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Comparing Ratios of Depression Between Female to Male MCI Patients and the General
Population

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Abstract

Mild Cognitive Impairment (MCI) is a condition that affects 20% of adults aged 60 and older. Patients with MCI find themselves in a place between healthy cognitive function and dementia. MCI is characterized by the forgetting of events and conversations, difficulty completing complex tasks, and trouble with remembering familiar environments. Previous studies on MCI suggest that patients are at a 40% greater risk of developing dementia, particularly Alzheimer's disease, as their condition progresses (Petersen, 1999). Accompanying that, MCI patients are often diagnosed with a mood disorder, commonly depression (Orgeta, Qazi, Spector, & Orrell, 2015). Prior studies have presented that in general, women, regardless of their cognitive state, are diagnosed with depression at a higher rate than men. Based on this, we predicted that the ratio of depression in female to male MCI patients would be different than the ratio of depression in the general population. We hypothesized that this rate will be amplified in female MCI patients due to the added stressors of their MCI diagnosis. The present study intends to make a broad impact on the preexisting literature, such as informing treatment options and improving quality of life in patients with cognitive impairment. Results were not significant, indicating that this specific sample displayed little to no symptoms of depression.

Introduction

Dementia and Alzheimer's Disease

Dementia is a general term regarding the cohort of symptoms leading to functional and cognitive impairment (Sperling et al., 2011). The disease affects the acuity of nearly all aspects of a person's cognitive abilities, such as memory, language, and critical thinking. Prevalence rates are exceedingly high; between 5-7% of the world's population are affected by dementia (Djukic, Wedekind, Franz, Gremke, & Nau, 2015). In the majority of cases, dementia is caused by neurodegeneration and can be progressive as well as fatal, although there are instances where the cause of dementia-like symptoms can be easily treated if the cause is ascertained early on (Arnold & Kumar, 1993). This scenario was documented in a patient exposed to harmful toxicants, like flame retardant and pesticides (DDT in particular). Once removed from the toxicants, normal physical and mental functioning was restored (Genius & Kelln, 2014). Diseases associated with dementia vary from specific causes, like lesions forming on the cortex in Dementia with Lewy bodies, to a variety of culprits, as in Mixed Dementia (Djukic et al., 2015). The present study focuses on the most common cause of dementia, Alzheimer's disease (AD).

AD is found in 50%-70% of patients who were diagnosed with dementia, and AD is in approximately 10% of persons aged 65 or older (Wang et al., 2015). Considering that AD is a progressive disorder with age as the main risk factor, the prior statistic increases to almost 50% in individuals aged 85 or older. Typically, the duration of time between diagnosis and death is 8.5 years. There is no singular cause of AD; however, genetic heritability and traumatic brain injury (TBI) are two known risk factors for developing the neurodegenerative disorder (Green et al., 2002; Plassman et al., 2000). Regarding genetic risk factors, a person carrying the hereditary

gene Apolipoprotein e4 (APOE-e4) poses a noticeably higher risk of developing AD than persons carrying the other two forms of the gene, e2 or e3. A 2008 study found that 65% of 1,770 patients diagnosed with AD carried a copy of the APOE-e4 gene.

To correctly diagnose AD, a patient must display significant cognitive decline documented through at least two standardized tests of cognitive ability. Other variations of diagnosing AD include utilizing a multitude of neuropsychological exams, combining the scores into a multivariate analysis, and examining cerebrospinal fluid (CSF) biomarkers. A biomarker refers to a biological criterion in determining whether a disorder is existent or nonexistent; to determine if a patient is at risk for AD, neurologists look for heightened levels of the protein beta-amyloid found in a patient's CSF. Research regarding the effectiveness of biomarker dissection is lacking (Blanco-Cantó et al., 2017). A standardized method of testing CSF has yet to be created, and there is still much debate on how to properly apply evidence of beta-amyloid to develop an appropriate treatment plan.

The primary treatment for AD is through pharmacological intervention. While none of the medications available can reverse the disorder's progression, Acetylcholinesterase inhibitors (AChEIs) are commonly used to slow down clinical progression. Some patients and their families prefer a non-pharmacologic method of treatment in the hopes to avoid external behavioral side effects caused by medication, which may include exercise, cognitive and memory stimulation, and listening to favorite music. The combination of the two therapies can provide successful stagnation of symptoms as well (Carmargo, Justus, & Retzlaff, 2015).

Mild Cognitive Impairment

Considering AD's prevalence in western society, it is important to examine its early warning signs and stages. In 1999, Petersen et al. first proposed the diagnostic criteria for Mild

Cognitive Impairment (MCI), an interim stage between normal cognitive function and AD. Particular attention has recently been directed toward regulating the prognosis and treatment for MCI. Inconsistencies between diagnostic materials used, length or lack of follow-up, and a wide discrepancy in conversion rates have proved to cause difficulties in determining a standard definition for MCI (Lopez-Anton et al., 2015). Conversion rates refer to the percentage of MCI patients whose condition progressed to a dementia; in general, approximately 40% of MCI patients later develop AD (Mitchell & Shiri-Feshki, 2009). Between 23% and 47% of MCI patients transition to AD in a matter of 2.6 years; 46% of MCI patients develop AD in 3 years (Busse, Bischkopf, Riedel-Heller, & Angermeyer, 2003; Cooper, Sommerlad, Lyketsos, & Livingston, 2015).

MCI is subdivided into two types: amnesic (aMCI) and nonamnesic. The deciding factor in diagnosing a patient with aMCI or nonamnesic MCI is dependent on whether or not memory is negatively affected. AD is predominantly the result of the progression of aMCI, as aMCI symptoms are more indicative of a prodromal form of AD. These signs are similar to the aforementioned symptoms: forgetting of conversations, names, and appointments that could have been effortlessly recalled in the past (Chen et al., 2016). Additionally, aMCI is separated into two different categories, single domain amnesic MCI (sda-MCI), and multiple domain amnesic MCI (mda-MCI). The prior type is diagnosed when MCI affects only a patient's memory; the latter is diagnosed when other cognitive functions are affected along with memory (Cooper, Sommerlad, Lyketsos, & Livingston, 2015). Diagnostic criteria for aMCI require that a patient display a decline of 1.5 standard deviations from the mean of either memory or non-memory related tasks (Murayama et al., 2010; Petersen et al., 1999). Nonamnesic MCI is considered when a patient's cognitive impairment does not involve memory. Patients with nonamnesic MCI

tend to experience difficulty in making solid judgments, planning how to complete complicated tasks, and perceiving the world visually. Nonamnesic MCI has the potential to lead to dementia with Lewy bodies and vascular dementia (Belden, Kahlon, Malek-Ahmadi, Tsai, & Sabbagh, 2015). The present study focuses on patients with aMCI, unless specified otherwise.

A concerning change in cognitive ability is required for MCI to be noticed within the patient (Petersen, 1999). A clinician, through a patient's friends, family, or caregiver, typically gathers this information. While MCI does not cause complications as intrusive as AD, patients with MCI can find themselves with memory concerns, which may include forgetting events, conversations, and interactions with friends. The cognitive impairment MCI patients confront reaches not only memory, but also on their attentional and lexical abilities; patients may experience difficulty in completing certain tasks, in finding the right words, and in repeating themselves throughout conversations (Petersen, 1999; Clément, Belleville, Bélanger, & Chassé, 2009). Diagnostic tools such as the Mini Mental State Exam (MMSE), the Montreal Cognitive Assessment (MoCA), and the Dementia Rating Scale (DRS-2) are commonly used as well. Known for its rapid and convenient assessment, the MMSE is the highest in popularity among the clinical community. The assessment asks patients to recall their current location, identify common objects, and follow verbal and written directions; the patients' responses are graded on a numerical scale. A high score between 24-30 indicates healthy cognitive function; 20-24 indicates mild dementia; 13-20 moderate dementia; less than 12 severe dementia (Folstein M., Folstein S., & McHugh, 1975). The MoCA encompasses similar measures as the MMSE, but also requires patients to complete a clock-drawing test and a trail test (Nasreddine, 2005). The DRS-2 measures patients on five subscales: attention, initiation/preservation, construction,

conceptualization, and memory. Low scores indicate the presence of cognitive impairment (Springate, Tremont, Papandonatos, & Ott, 2014).

Due to the variability in outcomes and testing, there is not an apparent treatment for MCI (Sachs-Ericsson & Blazer, 2015). Previous data collected from diagnosing MCI patients are heterogeneous, which makes it difficult to standardize a further course of action (Perri, Carlesimo, Serra, & Caltagirone, 2005). Because of these discrepancies, researchers have yet to determine what characteristics and prognosis correspond with which subtypes of MCI (Mansbach, Mace, & Clark, 2014). Despite the incongruities, clinicians are making progress towards developing treatment methods. Like in treating AD, AChEIs are used frequently to impede the progression of the disease (Allain, Bentue´-Ferrer, & Akwa, 2007). The use of antioxidants is on the rise as an alternative method of treatment. Food and drink such as green tea, wines, and Magnolia extract were found to produce anti-inflammatory bodies that had the potential to reduce degeneration of neural tissue (Choi, Lee, Hong, & Lee, 2012). Forlenza, de Paula, Machado-Vieira, Diniz, and Gattaz (2012) suggest the use of lithium salts can supplement neural tissue, reduce apoptosis (programmed cell death), and reinforce brain structures crucial to memory, like the hippocampus. However, the researchers in the latter study recommend more clinical testing to be completed before the regulation of lithium as an MCI treatment. Both physical and mental exercise has also been shown to help reduce effects of MCI as well (Sachs-Ericsson & Blazer, 2015).

Psychiatric Disorders in MCI

Persons with MCI are highly predisposed to psychiatric distress. Previous reports indicate that 36% of MCI patients experience moderate depression, while 63% experience severe depression; 74% experience similarly severe rates of anxiety (Orgeta, Qazi, Spector, & Orrell,

2015). Countless studies surrounding MCI concentrate on the cognitive profile of patients; few integrate psychiatric wellbeing. With this in mind, Clément, Belleville, Bélanger, and Chassé (2009) conducted a study that determined the relationship between psychiatric distress and cognitive function. After interviewing and testing 30 MCI patients, they found that the MCI patients faced higher rates of depression, anxiety, hostility, and lower self-esteem than the 27 controls interviewed. Another study with dementia patients reported that 60% of participants experienced symptoms of psychosis, and 42% experienced depression (Forsell, Palmer, & Fratiglioni, 2003). A recent study with 152 participants diagnosed with MCI found that these patients had significantly higher levels of depression, lower MMSE scores, and lower social functioning when compared to healthy control participants (Jayaweera et al., 2015).

Depression is particularly significant in MCI. Depression is often confused with apathy, a syndrome in which patients only experience a lack of motivation and goal-oriented behaviors; depression also includes emotional side effects, such as feeling guilty and worthless (Varanese, Perfetti, Ghilardi, & Di Rocco, 2011). Several studies support the idea that a depressed person also is at a noticeably higher risk of cognitive decline and dementia than a non-depressed person (DeLuca et al., 2005; Shiraishi, 2010; Kobayashi & Kato, 2011). In order for one to be diagnosed with depression, a client must face at least five related symptoms (anhedonia, insomnia, weight loss or gain, suicidal ideation, agitation, and the like) for a period of no less than two weeks (American Psychiatric Association, 2013). Additionally, significant distress or functional impairment must be present. A patient confronted with both depression and MCI has a higher resistance to antidepressants and a reduced likelihood of living independently (Orgeta, Qazi, Spector, & Orrell, 2015). In some cases, researchers report depression as a factor in increased conversion to AD (Yoon, Shin, & Han, 2017). Explanations for this linear relationship differ;

some clinicians believe depression in older adults is a precursor to dementia, while others believe that depression detracts from cognition, leaving vulnerability for AD (Yoon, Shin, & Han, 2017). With this being said, the integration of psychiatric treatment with treatment for MCI is imperative for a patient's prognosis (Orgeta, Qazi, Spector, & Orrell, 2015; Shahnawaz et al., 2013). It should also be noted that the cognitive deficits experienced in MCI do not diminish upon the treatment of depression (Jayaweera et al., 2015).

Depression in the General Population

Depression is increasing in prevalence in the United States. While treatment options are plenty, relapses are not uncommon; this is especially the case when depression co-occurs with other psychiatric disorders, such as anxiety and substance abuse disorder (Lin et al., 2016). Research on depression's gender disparity is vast. Studies tend to show that women in the general population (GP) are twice as likely to experience depression than men, and that the symptoms of depression women experience are often more debilitating than that of men (Ulbricht, Dumenci, Rothschild, & Lapane, 2016; Marcus et al., 2008). One study in particular found that over 12% of women in the United States have depression compared to 7.9% in men (Kim, Shin, & Song, 2015). Changes in hormones due to puberty, the menstrual cycle, and pregnancy are all cited in contributing to this statistic, in addition to standard risk factors (Ulbricht, Dumenci, Rothschild, & Lapane, 2016). These include socioeconomic as well as biological factors; around 40% of depression cases are linked to genetics (American Psychiatric Association, 2013). Cavanagh, Wilson, Caputi, and Kavanagh (2016) determined that depressed women also have a higher potential of facing problems with their appetite and weight maintenance.

Common treatments for depression in the GP are cognitive behavioral therapy (CBT) and medication (Bayliss & Holttum, 2015). Wuthrich, Rapee, Kangas, and Perini (2016), revealed that 54% of 113 depressed patients no longer met the criteria for depression after undergoing an 11-week CBT program. CBT is goal-oriented, challenges a patient's maladaptive mode of thinking, and replaces negative thoughts with positive affirmations to improve a patient's mood (Beck, Rush, Shaw, & Emery, 1979). Medications like Selective Serotonin Reuptake Inhibitors (SSRIs) facilitate the effects of CBT and aid in stabilizing a patient's mood (Bayliss & Holttum, 2015).

The present study examined the prevalence of depression in MCI patients. We hypothesized that the ratio of depression in female to male MCI patients would be different, and that the prevalence of depression in female MCI patients would differ from the ratio of depression in the general population. Specifically, we predicted that the rate would be amplified in female MCI patients due to the stress of their diagnosis and predisposition to depression. In order to support this, we compared our findings to the existing literature regarding the ratio of depression in the general population.

We used these prior studies as the basis for comparing rates of depression in MCI patients and the GP. We aimed to determine whether there were group differences in depression and apathy by gender. We intend to contribute to the literature on MCI by increasing the understanding of prevalence rate differences, and support treatment considerations of patient cognitive and psychiatric wellbeing.

Method

Participants

The University of Southern California previously gathered the data analyzed in this study through the Alzheimer's Disease Neuroimaging Initiative (ADNI). ADNI gathered its 822 volunteer participants from North American research centers throughout the study; additionally, the website for the Initiative provides referrals to those who are interested in participating in future studies. The participants agreed to several sessions of brain imaging and clinical testing, and they were followed over time to track the progression of their disease (ADNI, 2017). The range of participants' ages is between 71-75 years of age, and most participants are Caucasian (93%) and college educated (61%). Fifty-four percent of ADNI participants are diagnosed with MCI (ADNI, 2017). Identifying information about individual participants has already been redacted.

The institute conducts its research through the utilization of clinical, cognitive, biological, and genetic biomarkers to pinpoint the structure and function of the human brain throughout the stages of AD development (Cairns et al., 2015). With the goal of determining specific biomarkers that indicate very early stages of AD, ADNI intends for its data to be used towards research for more efficient AD treatment (Eskildsen et al., 2013). Beginning in 2003, ADNI is supported by several major health organizations, including the National Institute on Aging, General Electric Healthcare, and the National Institute of Biomedical Imaging and Bioengineering, along with other healthcare leaders; ADNI continues to receive funding from these sponsors to this day. ADNI breaks down the progression of AD into stages, respectively being Cognitively Normal (CN), Significant Memory Concern (SMC), Early Mild Cognitive Impairment (EMCI), Mild Cognitive Impairment (MCI), Late Mild Cognitive Impairment

(LMCI), and AD. Each stage adheres to its own definition and increases in neurological damage.

The study defines MCI as follows:

MCI participants have reported a subjective memory concern either autonomously or via an informant or clinician. However, there are no significant levels of impairment in other cognitive domains, essentially preserved activities of daily living and there are no signs of dementia. (ADNI, 2017)

The extent of the research ADNI conducts is evident in Eskildsen et al.'s 2013 study, which was supported by the initiative. Through an analysis similar to that of the present study, Eskildsen et al. utilized the preexisting data collected by ADNI in order to evaluate MRI in search of early physical signs of AD development. As a result of the study, Eskildsen and colleagues were able to determine similar patterns of visible neurological degeneration throughout test subjects that indicate warning signs of AD.

The present study will be selecting data gathered from a portion of the 822 total ADNI participants. Specifically, the responses recorded from 435 MCI-diagnosed participants on the Neuropsychiatric Inventory (NPI) will be analyzed.

Measures

The present study will be utilizing the data collected from ADNI volunteers who participated in taking the NPI. The NPI is a common tool used to measure the rates of depression and other psychiatric disturbances within MCI patients. Over the last decade, the use of the NPI became extensive in various professional psychological circles (Kørner et al., 2008). The NPI specializes in determining the indication of 12 psychiatric disorders in the presence of a neurodegenerative disorder in addition to evaluating the usefulness of some treatments (Cummings, 1997). The psychiatric disorders tested for are: delusions, hallucinations, agitation,

dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, nightly behavior disturbances, eating disorders, and abnormal motor behavior (Cummings, 1997). The assessment is conducted via interview with a third party, typically a patient's caregiver or a relative who knows the patient particularly well. The third party's responses are measured on several subscales, which in turn estimate the levels of severity and frequency of the patient's symptoms. Each subscale is rated on a scale of 12, with 144 being the highest possible total (12 subscales x 12 points); the higher the score, the more severe the symptom (Cummings, 1997). The patient's depression is rated through a measure called the dysphoria subscale, which is measured through the combination of scores from the psychiatric disorders that assess mood. Because many symptoms of depression and dementia overlap (e.g., weight loss, delusions, agitation), the dysphoria subscale utilizes questions that explicitly differentiate depression from dementia. An example is "Does the patient seem sad or say that he /she is depressed?" (Cummings, 1997).

Procedure

After reviewing an abstract we submitted for the data, the ADNI experimenters granted us access to the clinical data. Data recorded from NPI responses were retrieved and downloaded for investigation. Descriptive statistical analyses and a t-test to examine group differences between the male and female MCI patients were conducted through the *Statistical Package for the Social Sciences* (SPSS).

Results

After constructing a review of the relevant literature, we hypothesized that symptoms of depression were common in populations affected by MCI. Furthermore, based on the literature, we maintained the idea that depression affected female MCI patients at a higher rate than male MCI patients, and than the general population, due to their predisposition to the disorder and

added stress of the MCI diagnosis. Unexpectedly, the ADNI-collected data did not support either one of our hypotheses. We ran initial descriptive statistics (see Table 1), which indicated that the maximum score patients received on the NPI was 20 ($M = 2.3$; $SD = 3.30$). As previously noted, the highest score possible to receive on the NPI is 144, with a cutoff score of 50 signifying severe behavioral disturbances. A score of 20 or below implies mild to no behavioral disturbances.

Additionally, we ran a t-test focusing specifically on the results to the depression and apathy segment of the NPI. This was done to further investigate group differences in depression and apathy by splitting up the group by gender, male and female, with 1 signifying male and 2 female (see Table 2). While the female group had a higher mean than the male group, the difference was not statistically significant. Moreover, neither of the group's results indicated any sign of psychological distress, with the mean for male participants at 2.16 ($SD = 3.21$). While these results do not implicate that every MCI patient interviewed for the ADNI database does not experience psychiatric distress, they do suggest that depression and apathy were not as prevalent in the sample as expected.

Discussion

Overall, there were no significant group differences for depression or apathy. As previously stated, this is inconsistent with much of the literature regarding this cognitively impaired older adult sample (Orgeta, Qazi, Spector, & Orrell, 2015; Varanese, Perfetti, Ghilardi, & Di Rocco, 2011). After closer consideration, there are several possible explanations for the discrepancy between our hypotheses and the results. As noted in the Method, over half of the ADNI participants received a college education. Yang (2007) notes that a college education acts as a protective factor against late age depression because of the likelihood of having a higher

income and “less economic hardship.” This is because a college education tends to lead to more successful and fulfilling careers, therefore leaving a person of an older age less financial worries to develop stress over. The idea that a positive correlation exists between level of education and overall health is strongly supported, and could be a potential factor as to why the ADNI participants displayed little symptoms of depression.

Hughes-Morley, Young, Waheed, Small, and Bower (2015) ran a comprehensive literature review surrounding factors affecting recruitment for depression studies. After sorting through over 7,000 citations and analyzing 15 studies, the researchers found that a participant’s decision to volunteer for a depression experimental study depends on several variables; these variables mostly take into consideration the participant’s mood, state of mental health, and attitude toward the study, along with other typical considerations like personal benefits. Results indicated that participants who are on a regimented treatment plan for their depression are more likely to volunteer for depression trials. The willingness of the participants to volunteer could be a possible explanation for the results we found from the ADNI data.

Nearly all the ADNI participants identified as white, which could likewise be seen as a reason for the lower rates of depression in our sample. In his analysis, Yang (2007) also states that race, ethnicity, and socioeconomic status can play a role in the development of depression; members of a minority race or ethnicity tend to experience depression at a higher rate than those who are not. The ADNI population is majority white, college educated, and therefore presumably of a higher socioeconomic class, which is a combination of common protective factors that can deter depression. All the participants for the longitudinal study willingly volunteered and gave informed consent, which can suggest better treatment and resilience. Ultimately, there is no

single cause for the discrepancy between our hypothesis and the results, rather a multitude of factors.

Nonetheless, the implications of the current study are significant. Despite our patients not reporting signs of clinical depression or apathy, maintaining a continued awareness of mental health factors in older adults with cognitive impairment remains important because it helps highlight the importance of mood evaluation and treatment in this population. Evidence gathered by Arean and Cook (2002) supports the idea that CBT or interpersonal psychotherapy combined with medication is the strongest treatment for combating depression within older populations affected by cognitive impairment. Likewise, Teri, Logsdon, Uomoto, and McCurry (1997) suggested the use of CBT is effective in populations diagnosed a step further, with dementia.

Future studies with this sample may expand upon our hypothesis and investigate depression and apathy from multiple perspectives, including but not limited to clinicians, informants, and patients. Incorporating the viewpoints from these populations may elicit differing results; for example, if a patient does not report symptoms indicative of depression, their primary care practitioner may observe these signs and include it in the patient's report. Producing a well-rounded patient profile can lead to a more accurate reading of symptom onset, development, and treatment, and ultimately direct clinicians to a holistic outlook on MCI treatment, working to ease the strain of both cognitive and psychiatric impairment.

In summary, the current study analyzed the presence of depression or apathy in older adults diagnosed with Mild Cognitive Impairment, hypothesizing that female MCI-affected adults would display far higher rates of depression than in MCI-affected male adults and adults in the general population. An excess of prior research indicated that rates of clinical depression were found profoundly in cognitively impaired populations. With this hypothesis and previous

support, the current study took to the ADNI database to collect responses recorded on the NPI to determine if this specific population reflected what has been previously found. Unexpectedly, this particular MCI-affected population did not display symptoms of depression or apathy, for reasons we can only propose. As a result of this study, it was learned that not every MCI-affected population confronts psychiatric distress despite a serious diagnosis; although this finding did not reflect the hypothesis, it is encouraging to know that patients with cognitive impairment are not also battling with a disorder like depression or apathy.

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Table 1

Descriptive Statistics for NPI Responses

	<i>n</i>	Minimum	Maximum	Mean	Std. Deviation
GDTOTAL	917	0	12	1.50	1.90
PTEDUCAT	439	0	20	15.53	3.50
NPIA	742	0	2	.04	.210
NPISCORE	742	0	20	2.30	3.30
Valid N (listwise)	59				

Note. GDTOTAL = Grand Total; PTEDUCAT = Participant Education ; NPIA = NPI Apathy score; NPISCORE = Overall NPI score

Table 2

T-Test Results for Group Differences in Depression and Apathy Between Male and Female MCI Patients

	PTGENDER	<i>n</i>	Mean	Std. Deviation	Std. Error Mean
NPIA	1 (Male)	238	.04	.191	.012
	2 (Female)	190	.04	.189	.014
NPISCORE	1	238	2.16	3.208	.208
	2	190	2.18	3.631	.263
GDTOTAL	1	241	1.55	2.099	.135
	2	194	1.45	1.739	.125

Note. NPIA = NPI Apathy Score; NPISCORE = NPI Dysphoria Scale Score; GDTOTAL = Grand Total