV. Adverse effects\textsuperscript{17,18}
A. Gastrointestinal (GI) side effects (i.e. nausea, vomiting)
B. Renal dysfunction
C. Electrolyte abnormalities
D. Positional tremor
E. Hypothyroidism
F. Leukocytosis
G. Acne
H. Weight gain
I. Hyperglycemia
J. Cardiovascular conduction abnormalities

V. Concerns about use in the elderly\textsuperscript{17-19,24}
A. Toxicity: must monitor closely, adverse effects related to lithium plasma concentration

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{symptoms.png}
\caption{Common symptoms associated with increased serum lithium concentrations\textsuperscript{17,18}}
\end{figure}
B. Drug-drug and drug-food interactions
   1. Diuretics
   2. Angiotensin-converting enzyme (ACE) inhibitors
   3. Angiotensin-II receptor blockers (ARBs)
   4. Serotonergic agents
   5. Sodium intake
C. Renal function

LITHIUM AND NEUROLOGICAL FUNCTION

Figure 4. The pathophysiology of AD and potential targets for disease-modifying treatments\textsuperscript{21}

I. Biomarkers in AD and lithium’s effects
   A. Aβ accumulation
      1. Cleaved from APP by secretases
      2. Fragments link into plaques
      3. AD pathophysiology thought largely due to Aβ accumulation\textsuperscript{2,4,7,9,20}
      4. Aβ in patients with familial AD may be affected as many as 25 years prior to clinical onset of AD\textsuperscript{23}
      5. Lithium may decrease Aβ formation
   B. Glycogen synthase kinase-3 (GSK3) and tau
      1. Predominant tau kinase in the brain
      2. Pro-apoptotic protein
      3. GSK3 levels and activity altered in AD\textsuperscript{24,25}
      4. GSK3 overexpression associated with neurodegeneration and aberrant hyperphosphorylation of tau, causing aggregation into tangles\textsuperscript{24,25}
      5. GSK3 may also play a role in amyloid plaque deposition\textsuperscript{25}
      6. GSK3 inhibition appears to restore neuronal function\textsuperscript{24}
      7. Lithium inhibits GSK3 including affecting GSK3 interactions with APP cleavage\textsuperscript{19,24,25}
C. Brain derived neurotrophic factor (BDNF)
   1. Regulates neural development & survival (anti-apoptotic activities)
   2. BDNF decreases during acute episodes of bipolar disorder (BD) and with progression of BD during euthymic periods\textsuperscript{26}
      a. BDNF decrease may be marker of later-stage BD
      b. Normal serum BDNF levels after mean 21-year follow-up in excellent lithium responders\textsuperscript{27}
   3. Lithium
      a. Stimulation of BDNF helps increase cell survival and stimulate anti-apoptotic pathways\textsuperscript{28}
      b. Thought to protect mitochondria against oxidative damage\textsuperscript{25}
      c. Increases BDNF production in patients with and without BD with normal cognitive function \textit{and} in patients with early AD, with possibly as few as 10 weeks of treatment\textsuperscript{25,26,29}

D. N-methyl-D-aspartate (NMDA) receptor
   1. Glutamate (excitatory) channel which plays a role in development, neuroplasticity and excitotoxicity\textsuperscript{17,18,25}
   2. Excessive NMDA activation likely involved in stress-induced atrophy and neural apoptosis\textsuperscript{25}
   3. Lithium shown to protect cultured brain neurons from glutamate-induced NMDA receptor-mediated apoptosis\textsuperscript{25}

II. BD and Lithium
A. Inhibits GSK3, may increase or maintain BDNF levels and activity, and may protect against $\beta$-plaque formation
B. BD associated with decreased cognitive function with longer illness duration and/or increased numbers and/or severity of affective episodes, as this may decrease brain matter\textsuperscript{25}
   1. Long-term lithium treatment is associated with increased gray matter in the brain\textsuperscript{26}
   2. Patients with BD not taking lithium had significant reductions in glial cell counts, increased volume of gray matter, and increased brain levels of N-acetyl-aspartate (NAA), a marker of neuronal viability\textsuperscript{28}
### Table 6. Epidemiological studies of standard doses of lithium for cognitive function\textsuperscript{24,29-35}

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>Length of Follow-up</th>
<th>Sample</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dunn et al., 2005\textsuperscript{29}</td>
<td>Nested case-control</td>
<td>9954 cases, 9973 controls</td>
<td>10 years</td>
<td>General practice research database in UK; all age &gt;60</td>
<td>↑ dementia rate in those on Li (AD, VaD, and uncertain causes of dementia); OR 1.8 (1.1-2.8)</td>
<td>Few adjustments for variables; no Li levels or doses given</td>
</tr>
<tr>
<td>Terao et al., 2006\textsuperscript{30}</td>
<td>Controlled retrospective cohort study</td>
<td>36 current- or past Li-treated pts; 21 controls</td>
<td>Mean length Li tx: 4±4 years</td>
<td>University clinic outpatients, age ≥60, no dementia</td>
<td>MMSE ↑ in current + past Li-treated group (but not current Li alone) vs. controls; p=0.021</td>
<td>Small sample</td>
</tr>
<tr>
<td>Nunes et al., 2007\textsuperscript{31}</td>
<td>Case-control</td>
<td>66 Li, 48 no Li; total 114</td>
<td>Mean length Li tx: 6 years</td>
<td>Elderly, euthymic BD; age 68.2±5 years</td>
<td>Dementia: 5% with Li vs. 33% without recent continuous Li; p&lt;0.001</td>
<td>Only BD patients</td>
</tr>
<tr>
<td>Angst et al., 2007\textsuperscript{32}</td>
<td>Prospective controlled cohort study</td>
<td>406 bipolar and unipolar mood disorder pts</td>
<td>20 years</td>
<td>Outpatient cohort from Zurich followed 20 years</td>
<td>Li ↓ dem. severity in all, esp. BD (OR 0.23, 0.06-0.89); clozapine ↓ dem. severity in BD (OR 0.11, 0.01-0.84)</td>
<td>Longest prospective data available; bipolar and unipolar mood disorder patients</td>
</tr>
<tr>
<td>Kessing et al., 2008\textsuperscript{33}</td>
<td>Retrospective observational cohort study</td>
<td>16,238 patients</td>
<td>10 years</td>
<td>Denmark national prescription database</td>
<td>↓ dementia diagnosis to general population levels with long-term Li, but not AC, use; most p=NS</td>
<td>Use of claims data, no info about Li indication</td>
</tr>
<tr>
<td>Macdonald et al., 2008\textsuperscript{34}</td>
<td>Open-label trial</td>
<td>22 AD/Li and 300 AD comparators</td>
<td>1 year</td>
<td>Possible/probable AD, mild to moderate severity (MMSE 12-24); age ≥60 years</td>
<td>No difference in death or MMSE change between Li and comparison group; p=NS</td>
<td>High dropout rate (54.5%) but few 2/2 AEs; small number Li treated patients</td>
</tr>
<tr>
<td>Kessing et al., 2010\textsuperscript{35}</td>
<td>Retrospective observational cohort study</td>
<td>4856 patients</td>
<td>10 years</td>
<td>Denmark national prescription database; pts with main discharge diagnosis of manic or mixed episode or BD at first psychiatric hospital contact</td>
<td>50.4% exposed to Li, 36.7% to anticonvulsants; &gt;80% exposed to antidepressant or antipsychotic; continued Li, but not AC/D/P, ↓ dementia rate; RR 0.44 (0.23-0.85)</td>
<td>Largest sample size of BD patients studied in relation to Li for cognitive function; no dosing information</td>
</tr>
</tbody>
</table>

Li – lithium; pt – patient; tx – treatment; UK – United Kingdom; OR – odds ratio; RR – relative risk; dem – dementia; NS – not significant; AEs – adverse events; AC/D/P – anticonvulsants/antidepressants/antipsychotics

### Table 7. Randomized trial of lithium (Li) for cognitive function

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>Length of Follow-up</th>
<th>Sample</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nunes et al., 2013\textsuperscript{19}</td>
<td>Microdose lithium vs. placebo</td>
<td>58 Li, 55 placebo</td>
<td>15 months</td>
<td>Mild AD treated with lithium 300 mcg/day</td>
<td>No ↓ in MMSE in Li group; MMSE ↓ in placebo group; p&lt;0.001</td>
<td>Small trial, only tested MMSE, but potential benefit with low-dose Li</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Purpose</th>
<th>To test the treatment effect of lithium in AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Randomized, single-blind, placebo-controlled, parallel-group, multicenter 10-week study</td>
</tr>
</tbody>
</table>

**Population**

<table>
<thead>
<tr>
<th>Inclusion criteria:</th>
<th>Exclusion criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Informed consent</td>
<td>• Abnormal labs that may contraindicate lithium treatment</td>
</tr>
<tr>
<td>• If female, without childbearing potential</td>
<td>• Untreated hypothyroidism</td>
</tr>
<tr>
<td>• Age 5-85 years</td>
<td>• Electrocardiogram changes indicative of cardiovascular disease</td>
</tr>
<tr>
<td>• Clinical diagnosis of mild AD (MMSE 21-26) + meet NINCDS-ADRA criteria for probable AD</td>
<td>• Concomitant use of particular drugs (valproic acid, memantine, neuroleptics, coumarin anticoagulants, or NSAIDs)</td>
</tr>
</tbody>
</table>

Patients either treatment-naïve or had received limited or stable dose AChE inhibitor for at least 6 months

**Outcomes**

- **Primary:**
  - CSF levels of phosphorylated tau (p-tau)
  - GSK3 activity, measured by ratio of phosphorylated cyclic adenosine monophosphate (cAMP) response element binding protein (pCREB) to total CREB in lymphocytes
- **Secondary:**
  - CSF concentration of total tau and Aβ_{1-42}
  - Plasma levels of Aβ_{1-42}
  - ADAS-Cog summary scores
  - MMSE
  - NPI

**Methods**

- Patients randomized to lithium sulfate or placebo in 1:1 ratio
  - Titration phase of 6 weeks
  - Weekly visits during titration targeting serum lithium 0.5-0.8 mEq/L
  - If dose-limiting toxicity observed, reduced dose to maximal tolerated dose
- Maintenance phase for 4 weeks
  - Assessed biweekly
  - End-of-treatment assessment after total 10 weeks
- Follow-up visit or phone contact ~2 weeks after end-of-treatment visit
- Measured CSF markers (p-tau, total tau, and Aβ_{1-42}) at baseline and at week 10
- Measured GSK3 activity in lymphocytes at each visit
- Excluded missing data from the analyses

**Results**

- Enrolled 79, randomized 71
  - Placebo-lithium – 38:33
  - Completed – 37:30 (placebolithium)
  - All Caucasian, median age ~69 years in both groups, 54.5% females on lithium vs. 50% on placebo
  - Achieved lithium level 0.68 mEq/L (SD 0.23)
- **Primary outcome**
  - No statistically significant effect on CSF or blood-based measures for p-tau
  - No effect of lithium on GSK3 activity as measured by pCREB/total CREB ratio in lymphocytes
  - Mean estimated group difference in change of GSK3 levels=0 for lithium versus placebo
- **Secondary outcomes**
  - No statistically significant effect on any CSF or blood-based measures for total tau or Aβ_{1-42}
  - No statistically significant group differences in MMSE, ADAS-Cog, or NPI scores
    - Cognitive function (per ADAS-Cog) maintained in patients on lithium but seemed to decline in those on placebo
- **Adverse events (AEs)**
  - At least one AE in 11 patients on placebo and 15 on lithium
    - Difference between groups not significant
Most commonly reported: tremor, post-lumbar puncture syndrome, headache, nausea, hypokalemia, hyperhidrosis
- Drug-related adverse events, particularly GI, significantly greater in lithium group

**Author's Conclusion**
- Ten-week treatment with lithium did not change the level of CSF-based markers of AD pathology, including p-tau, total tau, and Aβ_{42}, in patients with mild AD
- No significant changes detected in global cognitive ability as measured by the ADAS-Cog

**Critique**
**Strengths:**
- CSF markers common to AD
- Study design
- Safety/tolerability of lithium ~0.6 mEq/L
- Outcome variables

**Weaknesses:**
- Sample size
- External validity
- Duration of study
- GSK3 activity from lymphocytes

**Take Home**
Short-term lithium did not have significant effects on cognition or core biologic markers (p-tau, total tau, and Aβ) in patients with mild AD

---


**Purpose**
To assess the neuroprotective effects of chronic low-dose lithium treatment in people with amnestic mild cognitive impairment (aMCI)

**Design**
Single-center, randomized, double-blind, placebo-controlled study

**Population**
Community-dwelling outpatients from a cohort studied for cognitive aging at University of Sao Paulo

**Inclusion criteria:**
- Age 60 years or older
- Diagnosis of aMCI per Mayo Clinic criteria
- Approval of general practitioner if medical comorbidities requiring continuous pharmacological treatment were present

**Exclusion criteria:**
- Sensory deficiencies which might preclude the administration of cognitive tests
- Active major psychiatric disorder
- Unstable clinical conditions (i.e. renal failure, cardiac insufficiency, uncontrolled diabetes)
- Previous use of lithium salts

**Outcomes**
- Primary outcomes
  - Modification of cognitive or functional status
  - Changes in CSF concentrations of Alzheimer's disease biomarkers
    - Total tau (T-tau)
    - P-tau
    - Aβ_{42}
- Secondary outcomes
  - Conversion from aMCI to AD
  - Safety and tolerability analysis

**Methods**
- Randomized to lithium starting at lithium carbonate 150 mg daily or placebo
  - Weekly visits during titration
    - Targeted serum lithium 0.25-0.5 mEq/L
    - Controlled for tolerability
  - Obtained serum lithium levels ~12 h after the last dose
    - Participants took doses at 0800 and 2000
- Once stable target levels achieved, maintained dose until next visit (every 3 months) to 12 months
- Assessed cognitive/functional status
  - Clinical Dementia Rating (CDR) scale, including the Sum of Boxes (SoB) score (CDR-SoB)
  - ADAS-Cog
- Further evaluated memory, attention and executive functioning
  - Consortium to Establish a Registry for Alzheimer's Disease (CERAD) delayed recall test
  - Sequence of Letters and Numbers (SLN)
  - Trail Making Test (TMT)

**Results**
- Recruited 51 patients, randomized 45
  - Randomized: 23 patients to lithium, 22 to placebo
- Completed: 21 on lithium, 20 on placebo
- Discontinuations: 1 death, 1 withdrawn secondary to stroke, 2 contact lost
- No statistically significant baseline differences; mean age ~71 years on lithium, ~74 years on placebo
- All participants with slight but significant worsening of global functional state per mean CDR-SoB scores
  - Magnitude of decline smaller in those treated with lithium
- Progressed to AD after 12 months of follow-up: N=11
  - Higher concentrations of T-tau and P-tau and lower Aβ42 at baseline vs. non-converters
  - More converters in placebo group (7/20) versus lithium (4/21) but not significant (p=0.2)

**Table 8. Baseline + f/u scores on cognitive tests, CSF markers according to treatment group (significant)**

<table>
<thead>
<tr>
<th>Cognitive test/CSF marker</th>
<th>Li baseline</th>
<th>Li follow-up</th>
<th>p*</th>
<th>Plac baseline</th>
<th>Plac follow-up</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAS-Cog</td>
<td>110 (6.7)</td>
<td>126 (6.6)</td>
<td>0.21</td>
<td>107 (5.1)</td>
<td>139 (8.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>Sequence of letters &amp; numbers</td>
<td>6.4 (2.1)</td>
<td>6.0 (2.9)</td>
<td>0.08</td>
<td>6.3 (2.6)</td>
<td>5.1 (2.6)</td>
<td>0.04</td>
</tr>
<tr>
<td>CDR-SoB score</td>
<td>1.4 (1.3)</td>
<td>2.2 (1.8)</td>
<td>0.05</td>
<td>1.9 (1.4)</td>
<td>2.8 (2.5)</td>
<td>0.04</td>
</tr>
<tr>
<td>Amyloid-β42</td>
<td>440.5 (150.3)</td>
<td>391.0 (106.1)</td>
<td>0.09</td>
<td>405.2 (162.0)</td>
<td>424.6 (167.4)</td>
<td>0.45</td>
</tr>
<tr>
<td>P-tau</td>
<td>62.9 (39.8)</td>
<td>54.0 (40.2)</td>
<td>0.15</td>
<td>58.1 (26.6)</td>
<td>63.7 (29.5)</td>
<td>0.07</td>
</tr>
<tr>
<td>T-tau</td>
<td>98.7 (57.6)</td>
<td>109.4 (79.5)</td>
<td>0.18</td>
<td>91.4 (46.2)</td>
<td>100.4 (51.9)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

*paired-sample t-tests; all scores shown as mean (SD); f/u – follow-up; Li – lithium; plac – placebo

- Decreased P-tau concentration in those on lithium versus increased P-tau in those on placebo
  - Significant at p=0.02
  - Lithium p-tau decrease by 8.9 pg/ml (SD 24.3) vs. placebo p-tau increase by 5.6 pg/ml (SD 11.4)
- All who progressed to AD had slight increase in CDR-SoB score (cognitive/functional worsening)
  - But, attenuated by lithium (3.3→4.4 on lithium, 3.4→5.6 on placebo, p=0.03)
- Safety
  - Overall good tolerability (91% completed 12 months of follow-up)
  - Occurrence of side effects similar in lithium and placebo groups (58% vs. 42%, p=0.13)
    - Most mild, transient, involved GI system, and no intervention needed
  - Serious AE thought unrelated to study drug
    - Ischemic stroke, death from sepsis secondary to pneumonia

**Author’s Conclusion**
Long-term lithium treatment at relatively lower serum levels may be a safe and inexpensive way to prevent, or delay, progression from pre-dementia stages to clinical AD

**Critique**
- Strengths:
  - Patient population (w/o dementia, with aMCI)
  - Included cognitive/functional status markers as well as biological markers
  - Study design, duration
  - Low-dose lithium, low dropout rate
- Weaknesses:
  - Sample size
  - External validity
  - Study duration

**Take Home**
- Lithium treatment for one year appeared to reduce cognitive decline in people with aMCI
- Long-term lithium treatment was associated with significant reduction in CSF concentration of P-tau
- Lithium treatment was safe and well-tolerated at serum concentrations of 0.25-0.5 mEq/L
- Contradicts prior negative RCT by Hampel et al., 2009

CSF – cerebrospinal fluid; RCT – randomized controlled trial

## Purpose
To examine the association of lithium and dementia risk in a large claims-based US cohort of older adults with bipolar disorder

## Design
Retrospective, population-based, observational cohort study

## Population
<table>
<thead>
<tr>
<th>Inclusion criteria:</th>
<th>Exclusion criteria, during 12-month pre-index period:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Continuous Medicaid eligibility during previous 395 days</td>
<td></td>
</tr>
<tr>
<td>• Diagnosis of bipolar disorder in pre-index period</td>
<td></td>
</tr>
<tr>
<td>• Age ≥50 years</td>
<td>• Diagnosis of dementia or mild cognitive impairment</td>
</tr>
<tr>
<td></td>
<td>• Treatment for dementia</td>
</tr>
<tr>
<td></td>
<td>• Any prescription claim for donepezil, galantamine, rivastigmine, memantine</td>
</tr>
</tbody>
</table>

Outcome

‘Incident dementia’: one in-patient or two out-patient claims for select ICD-9-CM diagnoses

## Methods
| • Retrospective review of combined service and pharmacy claims from 1/1/2001 to 12/31/2004 |
| CA, FL, GA, IL, NJ, NY, OH, and TX |
| 44 million individuals, ~40% of Medicaid insured population |
| Medicare Part A and B data were matched for all Medicaid insured individuals dually eligible for Medicare because Medicare is primary payer for physician/hospital services for individuals ≥65 years |
| Cumulative exposure defined time-dependently for each day of follow-up |
|   • Cumulative number of days of medication supply over previous 365 days in 4 categories |
|   • None = 0 days |
|   • Sporadic = 1-60 days |
|   • Intermittent = 61-300 days |
|   • Continuous = 301-365 days |
| • Anticonvulsants = negative control |
|   • Similar to lithium properties |
|   • Goal to reduce potential for confounding |
| • Covariates: demographics, other meds, residency in long-term care facility, psychiatric comorbidity, cardiovascular comorbidity, cerebrovascular disease, diabetes mellitus, Parkinson’s disease |
| • Sociodemographic and clinical characteristics calculated at baseline for full cohort |
|   • Stratified by use of lithium and anticonvulsants at any point during study period |
| • Calculated event rate and 95% confidence interval |
|   • Full cohort |
|   • Nonuse, sporadic use, intermittent use, and continuous use of lithium and anticonvulsants |
| • Follow-up |
|   • Beginning: index date |
|   • End: loss of service eligibility, death, end of study period or occurrence of study outcome, whichever came first |
| • Cox proportional hazard models to estimate hazard ratios for prior year exposure to (1) lithium and (2) anticonvulsants versus nonuse |
|   • Unadjusted model |
|   • Model adjusted for gender, age and ethnicity |
|   • Fully adjusted model |
|   • Controlled for all covariates |
|   • Age categorized in 5-year bands beginning with age 50-54 |
|   • Age and medications for BD as time-dependent variables, updated for each day of follow-up |

## Results
| Study cohort: 41,931 people |
| Not mainly female (71.4%) and white (66.4%), mean age 60.4 years at index |
| 3/4 Medicaid eligibility through disability and 18% resided in long-term care facility |
| Not exposed to lithium or any of the study anticonvulsants at any point: 18,119 patients |
| Lithium use in 6,900 patients: 12,748 person-years of follow-up |
| One or more prescription fills for anticonvulsants in 20,778 patients: 35,221 person-years of follow-up |
| Total 3,866 patients exposed to both lithium and anticonvulsants |
### Table 10. Incidence rates (IR) of dementia stratified by past-year exposure to lithium vs. ACs

<table>
<thead>
<tr>
<th>Days</th>
<th>0</th>
<th>1-60</th>
<th>61-300</th>
<th>301-365</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lithium, cumulative exposure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n⁰</td>
<td>37,485</td>
<td>2,925</td>
<td>4,808</td>
<td>3,766</td>
</tr>
<tr>
<td>Event</td>
<td>1,377</td>
<td>18</td>
<td>79</td>
<td>64</td>
</tr>
<tr>
<td>IR (95% CI)b</td>
<td>2.45 (2.32-2.58)</td>
<td>1.82 (0.98-2.66)</td>
<td>1.77 (1.38-2.16)</td>
<td>1.38 (1.04-1.72)</td>
</tr>
<tr>
<td><strong>Anticonvulsants, cumulative exposure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n⁰</td>
<td>28,046</td>
<td>8,604</td>
<td>13,920</td>
<td>11,014</td>
</tr>
<tr>
<td>Event</td>
<td>925</td>
<td>78</td>
<td>251</td>
<td>284</td>
</tr>
<tr>
<td>IR (95% CI)b</td>
<td>2.46 (2.30-2.61)</td>
<td>2.33 (1.82-2.85)</td>
<td>2.07 (1.82-2.33)</td>
<td>2.16 (1.91-2.41)</td>
</tr>
</tbody>
</table>

AC – anticonvulsants; a=not mutually exclusive for lithium and ACs (one individual could be in multiple categories); b=unadjusted incidence rate (95% confidence interval) expressed per 100 person years

- **Common concomitant meds**
  - Antidepressants – 64.9%
  - Antipsychotics – 53.6%
  - Anxiolytics – 49.5%
- **1,538 individuals newly diagnosed with dementia during follow-up**
  - 2.32 cases per 100 person years
- **Increased duration of lithium exposure associated with decrease in unadjusted incidence rate of dementia**
  - Similar but much less pronounced result for anticonvulsants
- **Cox proportional hazard models results**
  - In the unadjusted and age/gender/ethnicity adjusted models: generally decreasing hazards ratios with increasing lithium exposure
  - In the fully adjusted model: continuous but not intermittent or sporadic lithium exposure was associated with a significant decrease in dementia (HR=0.77, 95% CI 0.6-0.99)
  - No such effects shown with anticonvulsants
- **Among covariates, age = strongest predictor of dementia**
- **Other significant predictors = male gender, Black ethnicity, Medicaid eligibility through poverty, LTC residency, depression, alcohol-related disorders, cerebrovascular disease, diabetes mellitus, and Parkinson’s disease**

**Author’s Conclusion**
Continued lithium use, but not anticonvulsants, in older adults with bipolar disorder is associated with a reduced incidence of dementia diagnosis

**Critique**

**Strengths:**
- Sample size
- Internal validity, negative control
- External validity

**Weaknesses:**
- Use of claims data, no objective measurements
- Inclusion/exclusion/outcomes based on diagnosis codes
- Observational study design, duration
- External validity
- Channeling bias, healthy adherer effect, confounding
- No information regarding mechanism of neuroprotection

**Take Home**
Maintenance lithium treatment may delay or reduce the risk of dementia onset in older patients with BD
I. Is lithium an effective, and safe, means to prevent or delay the onset of dementia?
   A. Data only widely available for dementia associated with AD in particular, due to lithium’s apparent mechanisms in the pathophysiologic variables in AD
   B. Review of the literature demonstrates lithium’s effects on key biomarkers of AD, including Aβ accumulation, tau phosphorylation, and other anti-apoptotic and pro-apoptotic factors
   C. Studies demonstrate general tolerability of lithium to preserve cognitive function in adults >50 years of age
      1. Doses and serum levels varied from microdoses to full therapeutic doses, and plasma concentration ranged from negligible to therapeutic levels
      2. Dropouts were seen in all studies, albeit some with low rates, and even in patients with low serum lithium levels
      3. Lithium tolerability is quite patient-specific, as some patients with low levels experience drug-related intolerabilities leading to medication discontinuation, and others were able to stay on the medication at equal levels
      4. It is important to remain mindful of lithium’s detrimental effects and the common patient populations in which those effects may be more pronounced, specifically those with renal dysfunction, drug interactions, and major comorbidities associated with sodium imbalance or requiring sodium restrictions

II. Is there a subset of populations in which lithium may be most beneficial to prevent or delay the onset of dementia?
   A. Patients with bipolar disorder, especially those with increasing numbers and/or severity of affective episodes, may be at increased risk of dementia due to detrimental effects on brain composition
   B. Research particularly supports the benefits of lithium on slowing or preventing the progression to Alzheimer’s disease in patients with bipolar disorder who continuously use lithium as a mood stabilizer

III. What research still needs to be done?
   A. What dose and/or serum concentrations should we target for lithium neuroprotection?
   B. How early might lithium need to be started in patients – and at what stage in cognitive function – in order to obtain the full benefits of lithium neuroprotection?
   C. How long do patients need to be treated with lithium in order to benefit from lithium neuroprotection?
   D. Continued safety assessments will be an important factor when facing the data needs

IV. Clinical Recommendation

- Patients with bipolar disorder, especially those with greater numbers and/or severity of affective episodes
- If no contraindications, aim to initiate prior to age 65
- Continue lithium (even serum Li <0.6 mEq/L) as long as tolerated or until development of AD/dementia
REFERENCES


APPENDICES

Appendix 1. DSM-5 diagnostic criteria for specific NCDs

<table>
<thead>
<tr>
<th>Major or Mild NCD due to:</th>
<th>Diagnostic Criteria</th>
</tr>
</thead>
</table>
| Vascular dementia         | A. The criteria are met for major or mild neurocognitive disorder
|                           | B. The clinical features are consistent with a vascular etiology, as suggested by either of the following:
|                           | 1. Onset of the cognitive deficits is temporally related to one or more cerebrovascular events
|                           | 2. Evidence for decline is prominent in complex attention (including processing speed) and fronto-executive function
|                           | C. There is evidence of the presence of cerebrovascular disease from history, physical examination, and/or neuroimaging considered sufficient to account for the neurocognitive deficits
|                           | D. The symptoms are not better explained by another brain disease or systemic disorder
|                           | Probable vascular NCD is diagnosed if one of the following is present; otherwise possible vascular NCD should be diagnosed:
|                           | 1. Clinical criteria are supported by neuroimaging evidence of significant parenchymal injury attributed to cerebrovascular disease (neuroimaging-supported)
|                           | 2. The neurocognitive syndrome is temporarily related to one or more documented cerebrovascular events
|                           | 3. Both clinical and genetic evidence of cerebrovascular disease is present
|                           | Possible vascular NCD is diagnosed if the clinical criteria are met but neuroimaging is not available and the temporal relationship of the neurocognitive syndrome with one or more cerebrovascular events is not established |
| Frontotemporal Dementia | A. The criteria are met for major or mild neurocognitive disorder  
| B. Insidious onset and gradual progression  
| C. Either (1) or (2):  
| 1. Behavioral variant:  
| i. Three or more of the following behavioral symptoms:  
| ii. Behavioral disinhibition  
| iii. Apathy or inertia  
| iv. Loss of sympathy or empathy  
| v. Perseverative, stereotyped or compulsive/ritualistic behavior  
| v. Hyperorality and dietary changes  
| b. Prominent decline in social cognition and/or executive abilities  
| 2. Language variant:  
| a. Prominent decline in language ability, in the form of speech production, word finding, object naming, grammar, or word comprehension  
| D. Relative sparing of learning and memory and perceptual-motor function  
| E. The disturbance is not better explained by cerebrovascular disease, another neurodegenerative disease, the effects of a substance, or another mental, neurological, or systemic disorder  
| Probable FTD diagnosed if either of the following is present; otherwise, possible FTD should be diagnosed:  
| • Evidence of a causative frontotemporal NCD genetic mutation, from either family history or genetic testing  
| • Evidence of disproportionate frontal and/or temporal lobe involvement from neuroimaging  
| |
| Dementia with Lewy Bodies | A. The criteria are met for major or mild neurocognitive disorder  
| B. Insidious onset and gradual progression  
| C. The disorder meets a combination of core diagnostic features and suggestive diagnostic features for either probable or possible NCD with Lewy bodies  
| For probable major or mild NCD with Lewy bodies, the individual has two core features, or one suggestive feature with one or more core features.  
| For possible major or mild NCD with Lewy bodies, the individual has only one core feature, or one or more suggestive features.  
| 1. Core diagnostic features:  
| a. Fluctuating cognition with pronounced variations in attention and alertness  
| b. Recurrent visual hallucinations that are well formed and detailed  
| c. Spontaneous features of parkinsonism, with onset subsequent to the development of cognitive decline  
| 2. Suggestive diagnostic features:  
| a. Meets criteria for rapid eye movement sleep behavior disorder  
| b. Severe neuroleptic sensitivity  
| D. The disturbance is not better explained by cerebrovascular disease, another neurodegenerative disease, the effects of a substance, or another mental, neurological, or systemic disorder  
| |
| Parkinson’s Disease Dementia | A. The criteria are met for major or mild neurocognitive disorder  
| B. The disturbance occurs in the setting of established Parkinson’s disease  
| C. Insidious onset and gradual progression of impairment  
| D. The NCD is not attributable to another medical condition and is not better explained by another mental disorder  
| Major or mild NCD probably due to Parkinson’s disease should be diagnosed if 1 and 2 are both met. Major or mild NCD possibly due to Parkinson’s disease should be diagnosed if 1 or 2 are met:  
| 1. There is no evidence of mixed etiology (i.e., absence of other neurodegenerative or cerebrovascular disease or another neurological, mental, or systemic disease or condition likely contributing to cognitive decline).  
| 2. The Parkinson’s disease clearly precedes the onset of the NCD.  
|
## Appendix 2. Current pharmacological management of dementia\(^{17,18}\)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Indication(s)</th>
<th>MOA</th>
<th>Dose/Titration</th>
<th>Side Effects</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Donepezil</strong></td>
<td>Mild-severe AD*; mild-moderate PDD^, DLB^</td>
<td>Reversible, selective AChE inhibitor</td>
<td>5 mg/day x 4-6 wks, then 10 mg/d x ≥3 mo., then 23 mg/d</td>
<td>SLUDGE, insomnia, anorexia, bradycardia</td>
<td>At bedtime, with or without food; tablet or ODT formulations</td>
</tr>
<tr>
<td>(Aricept®)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Galantamine</strong></td>
<td>Mild-moderate AD*; severe AD^, PDD^ and DLB^</td>
<td>Reversible, selective AChE inhibitor and nicotinic ACh receptor modulator</td>
<td>IR: 4 mg BID x 4 wks, then 8 mg BID x 4 wks, then 12 mg BID</td>
<td>SLUDGE, insomnia, anorexia, bradycardia</td>
<td>IR: with breakfast and dinner ER: with breakfast</td>
</tr>
<tr>
<td>(Razadyne®)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rivastigmine</strong></td>
<td>Mild-severe AD*; mild-moderate PDD*; DLB^</td>
<td>Reversible AChE inhibitor, exact MOA unknown</td>
<td>PO: 1.5 mg BID, titrate by 3 mg q 2 wks, max 6 mg BID</td>
<td>SLUDGE, insomnia, anorexia, bradycardia</td>
<td>PO: with meals, swallow caps whole</td>
</tr>
<tr>
<td>(Exelon®)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Memantine</strong></td>
<td>Mod-severe AD*; mild-moderate VaD^</td>
<td>N-methyl-D-aspartate (NMDA) receptor antagonist</td>
<td>IR: 5 mg/d x ≥1 wk; ↑ by 5 mg/d after ≥1 wk; max 20 mg/d</td>
<td>Dizziness, confusion, headache, diarrhea, constipation</td>
<td>Take with or without food</td>
</tr>
<tr>
<td>(Namenda®)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FredA-approved indication; ^Off-label use

MOA – mechanism of action; AD – Alzheimer’s Disease; PDD – Parkinson’s Disease Dementia; DLB – dementia with Lewy bodies; VaD – vascular dementia; AChE – acetylcholinesterase; SLUDGE – salivation, lacrimation, urination, defecation, gastrointestinal upset, emesis

## Appendix 3. Mayo Clinic criteria for amnestic mild cognitive impairment (aMCI)\(^{36,37}\)

- Problems with memory or another mental function
- Cognitive decline over time from a previous level of functioning
- Overall mental function and daily activities are not affected
- Mental status tests show mild impairment for age/education level
- Not severe enough to be diagnosed as a subset of dementia

## Appendix 4. Comparison of the Clinical Dementia Rating (CDR) Scale and its subset Sum of Boxes score\(^{38,39}\)

<table>
<thead>
<tr>
<th>Exam Name</th>
<th>Description</th>
<th>Scoring</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Dementia Rating Scale</strong></td>
<td>• Global score used in clinical and research settings&lt;br&gt;• Stages dementia severity</td>
<td>• 5-point scale: 0=normal, 0.5=very mild dementia, 1=mild dementia, 2=moderate dementia, 3=severe dementia</td>
</tr>
<tr>
<td><strong>CDR Sum of Boxes score (CDR-SoB)</strong></td>
<td>• More detailed, quantitative index&lt;br&gt;• Provides more information in patients with mild dementia&lt;br&gt;• Simpler to calculate than CDR and can be treated as interval data in studies vs. CDR as ordinal data&lt;br&gt;• ↑ precision in tracking changes over time</td>
<td>• 6 domains: 0-3 point scale each, scored based on CDR scale&lt;br&gt;• 0-18 points overall&lt;br&gt;• ↑ score = ↑ cognitive impairment</td>
</tr>
</tbody>
</table>