SSRIs as Disease-Modifying Therapy for Alzheimer Disease

A. Study Purpose and Rationale
Alzheimer Disease (AD), characterized by a gradual and progressive decline in cognition and behavior with prominent early memory dysfunction, is the most common form of dementia in older adults. It represents a significant burden worldwide for health care systems. In 2000, an estimated 4.5 million people in the US were afflicted with AD, and projections suggest this number will rise to 14 million by 2050 [1]. AD predominantly affects older adults with a prevalence of at least 30% in populations 85 years and older [1]. As advances in medical technology have allowed people to live longer lives, there have naturally been numerous studies investigating possible disease-modifying therapies for AD. Intense interest has been focused on common FDA-approved medications already in widespread use. Unfortunately, while initial observational studies may have indicated some benefit, phase III clinical trials have not shown efficacy for statins, anti-inflammatory drugs, including steroids and NSAIDs, ginko biloba, valproate, and various other compounds [1,2]. Other pharmacologic interventions have targeted beta-amyloid and hyperphosphorylated tau proteins, both of which are hypothesized to be involved in the pathogenesis of AD [1]. Randomized trials of these experimental agents, including active vaccination against beta-amyloid, continue to be ongoing but have not been promising thus far [2].

Selective serotonin reuptake inhibitors (SSRIs) already have a well-recognized use as first-line treatment for depression, anxiety, and other behavioral disturbances in AD [1]. This may be explained by the fact that though acetylcholine is the most prominently depleted neurochemical in the cortex, there are also deficiencies in dopamine, norepinephrine, and serotonin. However, recent evidence from animal studies suggests that psychotropic agents such as mood stabilizers, antidepressants, and antipsychotics may also have neurotrophic/neuroprotective effects. Specifically, SSRIs activate the MAPK/ERK and Wnt/GSK signaling cascades ultimately modulating neuron protection and genesis through the upregulation of trophic/protective molecules such as brain-derived neurotrophic factor (BDNF) [3]. A study by Nelson et al. showed on 3xTgAD (transgenic AD) mice showed that treatment with intraperitoneal paroxetine for 5 months significantly enhanced spatial learning and memory ability compared to saline treatment alone. Paroxetine-treated mice also had reduced levels of hippocampal beta-amyloid and diminished tau pathology, though the latter was significant in male mice only [4]. Other studies have confirmed a reduction in amyloid plaque formation and have additionally shown a positive effect on hippocampal neurogenesis in animal models [5].

Trials examining the use of SSRIs on patients with existing AD show overall positive effects by various different measures, though these changes are often attributed to the lifting of depressive symptoms. However, no study has been able to distinguish between mood versus cognition as the substrate [5]. An epidemiological study published by Kessing et al. with data gathered from a large national Danish registry showed that patients prescribed an antidepressant at least once were more likely to be diagnosed with dementia, which they interpreted as depression being a risk factor for the development of dementia [6]. At the same time, they found that the relative risk of developing dementia was somewhat lower in groups who received more prescriptions for antidepressants (e.g. > 20 prescriptions versus 6-9), though the risk did not decrease to the level of those who had not received an antidepressant [6]. Their study further illustrates the difficulty in differentiating between depression, dementia, or both occurring concomitantly. Other studies suggest that depression may be a significant risk factor for the development of dementia [6], but this continues to be debated in the literature. There is clearly a need for further research investigating whether or not SSRIs are a clinically significant disease-modifying therapy for AD.

B. Study Design and Statistical Analysis

Hypothesis
Significant SSRI exposure (>1 year) will result in a decreased risk of developing Alzheimer Disease.

This will be a retrospective cohort study of adult elderly subjects enrolled in the Washington Heights-Inwood Columbia Aging Project (WHICAP) run by Dr. Richard Mayeux of the Columbia University
The study population will be divided into four groups:

- **Group 1** Subjects with depression (either diagnosed previously or on WHICAP assessment) and who have never received any type of antidepressant in the past.
- **Group 2** Subjects with depression (either diagnosed previously or on WHICAP assessment) and currently taking an SSRI and continued on it for at least 1 year as confirmed on follow-up visits. SSRIs will be defined as any of the following: citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline, or dapoxetine.
- **Group 3** Subjects with depression (either diagnosed previously or on WHICAP assessment) and currently taking an antidepressant of a class other than an SSRI and continued on it for at least 1 year as confirmed on follow-up visits. These include, but are not limited to, SNRIs, TCAs, and MAOIs.
- **Group 4** Subjects without depression (either diagnosed previously or on WHICAP assessment) and who have never received any type of antidepressant in the past.

A study by Paterniti et al. (2002) of approximately 1000 French adults aged 59-71 without cognitive impairment measured the change in MMSE scores upon initial survey and after 4 years. They attempted to correlate changes in MMSE with depression by screening with the Center for Epidemiologic Studies Depression Scale (CES-D). They found that the MMSE of those subjects with significant depression as predicted by the CES-D declined by -1.42 (N=122, SE=0.16) and significantly more than those without, whose scores decreased by -0.88 (N=881, SE=0.06) over those 4 years [8].

For our study, therefore, we can estimate that the Group 1 subjects not receiving antidepressants will decline in the MMSE by -1.42 (SD=0.16 × √(122) = 1.77). We will also estimate that Group 4 subjects will decline in the MMSE by -0.88 (SD=0.06 × √(881) = 1.78). Given that the effect size from depressed versus nondepressed subjects is approximately 0.40, we will estimate a significant effect size as 0.30, as we do not necessarily expect the treated depressed subjects of Group 2 and 3 in our study to approximate a change of a nondepressed population. For simplicity, we will assume that the means of Group 2 and 3 will be equal to the grand mean and also assume that the standard deviations are the same for all groups. The data will analyzed using a **one-way ANOVA test** for our four groups. Using the above estimates, approximately 1200 total individuals, or 300 individuals in each group, will be necessary to achieve α of 0.05 and power (1-β) of 0.8.

**C. Study Procedure**

This will be a retrospective review of data collected by WHICAP investigators. There will be no special procedures. The study will likely take place over the period of several months.
D. Study Drugs
Not applicable.

E. Medical Devices
Not applicable.

F. Study Questionnaires
Not applicable.

G. Study Subjects
Inclusion Criteria:
1) Ages 65 years or older as per WHICAP recruitment procedures

Exclusion Criteria:
1) Pre-existing diagnosis of dementia
2) Clinical diagnosis of dementia based on initial WHICAP assessment

H. Recruitment of Subjects
Not applicable.

I. Confidentiality of Study Data
All study data will be uniquely coded. All patient identifiers will be excluded. Data will be stored in a secure location on accessible only to the investigators.

J. Potential Conflict of Interest
None

K. Location of the Study
Columbia University Medical Center-Milstein Hospital

L. Potential Risks
There will be no risks to the study subjects.

M. Potential Benefits
None.

N. Alternative Therapies
Not applicable.

O. Compensation to Subjects
There will be no compensation to subjects.

P. Costs to Subjects
Subjects will not incur any additional costs.

Q. Minors as Research Subjects
Not applicable.

R. Radiation or Radioactive Substances
Not applicable.

References:


