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The effect of yoga on depression in mild cognitive impairment

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THE EFFECT OF YOGA ON DEPRESSION IN MILD COGNITIVE IMPAIRMENT

by

URVASHI K. SHUKLA

B.S., Rutgers University, 2013
M.S., Rowan University Graduate School of Biomedical Sciences, 2014

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Approved by

First Reader

John R. Weinstein, Ph.D., M.S.
Assistant Professor of Medicine

Second Reader

Anna Hohler, M.D., FAAN
Chair, Department of Neurology, St. Elizabeth Hospital

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ABSTRACT

Preclinical Alzheimer's Disease (AD) appears after a decade or more of brain degeneration and this is termed mild cognitive impairment (MCI). As it progresses, patients begin to lose their short term memory, motor skills and begin to become more disoriented and bed ridden. Thus, early diagnosis becomes paramount in preventing eventual disability. Individuals with MCI may have advanced brain degeneration and the presence of neuropsychiatric symptoms (NPS) may augment the progression to AD dementia compared to individuals without NPS. Of these NPS, depression is one of the main symptoms that greatly impacts quality of life but it is often overlooked and undertreated. The annual cost of pharmacologic treatments is rising and assessment tools for AD and depression are increasing as are rates of AD. It is crucial to execute compelling non-pharmacologic interventions that can be beneficial to the elderly population while acknowledging their endurance, fitness and enjoyment levels. Yoga is one such intervention that has been proven to improve depression and cognitive levels while simultaneously maintaining a positive and engaging atmosphere. Studies have found that consistent use of yoga can also increase GABA levels in the brain which serve to improve depression levels too. There have been no studies that have investigated the effects of yoga on depression in individuals with mild cognitive impairment.

This proposed trial will be a randomized controlled study and it will compare the quality of depression symptoms in elderly individuals with MCI and depression in elderly individuals without MCI with a yoga intervention combined with walking and in a control group with walking alone. Several assessment tools will be utilized to evaluate the outcomes including the PHQ-9, GDS, HAM-D, and MoCA. The effect on sleep will also be measured as a secondary outcome. If yoga is able to improve depression levels, it may have an impact in reversing MCI, delaying progression to AD dementia, and a potentially deep impact on the financial and public health burden of AD. Furthermore, it can reduce the need for anti-depressants and other medications for depression and eliminate their potentially harmful side effects. If this study proves to be clinically significant, yoga can also be recommended as an efficient intervention by clinicians in individuals with mild cognitive impairment and depression.

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LIST OF ABBREVIATIONS

AAMI …….. Age- Associated Memory Impairment

Aβ …….. Amyloid Beta

ADAS- cog …… Alzheimer's Disease Assessment Scale- Cognitive sub scale

AD ……... Alzheimer's Disease

ADC ……...…. Alzheimer's Disease Center

APOE ……... Apolipoprotein E

APP ……. Amyloid Precursor Protein

BBB …….…. Blood Brain Barrier

BMI …….. Body Mass Index

BU..... Boston University

CAIDE …… Cardiovascular Risk Factors Aging and Dementia

CDC …… Centers for Disease Control and Prevention

CDRS …….. Clinical Dementia Rating Scale

CIND …… Cognitive Impairment- No Dementia

CSF …….. Cerebrospinal Fluid

CVFT ……..….. Category Verbal Fluency Test

DBP …… Diastolic Blood Pressure

DST …… Digit Span Task

ECT …… Electroconvulsive therapy

FDA ……..... Food and Drug Administration

FRCP …… Framingham Cardiovascular Risk Profile

GDS …….. Geriatric Depression Scale

GDS ……... Global Deterioration Scale

HAM- D …… Hamilton Rating Scale for Depression

HVLT ……..... Hopkins Verbal Learning Test Total Recall

IRB ……..…….. Institutional Review Board

MCI …… Mild Cognitive Impairment

MMSE …… Mini Mental Status Exam

MOCA …… Montreal Cognitive Assessment Test

MRS ……. Magnetic Resonance Spectroscopy

NFT …… Neurofibrillary Tangles

NMDA ……..…. N- Methyl- D- Aspartate

NPI- Q …….. Neuropsychiatric Inventory Questionnaire

NPS …….. Neuropsychiatric symptoms

PHQ-9 …… Patient Health Questionnaire

PS1 …… Presenilin 1

PS2 …… Presenilin 2

RR …… Relative Risk

SBP ……. Systolic Blood Pressure

SCID …… Structured Clinical Interview for DSM- 5

SDMT ……. Symbol Digit Modalities Test

SPMSQ ……... Short Portable Mental Status Questionnaire

τ …… Tau protein

TMT …… Trail Making Test

WMS-R LM …… Wechsler Memory Scale- Revised Logical Memory Test

INTRODUCTION

Background

Alzheimer's Disease (AD) is a neurodegenerative disorder characterized by progressive cognitive decline and neuropsychiatric symptoms, eventually causing complete dependence for basic functions of life. It is the most common cause of dementia, and it accounts for about 75% of all cases of AD. Currently, AD affects more than 5.5 million Americans but that number is projected to triple to 14 million by 2060. AD disproportionately afflicts minority ethnic groups with a worldwide population of 24 million and affects more females than males.[4, 6, 15]AD is frequently associated with episodic memory impairment, executive and visuospatial functioning deficits, and neuropsychiatric symptoms (NPSs), such as depression, anxiety, apathy, irritability, and sleep disorder.

A prodromal phase of accelerated cognitive decline, known as mild cognitive impairment (MCI), precedes AD and acts as a translational stage to dementia with a conversion rate of 10-15% per year.[11] MCI is characterized by cognitive impairments that are not severe enough to require help with activities of daily life. NPSs, particularly depression, are the earliest precursor signs of progression to dementia in MCI, yet they are under recognized and difficult to treat.

Complex biological, genetic and structural constituents along with multifactorial risk factors encompass the pathogenesis of AD. Hallmarks of AD include neurofibrillary tangles and extracellular amyloid beta plaques in brain regions augmented by mitochondrial dysfunction causing oxidative stress and neuronal degeneration.[6, 12, 13] Genetic basis of AD is dependent on the type, Familial or Sporadic AD. Familial AD is rarer and is caused by mutations to Presenilin 1 (PS1), Presenilin 2 (PS2) and Amyloid Precursor Protein (APP). Sporadic AD affects more than 90% of AD patients and is found to be linked to the Apolipoprotein E (APOE) gene.[9] Modifiable risk factors include cardiovascular disease, diabetes obesity, hypertension, hypercholesterolemia, metabolic syndrome, and stress; non-modifiable risk factors include age, sex, family history, and genetics.[6, 11, 14, 16]

Currently, there is no pharmacologic therapy to halt progression or cure AD and treatment relies solely on symptomatic management.[25] Cholinesterase inhibitors and NMDA receptor temporarily aid with cognitive impairment but are associated with side effects and have not shown long- term promise. Moreover, clinical trials have not shown favorable results in these drugs halting progression of MCI to AD.[8, 25] Drug therapy of NPSs is highly related to adverse effects.[23, 24] Non-pharmacologic interventions for NPSs have gained increasing attention but it is unclear which is the most effective form. Some studies suggest that physical exercise in the form of dancing, walking, yoga or cognitive interventions, such as meditation and mindfulness, can provide short term benefits in improvement of NPSs and halt progression to AD long term.[32-34]

Statement of the Problem

The prevalence of NPSs is between 43% and 59% in patients with MCI.[21] Among these NPSs, depression greatly diminishes the quality of life of the elderly, prevents them from working and mingling, increases frustration levels, increases direct cost of care and institutionalization, and increases burden on their caregivers. Additionally, the combination of depression and MCI leads to a four-fold higher risk of progression to dementia.[21] Consequently, early detection and treatment of depression in elderly individuals with MCI is imperative. Unfortunately, it is often undervalued, overlooked, presumed to be a normal part of aging, and challenging to treat.

There is no direct standard of pharmacotherapy for NPSs treatment. Antipsychotics, antidepressants, benzodiazepines, cholinesterase inhibitors and anticonvulsants are used with minimal efficacy, have several adverse side effects, and increase the risk of death. Due to the high prevalence of comorbidities in the elderly, medication interaction risks, and low risk benefits of pharmacologic treatment, non-pharmacologic interventions such as yoga should be considered. The complexities of depression are interlinked with sleep disorder and, without proper treatment, worsening of all NPSs could result. While the use of yoga as a healthy form of exercise for the elderly has been recognized, further exploration is warranted regarding studies the effects of yoga in individuals diagnosed with both MCI and depression.

Hypothesis

Patients diagnosed both with MCI and depression participating in a yoga intervention twice a week with daily walking will have notable improvement in their depression levels after 3 months compared to patients who only execute daily walking.

Objectives and specific aims

The purpose of this research is to investigate whether a safe and manageable yoga routine can improve depressive symptoms in individuals diagnosed with mild cognitive impairment. If this study shows that yoga can improve depressive symptoms in mild cognitive impairment, it can be recommended by healthcare providers in individuals with mild cognitive impairment as a valid therapy. In a broader sense, yoga can also be incorporated as an exercise activity in senior activity centers and assisted living facilities. The specific aims of this thesis project include:

- Performing a literature review to provide evidence for the potential of yoga to reduce depression
- Proposing a randomized control trial to investigate the effectiveness of a twice a week yoga intervention for 3 months in improving depression in MCI patients
- As a secondary measure within the proposed study, investigate the effect of yoga on sleep disorder in patients with MCI and depression

REVIEW OF THE LITERATURE

OVERVIEW

Epidemiology of Alzheimer's Disease

There are currently more than 5.5 million Americans and 24 million people worldwide who are affected by Alzheimer's disease (AD).[6] According to the Centers for Disease Control and Prevention (CDC), that number is projected to triple to 14 million by 2060. AD is the 6th leading cause of death in the country among adults and the 5th leading cause of death among adults aged 65 or older.[17] Individuals between ages 60-85 have a 15-fold higher risk of getting AD dementia. It is estimated that about 1/10 people age 65 or older currently have AD dementia and 1/3 people age 85 or older have AD dementia.[6, 10]

Cases of AD are increasing worldwide but the prevalence greatly varies among low, middle, and high income countries. The prevalence of AD is greater in developed countries. This is largely due to the fact that developed countries have more risk factors such as hypertension, obesity, smoking, diabetes, metabolic syndrome, and cerebrovascular disease than developing countries. The prevalence of AD is low in less developed areas, such as Africa and the Middle East, while rising in China, India and Latin America. [14]

There are differences that exist in the epidemiology of AD among Whites, African Americans and Hispanics in the U.S., only a small fraction of which are accounted for by genetics. Recent studies suggest that AD may disproportionately burden minority ethno-racial groups.[4, 6] In individuals aged 65 and older, the prevalence

of AD dementia is: 13.8% in African Americans; 12.2% in Hispanics; 10.3% in non-Hispanic whites 10.3%; 9.1% in American Indian and Alaska Natives; and 8.4% in Asian and Pacific Islanders. In terms of gender differences, several studies have consistently found that more women have AD than men most likely because women survive longer.[15]

Definition of Alzheimer's Disease (AD)

AD is a progressive neurodegenerative disorder that is characterized by progressive cognitive decline leading to complete dependence for basic functions of daily life. AD can be classified as either mild, moderate or severe (Table 1).[11, 18] It is characterized by several cognitive and neuropsychiatric features and is the most common cause of dementia in 75% of cases.[6, 11, 13] Certain cognitive features include: episodic memory impairment (poor new learning), language difficulties, executive function deficits and visuospatial functioning deficits. Individuals with AD often repeat stories, have difficulties with word finding, problems with expression, and impaired planning or multi-tasking judgement. Additionally, they have poor awareness and insight into these problems. [6, 10, 11, 16]

Table 1. Cognitive, functional and behavioral deficits by disease stage in Alzheimer's disease [11]

Domain	MCI	Mild AD	Moderate AD	Severe AD
Duration	3–5 yrs	1–2 yrs	2–12 yrs	1 yr
Cognitive	Memory impairment (isolated deficit)	Recall/Learning Word finding difficulty Judgment and problem solving Calculation impairment	Moderate memory loss Anomia Visuospatial deficits Disorientation Confusion	Severe memory loss Agnosia Apraxia
Functional	Occasional loss of complex social or occupational skills	Difficulty in: Routine chores Complex meal preparation Financial matters Hobbies	Loss of IADL Getting lost Difficulty dressing Poor eating habits Poor hygiene habits	Loss of basic ADL: Dressing Grooming/bathing Eating Continence Mobility
Behavioral	Apathy, Irritability Withdrawal (mild)	Apathy Delusions Depression Withdrawal (moderate)	Agitation Delusions Depression Insomnia Wandering	Agitation: Verbal Physical Insomnia

Abbreviations: AD, Alzheimer's disease; IADL, instrumental activities of daily living; MCI, mild cognitive impairment.

Definition of MCI

The concept of MCI was first defined in 1962 as "benign senescent forgetfulness." [28] In 1986, the National Institute of Mental Health then transformed that definition into "age-associated memory impairment" (AAMI). AAMI encompassed all memory impairments but it was unable to differentiate individuals at risk of progressing to pathological conditions in the future from those who were undergoing the process of normal aging. [28] In an effort to overcome these shortcomings, the International Psychogeriatric Association originated the term "age-associated cognitive decline." The Canadian Study of Health and Aging also coined the term "cognitive impairment- no dementia" (CIND), which described individuals who were cognitively impaired but not to the extent of dementia. While this definition most closely resembles the definition of MCI, CIND encompasses a broader subset of individuals with lifelong cognitive impairment, static encephalopathy, and learning disabilities.[28]

The term MCI first originated in the 1980s by Reisberg and colleagues to characterize individuals with a Global Deterioration Scale (GDS) rating of 3 and Clinical Dementia Rating Scale (CDR) of 0.5, although those numbers alone do not determine a specific diagnosis. [28] MCI is presumed to be the transitional stage between normal aging and early AD, and although memory impairment exists, cognitive function is generally normal and the criteria for dementia is not formally met.[27, 28] MCI can be categorized into: amnestic MCI (memory loss is the main symptom) and non-amnestic MCI (memory loss is intact but other processing abilities like organizing, planning, reasoning, learning or judgement may not be). Amnestic MCI is the most common subtype with a prevalence of 10-14% in the elderly.[31]

In 1994, the Diagnosis and Evaluation of Dementia did not discuss guidelines for early detection of dementia. However, ample progress has been made since then in increasing attention to the evaluation and clinical monitoring of individuals with MCI. Literature reviews have found that there is insufficient data to make recommendations regarding cognitive screening of asymptomatic individuals but there is sufficient data to recommend evaluation and clinical monitoring of individuals with symptomatic MCI. The urgency for increased surveillance is due to increased risk of progression in individuals with MCI to AD when compared with similarly aged individuals in the general population.[27]

There have been a number of longitudinal, prospective, population and community- based studies investigating whether the presence of MCI predicts the development of AD dementia. [27] A recent review by the American Academy of

Neurology compiling a number of these studies showed that rate of conversion to AD dementia in individuals with MCI was 0.2% in the 65 to 69 age range and 3.9% in the 85 to 89-year range. [27] Another large prospective study from Germany found that subjects with MCI progressed to dementia at rates of 7.2%- 10.2% per year.[28] A meta- analysis of 60 cohort studies found strong positive associations between progression from MCI to AD and the following risk factors: abnormal cerebrospinal fluid (CSF), phosphorylated τ (relative risk (RR)= 2.43, 95% CI= 1.70 to 3.48), hippocampal atrophy (RR= 2.59, 95% CI= 1.95 to 3.44), medical temporal lobe atrophy (RR= 2.11, 95% CI= 1.70 to 2.63) and entorhinal atrophy (RR= 2.03, 95% CI =1.57 to 2.62). Conversely, negative associations were found for high body mass index (BMI) (RR= 0.85, 95% CI= 0.76 to 0.96) and higher auditory verbal learning test delay score (RR= 0.86, 95% CI= 0.77 to 0.96).[29] A limitation of this study was the inability to implement exposure assessment measures due to the large number of studies. Specifically, unmodifiable risk factors, such as lifestyle, alcohol use, smoking use, psychosocial factors, or any other variables that subjects were exposed to outside the controlled environment were not accounted for. Another limitation is that significant heterogeneity was found in ten of the meta-analyses that were performed due to differences between individual studies in study population characteristics, mean years of follow- ups, and the reporting of crude and adjusted risk estimates.[29]

Pathophysiology of AD

AD is a highly complex and heterogeneous disease with biological, genetic and structural components of its pathophysiology. Histologically, it is classified by

intracellular neurofibrillary tangles (NFTs) and extracellular amyloid beta (Aβ) plaques in the neocortex, hippocampus and other regions elemental in cognition. [6, 12] Mitochondrial dysfunction and oxidative stress cause neurons to accumulate lipofuscin, which exacerbates neuronal dysfunction.[13] The average time from diagnosis to death (which is dependent on disease stage, individual age and underlying comorbidities) is around 8 years but it can also last up to 20 years.[6, 8] The cascade of events that occurs in the pathophysiology starts from a molecular basis. Amyloid precursor proteins (APP) aid in neuronal growth and recovery. Normally, APP is proteolyzed by enzymes alpha and gamma secretase. These fragments of APP are soluble and are able to be recycled. However, if gamma secretase is combined with beta secretase instead, APP becomes insoluble. This insoluble APP creates monomers of amyloid beta (Aβ), which binds together to form an amalgamation of Aβ. This is the main histological feature: an abnormal extracellular accumulation of Aβ plaques in certain brain regions. An accumulation of plaques between neurons contributes to an impairment of brain signaling, loss of synaptic connections, and neuroinflammation, eventually leading to neuronal death. In a condition called amyloid angiopathy, Aβ plaques can deposit in blood vessels in the brain, increasing the risk of hemorrhage. [6, 8,10]

Neurons are held together by the cytoskeleton and the tau protein (τ) prevents the tracts from disassembling. Neurofibrillary tangles consisting of τ can deposit inside neurons. Aβ plaque buildup initiates pathways inside the neuron that cease supporting the cytoskeleton resulting in clumps and tangles of τ. This also impairs neuronal signaling

leading to apoptosis. With increased numbers of neurons undergoing apoptosis, the brain starts to atrophy, gyri become narrower, sulci get wider, and ventricles appear larger. [6, 10]

There are two distinct types of AD: familial and sporadic. Familial AD, the rarer type, usually affects people aged 30-60 and runs in families. It is caused by three known genes: Presenilin 1 (PS1), Presenilin 2 (PS2) and Amyloid Precursor Protein (APP). Sporadic AD (which represents more than 90% of AD patients) is much more common and affects individuals over age 55. The only gene that has been found to be linked with sporadic AD is the apolipoprotein E (APOE) gene, which mediates the processes of synapse formation, synaptic plasticity, destabilization of microtubules, and beta amyloid clearance. Humans are the only known species known to produce multiple alleles of the gene: APOE2, APOE3, and APOE4. The APOE2 isoform is relatively rare and may provide some protection. If AD dementia occurs in a person with APOE2, it most likely develops later in life than it would in someone with the APOE4 gene. The APOE3 allele is the most common allele and having this gene neither increases nor decreases the risk of getting AD dementia. APOE4, which is the strongest genetic risk factor, is associated with an earlier age of onset and results in a greater buildup of Aβ plaques. If an individual possesses one copy of the E4 allele, AD onset is accelerated by 2-5 years. If an individual possess two copies, AD onset is accelerated by 5-10 years.[9]

The various isoforms of APOE proteins can bind with Aβ forming APOE/Aβ complexes that enhance plaque formation. These complexes make the clearance of Aβ difficult, along with increasing the competition for the same clearance pathway. APOE4 and Aβ compete for the LRP1- dependent cellular uptake pathway in astrocytes, which

facilitates uptake and degradation within cells by modifying cytoskeletal enzymes. When APOE4 competitively inhibits LRP1/Aβ binding, it contributes to an increase in Aβ plaques. When APOE3 and APOE4 are in the same environment as Aβ, they bind LDL receptors, exert internalization and bind to hippocampal neurons with greater affinity. This interaction also impacts the intracellular amyloid precursor protein (APP) recycling process, causing a greater increase in Aβ load by enhanced Aβ production.[9, 16]

Risk factors of AD

Since there is currently no cure for AD, there has been an emerging approach towards mediating risk via modifiable risk factors. Any type of insult to the cerebral vasculature can serve as a risk factor contributing to cognitive impairments. These include: small and large cortical infarcts, vascular tortuosity, cerebral hemorrhage or ischemic stroke, hypo perfusion leading to cortical changes, and injuries or toxins that cause white matter changes. [6] Rodent models of neural ischemia due to cerebral hypo perfusion have showed an overexpression of p25 and cdk5 leading to increased levels of BACE1, which increase APP.[6, 11,14, 16]

Many of the risk factors found in cardiovascular disease are also applicable to AD. These include: obesity, decreased physical activity levels, metabolic syndrome, hypercholesterolemia, psychological stress, smoking, and alcohol abuse.[6, 7, 14] In the Framingham Heart Study, researchers focused on studying the risk factors for atherosclerosis as they thought it would offer insight to potential modifiable risk factors of AD. They developed the *Framingham Cardiovascular Risk Profile [FCRP*], which included the individual's age, gender, diabetes, smoking, treated and untreated systolic

blood pressure (SBP), total cholesterol, and high-density lipoprotein (HDL) cholesterol. Elevated scores of FRCP were associated with an increased risk for cardiovascular disease and smaller brain volume and increased white risk matter changes (evidenced by hyper intensities on imaging). FRCP scores and cognitive abilities had an inverse relationship establishing that cardiovascular disease increases parenchymal destruction.[14, 16]

Another risk assessment model, called the *Cardiovascular Risk Factors Aging and Dementia (CAIDE)* risk score, showed how blood pressure, cholesterol and diabetes contributes to AD pathophysiology. Reduced cerebral blood flow is one of the contributors to AD pathophysiology. Chronic hypertension causes reduced cerebral blood flow through reduced vessel elasticity, thickening of vessel walls, and narrowing of the lumen. It also impacts the blood brain barrier (BBB) by causing cerebral edema and allowing the inflow of systemic elements into the brain. The longer hypertension affects the individual, the smaller the brain volume becomes (especially in the hippocampus). [16]

Hypotension is also associated with a higher risk of AD as was evidenced in the *Bronx Aging Study*. Participants who had a diastolic blood pressure (DBP) of <70 mmHg and lower were twice as likely to get AD than those with DBP of >90 mmHg over a follow up of 2 years. The most reasonable explanation for this was that a DBP <70 causes decreased cerebral perfusion and this chronic ischemic state could lead to increased cerebral Aβ accumulation.[16]

Unfortunately, there are some non-modifiable risk factors, such as: age, sex, family history, and presence of APOE4.[9, 16] Conversely, the presence of protective risk

factors (which are modifiable) decrease an individual's chances of getting AD. These include: cognitive reserve and mental activity, educational attainment and lifelong learning, cognitive leisure activities, physical activity, social engagement, mindfulness, optimism, and diet including omega-3 intake. [6] Studies have found that increased intake of plant-based foods, increased fish intake due to increased amounts of omega 3, moderate red meat intake, reduced salt intake, and minimal alcohol intake can serve as protective factors.[6, 7]

Diagnosis of AD

While there is no single diagnostic test that can diagnose AD, healthcare professionals use a variety of approaches to make a diagnosis. Typically, the patient is brought in by family members who are concerned about a decline in thinking, memory problems or forgetfulness. Initially, the healthcare provider will delve into the patient's medical history asking questions on past medical history, psychiatric history, cognitive or behavioral changes, medication use, family history of similar symptoms, social history (diet, physical activity level, alcohol use or smoking). The healthcare provider will then assess reversible causes of memory loss, such as: depression, untreated sleep apnea, delirium, hypothyroid, other neurological disorders, vitamin deficiencies, and vitamin B12 deficiency.[25] It is also important to rule out possible infectious causes. One of two highly sensitive neuropsychological screening tests, the Mini-Mental State Exam (MMSE) and Montreal Cognitive Assessment Test (MOCA) will be conducted which have subtle differences (Table 2). [1, 5] Both these tests are used to assess the overall activity of the higher cortical functions. In both the MMSE and MOCA, a maximum

score of 30 is considered normal, a score of 20-24 suggests mild dementia, 13-20 suggests moderate dementia, and less than 12 indicates severe dementia.

Table 2: Comparison of MMSE and MOCA in terms of the studied areas of cognition and scoring [5]

Cognitive function		MMSE (No. of points/trials)	MoCA (No. of points/trials)
Orientation		10 tasks (10 points)	6 tasks (6 points)
Memory	Learning	Learning of 3 words (3points/1 trial allowed)	learning of 5 words (no points/2 trials allowed)
	Delayed recall	3 words (3 points)	5 words (5points)
	Cued recall (optional)	not present	5 words (no points)
	Recognition (optional	not present	5 words (no points)
Naming		2 items (2 points)	3 pictures (3 points)
Visuospatial functions		copy of pentagons (1 point)	copy of cube (1 point) clock drawing (3 points)
Comprehension		3-stage command (3)	not present
Vigilance		not present	tapping with hand at letter A (1 point)
Language		repetition of sentence (1 point)	Repetition of 2 sentences (2 points)
Reading		Sentence (1 point)	not present
Abstract thinking		not present	similarities (2 points)
Writing		patient's sentence (1 point)	not present
Alternating Trial Making		not present	1 trial (1 points)

Lastly, the medical workup includes brain imaging with MRI or CT to rule out other conditions, such as tumor, hemorrhage, stroke, or hydrocephalus, that may be causing memory loss but require different treatment. Some AD abnormalities include: hippocampal/temporal lobe atrophy in MRI, decreased amyloid/increased tau in CSF, and

amyloid plaques in PET scans. A metanalysis found that hippocampal volume can detect an average of 73% of MCI subjects who progress to AD. [20]

Neuropsychiatric (NPS) symptoms in AD

NPSs are among the earliest signs of cognitive decline and affect 97% of individuals with dementia, yet they are often under-recognized and difficult to treat. [23] AD NPSs may manifest as a lack of emotional connection to people or things (apathy), disinterest, aggression, paranoia, impulsivity, depression, anxiety, disinhibition, irritability, motor disturbance, sleep disorder, appetite disorder, aberrant vocalization, motor problems, delusions, and hallucinations later in the course. [6, 10, 11, 16, 23]

There is a prodromal phase of accelerated decline in multiple cognitive functions (otherwise known as mild cognitive impairment or MCI) before developing AD which can be last for as little as 6 months and up to 10 years. [18] According to the Alzheimer's Association, about 15- 20% of people age 65 or older have MCI.[11]A cohort study done by Tarango et al found that among people with MCI, the presence of NPS may increase the risk of progression to AD dementia. [21] One MCI study found NPSs in 59% of participants and their presence forecasted faster progression from MCI to AD dementia in two large cohort studies. [23]

Depression and Sleep Dysfunction in MCI

There are 15-30% of patients with MCI who experience feelings of anxiety and depression and, among this group, the conversion rate of MCI to dementia can be as high as 50%. A compilation of literature reviews found that yoga improves depressive

symptoms by downregulating the hypothalamic axis and sympathetic nervous system leading to decreased cortisol levels, blood pressure and inflammatory markers.[37]

Up to 45% of patients with MCI report sleep disturbance. These complaints include insomnia, sleep fragmentation, daytime sleepiness, and cognitive dysfunction. The connection between yoga, sleep and cognitive function is interlinked; therefore, yoga could be an ideal complement to the treatment plan. This was evidenced in a study done by Janelsins and colleagues who found that cancer patients who had undergone 2-24 months of treatment and complained of sleep disturbances reported improved sleep and memory after participating in yoga. [37] Other benefits of yoga on sleep include: reduced sleep latency, improved sleep quality, and increased feelings of restfulness in the mornings. [37]

Treatment of AD

Currently, treatment for AD relies solely on symptomatic management and there is no definitive treatment that halts progression. Some medications exist but their benefits are small. There is an immense need for therapies to prevent and/or slow the progression of AD.[25] Treatment is branched into pharmacologic therapy and non-pharmacologic (behavioral) interventions.

Pharmacologic therapy

Currently, there are four Food and Drug Administration (FDA) approved medications available specifically for AD dementia. These treatments provide symptomatic relief but they do not modify the disease course. The medications are divided into two categories based on their respective mechanisms of action:

Cholinesterase inhibitors and NMDA (N-methyl-D-aspartate) receptor antagonists. While these drugs are not addictive, the following side effects have been reported: loss of appetite, nausea, vomiting, diarrhea, constipation, dizziness, headaches, and fatigue.[25] These drugs might be one strategy to temporarily aid with cognitive impairment but they may not work for everyone. Another short coming of these drugs is that their effects wear off over time. While the drugs are approved for specific AD stages (mild, moderate and severe), they are not approved for mild cognitive impairment. Clinical trials that have tested whether these drugs could prevent progression of the translational stage to AD have shown no lasting benefit.[8] This is why there is an immense need to focus on effective lifestyle approaches to slow disease.

There are also new therapeutic approaches directed towards the pathogenesis of AD undergoing clinical trials. These include medications that are: anti-amyloid aggregates, anti-tau, β and γsecretase inhibitors, Aβ vaccination, amyloid cholesterol-lowering drugs, anti-inflammatories, and neuroprotective drugs. [2]

Cholinesterase inhibitors

In the cholinergic hypothesis a neurochemical feature of AD is a deficit in cholinergic transmission, which relates to memory impairment. Cholinesterase inhibitors were implemented in an effort to inhibit the synaptic enzymatic breakdown of acetylcholine (a neurotransmitter key to neurons involved with learning and memory) and improve cholinergic transmission. However, as increasing numbers of neurons die, the continued efficacy of these drugs discontinues. A review by the Quality Standard Subcommittee of the American Academy of Neurology concluded that despite the small

degree of benefit of treatment with acetylcholinesterase inhibitors, they should be first line treatment in patients with mild to moderate AD. There are four cholinesterase inhibitors that are approved by the FDA: Tacrin, Donepezil, Rivastigmine, and Galantamine. Data show that these cholinesterase inhibitors have similar efficacy in short term use but more data is needed to understand long term effects on disease progression. In 1/3 of patients, symptoms were shown to worsen in the first 6 months of treatment with a variable response to a second inhibitor. Clinical research studies have limited guidance on the safety of switching drugs. [8, 25, 26]

NMDA receptor antagonists

Increased extracellular amounts of glutamate, the main CNS excitatory neurotransmitter, can lead to exaggerated activation of NMDA receptors, which results in intracellular accumulation of Ca^{2+}. This intracellular Ca^{2+} accumulation further results in neuronal death. Thus, Memantine, an NMDA- receptor antagonist, regulates the activity of glutamate and reduces the cascade of events (by partially blocking NMDA receptors) that would lead to the chronic increased influx of calcium and subsequent neuronal death. It can be used in moderate to severe AD although a systematic review by the Cochrane Dementia Group published that the trials were unable to detect clinically significant benefit due to their short nature and small sample size. [25, 26]

Treatment of NPS

Currently, only a few pharmacologic treatments for NPSs exist with proven efficacy and acceptable levels of risk, such as antipsychotics, antidepressants, benzodiazepines, cholinesterase inhibitors, and anticonvulsants.[22] Antipsychotics (such as

Olanzapine, Aripiprazole, and Haloperidol) were found to have minimal efficacy on psychotic symptoms but were associated with several adverse side effects and an increased risk of death. [23]

Treatment of Depression and Sleep Disorder

Some studies have suggested that antidepressants may worsen the course of cognitive decline in certain patients and are even associated with QT interval prolongation. [23, 24] A meta-analysis of drug treatment versus placebo in patients with AD found insufficient evidence to help guide drug treatment of sleep problems in AD. [23] Nonpharmacological interventions are considered the first line treatment but there has not been much real-world application due to insufficient funds to study their efficacy. [23] Investigating the effects of yoga, electroconvulsive therapy (ECT), and drug therapy (Imipramine) for 4 weeks, a study done by Janakiramaiah et al found that respective remission rates were 67% for yoga, 93% for ECT, and 73% for drug therapy. [43]

EXISTING RESEARCH

While several treatment trials are advancing to determine which therapeutic measure can effectively halt progression from MCI to AD dementia, there has not been a clear answer. [27] The significance of early intervention in the MCI timeline is that sooner application of therapeutic interventions can prevent long term damage to the central nervous system.[28] A systematic review found that no randomized controlled trials showed protective effects of dementia medication, anti- hypertensives, nonsteroidal anti-inflammatory drugs, or aspirin.[30] Despite inconsistencies in data on antioxidants in

cognitive function, there have been suggestions that vitamin E, vitamin C, gingko biloba and curcumin may be beneficial in early MCI stages to reduce oxidative stress levels. [31]

Since no medications have been proven to effectively treat MCI, researchers have shifted their attention towards non-pharmacologic options. Certain non-pharmacologic interventions, such as moderate-intensity exercise, Mediterranean diet, social activities, and cognitive exercises have shown favorable results through observational research. [31] A study found that 6 months of a behavioral intervention consisting of regular intervals of increased heart rate improved executive function for patients with MCI without the cost and side effects of pharmaceutical therapies. [32] The participants in this randomized, controlled trial included 33 adults (17 women and 16 men) who ranged from the ages of 55 to 85 years old and were diagnosed with MCI in memory disorder clinics by the Petersen criteria. The study aimed to analyze the impact of aerobic exercise on cognition in elderly adults who were had MCI. The subjects were randomized to one of two groups: either a high-intensity aerobic exercise group or a stretching control group. A fitness instructor supervised the aerobic exercise group and instructed exercises on treadmills and ellipticals for 45-60 mins 4 days a week for a duration of 6 months, while ensuring their heart rate was sustained 75%-85% of their heart rate reserve. Meanwhile, the stretching control group was supervised to maintain 50% or below of their heart rate reserve.[32]

Cognitive assessment testing measured both executive function and short-term memory at baseline, 3 months and 6 months. Executive function testing included the Trail Making Test (which consisted of drawing lines to connect alphanumeric stimuli that

were randomly placed on a page), the Stroop Color and Word Test (which tested selective attention and response inhibition using a computer), Task Switching (measured the ability to switch between tasks), and Symbol Digit Modalities (which tested processing speed by enabling subjects to draw symbols for a series of numbers). Short-term memory was tested using Story Recall (which tested the ability of subjects to recall a narrative after a 30 min delay), List Learning (which tested the ability of subjects to hear 12 words and remember them across 3 trials), and Delayed-Match-To-Sample (which tested visual memory). Remarkable positive effects of aerobic exercise were assessed for Symbol-Digit Modalities ($F_{1,26}=4.18$; $P=.05$), Verbal Fluency ($F_{1,25}=4.87$; $P=.04$), and Trail Performance ($F_{1,25}=4.58$; $P=.04$) compared to the stretching control group. A small sample size was a limitation of this study. Since the inclusion criteria of the study was limited to elderly adults without medical problems and those able to undergo physical exercise, the results might not be generalizable to population-based samples. Additionally, population-based samples will have less structure and supervision than this controlled trial did. There could also have been a potential misclassification bias if those in the control group exercised on their own time. This study found that non-pharmacological treatment (aerobic exercise) was able to serve as a protective factor in preserving cognitive function in subjects with MCI.[32]

A single-blind randomized controlled trial by Zhu et al was designed to assess the effectiveness of a specifically designed moderate-intensity aerobic dance routine on cognitive function compared to the usual care in 56 patients with amnestic MCI for 3 months. While both groups were counseled by physicians at baseline in promoting

healthy lifestyles, the treatment group attended a 35-minute dance session 3 times a week for 3 months. The dance session included head movement, side bending, knee bending, heel up, boxing, shoulder movement, kicking, square-stepping, and sculling exercises. The Wechsler Memory Scale- Revised logical memory test (WMS-R LM subtest), MoCA, Symbol Digit Modalities Test (SDMT), Trail Making Test (TMT), and forward and backward digit span tasks (DST) were used to measure outcomes.[40]

In order to detect an effect size of 0.75 SD, a sample size of 56 (28 per group) was required to achieve 80% power at the significance level of 0.05. Patients in the treatment group showed greater improvements in memory (95% CI 1.6, 5.1; $p<0.05$) and cognitive function (95% CI 0.8, 2.3; $p<0.001$) both at 3 months compared to the group that only received the usual care. Furthermore, these patients were followed up for another 3 months after the discontinuation of the dance intervention and it was found that their previously obtained memory improvement had diminished, and quality of life was also improved compared to baseline (95% CI 1.1, 11.2, $p<0.05$). Only individuals with amnestic MCI were studied, so these findings may not be generalizable to those with non-amnestic MCI. Selection bias was also another limitation of this study because only elderly adults who were able to execute the aerobic dance routine were chosen. Those with increased sensitivity to fatigue or pre-existing medical conditions were unable to pass the screening criteria. However, these results confirm that the cognitive function of individuals with amnestic MCI in the treatment group substantially improved compared to the control group.[40]

Existing research confirms the presence of NPS in patients with MCI and one study found that NPS occur with a prevalence between 43% and 59% in those patients. Patients with MCI and NPS have a four-fold higher risk of progression to dementia.[21] Studies have suggested that several NPS including anxiety, depression, apathy, and agitation have been linked to a higher risk of progression to AD. However, findings have still been inconsistent.[34] A longitudinal population- based study by Palmer et al evaluated mood-related, depressive, and motivation-related symptoms in 185 people without MCI and 47 with MCI ages 75 to 95 from Stockholm, Sweden for 3 years. At the end of the 3-year follow up, AD was diagnosed according to Diagnostic and Statistical Manual for Mental Disorders-III-R criteria. [33]

More NPS occurred in individuals with MCI (36.2% mood, 36.2% motivation, and 46.8% anxiety) than in cognitively intact individuals (18.4% mood, 13% motivation, and 24.9% anxiety). At the 3- year follow up, 56.2% of individuals with multi-domain MCI developed AD compared to only 5.9% of individuals without baseline cognitive impairments.[33] While investigating whether all NPS predicted progression to AD among individuals with MCI over 3 years, it was found that only the symptom of anxiety predicted AD in subjects with MCI (Figure 1). [33]

Figure 1: NPS in relation to progression to AD in individuals with and without MCI [33]

Presence of clinically severe symptoms as predictors of AD	MCI-amnestic or -multidomains, n = 47		No cognitive impairment, n = 185	
	RR	95% CI for AD	RR	95% CI for AD
Mood symptoms: 0–4 symptoms	0.9	0.6–1.5	1.9	1.0–3.6
Motivation-related symptoms: 0–4 symptoms	1.1	0.7–1.8	1.9	0.5–7.4
Anxiety symptoms: 0–4 symptoms	1.8	1.2–2.7	1.1	0.5–2.3

Relative risks (RRs) estimated from hazard ratios calculated with Cox proportional hazard models adjusted for age, sex, and education.
AD = Alzheimer disease; MCI = mild cognitive impairment.

The risk of AD nearly doubled for every anxiety symptom (RR: 1.8, 95% CI: 1.2 to 2.7). Individuals with MCI who had problems with decision making had a 5-fold risk of AD compared to those without (RR: 5.6, 95% CI: 1.1 to 29). Moreover, individuals with MCI and persistent worrying also had a 5-fold increased risk (RR: 5.3, 95% CI: 18 to 15.6). About 6% of cognitively intact individuals, 40.9% of individuals with MCI without anxiety, and 83.3% of individuals with MCI and anxiety progressed to AD. Notably, this translated to a 30 times higher risk in individuals with MCI and anxiety (RR: 34.4, 95% CI: 13.9 to 85.8) than those cognitively intact. [33]

This study suggests that the presence of anxiety symptoms with MCI enhances the predictive validity of identification of AD. This study was based off performance on neuropsychological tests and self-reported symptoms; moreover, it included data from a population-based study instead of a clinical sample, so the results have a higher likelihood of being generalizable to the general population compared to other studies that have used clinical samples. A limitation is that these results may not be representative of the general population due to the small sample size, and it is likely underpowered. [33]

Depression is another NPS that was found to be a precocious indicator of progression to AD in individuals with MCI. A prospective study done by Chan et al was conducted to assess the 2-year impact of NPS on clinical deterioration to AD in 321 community-dwelling Chinese people aged 60 and older with MCI.[34] Cognitive and functional assessment of the subjects was measured by a Chinese version of the MMSE, delayed recall of list learning of the Alzheimer's Disease Assessment Scale- Cognitive subscale (ADAS-cog), Category Verbal Fluency Test (CVFT), and assessment by a geriatric psychiatrist with Clinical Dementia Rating (CDR). Of the 321 subjects, 270 (84.1%) remained stable or improved, while 51 (15.9%) developed dementia over the 2 years. These subjects presented with depression, apathy, and anxiety at baseline but 27.5% of subjects with depression at baseline developed dementia in comparison with 14.8% of those without depression at baseline. Dementia converters exhibited more delusions, agitation, depression, irritability, aberrant motor behavior and appetite changes and less apathy, anxiety, and night-time behavior disturbance (Figure 3). Particularly, depression and aberrant motor behaviors (although not as significant) at baseline were correlated with conversion to dementia in 2 years, whereas the other NPS prevalence was mild. [34]

Figure 3: Baseline NPS outcome at follow-up [34]

	Stable group (n = 270)	Deteriorated group (n = 51)	Statistics[a] (P-value)
Delusion, n (%)	9 (3.3)	3 (5.9)	0.38
Hallucination, n (%)	1 (0.4)	0 (0)	0.66
Agitation, n (%)	9 (3.3)	4 (7.8)	0.13
Depression/dysphoria, n (%)	40 (14.8)	14 (27.5)	0.03
Anxiety, n (%)	37 (13.7)	4 (7.8)	0.25
Euphoria/elation, n (%)	1 (0.4)	0 (0)	0.66
Apathy/indifference, n (%)	42 (15.6)	3 (5.9)	0.07
Disinhibition, n (%)	3 (1.1)	0 (0)	0.45
Irritability/lability, n (%)	13 (4.8)	5 (9.8)	0.16
Aberrant motor behaviour, n (%)	1 (0.4)	2 (3.9)	0.02
Night-time behaviour, n (%)	61 (22.6)	10 (19.6)	0.64
Appetite/eating change, n (%)	8 (3.0)	3 (5.9)	0.29

[a] χ^2 test.

This study provides evidence that depression in individuals with MCI is an early predictor of progression to dementia. Additionally, it was recommended that further studies still need to assess whether effective management of NPS in MCI could prove to delay progression to dementia. The limitation of this study was that the small sample size included elderly individuals from Hong Kong. Cultural differences and underlying genetic or environmental factors could have affected the reporting of NPS, thereby introducing a potential bias. Additionally, the study had a short follow-up of 2 years which raises concerns of inadequately capturing all dementia converters. Thus, these results may not be generalizable to other cultural populations. [34] Lastly, the researchers might have been using incorrect statistics. This study used Chi square but many of the

comparisons would have small numbers in the cells. Thus, Fisher's Exact might have been the more appropriate statistical test.

A 2-year cohort study done by Taragano et al evaluated three clusters of patients with MCI and NPS and examined their risk of progression to dementia: a severe cluster (agitation, anxiety, apathy, nighttime behaviors, inhibition), an affective cluster (depression, anxiety, irritability, nighttime behaviors), and an asymptomatic cluster. The sample consisted of 540 volunteers who were 60 years and older and diagnosed with MCI at an Alzheimer's Disease Center (ADC). Data collection took place at the ADC between September 2005 and August 2013. The Neuropsychiatric Inventory Questionnaire (NPI-Q), Mini-Mental State Examination (MMSE), and the Geriatric Depression Scale (GDS) were conducted at each visit. [21]

Of the 540 individuals with MCI, 121 (22%) were diagnosed with dementia; those of the severe class had more than twice the risk of the asymptomatic class (2.69, CI: 1.65-4.37) and the affective class had more than one and half times the hazard of the asymptomatic class (1.75, CI: 1.12-2.70). [21] This study highlights the finding that targeting patients with NPS from the severe cluster (agitation, anxiety, apathy, nighttime behaviors, inhibition) with effective management may decrease the risk of conversion to dementia due to its association, assuming that intervening on NPS modifies a similar underlying pathology to AD. The sample also consisted of volunteers who were diagnosed with MCI after at least one visit where they were considered cognitively normal, so these results may not be generalizable to later stages of MCI. [21]

Yoga is an ancient mind body practice that has been identified as a complementary health approach by the National Center for Complementary and Integrative Health. Yoga has been affiliated with physical postures (asanas), breathing techniques (pranayama), and meditation (dyana). While there are several branches of yoga practices, Hatha yoga is the most common branch practiced in the US that encompasses physical posturer, breathing and meditation. Yoga is an exercise used and recommended by several people to approach and prevent health conditions such as, depression, anxiety, asthma, low back pain, cancer, cardiovascular disease, and insomnia. Yoga may improve multiple cognitive domains, such as attention, processing speed and verbal memory. [42]

Mood disorders have been linked with reduced GABA levels and they have been shown to respond to drugs that increase GABA levels.[36] A yoga intervention done by Gautam et al found the experimental group of yoga practitioners to have a 27% increase in GABA levels after a 60-minute session of yoga as opposed to change in GABA levels in controls after a 60 minute reading session. [35] These results show that the effects of yoga are comparable to pharmacologic treatment evidencing that a yoga intervention can prove to be as efficacious on depression as pharmacologic treatment with the benefit of no side effects. Eight studies in a literature review showed that yoga had beneficial effects on cognitive function in individuals with MCI by improving sleep, mood, and neural connectivity. [37]

Mind-body interventions have increasingly been used to manage depressive symptoms but no studies have investigated the effects of a yoga intervention in

depressive symptoms in the elderly with mild cognitive impairment. While several studies have found an association between the presence of depression in individuals with MCI and progression to dementia, this randomized controlled trial will be the first yoga intervention study to measure depression severity in patients with MCI.

METHODS

Study design

This proposed study will be a randomized-controlled trial with two arms to assess the effects of a yoga intervention in improving depression symptoms and GABA levels in the brain. The control arm will not undergo a yoga intervention but will participate in walking twice a week for 9 months. The experimental arm will utilize a yoga intervention in combination with walking for the same duration of time. Both treatment groups will continue to receive normal baseline standard of care throughout the duration of the study. Patients will be assessed using the following validated standardized tools: Patient Health Questionnaire (PHQ-9), Geriatric Depression Scale (GDS), Hamilton Rating Scale for Depression (HAM-D), and Montreal Cognitive Assessment Test (MoCA). The HAM-D and GDS are both subjectively completed by the participant and the HAM-D is completed by a healthcare professional. Magnetic Resonance Spectroscopy (MRS), a non-invasive method to measure neurotransmitter concentrations in the brain, will be used to measure GABA levels throughout the experiment. [44] The subjects will be evaluated at baseline, at 3 months, and at 6 months to determine whether depression levels improved, were unchanged, or worsened.

Study population, recruitment and sampling

Patients will be recruited from the Neurology and Family Medicine outpatient departments of several Boston hospitals including Boston Medical Center, St. Elizabeth's, and Massachusetts General Hospital. A healthcare practitioner will have diagnosed the patients with both MCI using the Petersen criteria and depression using the DSM-5 criteria. Additionally, their depression will be poorly controlled over time, which are defined by persistent depressive symptoms (feeling sad, inability to concentrate, excessive feelings of guilt, extreme mood changes, fatigue, sleep changes, decreased interest and appetite levels, etc.) despite lifestyle modification and anti-depressant trials.

Patients who have exhausted their pharmacologic and non-pharmacologic treatment options for both MCI and depression will be asked to participate in this study at their next follow up visit with either the Neurologist or General Practitioner. If agreed, they will be asked to fill out a PHQ-9, GDS, and MoCA test. Patients with a MMSE or MOCA score of 20-26 will be asked to participate in the study to ensure that they are early in the process of MCI to be able to follow through with the yoga program. A score of <20 would make it difficult for patients to follow the steps of the session. Physicians will give their contact information to the research coordinators who will consequently reach out to the patients' by phone to determine if they meet the inclusion criteria listed below. If they do, the patients' will be asked to provide consent and will be enrolled into the study.

Prior to the start of the study, baseline MCI and depressive symptoms will be re-evaluated in these patients. Each participant will undergo a medical evaluation to ensure

there are no contraindications that could lead to postural instability or difficulties following instructions. The first will be with their respective Family Medicine or Neurology practitioner to assess baseline symptoms and a research assistant with at least 1-2 years of clinical research experience. The research assistant will explain the specific aims of the study with the participants and their families individually and answer all of their questions. After this meeting has been completed with all the participants, the intervention-based study will start in a few days. They will then be randomly assigned to the yoga group, and both groups will be given instructions regarding weekly text messages for walking reminders.

The inclusion criteria will include: (1) Patients of any gender between the ages of 65-80 years old; (2) with a diagnosis of MCI according to a MoCA test score of 20-24 to ensure that they can follow commands properly; (3) with intact cognition according to a score of 8 or higher on the Short Portable Mental Status Questionnaire (SPMSQ); (4) a diagnosis of depression from the DSM-5 criteria; and (5) the ability to walk independently and perform yoga safely. Patients must also have a means of transportation to assisted living facilities where the yoga intervention will take place and access to a cell phone on which they can receive text messages for reminders of biweekly walks. The exclusion criteria will include: (1) patients with a history of uncontrolled cardiovascular, postural, orthopedic, neurological, or pulmonary conditions that affect the individual's ability to balance and think clearly; and (2) patients with a prior history of yoga training as it may bias the study.

Based on a Cohen's D of 0.54, the study will require a sample size of 110 with 55 subjects in each arm to detect a significant difference by the student's t test in improvement of depression symptoms. This is calculated with a beta of 0.2 and an alpha of 0.05. These numbers are generated based on the results from Eyre et al that found that level of improvement on the effects of depressed mood with kundalini yoga in individuals with MCI at 24 weeks using the Hopkins Verbal Learning Test Total Recall (HVLT) Total. [41] We predict that our intervention method will show similar or superior results in improvements in depression levels.

Intervention

The intervention of this study is based on the study performed by Chen et al which investigated the effects of silver yoga exercises in the sleep quality, depression levels and mental health status in elderly individuals over 6 months, which found that improved mental health indicators after 3 months and were maintained throughout 6 months. [40] Individuals who meet the inclusion criteria will be randomized into the two arms. A 40-minute yoga exercise program will be implemented twice a week for 6 months as the intervention for the subjects in the experimental group in a senior assisted living facility. Each yoga session will have a trained yoga instructor who is specialized in geriatric exercise. The exercise program will include a warm up phase (10 mins) with 4 postures to loosen up tight muscles, 7 gentle stretching postures (20 mins), and a relaxation phase (10 mins) with 4 postures. Inhalation and exhalation breathing techniques will be encouraged throughout the sessions and the yoga postures will be less arduous keeping in consideration the toleration and exhaustion levels of the elderly. Daily

walking will be implemented in all participants in both groups. Instructions on walking will be set via text message twice a week.

Study variables and measures

Baseline demographics, such as age, gender, ethnicity, medical comorbidities (heart disease, lung disease, etc.), medications, level of physical activity and fitness, and pre-treatment scores for the PHQ-9, GDS, HAM-D, and PQSI will be obtained for all participants enrolled in this trial.

The dependent variable in this study will be level of depression, which will be measured by the PHQ-9, GDS, and HAM-D. The PHQ-9 consists of 9 questions that screens for the presence and severity of depression (see Appendix 1). The survey items ask about the patient's level of interest in doing things, feeling depressed, difficulty sleeping, energy levels, eating habits, concentration abilities, self-perception, speed of functioning and thoughts of suicide. Responses can range from 0 (not at all) to 3 (almost every day). Total score can range from 0 to 27. A test of 10 or above is associated with the presence of depression and indicates that a treatment plan is needed.

The GDS is a 30-item instrument (see Appendix 2), but there is also a short 15-item instrument in case the other version proves difficult for patients to complete. Patients can answer either yes or no and one point is assigned to each answer. A score of 0-9 indicates "normal", 10-19 "mildly depressed", and 20-30 "severely depressed."

The HAM-D will be administered by a healthcare professional (see Appendix 3). It asks questions in 21 areas with a choice of varying rating scores. A score of 0-7 indicates "normal", 8-13 indicates "mild depression", 14-18 indicates "moderate

depression", 19-22 indicates "severe depression", >/= 23 indicates "very severe depression."

Sleep quality will be measured as a secondary outcome by using the Pittsburgh Sleep Quality Index (PQSI) with scores ranging from 0-21 and higher numbers correlating with worsening sleep quality. The independent variable of this study is participation in the yoga intervention.

Data collection

The subjects will undergo assessments using the PHQ-9 and GDS, which will be individually filled out by the participant, and the HAM-D, which will be filled out by the healthcare provider. Each participant will also have blood work done to evaluate baseline values and MRS imaging to determine baseline GABA levels.

The clinical coordinator of the study will be responsible for scheduling and arranging follow up visits at baseline, 3 months, and 6 months with a clinical research assistant. The research assistant will provide each of the clinical assessments at all follow up visits. Either a family care physician or neurologist will be present at each of these follow-ups so they can assess symptoms and fill out the HAM-D. At subsequent follow up visits, scores from the prior visits will be assessed. The MoCA test will be assessed at each visit to ensure adequate levels of cognitive functioning. As long as the participants' are not losing significant cognitive function, they will be allowed to continue in the study. If they do start to lose cognitive function, only data up to the point of loss of cognitive function will be included. In subsequent follow up visits, participants will complete the

assessments and speak to their relative healthcare practitioners about any difficulties or symptoms they are experiencing. Input on memory complaints or depressive symptoms will also be taken from their family members. At every follow up appointment, baseline MoCA and MMSE will be done.

To ensure adequate attendance for the entirety of the class, participants will be asked to sign in and sign out. In order to incentivize attendance, they will receive a member ID card that allows them to take part in the yoga classes free of charge. They will also be asked to keep track of their walking activity and any extraneous physical activity they may take part in.

Data analysis

To calculate the improvement in depression symptoms outcome, the data collected using the assessments will include the mean and standard deviation of the total score at baseline, 3 months, and 6 months. In order to compare the difference in depression scores between the study arms, the independent t-test will be used. Percentages of both treatment arm outcomes (improvement, no improvement or worse outcomes) will be summarized in a table. The comparisons among baseline, 3 month, and 6 month outcomes will be conducted using the Chi square test showing percentages. To compare demographic information (such as age, race, sex, ethnicity, pre- intervention PHQ-9, GDS, and HAM-D scores) and assessment scores prior to the yoga intervention, means and standard deviations will be used to compare continuous variables and proportions will be used to compare categorical variables. Sleep and GABA levels will be analyzed by using the t-test.

Timeline and resources

This study will take place for a duration of 6 months (24 weeks) following recruitment. IRB approval is anticipated to take 6 months, recruitment should take 2-3 months, and data analysis should take approximately 3 months. Approximately 5 yoga instructors and physical therapists with at least 1-2 years of experience will be recruited to teach the yoga routine. These instructors and therapists will be required to have worked with senior citizens in the past. The specified 40-minute yoga routine will be taught to the yoga instructors and physical therapists, and they will also be explained the safety protocols.

Institutional Review Board

An outline of the detailed protocol and aims of the study will be submitted for full board review to the Boston University Medical Campus Institutional Review Board (IRB). Approval will be obtained prior to subject recruitment.

CONCLUSION

Discussion

The results of this study will provide information about the possible applicability of a non-pharmacologic therapeutic intervention in improving depression in individuals with mild cognitive impairment. Yoga has been associated with remarkable outcomes for improving depression and sleep outcomes in individuals with a wide variety of medical conditions compared to pharmacological interventions. The current pharmacologic therapeutic interventions aimed at alleviating depression and other neuropsychiatric symptoms of MCI are associated with a wide range of serious side effects and there has not been much investigation into non-pharmacologic interventions. This study is the first study to measure the outcome of yoga in depression symptoms in individuals with mild cognitive impairment. Since there is a strong association between depression and quality of sleep, it is predicted that the intervention group will have improved sleep quality as well.

Depression and mild cognitive impairment both lack an ability to be biologically tracked; they must be evaluated using standardized assessments. A limitation is that although the PHQ-9 and GDS are generally used, their ability to correctly identify depression compared to some established criteria has not been thoroughly investigated. For instance, no studies in the US have investigated the diagnostic accuracy of the PHQ compared to the gold standard, the Structured Clinical Interview for DSM-5 (SCID). However, SCID was not used in this study due to its increased length of completion time, which may not be sustainable for the elderly population. False positives and false negatives can occur in these assessments which can also be problematic. On the contrary, strengths of these assessments are that they are simple and cost-effective tools.

Patient compliance and adherence to the yoga intervention may also be another limitation. The population of the study is elderly with mild cognitive impairment and depression among other neuropsychiatric symptoms so they may display decreased levels of motivation at times. Moreover, they may fatigue more easily and have lower levels of physical stamina. Yoga has been shown to boost endorphin levels and the ability to engage in social activity with their peers and instructors may boost motivation.

The strengths of this study include the wide range of diverse ethnic, racial and socioeconomic backgrounds of the patients, which will allow for the results of the study to be generalizable to diverse population-based communities. While the participants will continue to receive standard of care by their practitioners, they will also be on pharmacological therapy to avoid potential biases if their depression or MCI become resistant to treatment. This is contrary to other studies that have evaluated the use of

non-pharmacologic treatment in individuals with mild cognitive impairment and depression where the participants have not been simultaneously taking both pharmacologic therapy and non-pharmacologic therapy.

Summary

MCI is the translational stage in the progression to dementia and it is associated with NPS, including depression. Research has found that the presence of these NPS is associated with eventual progression to AD dementia and targeting them could prevent progression to dementia, if the intervention targets underlying shared pathophysiologies of the conditions. Existing pharmacologic treatment for NPS is replete with adverse side effects and minimal resolutions. Research has also found that yoga has been effective in improving depression symptoms in individuals with various kinds of diseases but these have been limited in study duration, design and demographics of participants. Yoga has also been chosen as an intervention for this study because it fosters the ability to build relationships and interact in a social setting, which may increase GABA levels in the brain. This study will be the first to investigate the effects of yoga on depression in individuals with mild cognitive impairment. The population in this study will be from various racial, ethnic and socioeconomic backgrounds, on pharmacologic agents for depression and MCI, and with varying levels of depression. They will be randomized into a treatment group, which will be exposed to a biweekly yoga intervention with walking, and a control group, which will be exposed to just walking weekly, both for a total duration of 9 months. Thus, the potential for bias will be accounted for by eliminating the

possibility of participants being resistant to treatment for depression and outcomes will be measured using standardized assessments, the PHQ-9, GDS and HAM-D.

Clinical and/or public health significance

After heart disease and cancer, AD is the 3rd most expensive disorder in the country. It is the only cause of death in the top 10 that cannot be cured, reversed or slowed and approximately 100,000 patients die of AD each year. There are significant economic, social and health care burdens to prevent, diagnose, treat and manage AD dementia.[19] As per the CDC, the costs of treating AD in 2010 were projected to be between $159 and $215 billion.[17] However, by 2040, these costs will jump to between $379 and more than $500 billion annually.[3, 17, 19] Total costs include: direct costs (medications, physician visits, home health aides), indirect costs (caregiver lost productivity), and intangible costs (suffering and decreased quality of life endured by caregivers). A Medicare study showed that each comorbid condition in patients with AD (which also costs more to manage) was associated with a higher cost ($10,435) than in patients without AD ($526). [3, 19]

Healthcare systems are increasingly examining non-pharmacologic interventions as a more effective option. Exercise has been linked with improving cognition and reducing depression levels in individuals with MCI. Studies have examined the interventions of aerobic exercises in patients with MCI, but the use of yoga in individuals with MCI and depression have yet to be studied. Commitment to exercise regimens can be difficult for the elderly with MCI, and high intensity aerobic exercise can prove to be challenging. Studies have linked yoga with high enjoyment levels and feasibility levels

which increase the likelihood of the elderly being consistent with the exercise. If this study proves to utilize yoga to reduce depression levels in patients with MCI, healthcare professionals could recommend yoga exercises to target depression levels that have been associated with eventual progression of MCI to AD dementia. Thus, this highlights the importance of enforcing effective non-pharmacologic interventions both for the individual and the healthcare system.[17]

APPENDIX

Appendix 1:

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✔" to indicate your answer)*	**Not at all**	**Several days**	**More than half the days**	**Nearly every day**
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING 0 + _____ + _____ + _____

=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	**Somewhat difficult**	**Very difficult**	**Extremely difficult**
☐	☐	☐	☐

Appendix 2:

Geriatric Depression Scale (Long Form)

Patient's Name:_____ Date:_____

Instructions: Choose the best answer for how you felt over the past week.

No.	Question	Answer	Score
1.	Are you basically satisfied with your life?	YES / NO	
2.	Have you dropped many of your activities and interests?	YES / NO	
3.	Do you feel that your life is empty?	YES / NO	
4.	Do you often get bored?	YES / NO	
5.	Are you hopeful about the future?	YES / NO	
6.	Are you bothered by thoughts you can t get out of your head?	YES / NO	
7.	Are you in good spirits most of the time?	YES / NO	
8.	Are you afraid that something bad is going to happen to you?	YES / NO	
9.	Do you feel happy most of the time?	YES / NO	
10.	Do you often feel helpless?	YES / NO	
11.	Do you often get restless and fidgety?	YES / NO	
12.	Do you prefer to stay at home, rather than going out and doing new things?	YES / NO	
13.	Do you frequently worry about the future?	YES / NO	
14.	Do you feel you have more problems with memory than most?	YES / NO	
15.	Do you think it is wonderful to be alive now?	YES / NO	
16.	Do you often feel downhearted and blue?	YES / NO	
17.	Do you feel pretty worthless the way you are now?	YES / NO	
18.	Do you worry a lot about the past?	YES / NO	
19.	Do you find life very exciting?	YES / NO	
20.	Is it hard for you to get started on new projects?	YES / NO	
21.	Do you feel full of energy?	YES / NO	
22.	Do you feel that your situation is hopeless?	YES / NO	
23.	Do you think that most people are better off than you are?	YES / NO	
24.	Do you frequently get upset over little things?	YES / NO	
25.	Do you frequently feel like crying?	YES / NO	
26.	Do you have trouble concentrating?	YES / NO	
27.	Do you enjoy getting up in the morning?	YES / NO	
28.	Do you prefer to avoid social gatherings?	YES / NO	
29.	Is it easy for you to make decisions?	YES / NO	
30.	Is your mind as clear as it used to be?	YES / NO	
		TOTAL	

This is the original scoring for the scale: One point for each of these answers.
Cutoff: normal-0-9; mild depressives-10-19; severe depressives-20-30.

1. NO	6. YES	11. YES	16. YES	21. NO	26. YES
2. YES	7. NO	12. YES	17. YES	22. YES	27. NO
3. YES	8. YES	13. YES	18. YES	23. YES	28. YES
4. YES	9. NO	14. YES	19. NO	24. YES	29. NO
5. NO	10. YES	15. NO	20. YES	25. YES	30. NO

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Appendix 3:

HAMILTON DEPRESSION RATING SCALE (HAM-D)

(To be administered by a health care professional)

Patient Name _____ Today's Date _____

The HAM-D is designed to rate the severity of depression in patients. Although it contains 21 areas, calculate the patient's score on the first 17 answers.

☐ 1. DEPRESSED MOOD
(Gloomy attitude, pessimism about the future, feeling of sadness, tendency to weep)
0 = Absent
1 = Sadness, etc.
2 = Occasional weeping
3 = Frequent weeping
4 = Extreme symptoms

☐ 2. FEELINGS OF GUILT
0 = Absent
1 = Self-reproach, feels he/she has let people down
2 = Ideas of guilt
3 = Present illness is a punishment; delusions of guilt
4 = Hallucinations of guilt

☐ 3. SUICIDE
0 = Absent
1 = Feels life is not worth living
2 = Wishes he/she were dead
3 = Suicidal ideas or gestures
4 = Attempts at suicide

☐ 4. INSOMNIA - Initial
(Difficulty in falling asleep)
0 = Absent
1 = Occasional
2 = Frequent

☐ 5. INSOMNIA - Middle
(Complains of being restless and disturbed during the night. Waking during the night.)
0 = Absent
1 = Occasional
2 = Frequent

☐ 6. INSOMNIA - Delayed
(Waking in early hours of the morning and unable to fall asleep again)
0 = Absent
1 = Occasional
2 = Frequent

☐ 7. WORK AND INTERESTS
0 = No difficulty
1 = Feelings of incapacity, listlessness, indecision and vacillation
2 = Loss of interest in hobbies, decreased social activities
3 = Productivity decreased
4 = Unable to work. Stopped working because of present illness only. (Absence from work after treatment or recovery may rate a lower score).

☐ 8. RETARDATION
(Slowness of thought, speech, and activity; apathy; stupor.)
0 = Absent
1 = Slight retardation at interview
2 = Obvious retardation at interview
3 = Interview difficult
4 = Complete stupor

☐ 9. AGITATION
(Restlessness associated with anxiety.)
0 = Absent
1 = Occasional
2 = Frequent

☐ 10. ANXIETY - PSYCHIC
0 = No difficulty
1 = Tension and irritability
2 = Worrying about minor matters
3 = Apprehensive attitude
4 = Fears

Appendix 4:

Name_____ Date_____

Sleep Quality Assessment (PSQI)

What is PSQI, and what is it measuring?

The Pittsburgh Sleep Quality Index (PSQI) is an effective instrument used to measure the quality and patterns of sleep in adults. It differentiates "poor" from "good" sleep quality by measuring seven areas (components): subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction over the last month.

INSTRUCTIONS:

The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

During the past month,

1. When have you usually gone to bed? _____
2. How long (in minutes) has it taken you to fall asleep each night? _____
3. What time have you usually gotten up in the morning? _____
4. A. How many hours of actual sleep did you get at night? _____
   B. How many hours were you in bed? _____

5. During the past month, how often have you had trouble sleeping because you	Not during the past month (0)	Less than once a week (1)	Once or twice a week (2)	Three or more times a week (3)
A. Cannot get to sleep within 30 minutes				
B. Wake up in the middle of the night or early morning				
C. Have to get up to use the bathroom				
D. Cannot breathe comfortably				
E. Cough or snore loudly				
F. Feel too cold				
G. Feel too hot				
H. Have bad dreams				
I. Have pain				
J. Other reason (s), please describe, including how often you have had trouble sleeping because of this reason (s):				
6. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?				
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
8. During the past month, how much of a problem has it been for you to keep up enthusiasm to get things done?				
9. During the past month, how would you rate your sleep quality overall?	Very good (0)	Fairly good (1)	Fairly bad (2)	Very bad (3)

Scoring

Component 1	#9 Score	C1 _____
Component 2	#2 Score (<15min (0), 16-30min (1), 31-60 min (2), >60min (3)) + #5a Score (if sum is equal 0=0; 1-2=1; 3-4=2; 5-6=3)	C2 _____
Component 3	#4 Score (>7(0), 6-7 (1), 5-6 (2), <5 (3)	C3 _____
Component 4	(total # of hours asleep) / (total # of hours in bed) x 100 >85%=0, 75%-84%=!, 65%-74%=2, <65%=3	C4 _____
Component 5	# sum of scores 5b to 5j (0=0; 1-9=1; 10-18=2; 19-27=3)	C5 _____
Component 6	#6 Score	C6 _____
Component 7	#7 Score + #8 score (0=0; 1-2=1; 3-4=2; 5-6=3)	C7 _____

*Add the seven component scores together*_____ *Global PSQI* _____

A total score of "5" or greater is indicative of poor sleep quality.
If you scored "5" or more it is suggested that you discuss your sleep habits with a healthcare provider

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