CHANGE IN COGNITIVE FUNCTIONING FOLLOWING ACUTE ANTIDEPRESSANT TREATMENT IN LATE-LIFE DEPRESSION

by

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ABSTRACT

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Michelle Erin Reinlieb

Advisor: Dr. Joel R. Sneed

The purpose of this dissertation was to examine the cognitive impact of antidepressant medication among depressed older adults. We explored the following questions in a series of 3 studies: 1) what impact does medication have on cognition (Study 1); 2) is there a differential impact of antidepressant medication on cognitive functioning depending on medication class (Study 2); 3) is there a differential impact of antidepressant medication on cognitive functioning depending on diagnostic subtype (Study 3)? Across all three studies, we examined whether change in cognition following antidepressant treatment depended on medication response. In Study 1, an 8-week placebo-controlled trial of citalopram in the treatment of depressed adults 75 years and older (mean age = 79.6), we found that medication non-response was associated with a decline in verbal learning and psychomotor speed. In Study 2, a 12-week randomized, double-blind, parallel-group design comparing sertraline and nortriptyline in the treatment of depressed older adults (mean age = 64.2), we found that sertraline responders showed significantly more improvement in verbal learning compared to nortriptyline responders; to our surprise, nortriptyline responders were the only treatment by responder status group to show no improvement in verbal learning from baseline to endpoint. Finally, in Study 3, an 8-week, open

treatment trial of antidepressant medication in depressed older adults (mean age = 62.3), we found that change in cognition by diagnostic status depended on response. Specifically, vascular depressed non-responders declined in one aspect of executive functioning (i.e., set-shifting) relative to the improvement observed across all other patient groups.

Overall, these findings suggest that antidepressant medication may be cognitively benign among 'young-old' depressed patients, particularly in the absence of significant cerebrovascular disease. The presence of extensive cerebrovascular disease may negatively interact with medication non-response to influence cognitive outcomes. Among 'old-old' patients, medication may have a deleterious effect on cognition, but only among those who do not respond to treatment. This supports the contention that 'old-old' patients, or depressed older adults with extensive cerebrovascular disease, should not be maintained on a medication if they have not responded following an adequate trial as it may negatively impact some aspects of cognition.

DEDICATION

I dedicate this dissertation to my patient and supportive family.

Without you, the following pages would undoubtedly be blank.

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I first want to thank my advisor and dissertation chair, Dr. Joel Sneed, as this dissertation would not have been possible without his guidance. His mentorship and support throughout my graduate career have been tremendous. I cannot thank him enough for his unending dedication to my training and development.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

GLOSSARY OF ABBREVIATED TERMS

Beck Depression Inventory-II – BDI-II
Buschke Selective Reminding Test – Buschke SRT
Choice Reaction Time Test – CRT
Clinical Global Impression Scale – CGI
Continuous Performance Test – CPT
Dementia Rating Scale-2, Initiation/Perseveration Subtest – DRS-I/P
Diagnostic and Statistical Manual, Fourth Edition-Text Revision - DSM-IV-TR
Hamilton Rating Scale for Depression – HRSD
Judgment of Line Orientation – JLO
Late-life depression – LLD
Magnetic Resonance Imaging – MRI
Mini Mental State Examination – MMSE
Monoamine oxidase inhibitors – MAO-I
Selective Serotonin Reuptake Inhibitors – SSRI
Serotonin-norepinephrine reuptake inhibitors – SNRI
Simple Reaction Time Test – SRTT
Statistical Package for the Social Sciences – SPSS
Statistical Analysis System – SAS
Stroop Color/Word Test – Stroop
Structured Clinical Interview for DSM-IV Axis 1 Disorders – SCID
Trail Making Test A – TMT A
Trail Making Test B – TMT B
Tricyclic antidepressants – TCA
Wechsler Adult Intelligence Scale-III – WAIS-III

GENERAL INTRODUCTION

Depression is prevalent in late-life and is a major public health concern (Lebowitz et al., 1997). Approximately 8% to 16% of older adults in community samples experience clinically significant depressive symptoms (Blazer, 1994; Blazer, Burchett, Service, & George, 1991) and major depression has been reported to occur in approximately 2% of adults aged >65 years (Blazer, Hughes, & George, 1987; Steffens, Fisher, Langa, Potter, & Plassman, 2009). Late-life depression often goes undiagnosed or inadequately treated and is associated with decreased quality of life, cognitive and functional decline, increased hospitalization and service use, and higher rates of mortality from comorbid medical conditions or suicide (Blazer, 2003; Blazer, Hybels, & Pieper, 2001; Ganguli, Dodge, & Mulsant, 2002; Huang et al., 2000; Unützer et al., 2000). As such, the cost ascribable to depression is approximately $43 billion annually in the United States (Hirschfeld et al., 1997).

Major depression is diagnosed in the DSM-IV-TR (Association, 2000), when five or more of the following symptoms present during the same two week period: depressed mood, loss of interest or pleasure in activities, significant increase or decrease in weight or appetite, feelings of worthlessness or excessive or inappropriate guilt, diminished ability to concentrate or make decisions, fatigue or loss of energy, psychomotor agitation or retardation, insomnia and hypersomnia, and recurrent thoughts of death or suicidal ideation. To meet diagnostic criteria for major depression, at least one of the five symptoms must include depressed mood or loss of interest in activities. Symptoms must represent a decline from previous functioning, cause significant distress or functional impairment, and cannot be accounted for by a medical condition, psychoactive substances, or bereavement.

There are notable differences between the clinical presentation of early- and late-life depression. For example, older depressed adults often present with multiple somatic complaints such as sleep or appetite disturbance and fatigue and may more readily report physical symptoms than depressed mood (Gallo & Rabins, 1999). Furthermore, depressive symptoms in the elderly may be incorrectly attributed to medical comorbidities or normal aging processes (Barry, Abou, Simen, & Gill, 2012; Kennedy & Marcus, 2005). It is also possible that impairment secondary to depression may be overlooked because of lower functional expectations of the geriatric population (NIH, 1991). Finally, current healthcare systems may represent a barrier to effective treatment of depression given such factors as poor coordination between service providers and lack of infrastructure to support depression care (e.g., use of standard screening measures) (McEvoy & Barnes, 2007). As a result, LLD is often unrecognized and under treated, particularly in primary care settings as a result of brief patient visits and lack of expertise in the diagnosis of late-life mental illness (Lemeliln, Hotz, Swensen, & Elmslie, 1994). Although the prevalence of depression is substantially higher in primary care patients than the general elderly population (Bruce & Pearson, 1999), approximately 30-50% of patients with major depression go undiagnosed in a medical setting (Boswell & Stoudemire, 1996).

The first-line of treatment for depression is antidepressant medication, particularly in the older adult community where the majority of treatment is provided by primary care doctors. There are multiple classes of antidepressant medications including SSRIs, SNRIs, TCAs, and MAO-Is. Important considerations when treating the geriatric depressed include the effect of medication on comorbid medical illnesses, increased sensitivity to adverse drug interactions,

age-associated changes in pharmacokinetics and drug metabolism, and increased vulnerability to side effects (Montgomery, 2002; Pollock, 2004).

Selective serotonin reuptake inhibitors are the most frequently used antidepressant medication and have proven safety and efficacy in the geriatric depressed (Newhouse, 1996); the limited anticholinergic and antihistaminergic side effects result in better tolerability and compliance. Tricyclic antidepressants, on the other hand, have demonstrated efficacy in the elderly that is similar to that of SSRI antidepressants (Mottram, Wilson, & Strobl, 2006). However, the side effect profile of TCAs, which includes anticholinergic and cardiac effects and sedative properties, limits their use in a geriatric population (Roose, 2003; Roose & Spatz, 1998). In fact, comparator trials have shown that SSRIs have a better overall tolerability profile than TCAs in the elderly depressed (Montgomery, 2002).

Other classes of antidepressants that are efficacious for the elderly depressed include SNRIs and MAO-Is (Georgotas et al., 1986; Mukai & Tampi, 2009). Although there is limited evidence for the use of SNRIs in the treatment of geriatric depression, evidence suggests that there is no significant difference in efficacy or safety between SNRIs and SSRIs (Dhillon, 2013; Mukai & Tampi, 2009). Monoamine oxidase inhibitors have the advantage of minimal anticholinergic activity (Thase, Trivedi, & Rush, 1995) and cardiac effect (Halper & Mann, 1988). However, clinicians have avoided using MAO-Is in elderly patients because of the potential to produce a hypertensive crisis from food and drug interactions (Thase, et al., 1995).

Antidepressant treatment can have an impact on both depressive symptoms and neurocognitive functioning in LLD. However, the field has primarily focused on improvement of depressive symptoms following antidepressant therapy; few studies have examined the effect of

antidepressants on cognitive function. Because the depressed elderly are a cognitively vulnerable population whose first line of treatment is antidepressant medication, it is important to consider the impact that antidepressant treatment can have on cognition when treating that patient group.

PROPOSED STUDIES

The purpose of this dissertation is to determine the impact of antidepressant medication on the cognitive functioning of depressed older adults. The first question I considered is what impact the medication itself (i.e., pharmacological properties) has on cognition. Many studies that have examined this issue have been limited by methodological constraints including lack of a control group for comparison (e.g., age-matched control group and/or placebo control group) (Bondareff et al., 2000; Doraiswamy et al., 2003; Georgotas et al., 1989; Nebes et al., 1999). Some studies have included an age-matched (non-depressed) control group, but such designs make it difficult to conclude whether change in cognitive functioning over the course of treatment is a result of the medication (e.g., its pharmacological properties) or non-specific factors related to participation in the trial (e.g., more frequent interaction with doctors than controls). It is possible to control for the impact of non-specific factors on cognition through the use of a placebo control group; any cognitive changes observed within the experimental group above and beyond the placebo group can be attributed to the medication itself. To our knowledge, however, there have been few placebo-controlled trials examining the cognitive impact of antidepressant medication in geriatric depression.

Study 1 will examine the impact of SSRIs, the first-line of antidepressant treatment in the geriatric depressed, on the cognitive functioning of depressed older adults using data from an eight-week, randomized, placebo-controlled trial of citalopram (Culang et al., 2009). Given its placebo-controlled design, the data from this study will allow me to determine whether cognitive change is caused by SSRI administration or non-specific factors related to participation in the

treatment trial; any change in cognitive functioning above and beyond the placebo group could be attributed to the effects of the antidepressant treatment.

The second question is whether there is a differential impact of antidepressant medication on cognitive functioning depending on medication class (e.g., SSRIs, SNRIs, TCAs, MAOs). This is especially important because some major depressive subtypes preferentially respond to different antidepressant medications. For instance, MAO-Is demonstrate superior efficacy than both placebo and TCAs in the treatment of atypical depression (Liebowitz et al., 1984; Quitkin et al., 1988). On the other hand, patients with melancholic depression show a favorable response to TCAs (Abou-Saleh & Coppen, 1983; Guelfi, Ansseau, Timmerman, Kørsgaard, & Group, 2001), and there is evidence to suggest that SSRIs are less effective than TCAs in the treatment of melancholia in late-life (Joyce, Mulder, Luty, McKenzie, & Rae, 2003; Parker, Roy, Hadzi-Pavlovic, Wilhelm, & Mitchell, 2001). Finally, vascular depression (Alexopoulos, Meyers, Young, Campbell, et al., 1997; Sneed, Rindskopf, Steffens, Krishnan, & Roose, 2008; Sneed, Roose, & Sackeim, 2006) may be a subtype of LLD that, especially in the presence of executive dysfunction, may demonstrate an overall lower rate of antidepressant response (Alexopoulos et al., 2005; Sneed et al., 2010; Sneed, Keilp, Brickman, & Roose, 2008; Sneed et al., 2007). These findings suggest the first line of treatment for depression may depend on diagnostic subtype and, therefore, it is important to understand the cognitive impact of different medication classes.

In Study 2, I will examine the differential impact of antidepressant medication class (TCA or SSRI) on the cognitive functioning of depressed older adults. I will address this issue using data from a twelve-week, randomized, double-blind, parallel-group design comparing

sertraline and nortriptyline in the treatment of geriatric depression (Culang-Reinlieb, Sneed, Keilp, & Roose, 2012).

The third question I considered is whether diagnostic subtype has a differential impact on cognitive functioning following antidepressant treatment. For instance, patients with vascular depression may show less improvement or even a decline in cognitive functioning following antidepressant treatment when compared to patients with nonvascular depression. This hypothesis is supported by the progressive nature of the MRI hyperintensities that define the subtype (Awad, Johnson, Spetzler, & Hodak, 1986) and the association between MRI hyperintensities and cognitive decline (De Groot et al., 2002; Kohler et al., 2010). Melancholic depression, a subtype of MDD that requires the presence of either anhedonia or lack of mood reactivity in addition to 3 of 6 additional symptoms, is another subtype that may demonstrate poor cognitive outcomes following antidepressant treatment. Previous research suggests that depressed patients with melancholia have verbal learning deficits at baseline when compared to depressed patients without melancholia (Withall, Harris, & Cumming, 2010). Given these baseline deficits, patients with melancholic depression may require a longer time for cognitive recovery and, therefore, may show little change in cognitive functioning over an acute treatment trial when compared to non-melancholics (Withall, et al., 2010).

In Study 3, I will examine the differential impact of diagnostic subtype on change in cognition following acute antidepressant treatment using data from a 2-site (Harlem Hospital and the New York State Psychiatric Institute), 8-week, open-treatment trial I have coordinated under the guidance of Dr. Sneed. The purpose of this study is to examine the impact of medication on

cognitive functioning in patients with and without vascular depression, who we hypothesized would be overrepresented among African American patients in the Harlem Hospital sample.

Finally, in each of the three studies, we will attempt to disentangle the cognitive effects of medication from that of symptom remission. A number of studies that have examined the impact of antidepressant medication on cognition have not fully examined whether change in cognition following treatment depends on medication response. For example, some studies did not even explore the potential impact of responder status (Bondareff, et al., 2000; Raskin et al., 2007). Other studies included only responders in their analyses rather than comparing change in cognition among medication responders and non-responders, which would have helped to differentiate the impact of medication versus response on change in cognitive functioning (Bhalla et al., 2006; Butters et al., 2000; Gallassi, Di Sarro, Morreale, & Amorec, 2006; Nebes et al., 2003). Therefore, the interaction between response and the impact that antidepressant medication has on cognition will be examined in each of the three following studies.

STUDY 1

CHANGE IN COGNITIVE FUNCTIONING FOLLOWING ACUTE ANTIDEPRESSANT TREATMENT IN LATE-LIFE DEPRESSION[1]

[1]Culang, M.E., Sneed, J.R., Keilp, J.G., Rutherford, B.R., Pelton, G.H., Devanand, D.P., Roose, S.P. (2009). Change in cognitive functioning following acute antidepressant treatment in late-life depression. *American Journal of Geriatric Psychiatry, 17, 881-888.*

INTRODUCTION

Selective Serotonin Reuptake Inhibitors are the first-line of treatment in the geriatric depressed due to the efficacy, safety and tolerability of its class. Cognitive impairment is common in LLD, particularly in memory (Gallassi, et al., 2006; Kramer-Ginsberg et al., 1999; Salloway et al., 1996), visuospatial functioning (Butters et al., 2004; Kramer-Ginsberg, et al., 1999), information processing speed (Lesser et al., 1996; Nebes et al., 2000), and executive functioning (Lesser, et al., 1996; Lockwood, Alexopoulos, & van Gorp, 2002). It is important to consider the impact that antidepressant treatment can have on cognition when treating depressed older adults.

Research that has examined the impact of SSRIs on the cognitive functioning of depressed older adults has been inconclusive because most studies have been limited by methodological constraints including small sample size or lack of an age-matched control group for comparison (Bondareff, et al., 2000; Doraiswamy, et al., 2003; Georgotas, et al., 1989; Nebes, et al., 1999). For instance, treatment of LLD with sertraline led to an improvement in short- and long-term memory storage and retrieval and speed of processing (Doraiswamy, et al., 2003). Although these results suggest that some aspects of cognition (i.e. memory and processing speed) improve with antidepressant treatment, it is difficult to determine if the improvement was a function of repeat testing or medication because the design lacked a control group for comparison. Studies using age-matched controls have shown that cognitive functioning of depressed older adults does not improve beyond the expected practice effect[2] (Butters, et al.,

[2]Practice effects refer to improvement due to repeat testing and are defined by the performance of a comparison condition, either an age-matched control group (12-14) or a placebo comparison group (8, 15), that is not being treated with medication.

2000; Nebes, et al., 2003; Portella et al., 2003). For example, working and episodic memory, attention shifting, and processing speed did not improve following treatment with paroxetine to a greater degree than normal controls did with practice, regardless of responder status (Nebes, et al., 2003). Similarly, cognitive functioning showed no improvement beyond a practice effect among responders to either nortriptyline or paroxetine (Butters, et al., 2000). These studies suggest that depressed older adults show little improvement as a function of treatment and cognitive impairment persists following an adequate trial of antidepressant medication.

Although such designs allow us to determine whether cognition changes as a function of antidepressant treatment, it does not allow us to conclude that the change (if any) is a result of treatment due to a lack of a placebo condition. However, there have been few placebo-controlled trials examining this issue. In one study, nortriptyline and phenelzine produced no change in cognition in depressed older adults when compared to placebo, and this effect did not depend on responder status (Georgotas, et al., 1989). However, the small sample size and limited number of responders made it difficult to determine the impact of responder status on change in cognition. Furthermore, this study was restricted to the use of a TCA and MAO-I. In another study, patients taking duloxetine showed significant improvement in verbal learning and memory compared to the placebo group (Raskin, et al., 2007). Therefore, it is unclear what impact medication, SSRIs in particular, has on cognitive functioning.

The purpose of this study was to examine the impact of antidepressant treatment on change in cognitive functioning. To accomplish this aim, we used neuropsychological data collected as part of the Old-Old Depression Study (Roose et al., 2004), a large (n=174), randomized, double-blind, placebo-controlled trial of citalopram in depressed older adults (age

>75). These data provided us with the methodological strength to address two questions: 1) Do patients treated with citalopram show differential change in cognitive functioning over the 8 weeks when compared to patients treated with placebo? 2) Does change in cognitive performance depend on responder status? To our knowledge, this is the first attempt to approach these issues using a placebo-controlled trial of an SSRI in an old-old (>75 years old) depressed population.

METHODS

Procedure

This study was a multi-center, double-blind, randomized eight-week trial comparing citalopram to placebo in 174 community dwelling depressed patients 75 and older. At the initial visit, a comprehensive psychiatric evaluation, including a SCID, a HRSD, MMSE, and a medical history, were performed to confirm diagnosis, severity and preliminary eligibility. If the patient met inclusion criteria and signed informed consent, a physical examination, an ECG, and routine blood work were performed. Patients who met inclusion and exclusion criteria (see below) entered a one-week single-blind placebo lead-in. If at the end of this week, a patient continued to meet inclusion and exclusion criteria, they were randomized to citalopram 20 mg/d or matched placebo. At the end of week four, patients with a HRSD score > 10 had their dose increased to two pills per day, i.e., 40 mg of citalopram or 2 placebo pills. After randomization, patients returned for study visits at week one, two, three, four, five, six, and eight (final week). Mood was assessed at each patient visit, neuropsychological functioning was assessed at baseline and week 8, and structural imaging was obtained at baseline.

Inclusion criteria were a) male or female 75 years or older and not living in a residential setting, b) unipolar depression, single or recurrent, non-psychotic, current episode at least four weeks, c) score of ≥ 20 on the 24-item HRSD at initial visit and at the end of the one week placebo lead-in, and d) willing and able to give informed consent. Exclusion criteria were a) bipolar disorder, obsessive compulsive disorder, psychotic disorder, current substance abuse or dependence within past year, b) current suicide intent or serious attempt within past year, c) probable Alzheimer's disease or vascular dementia based on NINCDS/ADRDA criteria, d) MMSE score ≤ 18, e) Parkinson's disease, f) acute, severe or unstable medical illness, and g) failed to respond to either a trial of an SSRI or trials of two or more different classes of antidepressants other than SSRI's for the current depressive episode.

Neuropsychological Test Battery

The test battery was designed to assess a number of cognitive functions pertinent to aging and major depression including mental status, psychomotor speed, reaction time, visual-spatial skill, attention, and memory. Three of the tests (CRT, JLO, Stroop) were presented on a Macintosh laptop computer and were written in the PsyScope programming language (J. D. Cohen, MacWhinney, Flatt, & Provost, 1993) whereas the other three tests (MMSE, Buschke SRT, Digit Symbol subtest of the WAIS-III) were administered by hand.

1) 30-item Folstein Mini-Mental State Exam (Folstein, Folstein, & McHugh, 1975): The MMSE is a brief, structured 30-item mental status examination. The total score possible on the 30-item MMSE is 30.

2) WAIS-III Digit Symbol Subtest (Wechsler, 1997): The Digit Symbol test is a measure of psychomotor speed, which requires subjects to transcribe number-coded figures on to a blank

number-coded grid. The total Digit Symbol score corresponds to the total number of items completed correctly within 120 seconds.

3) Choice Reaction Time Test (Thorne, Genser, Sing, & Hegge, 1998): In this task, subjects are instructed to "catch the X" that is presented on successive trials in different areas of the screen by hitting the correct corresponding key. A total of 60 items are presented and median reaction time is computed from all correct individual responses. The median reaction time was log transformed for use in statistical analyses.

4) Stroop Color/Word Test (MacLeod, 1991): The Stroop is a measure of attention, concentration, and behavioral inhibition under distracting conditions that is sensitive to frontal lobe dysfunction (Lezak, Howieson, & Loring, 2004). The Stroop presents stimuli individually, allowing reaction time to be recorded for each trial. By key press, subjects identify on each trial the name or color of the stimulus. There are three blocks of trials, each with a 50 millisecond inter-stimulus interval. In the first block, printed color names (Red, Blue, Green) are presented in black. In the second block, a string of XXXs is presented in different colors (Red, Blue, Green). In the third block, color names are again presented, but this time printed in incongruous colors. Subjects are given feedback on each trial (beep for correct; buzz for error), and this task produces consistent interference effects. The degree of interference (percent increase in reaction time between the control conditions and the incongruent condition) was computed for use as the dependent measure.

5) Judgment of Line Orientation (Benton, Sivan, Hamsher, Varney, & Spreen, 1983): This task is a measure of spatial judgment and requires subjects to characterize the orientation of

isolated line segments. The total score on this measure is the number of correct responses out of 30.

6) Buschke Selective Reminding Test (Buschke & Fuld, 1974): The Buschke SRT uses 12-word lists with 6 trials, followed by free recall after a 15 minute delay. Since subjects are only reminded of words not recalled on the previous trial, this task is more demanding and provides more information on encoding strategies than other list learning tasks. Total words recalled across the 6 trials will be the dependent measure.

Data Analysis

Missing Data

Missing data at baseline ranged from 0.6% on the MMSE and SRT to 9.8% on the JLO and from 11.5% on the MMSE to 19.0% on the Stroop at follow-up. To accommodate missing data, we used multiple imputation using the PROC MI and MIANALYZE procedures in SAS. Multiple imputation is a simulation technique that replaces each missing datum with a set of $m > 1$ plausible values (Schafer & Olsen, 1998). This report is based on five imputed data sets ($m = 5$), which is sufficient to obtain excellent results unless rates of missing data are exceptionally high (Schafer, 1999). The imputed data sets are analyzed using standard statistical analyses and results from the analyses from the *m* complete data sets are combined using Rubin's rules (Schafer & Graham, 2002; Schafer & Olsen, 1998) to generate valid statistical inferences that reflect uncertainty due to missing values and improve the accuracy of the results.

Statistical Analyses

Prior to testing for differences in change in neuropsychological test performance, we used the PROC REG and PROC LOGISTIC procedures in SAS to test for differences at baseline

between the two treatment conditions as well as the four treatment condition by responder status groups (see below). There were no differences on age, education, gender, baseline depression severity, responder status, or on any of the neuropsychological tests with the exception of baseline scores on the MMSE and Digit Symbol subtest of the WAIS-III. Therefore, we adjusted for baseline Digit Symbol and MMSE scores in the two treatment group analyses. When comparing the four patient groups (responder status by treatment condition), we found differences on education and baseline MMSE, CRT, and SRT scores. We therefore included these variables as covariates in the four group analyses. We also adjusted for site of study in all analyses, which we know from previous reports to be associated with outcome (Roose, et al., 2004).

To test for differences in change in neuropsychological test performance, we used data from the multiply imputed data sets and adopted a partial or regressed change approach to analyzing two time-point data (J. Cohen, Cohen, West, & Aiken, 2003) using the PROC REG procedure in SAS. According to this approach, the endpoint neuropsychological test score is treated as the outcome variable and the baseline test score is treated as a covariate. This effectively removes all correlation of the endpoint score from the baseline score and represents an improvement over simple change scores (subtracting baseline from endpoint), which tend to overcorrect the endpoint score by the baseline score due to unreliability of measurement (J. Cohen, et al., 2003). We first tested for differences in endpoint scores between treatment conditions using a dummy coded (citalopram = 1, placebo = 0) variable. To test whether change in neuropsychological test performance depends on responder status (50% reduction from baseline HRSD score), we again used a dummy coded variable to designate the four patient

groups (citalopram responders, citalopram non-responders, placebo responders, and placebo non-responders). Each covariate was centered at its respective mean so the intercept corresponded to the mean of the reference group at endpoint and the unstandardized regression weights reflected the difference between the groups included in the model and the reference group (excluded from the model). All significance tests were evaluated at the 5% level.

RESULTS

Descriptive Statistics

Table 1 presents baseline demographic and clinical characteristics of the total sample, placebo and citalopram groups, and the four groups of patients classified by treatment condition and responder status. The average study participant was 79.57 years and completed about 2 years of college. Approximately 58% of the sample were women, average baseline depression severity was 24.32 on the 24-item HRSD, and 40% of the sample was classified as responders. The average MMSE score of the sample at baseline was 27.99 and 6.9% had a score of 24 or below.

To facilitate interpretation of the pattern of change in neuropsychological test performance as a function of treatment group, all neuropsychological scores were converted to z-scores based on mean values at baseline in the total sample. For variables in which good performance was represented by lower values (e.g., CRT), *z*-scores were reversed so that a high *z*-value represented a good performance for those measures. As can be seen in Figure 1, neuropsychological test performance improved on each test in the placebo group, which is consistent with a practice effect. For the purposes of this report, practice effects refer to improvement in performance due to repeat testing and are defined on the basis of the performance of the placebo group. Differences from the placebo group (both positive and

negative) reflect deviations from a practice effect and represent either improvement beyond a practice effect or the absence of a practice effect, possibly even decline. As can be seen in Figure 1, the citalopram group improved on some tests and declined on others.

Hypothesis Testing

Table 2 shows the unadjusted means and standard deviations for all neuropsychological tests both pre and post-treatment for the citalopram and placebo groups as well as the four patient groups (treatment group by responder status). Adjusting for site and baseline MMSE and Digit Symbol, there was a statistically significant difference between the placebo and citalopram conditions at endpoint on the Buschke SRT. Specifically, patients treated with citalopram scored lower at endpoint than patients treated with placebo [B=-2.74 SE=1.41, t(1087)=-1.94, 95% CI -5.52, 0.03, p=0.05].

We next compared the four groups of patients classified according to treatment condition and responder status on endpoint neuropsychological test performance. As can be seen in Table 2, citalopram responders scored significantly higher than both citalopram non-responders [B=-2.54, SE=0.97, t(80.46)=-2.54, 95% CI -4.38, -0.53, p=0.01] and placebo non-responders [B=-2.47, SE=0.89, t(217.31)=-2.77, 95% CI -4.23, -0.71, p=0.01] on the JLO at endpoint. However, citalopram responders were not statistically significantly different than placebo responders at endpoint [B=-1.81, SE=1.02, t(111.56)=-1.78, 95% CI -3.83, 0.20, p=0.08]. Looking at endpoint performance on the Buschke SRT, citalopram non-responders were the only group to decline from pre-test to post-test. Specifically, citalopram non-responders scored lower (3.64 points) than placebo non-responders at study end [B=-3.64 SE=1.83, t(472.15)=-1.99, 95% CI -7.23, -0.05, p=0.05]. Similarly, citalopram non-responders were the only group to decline from pre-test

to post-test on the Digit Symbol. In particular, citalopram non-responders scored lower than citalopram responders at endpoint [B=-5.62 SE=2.65, t(233.31)=-2.12, 95% CI -10.84, -0.40, p=0.04].

DISCUSSION

This was the first study to examine the impact of antidepressant treatment on change in cognitive functioning in depressed adults 75 years and older using data from an eight-week, randomized, placebo-controlled trial. While the placebo group showed a distinct practice effect from baseline to endpoint on all neuropsychological tests, the citalopram group improved on some tests but declined on others. However, the pattern of change depended on responder status. Specifically, citalopram non-responders were the only group to decline in performance on verbal learning (Buschke SRT) and psychomotor speed (Digit Symbol). Citalopram responders showed significant improvement in visuospatial functioning (JLO) when compared to non-responders in either condition, but their improvement was not greater than responders on placebo. Similarly, citalopram responders showed greater improvement on psychomotor speed (Digit Symbol) than citalopram non-responders, but their improvement was not greater than placebo responders or non-responders. The findings indicate that the practice effect is impaired in some domains among non-responders on medication. Therefore, these findings suggest that patients should not be maintained on a medication if they have not had an adequate response.

One possible explanation for the observed decline in verbal learning and psychomotor speed is that the overall level of cognitive functioning in the sample was low and the citalopram group had a disproportionately high number of cognitively impaired patients. This might explain why there was inconsistent improvement in the citalopram condition and why this study differs

from previous placebo-controlled trials (Georgotas, et al., 1989; Raskin, et al., 2007). However, the average MMSE score at baseline for the sample was 28, which is well within normal limits. Moreover, although there was a significant difference in MMSE scores between the treatment groups at baseline, it was the citalopram group that scored higher at baseline than the placebo group. Similarly, the citalopram group (30%) had a lower number of patients with memory impairment (i.e., a baseline Buschke SRT score ≤1.5 standard deviations below the normative sample) than the placebo group (40%) (Larrabee, Trahan, & Levin, 2000). This suggests that the medication group did not include a disproportionate number of individuals demonstrating medial temporal lobe dysfunction above and beyond what would be expected with late-life depression alone.

Another possibility is that brain lesions, which are associated with age (Taylor, MacFall, et al., 2003) and other risk factors such as hypertension and diabetes (Murray et al., 2005), were disproportionately represented in the citalopram condition. White matter hyperintensities that are characteristic of LLD may interrupt frontal-striatal pathways that mediate cognitive functions that are commonly impaired in LLD. Furthermore, cognitive impairment is associated with the presence of white matter hyperintensities in LLD and deficits worsen as the lesions become more severe (Kramer-Ginsberg, et al., 1999; Lesser, et al., 1996). However, there were no statistically significant differences in the percentage of patients in the citalopram group and the placebo group classified as having high lesion load, which was defined as a deep white matter hyperintensity rating of 2 or a subcortical gray matter rating of 3 on the Fazekas modified Coffey Rating Scale for Signal Hyperintensities (Krishnan, Hays, & Blazer, 1997).

The decline in verbal learning may be particularly attributed to the anticholinergic effects of SSRIs. Selective serotonin reuptake inhibitors have unique non-serotonergic pharmacological profiles that are associated with distinct effects on cognitive functioning (Chew et al., 2008). Paroxetine, for example, may cause impairment in delayed verbal recall in healthy middle-aged adults and elderly subjects whereas sertraline is associated with improvement in immediate and delayed verbal recall and verbal fluency (Furlan et al., 2001; Schmitt, Kruizinga, & Riedel, 2001). Although administration of citalopram is associated with improvement in working memory in depressed adults (Zobel et al., 2004) and increased memory consolidation in healthy adults (Harmer, Bhagwagar, Cowen, & Goodwin, 2002), it is still unclear what effect citalopram can have on cognitive functioning of the geriatric depressed, a population that is especially vulnerable to the adverse effects of antidepressant medication (Baldwin & Johnson, 1995).

The observed decline in verbal learning and psychomotor speed in the citalopram group is consistent with a recent report from an epidemiological study of elderly depressed patients examining the relationship between depressive symptoms, cognitive impairment, and antidepressant use (Ravaglia et al., 2008). Findings revealed that baseline depression scores predicted future mild cognitive impairment but only among those using antidepressant medications at baseline. Taken together, these findings support the contention that non-responders should not be maintained on medication that may have a negative impact on some aspects of cognitive functioning, which may facilitate the development of mild cognitive impairment (Devanand et al., 2003).

This study should be interpreted in the context of several limitations. First, there were statistically significant differences between the two treatment conditions as well as the four

patient groups at baseline on several neuropsychological tests. However, these differences were adjusted for in the statistical models by including those tests as covariates. Second, it may be possible that including a small number of patients with mild cognitive impairment or in the early stages of a neurodegenerative disorder such as Alzheimer's disease (MMSE $\leq$ 24) in this study (n=12) might have influenced our results. However, we ran the analyses with and without this group of patients and the results were not different. Third, there was missing data, as is typically the case in clinical trials, and we accommodated for missing data using multiple imputation, a far superior method compared to traditional approaches using mean substitution or complete case analysis. Fourth, a somewhat limited neuropsychological battery was used. Only one aspect of executive functioning (i.e. response inhibition) was evaluated and no formal test of attention was included in the study. These limitations, however, are balanced by using data from the only randomized, placebo-controlled clinical trial of antidepressant treatment among depressed patients age 75 or older. Moreover, unlike other studies, there were an approximately equal number of responders in both treatment conditions, allowing for an adequate test of whether change in cognitive function across two treatments depends on responder status.

Our findings indicate that citalopram may interfere with the normal practice effect in verbal learning and psychomotor speed among patients who do not respond on medication. While responders on medication may improve in some domains, their improvement does not exceed the expected practice effect observed in patients randomized to placebo. This raises the important clinical issue that, although two treatments may be equivalent with regard to response, they may have differential effects on cognitive functioning, especially in a cognitively vulnerable

population. Our findings suggest that non-responders should not be maintained on medication that may have a negative effect on some aspects of cognitive functioning.

Table 1. Baseline clinical and demographic characteristics of the total sample, the citalopram and placebo subsamples, and the four patients groups classified by treatment condition and responder status

Variable	Total Sample (n=174)	Citalopram (n=84)	Placebo (n=90)	Citalopram Responders	Citalopram Non-responders	Placebo Responders	Placebo Non-responders
Age	79.57 (4.36)	79.82 (3.97)	79.33 (4.69)	79.30 (3.74)	80.19 (4.08)	80.05 (5.42)	78.89 (4.13)
Women (%)	58	54	62	60	49	61	63
Education	13.77 (3.27)	13.82 (2.76)	13.72 (3.67)	12.76 (2.61)	14.56 (2.67)	13.30 (4.17)	13.99 (3.30)
HRSD	24.32 (4.12)	24.40 (4.31)	24.25 (3.93)	24.04 (4.50)	23.96 (4.13)	23.33 (3.46)	24.82 (4.10)
Responder (%)	40	41	38	100	0	100	0
MMSE	27.99 (2.13)	28.37 (1.61)	27.62 (2.46)	28.46 (1.40)	28.31 (1.74)	27.35 (2.38)	27.79 (2.50)

Table 2. Unadjusted neuropsychological test performance scores at baseline and endpoint of the citalopram and placebo subsamples and the four patient groups classified by treatment condition and responder status

NP Test	Citalopram (n=84)		Placebo (n=90)		Citalopram Responders		Citalopram Non-responders		Placebo Responders		Placebo Non-responders	
	PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST
MMSE	28.37 (1.61)	28.35 (1.67)	27.62 (2.46)	27.67 (2.15)	28.46 (1.40)	28.59 (1.26)	28.31 (1.74)	28.19 (1.88)	27.35 (2.38)	27.58 (2.28)	27.79 (2.50)	27.78 (2.06)
Digit Symbol	45.17 (16.83)	45.86 (16.91)	40.14 (16.22)	41.49 (17.98)	45.38 (17.21)	48.92 (16.20)	45.02 (16.59)	43.75 (17.11)	39.87 (17.23)	42.20 (19.02)	40.31 (15.57)	41.04 (17.32)
Stroop	0.87 (0.58)	0.69 (0.54)	0.82 (0.64)	0.64 (0.61)	0.84 (0.61)	0.61 (0.61)	0.89 (0.55)	0.75 (0.47)	0.92 (0.72)	0.63 (0.66)	0.77 (0.59)	0.65 (0.58)
CRT	6.76 (0.31)	6.79 (0.36)	6.82 (0.37)	6.80 (0.39)	6.77 (0.34)	6.77 (0.36)	6.74 (0.29)	6.80 (0.36)	6.90 (0.43)	6.83 (0.50)	6.77 (0.32)	6.78 (0.31)
JLO	19.49 (5.61)	21.55 (5.41)	19.76 (6.63)	20.50 (5.75)	19.21 (5.46)	22.59 (5.09)	19.69 (5.72)	20.82 (5.53)	18.71 (7.18)	19.93 (5.90)	20.42 (6.18)	20.85 (5.63)
Buschke SRT	36.37 (8.78)	35.23 (10.73)	34.23 (10.83)	35.71 (11.86)	37.04 (7.66)	37.46 (10.61)	35.90 (9.47)	33.68 (10.57)	31.68 (9.46)	33.78 (11.47)	35.83 (11.33)	36.92 (11.96)

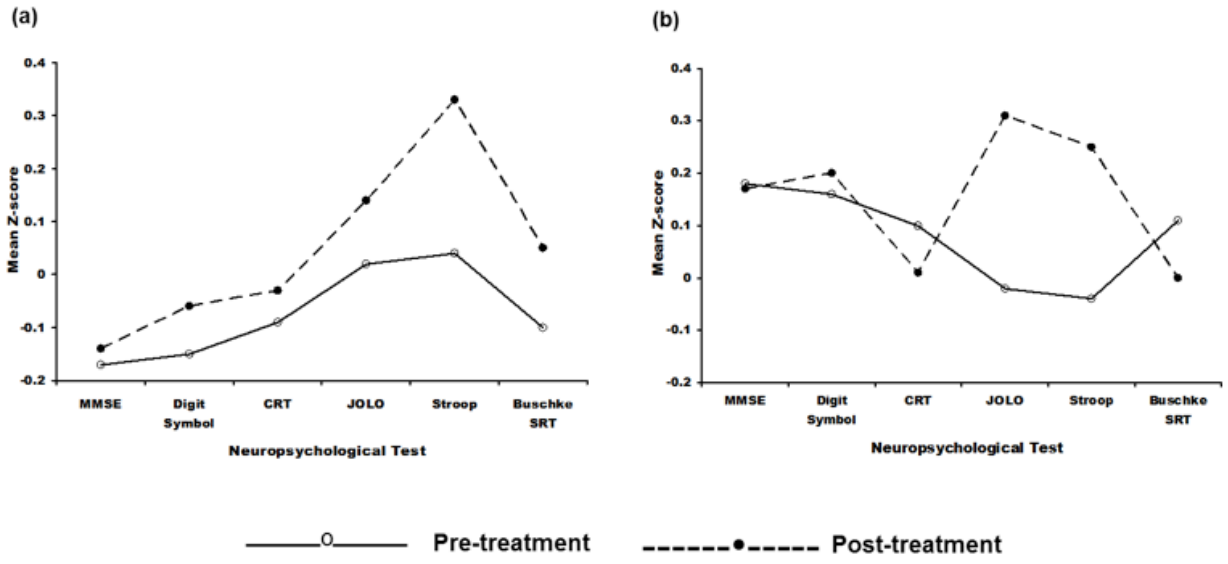

Figure 1. Change in cognitive performance from pre- to post-treatment in the (a) placebo condition and (b) citalopram condition across six neuropsychological tests

STUDY 2

CHANGE IN COGNITIVE FUNCTIONING IN DEPRESSED OLDER ADULTS FOLLOWING TREATMENT WITH SERTRALINE OR NORTRIPTYLINE[3]

[3]Culang-Reinlieb, M.E., Sneed, J.R., Keilp, J.G., Roose, S.P. (2011). Change in cognitive functioning in depressed older adults following treatment with sertraline or nortriptyline. *International Journal of Geriatric Psychiatry, 27(8),* 777-84. .

INTRODUCTION

Cognitive impairment is common in geriatric depression. Cognitive domains reported to be affected include memory (Gallassi, et al., 2006; Kramer-Ginsberg, et al., 1999; Salloway, et al., 1996), visuospatial functioning (Butters, et al., 2004; Kramer-Ginsberg, et al., 1999), information processing speed (Lesser, et al., 1996; Nebes, et al., 2000), and executive functioning (Lesser, et al., 1996; Lockwood, et al., 2002). The conversion rate of LLD into dementia among those with cognitive impairment is much higher than those without cognitive impairment (Modrego & Ferrandez, 2004). Antidepressant medication is the first line of treatment for depression, particularly in the older adult community where primary care doctors provide the majority of treatment. Therefore, it is important to understand the effects of antidepressant medication on cognition among the depressed elderly, a cognitively vulnerable population.

When examining the effect of antidepressant medication on cognition in depressed older adults, two interrelated sets of questions arise. The first set of questions focuses on within-treatment changes in cognitive functioning: a) does cognitive functioning change from pre- to post-treatment? and b) is there a differential impact of medication on cognition depending on whether or not the patient responds? Within the second set of questions, the focus is on between-treatment changes in cognitive functioning: a) is there a differential impact of antidepressant medication on cognitive functioning depending on medication class (e.g., SSRIs, SNRIs, TCAs, MAO-Is)? b) does change in cognitive functioning between treatment conditions depend on responder status? Of course, the concept of cognitive functioning is broad and consists of a number of functions including but not limited to memory, attention, processing speed, executive

functioning, and visuospatial/visuoconstructional skills. Therefore, it is important to examine each of the above questions within the context of a multi-domain assessment to address how antidepressant medication (including whether or not the patient responds) differentially affects each of these cognitive domains.

A number of studies have examined the impact of antidepressant medication on cognition but have not fully addressed the two interrelated sets of questions we have outlined (Bhalla, et al., 2006; Bondareff, et al., 2000; Butters, et al., 2000; Doraiswamy, et al., 2003; Gallassi, et al., 2006; Nebes, et al., 2003; Raskin, et al., 2007). For example, some studies did not address whether change in cognition depends on response to treatment (Bondareff, et al., 2000; Raskin, et al., 2007). Other studies included only responders in their analyses rather than comparing change in cognition among responders and non-responders, which would have helped to differentiate the impact of medication versus response on change in cognitive functioning (Bhalla, et al., 2006; Butters, et al., 2000; Gallassi, et al., 2006; Nebes, et al., 2003). Finally, another study used a composite cognitive score in its analyses and thus did not address the differential impact of medication on different cognitive domains (Doraiswamy, et al., 2003).

To our knowledge, few studies have fully tested the impact of medication on cognitive function in depressed older adults. For example, in an 8-week randomized placebo-controlled trial of citalopram (Culang, et al., 2009), antidepressant non-response was associated with cognitive decline in verbal learning and psychomotor speed. Although responders on medication improved on some domains (psychomotor speed and visuospatial functioning), their improvement did not exceed the expected practice effect observed among patients randomized to placebo. This study, therefore, shows decline in some domains and improvement in other

domains, and is an example of a differential impact of medication on cognition. In another study, nortriptyline and phenelzine produced no change in any cognitive domain assessed (verbal learning, psychomotor speed, visual memory) in depressed older adults when compared to placebo, and this effect did not depend on responder status (Georgotas, et al., 1989). In a third study, an uncontrolled trial in depressed older adults showed no change in any cognitive domain assessed (processing speed, executive functioning, verbal and visual memory, visuoperceptive functioning, and attention) over 12 months of treatment when compared to age-matched controls (Portella, et al., 2003). Furthermore, there were no differences in change among remitted and non-remitted patients.

The purpose of this study was to examine the impact of a TCA and SSRI on cognition and to determine whether change in cognition depends on response to treatment and cognitive domain. To accomplish this aim, we used pre-post neuropsychological data on global cognitive functioning, verbal learning, attention, psychomotor speed, and executive functioning (the switching and response inhibition components), collected as part of a 12-week, randomized, double-blind, parallel-group design comparing sertraline and nortriptyline in the treatment of depressed older adults. In the context of this multi-domain assessment, we addressed the two sets of questions outlined above: 1.a) whether there were pre- to post-treatment changes in cognitive functioning within the sertraline and nortriptyline conditions, 1.b) whether change in cognitive functioning within each treatment condition depended on responder status, 2.a) whether there were differences in change in cognitive functioning between the nortriptyline and sertraline conditions, and 2.b) whether change in cognitive functioning between treatment conditions depended on responder status.

METHODS

Procedure

This study was a double-blind, randomized, 12-week clinical trial comparing nortriptyline to sertraline in depressed older adults. Patients were recruited by radio and newspaper advertisements and/or through referral from other physicians. At the initial visit, a comprehensive psychiatric evaluation, including a SCID, HRSD, MMSE, Newcastle I scale for the assessment of melancholia, and a medical history were performed. If the patient met inclusion criteria and signed informed consent, a physical examination, electrocardiogram, complete blood count, chemistries, electrolytes, and thyroid panel were performed.

Inclusion criteria were 1) age > 45; 2) unipolar depression, single or recurrent, nonpsychotic, by DSM-IV criteria; 3) HRSD ≥ 16 at the initial visit and at the end of 1 week of placebo; 4) MMSE score ≥ 24; and 5) willing and able to give informed consent. Exclusion criteria were 1) current or history of obsessive-compulsive disorder, psychotic disorder, or substance dependence within the past year (other than nicotine) by DSM-IV criteria; 2) judged to be a current suicide risk or serious suicide attempt within the past year; 3) patients status post myocardial infarction, coronary artery bypass, or angioplasty, or with a positive history of angina or positive stress test; 4) QRS interval greater than 0.12 sec or QTc interval ≥ 46 msec; 5) treatment with coumadin, heparin or type 1 antiarrhythmic medications; 6) diagnosis of narrow angle glaucoma; 7) stroke, epilepsy or Parkinson's disease; 8) acute, severe or unstable medical condition; 9) positive urine toxicology screen for drugs of abuse including amphetamine, barbiturates, cocaine, marijuana, methadone, methaqualone, opioids, and phencyclidine; 10) treatment in the current episode of depression with either nortriptyline with a plasma level

between 50 and 150 ng/ml, desipramine or imipramine with a plasma level of 250 ng/ml or greater, paroxetine 40mg, fluoxetine 40mg, or sertraline 200mg for at least 4 weeks.

Patients who met inclusion/exclusion criteria and signed informed consent were given one week of single-blind placebo. If patients still met inclusion/exclusion criteria at the end of the placebo week and did not reduce their HRSD score by 25%, they were randomized. The assessments performed at the end of the placebo week and every visit thereafter included the HRSD, the Montgomery-Åsberg Depression Rating Scale, the BDI-II, and the CGI of severity and improvement. The Hamilton Anxiety Rating Scale was performed at baseline and at the end of weeks 2, 4, and 8 of treatment; the Medical Outcomes Study 36-Item Short-Form Health Survey and the MMSE were performed at baseline and at the end of week 12 or upon early termination. The CIRS-G was also administered at baseline. Stratification of the sample was based on diagnosis of melancholia by DSM-IV criteria (questions resolved by case conference). Randomization was done using permuted blocks of ten.

Participants randomized to sertraline received 50 mg for one week and then 100 mg for the next 4 weeks. If the patient did not meet criteria for remission (HRSD < 10) by week 5, the dose was increased to 150 mg/day. If the patient did not show evidence of response by week 9, the dose was increased to 200 mg/day. The nortriptyline dose was calculated at 1 mg/kg; 1/3 of that dose was given days 1 through 3, 2/3 on days 3 through 6, and the full dose of medication was given on day 7. A plasma level was drawn 7 days later and the dose of nortriptyline was adjusted so that the plasma level was within 80-120 ng/ml. The New York State Psychiatric Institute IRB approved this study.

Neuropsychological Test Battery

The test battery was designed to test a number of cognitive functions pertinent to LLD including mental status, psychomotor speed, attention, and memory. Two of the tests (CPT and Stroop) were presented on a Macintosh laptop computer and were written in the PsyScope programming language (J. D. Cohen, et al., 1993) whereas the other five tests (MMSE, Buschke SRT, TMT A and B, and Purdue Pegboard) were administered by hand. The MMSE, Buschke SRT, and Stroop were previously described in detail (refer to Procedures section, Study 1). The remaining neuropsychological tests are described below:

1) Purdue Pegboard (Tiffin & Asher, 1948):The Purdue Pegboard Test assesses fine and gross motor dexterity and coordination and psychomotor speed. In this task, subjects are instructed to place as many pins in the holes within a 30 minute time period. Five separate scores can be obtained with the Purdue Pegboard: (1) right hand; (2) left hand; (3) both hands; (4) right plus left plus both hands (R+L+B); and (5) assembly. The dependent measure will be the number of pins placed using both hands.

2) Continuous Performance Test (Cornblatt, Risch, Faris, Friedman, & Erlenmeyer-Kimling, 1988): The CPT is a standard research measure of sustained attention. In this task, 4-digit numbers are flashed for 50 ms at a rate of 1 per second. Subjects are instructed to respond only when the same 4-digit number appears on consecutive trials. A total of 150 trials are presented, containing 28 targets and 26 "catch" trials (very similar but no identical number pairs). The dependent measure is d', a signal detection index of sensitivity and response bias.

3) Trail Making Test A (Reitan & Wolfson, 1985): In the TMT A, a measure of attention, there are 25 circles that are numbered 1 – 25, and the patient should draw lines to connect the

numbers in ascending order as quickly as possible. The dependent measure is the total time taken to complete the task.

4) Trail Making Test B (Reitan & Wolfson, 1985): The TMT B, a measure of executive functioning, requires the subject to connect numbers and letters in an alternating pattern (1-A-2-B-3-C, etc.) as quickly as possible. The dependent measure is the total time taken to complete the task.

Data Analysis

Missing Data

One hundred and twelve patients were randomized to treatment with either nortriptyline or sertraline. Forty-nine patients were missing all neuropsychological data across the two time-points (baseline and week 12) and were excluded from this study. No differences between those patients with neuropsychological data (n=63) and those without neuropsychological data (n=49) were detected on any clinical or demographic variable. To accommodate missing data for the remaining sample (n=63), we used the multiple imputation (Schafer & Olsen, 1998) procedure in SPSS. Multiple imputation replaces missing data with a set of plausible values based on all variables in the working dataset, which includes demographic, clinical outcome, and neuropsychological test variables. To capture the uncertainty in the estimated values, multiple imputation is conducted several times yielding similar but not identical datasets. This report is based on five imputed data sets, which is sufficient to obtain excellent results unless rates of missing data are exceptionally high (Schafer, 1999). The five imputed data sets are analyzed separately using standard statistical analyses. Results from the analyses are then combined using

Rubin's rules (Schafer & Graham, 2002; Schafer & Olsen, 1998) to generate valid statistical inferences that reflect uncertainty due to missing values and improve the accuracy of the results.

Statistical Analyses

Prior to testing for differences in change in neuropsychological test performance, we used simple and logistic regression in SPSS to test for differences at baseline between the two treatment conditions as well as the four treatment condition by responder status groups (see below). There were no differences on age, education, gender, baseline depression severity, responder status, or on any of the neuropsychological tests when comparing the two (treatment condition) and four (responder status by treatment condition) patient groups. Therefore, we did not adjust for demographic, clinical, or neuropsychological tests in the subsequent analyses.

To test whether antidepressant medication (sertraline or nortriptyline) had an impact on cognition, pre- and post-treatment performance on each of the neuropsychological tests were compared using paired t-tests. Independent samples t-tests were used to determine whether change in cognitive performance within each treatment condition depended on responder status; in this model, change scores were computed for each neuropsychological test (t2-t1) and used as the outcome variable and responder status was treated as the independent variable. We next tested for differences in change in neuropsychological test performance between the two treatment conditions using an independent samples t-test. In these analyses, treatment condition (nortriptyline=0, sertraline=1) was treated as the independent variable and the change score as the outcome variable. Finally, to test whether change in neuropsychological test performance between treatment conditions depended on responder status, we used a dummy-coded variable to designate the four patient groups (sertraline responders, sertraline non-responders, nortriptyline

responders, and nortriptyline non-responders). Multiple regression was used and the neuropsychological test change scores were again treated as the outcome variable.

The partial or regressed change approach to two time point data is often recommended (J. Cohen, et al., 2003). In this procedure, the endpoint neuropsychological test score is treated as the outcome variable and the baseline test score is treated as a covariate. This effectively removes all correlation of the endpoint score from the baseline score and represents an improvement over simple change scores (subtracting baseline from endpoint) which tend to overcorrect the endpoint score by the baseline score due to unreliability of measurement (J. Cohen, et al., 2003). We used a change score model in order to be consistent throughout our statistical analyses and to facilitate the presentation of results. Furthermore, conducting the analyses using both strategies did not yield substantively different findings. Throughout our analyses, significance tests were evaluated at the 5% level.

RESULTS

Descriptive Statistics

Table 3 presents baseline demographic and clinical characteristics of the total sample (n=63) and sertraline and nortriptyline subgroups. The average study participant was 64 years old and completed about 4 years of college. Approximately 60% of the sample were women, average baseline depression severity was 24.37 on the 24-item HRSD, and 43% of the sample were classified as responders. The average MMSE score of the sample at baseline was 27.71.

Table 4 presents complete case pre- and post-treatment data for all neuropsychological tests by medication group and responder status. As can be seen from Table 4, test scores remained relatively stable in both treatment conditions and in the treatment condition by

responder status groups with the exception of scores on the Buschke SRT, CPT and TMT B. Qualitatively, nortriptyline responders showed no improvement on the Buschke SRT as compared to patients treated with sertraline or nortriptyline non-responders. On the TMT B, nortriptyline responders seemed to decline as compared to the improvement seen among nortriptyline non-responders. Finally, both nortriptyline and sertraline responders appeared to improve on the CPT whereas non-responders across treatment conditions declined. To formally test these apparent differences in change based on complete case data, we ran a series of analyses using change scores on each test as the outcome variable and accommodated missing data using multiple imputation.

Hypothesis Testing

We first compared pre- and post-treatment neuropsychological test scores within each treatment condition to address whether antidepressant medication has an impact on cognitive functioning. Within the sertraline condition, significant change occurred on the Buschke SRT [$t(2082)=-6.30$, $p=.001$]. No change was observed on the other neuropsychological tests. Within the nortriptyline condition, no significant change was observed on any of the neuropsychological tests. These results are graphically displayed in Figure 2, which depicts pre- to post-treatment change in cognitive performance within each treatment condition across the seven neuropsychological tests. For variables in which good performance was represented by lower values (e.g., Trail Making Test A and B), *z*-scores were reversed so that a high *z*-value represented a good performance for those measures.

Next, we examined whether change in cognitive functioning within treatment depended on response. In the sertraline condition, 33% of patients responded compared to 53% in the

nortriptyline condition ($\chi^2(1)=2.57$, p=.11). Change in cognitive performance from baseline to endpoint on the Buschke SRT did not depend on response to sertraline [t(40)=-0.54, p=.60]. Although there were no statistically significant changes in cognition within the nortriptyline condition, we nevertheless examined whether there were differences depending on response; however, no significant findings were observed.

We next examined whether there were differences in change in cognitive functioning between the nortriptyline and sertraline conditions. There was a statistically significant difference between the sertraline and nortriptyline conditions at endpoint on the Buschke SRT. Although both treatment conditions improved on the Buschke SRT from baseline to endpoint, patients treated with sertraline improved significantly more than patients treated with nortriptyline [t(8803)=-2.44, p=0.02]. No other comparisons between sertraline and nortriptyline were statistically significant.

Finally, we examined whether change in cognitive functioning between treatment conditions depended on responder status. Patients who responded on sertraline improved significantly more on the Buschke SRT than patients who responded on nortriptyline [B=-15.73, SE=6.14, t=-2.56, p=0.01] but no more than sertraline non-responders or nortriptyline non-responders. No other comparisons were statistically significant.

DISCUSSION

The purpose of the present study was to examine the impact of nortriptyline and sertraline on change in cognitive functioning of depressed older adults using data from a twelve-week, double-blind, randomized clinical trial. Within this multi-domain assessment, we addressed two interrelated sets of questions: 1) Within treatment condition, does cognitive functioning change

from pre- to post-treatment and does it depend on medication response? 2) Between treatment conditions, is there a differential effect of medication on change in cognition and does it depend on medication response?

We found that patients treated with sertraline showed a significant change in verbal learning from pre- to post-treatment, but this change did not depend on responder status. Therefore, taking sertraline improved memory regardless of whether the patient responded to the medication. Of course, this effect could be because of sertraline or non-specific factors associated with participating in a clinical trial. However, improvement in memory (or any other cognitive domain) was not observed in the nortriptyline condition. Therefore, we can infer that memory improvement is likely to be associated with taking sertraline because we did not see a similar effect in the nortriptyline condition, which shared the same non-specific factors. This finding is consistent with previous reports showing improvement in memory on sertraline in non-depressed older adults (Furlan, et al., 2001; Schmitt, et al., 2001).

We next compared change in cognitive functioning between the nortriptyline and sertraline conditions and found that patients treated with sertraline showed significantly more improvement in verbal learning compared to patients treated with nortriptyline. This finding is consistent with previous studies comparing the impact of sertraline to nortriptyline on the cognitive functioning of older adults. For example, treatment with sertraline in the geriatric depressed led to greater improvement in verbal learning (as measured by the Shopping List Task) when compared to treatment with nortriptyline (Doraiswamy, et al., 2003). In another study of depressed older adults, sertraline treatment led to improvement in verbal learning (as measured

by the Shopping List Task) whereas nortriptyline treatment led to a mild decline over 12 weeks of treatment (Finkel, Richter, & Clary, 1999).

Finally, we compared change in cognition as a function of medication condition and responder status and found that sertraline responders showed significantly more improvement in verbal learning compared to nortriptyline responders but no more than sertraline non-responders or nortriptyline non-responders. To our surprise, nortriptyline responders were the only treatment by responder status group to show no improvement in verbal learning from baseline to endpoint.

The most cogent explanation for this unexpected finding is that memory improvement is blocked by the anticholinergic effect of nortriptyline. Tricyclic antidepressants have five times the anticholinergicity of SSRIs in older adults (Pollock et al., 1998). More specifically, sertraline has been found to produce no anticholinergic activity at therapeutic doses whereas nortriptyline demonstrates a moderate anticholinergic activity (5-15 pmol/ml) (Chew, et al., 2008). Furthermore, drug-induced anticholinergic activity has been associated with cognitive impairment in older adults (Oxman, 1996); greater anticholinergic effect was significantly (negatively) associated with endpoint cognitive improvement (in verbal learning and processing speed) in depressed older adults (Doraiswamy, et al., 2003). In another study of the geriatric depressed, higher plasma nortriptyline concentration over 6 weeks of treatment was associated with poorer free recall but better affective outcome (Young et al., 1991) indicating that the therapeutic and cognitive effects of nortriptyline may have different mechanisms. Even very low anticholinergic activity has been associated with specific cognitive deficits. In one study, depressed elderly subjects with serum anticholinergic activity performed more poorly in verbal learning than did those without anticholinergic activity (Nebes et al., 1997). However, plasma

drug levels of nortriptyline were blood-controlled in the present study, and it is unlikely that the anticholinergic effect differentially impacted the cognitive functioning of responders and non-responders on nortriptyline.

Another possible explanation for the unexpected finding is that the nortriptyline responder group had a disproportionately high number of cognitively impaired patients. However, the average MMSE score at baseline for the sample was 27.01, which is within normal limits and there was no significant difference in MMSE score between the four treatment by responder status groups at baseline. Similarly, there were no significant differences in the number of patients with memory impairment (a score $\leq$ 1.5 standard deviations below the mean on the Buschke SRT) between the nortriptyline responder group (3 of 16 patients with memory impairment) than the other patient groups. There were also no differences between the four groups in age or education. It is also possible that the overall medical burden was higher among nortriptyline responders compared to the other three groups. The interaction between medical illness and antidepressant medication could adversely affect cognitive functioning. However, there were no significant differences in medical burden (as assessed by the CIRS-G) between the four groups.

This study should be interpreted in the context of several limitations. First, the sample size was relatively small and this study was not specifically powered to detect between drug differences in cognitive function by responder status. The responder analyses should therefore be interpreted with caution. Furthermore, the small sample size did not allow for a test of the interaction between depressive subtype, responder status, and treatment condition on change in cognitive function nor did it allow us to take into account differences due to depressive subtype

(melancholia vs. non-melancholia). Second, the findings of this study may have been only a statistical anomaly. These were post-hoc analyses involving a multiplicity of statistical tests. Therefore, the findings are intended to be hypothesis generating only and are clearly in need of replication. Third, although multiple cognitive domains were examined, the assessment within each domain was relatively limited. Fourth, there was no placebo control group making it difficult to determine whether the observed improvement in verbal learning was nothing more than a practice effect. However, treatment with sertraline led to an improvement on the Buschke SRT that exceeded the improvement observed in patients randomized to placebo in our previous study (Culang, et al., 2009) (¾ and ¼ of a standard deviation, respectively), suggesting there was significant change from pre- to post-treatment beyond a practice effect.

Table 3. Baseline clinical and demographic characteristics of the total sample, the sertraline and nortriptyline subsamples, and the four patients groups classified by treatment condition and responder status

Variable	Total Sample (n=63)	Sertraline (n= 33)	Nortriptyline (n= 30)	Sertraline Responders (n=11)	Sertraline Non-responders (n=22)	Nortriptyline Responders (n=16)	Nortriptyline Non-responders (n=14)
Age	64.19 (8.47)	64.85 (8.83)	63.47 (8.15)	65.82 (9.19)	64.36 (8.82)	63.25 (8.94)	63.71 (7.47)
Women (%)	60	61	60	45	68	63	57
Education	16.17 (2.42)	16.29 (2.14)	16.04 (2.73)	17.40 (.52)	15.67 (2.45)	16.23 (2.35)	15.83 (3.19)
HRSD Baseline	24.37 (4.87)	23.91 (4.38)	24.87 (5.39)	23.18 (4.56)	24.27 (4.36)	24.81 (4.45)	24.93 (6.47)
Responder (%)	43	33	53	100	0	100	0

Table 4. Unadjusted neuropsychological test performance scores at baseline and endpoint of the sertraline and nortriptyline subsamples and the four patient groups classified by treatment condition and responder status (complete case data)

NP Test	Sertraline (n=33)		Nortriptyline (n=30)		Sertraline Responders (n=11)		Sertraline Non-responders (n=22)		Nortriptyline Responders (n=16)		Nortriptyline Non-responders (n=14)	
	PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST
MMSE	27.9 (2.6)	28.3 (1.8)	27.6 (2.9)	28.0 (2.8)	28.5 (2.1)	28.6 (2.3)	27.6 (2.8)	27.8 (2.0)	27.1 (3.4)	28.0 (2.9)	28.1 (2.2)	29.2 (.8)
TMT A	48.2 (36.4)	48.6 (24.3)	49.9 (20.6)	51.0 (20.7)	38.3 (9.8)	36.8 (12.1)	53.1 (43.5)	61.5 (28.1)	50.2 (21.5)	55.1 (21.7)	49.5 (20.4)	40.1 (13.7)
TMT B	106.4 (52.5)	101.8 (49.4)	109.5 (63.9)	126.2 (80.7)	89.6 (49.0)	90.2 (29.5)	114.8 (53.3)	115.9 (58.6)	118.2 (72.7)	143.0 (87.4)	100.2 (54.1)	81.4 (34.1)
CPT	561.8 (100.6)	578.5 (98.3)	569.0 (107.0)	548.2 (99.3)	573.1 (80.9)	562.4 (91.5)	556.4 (110.6)	601.5 (110.4)	573.3 (117.1)	539.9 (102.7)	565.1 (101.9)	575.3 (95.5)
Purdue Pegboard	10.1 (3.1)	10.0 (3.1)	10.7 (3.1)	11.2 (3.8)	10.9 (3.3)	10.1 (3.5)	9.7 (3.0)	9.9 (2.9)	11.0 (3.4)	10.9 (4.0)	10.3 (2.8)	11.8 (3.5)
Buschke SRT	102.2 (16.4)	121.6 (9.6)	109.0 (23.2)	114.3 (21.4)	105.4 (15.1)	122.7 (19.9)	100.5 (17.1)	120.4 (12.9)	112.1 (18.0)	112.2 (24.1)	105.6 (19.9)	119.8 (11.4)
Stroop	.5 (.3)	.6 (.3)	.5 (.3)	.4 (.3)	.5 (.3)	.4 (.2)	.6 (.4)	.7 (.3)	.4 (.4)	.4 (.3)	.5 (.3)	.4 (.2)

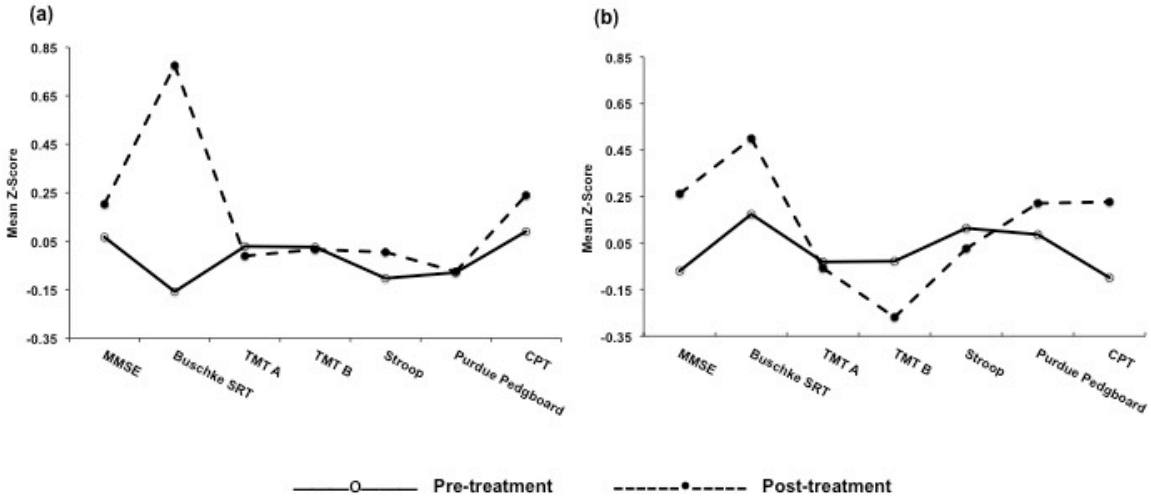

Figure 2. Change in cognitive performance from pre- to post-treatment in the (a) sertraline condition and (b) nortriptyline condition across seven neuropsychological tests

STUDY 3

THE IMPACT OF VASCULAR DEPRESSION ON CHANGE IN COGNITIVE FUNCTIONING FOLLOWING ACUTE ANTIDEPRESSANT TREATMENT

INTRODUCTION

The vascular depression hypothesis proposes that some geriatric depressives syndromes are predisposed, precipitated, or perpetuated by cerebrovascular disease (Alexopoulos, Meyers, Young, Campbell, et al., 1997). This hypothesis originated from the finding that patients with late-onset depression had higher rates of hyperintensities on T2-weighted brain MRI when compared with patients with early-onset depression (Hickie et al., 1995; Krishnan, et al., 1997; Salloway, et al., 1996). It was further observed that patients with late-onset depression and MRI hyperintensities demonstrated greater neuropsychological impairment than patients with early-onset depression (Alexopoulos, Meyers, Young, Kakuma, et al., 1997; Lesser, et al., 1996; Salloway, et al., 1996). Greater severity of hyperintensities was also associated with poor response to treatment (Hickie, et al., 1995). Therefore, a coherent hypothesis of vascular depression began to emerge (Alexopoulos, Meyers, Young, Campbell, et al., 1997; Alexopoulos, Meyers, Young, Kakuma, et al., 1997; Krishnan, et al., 1997; Krishnan & McDonald, 1995; Steffens & Krishnan, 1998) in which late-onset depression was seen as a consequence of structural damage to frontal subcortical systems due to cerebrovascular disease, which in turn led to executive dysfunction and poor antidepressant treatment response (see Figure 3).

Not surprisingly, vascular depression may represent a cognitively vulnerable subtype of LLD. For instance, one study found that patients with MRI-defined vascular depression demonstrated significantly worse performance across measures of executive functioning and nonverbal memory when compared to nonvascular depressed patients (Potter, McQuoid, Steffens, Welsh-Bohmer, & Krishnan, 2009). Although this is the only study to date that has examined this issue among patients classified as vascular depressed (as defined by MRI

hyperintensities), numerous other studies have shown that depressed older adults with white matter hyperintensities demonstrate worse performance on measures of executive functioning and processing speed compared to both age-matched controls and depressed older adults without such lesions (Kramer-Ginsberg, et al., 1999; Lesser, et al., 1996; Sheline et al., 2008).

Patients with vascular depression may also respond poorly to antidepressant treatment as several studies have found an association between MRI hyperintensities and poor medication response among depressed older adults (Alexopoulos, Kiosses, Choi, Murphy, & Lim, 2002; Alexopoulos et al., 2008; Gunning-Dixon et al., 2010; Hickie, et al., 1995; Navarro et al., 2004; Simpson, Baldwin, Jackson, & Burns, 1998; Sneed et al., 2011; Taylor, Steffens, et al., 2003). Specifically, one study found that depressed older adults classified as having high deep white matter hyperintensity load were approximately 7 times more likely not to remit following antidepressant treatment compared to patients classified as having low deep white matter hyperintensity load (Sneed, et al., 2011). In another recent study, depressed older adults who failed to remit following antidepressant treatment had significantly greater MRI hyperintensity burden than both patients who remitted and age-matched controls (Gunning-Dixon, et al., 2010). Furthermore, MRI hyperintensity burden did not differ between depressed patients who remitted and elderly comparison subjects.

As the findings of Study 1 suggest (Culang, et al., 2009), there may be a deleterious interaction between medication non-response and the impact that antidepressant medication has on the cognitive functioning of older adults. Taken together with the definition of vascular depression (i.e., MRI hyperintensities) and the executive dysfunction that characterizes the subtype, vascular depression may represent a subtype of LLD that is particularly vulnerable to

cognitive decline. It is therefore important to determine the impact that antidepressant medication can have on cognitive functioning when treating this population.

We will examine this issue using data from an 8-week, multi-ethnic, open-treatment trial of antidepressant medication in depressed older adults (PI: Dr. Sneed). The principle aim of the clinical trial was to test the association between African Americans and vascular depression. This is based on the fact that African Americans have higher rates of vascular risk factors than Caucasians, which may put them at greater risk for vascular depression. This issue will therefore be addressed within the present study, which has the following aims and hypotheses:

Aim 1: To examine baseline difference between patients with and without vascular depression on demographic and clinical variables.

Hypothesis 1: Vascular depression will be overrepresented among a clinical sample of African Americans.

Hypothesis 2: Patients with vascular depression will demonstrate worse performance on measures of executive functioning and psychomotor speed than patients with nonvascular depression.

Aim 2: To determine differences in response rates to antidepressant treatment between patients with and without vascular depression.

Hypothesis 1: Patients with vascular depression will respond less well to antidepressant medication than patients with nonvascular depression.

Aim 3: To determine the impact of medication on cognitive functioning by vascular depression status and whether the observed change in cognitive functioning (if any) depends on response to treatment.

Hypothesis 3: Patients with vascular depression will show less change (i.e., improvement) or a decline in performance across measures of executive functioning and psychomotor speed over the 8-week trial when compared to patients with nonvascular depression.

METHODS

Procedure

This study was a 2-site, multi-ethnic, open 8-week trial of antidepressant medication in older adults with depression. At the screening visit, a comprehensive psychiatric evaluation, including a SCID, HRSD, and MMSE, and a medical history were performed to confirm diagnosis and assess eligibility. If the patient was considered to have an affective disorder, a SCID was completed to document diagnostic status.

Patient were considered eligible if they were a) male or female 50 years or older, b) current diagnosis of major depression disorder, dysthymia, or depression NOS, c) score of ≥ 14 on the 24-item HRSD at initial visit, and d) willing and able to give informed consent, complete neuropsychological testing, and complete the medical exam, electrocardiogram, blood tests, and urine screen. Exclusion criteria were a) bipolar disorder, obsessive compulsive disorder, psychotic disorder, current substance abuse or dependence within past year, b) meets criteria for psychotic depression, c) current suicide intent or serious attempt within past six months, d) probable Alzheimer's disease or vascular dementia based on NINCDS/ADRDA criteria, e) MMSE score < 24, f) in psychotherapy less than 3 months, g) currently taking Triptans, h) acute, severe or unstable medical illness, and i) MRI contraindications.

If a patient met inclusion and exclusion criteria, informed consent was obtained and the patient entered the treatment protocol. Patients who were on psychotropic medication at the time of the initial evaluation entered a washout period. The baseline assessment included a physical examination, an electrocardiogram, and routine blood work. The patient completed a BDI-II and the study physician completed the CIRS-G and CGI. Finally, patients received baseline structural MRI and neuropsychological testing.

Upon completion of the baseline evaluation, the patient began open treatment with either citalopram or escitalopram. If a patient failed to respond to an adequate trial of escitalopram or citalopram in the current depressive episode, he or she was alternatively treated with duloxetine or desvenlafaxine. Treatment with citalopram began at 20 mg/day for the first 4 weeks. At the end of 4 weeks, patients who did not meet remission criteria (HRSD < 8) had their citalopram dose increased to 40 mg/day for the remainder of the trial (4 weeks). If treated with escitalopram, the dosage began at 10mg/day for 4 weeks and was increased to 20mg/day at the end of week 4 if the patient did not meet remission criteria. Duloxetine dosing began at 30mg/day for the first week followed by increasing doses up to a maximum of 120mg/day, as was clinically determined by the study physician. Desvenlafaxine dosing began at 50mg/day for 4 weeks and then was increased to 100mg/day at the end of week 4.

At each weekly visit, depression severity was evaluated using the HRSD and BDI-II. Global improvement ratings were also collected (CGI). At week 4 and 8, follow-up neuropsychological testing was completed.

Neuropsychological Test Battery

The test battery included a total of ten measures that assessed global cognitive function, attention, memory, language, executive functions, psychomotor speed, and visuospatial functioning. Since the primary goal of this study was to examine change in executive functioning and psychomotor speed between vascular depressed and nonvascular depressed patients, we only included six of the ten neuropsychological measures in our analyses. Three of the six tests (SRTT, CRT, and Stroop) were presented on a Macintosh laptop computer and were written in the PsyScope programming language (J. D. Cohen, et al., 1993) whereas the other three tests (DRS-I/P, TMT A and TMT B) were administered by hand. The CRT and Stroop were previously described in detail (refer to Procedures, Study 1) as were the TMT A and TMT B (refer to Procedures, Study 2; mean reaction time was log transformed for use in these statistical analyses). The remaining neuropsychological tests are described below:

1) Mattis Dementia Rating Scale –Initiation and Perseveration subtest (Mattis, 1989): The DRS-I/P subscale consists of items that assess a) verbal generative fluency (e.g., naming supermarket items over 1 minute), b) auditory articulation of vowel and consonant patters, c) double alternating motor movements, and c) simple graphomotor skills (e.g., XOXO). The total possible score is 37.

2) Simple Reaction Time Test: The SRTT is a test which measures simple reaction time through delivery of a known stimulus to a known location to elicit a known response. The only uncertainty is with regard to when the stimulus will occur, by having a variable interval between the trial response and the onset of the stimulus for the next trial. In this task, as soon as subjects see the X on the screen, they must press the '0' on the keypad. A total of 60 items are presented

and median reaction time is computed from all correct individual responses. The median reaction time was log transformed for use in statistical analyses.

MRI and VD Classification

T2-weighted FLAIR images were acquired at baseline and evaluated for the presence of deep white matter hyperintensities. The severity of lesions was graded by a neuroradiologist using the Fazekas modified Coffey Rating Scale for signal hyperintensities (Krishnan, et al., 1997). Deep white matter hyperintensities were defined as abnormalities in the frontal, parietal, temporal, or occipital lobes, and scored as 0 (absent), 1 (punctate foci), 2 (beginning confluence of foci), and 3 (large confluent areas). Participants were classified as having vascular depressed if they received a score of 2 or more on their deep white matter hyperintensity rating (Krishnan, et al., 1997; Sneed, Rindskopf, et al., 2008).

Data Analysis

Missing Data

To accommodate missing data, we used multiple imputation (Schafer & Olsen, 1998) using the Multiple Imputation procedure in SPSS. This report is based on twenty imputed data sets (m =20), which is sufficient to obtain excellent results unless rates of missing data are extremely high (Schafer, 1999). The imputed data sets were analyzed using standard statistical analyses were used to analyze the twenty imputed data sets and results were combined using Rubin's rules (Schafer & Graham, 2002; Schafer & Olsen, 1998).

Statistical Analyses

Descriptive statistics were calculated to characterize the total sample, the vascular depression and nonvascular depression subsamples, and the four patient groups classified by vascular depression and responder status (see below) on all clinical, demographic, and

neuropsychological test variables. Simple and logistic regression analyses as well as chi-square tests of independence were used to examine baseline differences between the vascular depression and nonvascular depression subsamples on demographic and clinical characteristics.

Aim 1

To compare the racial make-up of the vascular depression and nonvascular depression subgroups, we first conducted an omnibus chi-square test. To specifically compare the rate of vascular depression between Caucasian and African American patients, we conducted a follow-up chi-square test on vascular depression (nonvascular depression=0, vascular depression=1) and race (Caucasian=0, African American=1).

To test for differences in neuropsychological test performance at baseline between patients with and without vascular depression, we used a simple regression analysis in which vascular depression was treated as the independent variable (nonvascular depression=0, vascular depression=1) and the given neuropsychological test score as the dependent variable.

Aim 2

To test for differences in treatment response rates between patients with and without vascular depression, we conducted a logistic regression analysis on medication response (50% reduction in HRSD from baseline).

Aim 3

To test for differences in change in neuropsychological test performance, we used data from the multiply imputed data sets and adopted a partial or regressed change approach to analyzing two time-point data (J. Cohen, et al., 2003) (see Study 1 Procedures) using the linear regression procedure in SPSS. According to this approach, the endpoint neuropsychological test

score is treated as the outcome variable and the baseline test score is treated as a covariate. We first tested for differences in endpoint scores between patients with and without vascular depression using a dummy coded variable (nonvascular depression = 0, vascular depression = 1). To test whether change in neuropsychological test performance by vascular depression depends on responder status (50% reduction from baseline HRSD score), we again used a dummy coded variable to designate the four patient groups (vascular depression responders, vascular depression non-responders, nonvascular depression responders, and nonvascular depression non-responders). We adjusted for select demographic variables that are known to have an impact on neuropsychological test performance including age, education, and gender. Each covariate was centered at its respective mean so the intercept corresponded to the mean of the reference group at endpoint and the unstandardized regression weights reflected the difference between the groups included in the model and the reference group (excluded from the model). All significance tests were evaluated at the 5% level.

RESULTS

Descriptive Statistics

Forty-six participants met inclusion and exclusion criteria. Forty-two of these patients received an MRI at baseline. Table 1 presents unadjusted baseline demographic and clinical characteristics of the total sample as well as the vascular depression and nonvascular depression subgroups. Within the total sample, the average study participant was 62 years old (SD=9.4) and completed 3 years of college (SD=2.9). Fifty-two percent of the sample was women, the average depression score at baseline was 23.4 (SD=5.5) on the 24-item HRSD, and the average MMSE

score was 28.5 (SD=1.3). Of the 42 patients, 30 (71%) were administered escitalopram, 9 (21%) citalopram, 2 (5%) duloxetine, and 1 (2%) desvenlafaxine.

As can be seen in Table 1, 16 (38%) patients were classified as vascular depression and 26 as nonvascular depression (62%). Patients with vascular depression were significantly less educated than those with nonvascular depression [B=-2.0, SE=.89, 95% CI -3.72, -.25, p=.03]. Patients with vascular depression were also significantly more likely to be female [B=1.57, SE=.70, 95% CI 1.21, 19.08, p=.03]. We therefore adjusted for education and gender in all neuropsychological test analyses. There were no statistically significant differences in age, baseline depression severity or medical burden between vascular and nonvascular depressed patients.

Hypothesis Testing

Aim 1

We first tested the association between vascular depression and race. The omnibus test revealed a statistically significant difference in the racial make-up of the vascular depression and nonvascular depression subgroups (p=.001, Fisher's Exact Test). Specifically, the vascular depression subgroup (n=16) was composed of 2 Caucasians, 11 African Americans, 2 Hispanics and 1 biracial individual whereas the nonvascular depression subgroup (n=26) was composed of 18 Caucasians, 7 African Americans, and 1 Hispanic. A follow-up test (2x2 chi-square) revealed a significant difference in the rate of vascular depression among African Americans and Caucasians ($\chi^2(1)=11.0$, p=.001). Specifically, 11 of 18 or 61% of African Americans in this sample had vascular depression whereas 2 of 20 or 10% of Caucasians were classified as vascular depressed.

Next, we compared baseline neuropsychological test performance between the vascular and nonvascular depressed subsamples. Table 6 presents unadjusted pre- and post-treatment neuropsychological test scores of the vascular depression and nonvascular depression subsamples and the four patients groups classified by vascular depression and responder status. Adjusting for education and gender, patients with vascular depression demonstrated significantly worse performance on the Stroop [B=.64, SE=.28, 95% CI .08, 1.19, p=.02, *d*=.93], DRS-I/P subtest [B=-2.53, SE=.80, 95% CI -4.09, -.96, p=.002, *d*=1.01], and CRT [B=.14, SE=.07, 95% CI 0.0, .28, p=.05, *d*=.66] at baseline when compared to patients with nonvascular depression.

Aim 2

We next examined differences in medication response rates between patients with and without vascular depression. Seven of 16 (44%) patients with vascular depression responded to antidepressant treatment whereas 19 of 26 (73%) patients with nonvascular depression responded. This 29% difference in response rates, however, was not statistically significant [B=-.98, SE=.70, 95% CI .37, .09, p=.16].

Aim 3

Finally, we examined whether change in cognitive functioning following antidepressant treatment depended on vascular depression and responder status. Adjusting for age, education, gender, and baseline performance, there were no statistically significant difference on endpoint performance between patients with and without vascular depression on any neuropsychological test.

When comparing change in cognitive functioning among the four patient groups classified by vascular depression and responder status, there was also a statistically significant

difference between the four patient groups on the TMT B at endpoint. Specifically, both the vascular depressed [B=44.08, SE=22.01, 95% CI .72, 87.45, p=.05, *d*=.64] and nonvascular depressed responders [B=41.35, SE=17.99, 95% CI 5.99, 76.70, p=.02, *d*=1.67] improved from baseline to endpoint, which was significantly different from the decline observed among the vascular depressed non-responders. Qualitatively, the vascular depressed non-responders were the only patient group to decline from baseline to endpoint on TMT B. We further controlled for baseline TMT A performance in these analyses to see if the effect was mediated by differences in processing speed (rather than executive functioning per se), but this did not substantively change the results. No other comparisons were statistically significant.

DISCUSSION

The overall goal of the present study was to examine change in cognitive functioning following acute antidepressant treatment using data from an eight-week, multi-ethnic, open-treatment trial of antidepressant medication. We addressed three aims: 1) examine baseline differences between patients with and without vascular depression on key clinical and demographic variables; 2) determine differences in medication response rates between patients with and without vascular depression; and 3) determine the impact of medication on cognitive functioning by vascular depression and responder status.

First, we tested the association between vascular depression and African Americans and found the rate of vascular depression to be significantly higher among a clinical sample of African Americans than Caucasians. Specifically, 61% of African Americans and 10% of Caucasians were classified as having vascular depression. This discrepancy is consistent with previous findings that document higher rates of vascular risk factors in African Americans than

Caucasians. For instance, African Americans have higher rates of hypertension (Kramer et al., 2004), diabetes (Brancati, Kao, Folsom, Watson, & Szklo, 2000), and obesity (Hedley et al., 2004) than Whites. Not surprisingly, they also have higher rates of cardiovascular disease compared to Whites (AHA, 2007) and cardiovascular disease is the leading cause of death in African Americans (AHA, 2005). Finally, stroke is 1.5 times more prevalent in African Americans at every age group (Kissela et al., 2004), which significantly increases risk for the development of vascular dementia. It stands to reason that the high rates of vascular risk factors also leaves African Americans at higher risk for vascular depression than Caucasians. This hypothesis is substantiated by the findings of this study, which is the first to document the association between vascular depression and African Americans.

Our second finding was that patients with vascular depression demonstrated worse performance on two measures of executive functioning (Stroop, DRS-I/P) and one measure of psychomotor speed (CRT). This is consistent with previous reports that document a negative association between white matter hyperintensities and both psychomotor speed (Hickie, et al., 1995) and executive ability (Lesser, et al., 1996) among depressed older adults. Furthermore, in the one study to date that has examined the neuropsychological profile of MRI-defined vascular depression (Potter, et al., 2009), the authors found that patients with vascular depression exhibited worse performance on measures of executive functioning (i.e., working memory and set-shifting) after controlling for age, depression severity and medical burden than patients with nonvascular depression.

The observed neuropsychological profile of the vascular depression subgroup is also consistent with the vascular depression hypothesis as it reflects the proposed underlying

cerebrovascular pathology of the subtype. In particular, functional deficits in vascular depression have been hypothesized to reflect lesions within frontostriatal circuits that are integral to emotion regulation and many cognitive functions, including executive skills and processing speed (Alexopoulos, Meyers, Young, Campbell, et al., 1997). In fact, studies have documented neuroimaging evidence of cerebrovascular irregularities in the form of deep white matter hyperintensities and/or reduced volume in frontal and subcortical regions (Artero et al., 2004; Firbank, Lloyd, Ferrier, & O'brien, 2004; Greenwald et al., 1998; Hannestad et al., 2006; Taylor et al., 2007). Previous reports of morphometric studies in LLD have also described neuronal abnormalities within the prefrontal cortex and striatum (Khundakar, Morris, Oakley, McMeekin, & Thomas, 2009; Rajkowska, Miguel-Hidalgo, Dubey, Stockmeier, & Krishnan, 2005). In support of the vascular depression hypothesis, the pattern of test performance among vascular depressed patients in this study is consistent with disrupted frontal-subcortical circuitry.

Although this study documented a 29% difference in response rates to antidepressant medication between vascular and nonvascular depressed patients, this difference was not statistically significant. Seventy-three percent of the nonvascular depression group responded whereas 44% of the vascular depression group responded. Although statistically nonsignificant, these findings are consistent with the idea that patients with vascular depression respond less well to antidepressant medication than patients with nonvascular depression. However, they also suggest that patients with vascular depression may respond better to an initial trial of medication than is commonly reported in the literature (Gunning-Dixon, et al., 2010; Sneed, et al., 2011). It should be noted, however, that the response rate of the vascular depression subgroup (44%) was relatively lower than that in other open treatment trials (63%) (Karp et al., 2010; Wohlreich,

Mallinckrodt, Watkin, & Hay, 2004) in geriatric depression indicating that, while they do respond, their response may not be as robust as patients with nonvascular depression. Future studies should examine whether augmenting antidepressant therapy with a non-pharmacological treatment such as problem solving therapy is effective in the treatment of vascular depression.

Finally, we examined change in cognitive functioning and found that vascular depressed non-responders demonstrated a decline in one aspect of executive functioning (i.e., rapid set-shifting) relative to the improvement seen across the other patient groups. This finding is consistent with a recent study, which found that higher vascular risk scores predicted less change in executive functions among depressed older adults treated with sertraline (Barch et al., 2012). Similarly, other studies have documented an association between baseline MRI hyperintensities and subsequent cognitive decline (De Groot, et al., 2002; Kohler, et al., 2010). Based on these past studies, one possible explanation for our finding is that the vascular depressed non-responders had greater severity of MRI hyperintensities than the vascular depressed responders. However, there were no significant differences in deep white matter or total hyperintensity load between the two groups. Importantly, no prior study has examined whether the impact of vascular disease on change in cognitive functioning depends on response to treatment.

Another possible explanation for this finding is that the vascular depressed non-responder group had greater risk factors for neuropsychological impairment than the other patient groups. Not surprisingly, age, education, age of onset for depression, depression severity, and medical burden have been associated with neuropsychological deficits in LLD (Boone et al., 1995; Butters, et al., 2004; King, Caine, & Cox, 1993; Lesser, et al., 1996; Lesser et al., 1991; Potter, et al., 2009). However, there were no statistically significant differences between the vascular

depressed non-responders and the other three patient groups on baseline depression severity (HRSD), medical burden (CIRS-G), years of education, or age of onset for depression. Although vascular depressed non-responders were significantly older than vascular depressed responders, we controlled for age across analyses.

This study should be interpreted in the context of several limitations. First, the sample size was small and this study was not specifically powered to detect between subtype differences in cognitive functioning by responder status. Therefore, responder analyses should be interpreted with caution and the findings are in need of replication in a larger sample. Second, the small sample size did not allow for a test of the interaction between depressive subtype, responder status, and medication type/dose on change in cognitive function. Participants were enrolled in an open-treatment program in which treatment regimens differed. Although most participants were taking an SSRI, it is possible that variation in specific agents may have impacted change in cognitive functioning. Third, there was no healthy age-matched comparison group making it difficult to determine the extent (if any) of baseline neurocognitive "impairment" among the vascular depression subgroup. Finally, the rate of response among the nonvascular depressed group (73%) was significantly higher than that observed in other open treatment (63%) and comparator trials (60%) in geriatric depression. Although the reason for this discrepancy is unclear, one possible explanation may be that our study included patients with dysthymic disorder, depressive disorder NOS, and major depressive disorder whereas other comparable studies in LLD limited their sample to those with major depressive disorder.

In conclusion, the findings of this study suggest that vascular depression is associated with African American status and frontal systems dysfunction, which is consistent with the

vascular depression hypothesis. Change in cognitive functioning by diagnostic subgroup depended on responder status in that vascular depressed non-responders demonstrated a decline in one measure of executive functioning (i.e., set-shifting) relative to the improvement seen across the other patient groups. Finally, contrary to our hypotheses, patients with vascular depression demonstrated somewhat favorable affective outcomes following acute antidepressant treatment. Although the vascular depressed group did not achieve an adequate response to antidepressant treatment, it was higher than expected based on the vascular depression literature (Gunning-Dixon, et al., 2010; Sneed, et al., 2011). Based on the cognitive and affective outcomes of vascular depressed patients in this study, future research may want to examine the effectiveness of augmentation therapy using a combination of antidepressant medication and a non-pharmacological approach (e.g., problem-solving therapy) in the treatment of vascular depression. Alternative treatments that target cognitive deficits may be particularly effective as they may reduce the risk of cognitive decline and extend quality of life.

Table 5. Baseline clinical and demographic characteristics of the vascular depression and nonvascular depression subsamples and the four patient groups classified by vascular depression and responder status (complete case data)

Variable	Total Sample (n=42)	Vascular Depression (n= 16)	Nonvascular Depression (n= 26)	Vascular Depression Responders (n=7)	Vascular Depression Non-responders (n=9)	Nonvascular Depression Responders (n=19)	Nonvascular Depression Non-responders (n=7)
Age	62.3 (9.4)	63.5 (10.8)	61.5 (8.6)	56.3 (9.3)	68.4 (11.3)	60.1 (9.5)	63.5 (9.6)
Women (%)	52	75	38	33	86	38	50
Education	15.0 (2.9)	13.8 (3.0)	15.7 (2.7)	13.3 (1.2)	15.1 (3.0)	15.1 (3.2)	16.0 (2.2)
African American White Hispanic	 43 48 7	 69 13 13	 27 69 4	 71 14 14	 67 11 11	 32 63 5	 14 86 0
HRSD Baseline	23.4 (5.5)	23.6 (7.0)	23.3 (4.5)	19.3 (3.2)	25.1 (6.4)	23.9 (4.0)	20.3 (4.8)
Responder (%)	62	44	73	100	0	100	0

Table 6. Unadjusted neuropsychological test performance scores at baseline and endpoint of the vascular depression and nonvascular depression subsamples and the four patient groups classified by vascular depression and responder status (complete case data)

NP Test	Vascular Depression (n=16)		Non-Vascular Depression (n=26)		Vascular Depression Responders (n=7)		Vascular Depression Non-responders (n=9)		Nonvascular Depression Responders (n=19)		Nonvascular Depression Non-responders (n=7)	
	PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST
Stroop	.47 (.27)	.29 (.24)	.25 (.17)	.25 (.18)	.34 (.21)	.12 (.08)	.53 (.35)	.43 (.24)	.29 (.19)	.25 (.14)	.22 (.14)	.29 (.32)
TMT A	50.51 (22.02)	53.16 (31.26)	36.20 (16.30)	32.53 (12.53)	45.28 (18.53)	46.85 (22.07)	55.60 (24.36)	63.57 (38.56)	43.05 (8.92)	31.88 (11.77)	36.70 (22.19)	36.86 (17.34)
TMT B	158.41 (84.95)	133.09 (64.95)	103.96 (64.66)	80.41 (52.90)	176.36 (94.22)	127.39 (46.33)	156.19 (101.43)	161.61 (59.49)	97.73 (62.28)	74.88 (43.27)	128.43 (105.24)	110.71 (81.26)
DRS I/P	34.27 (3.47)	35.47 (2.39)	36.82 (.85)	36.43 (1.27)	34.20 (4.38)	36.00 (1.73)	33.86 (3.44)	34.75 (2.87)	37.00 (0.0)	36.38 (1.36)	37.00 (0.0)	36.40 (1.34)
SRTT	478.66 (119.47)	470.64 (76.50)	417.42 (67.55)	419.90 (79.00)	516.20 (202.01)	512.70 (81.25)	463.69 (64.12)	427.13 (30.89)	408.39 (58.66)	416.54 (89.27)	402.25 (60.76)	444.63 (33.84)
CRT	963.00 (245.91)	848.39 (184.59)	816.20 (139.94)	733.17 (128.90)	996.30 (328.73)	849.50 (267.85)	1006.25 (226.39)	846.31 (149.21)	810.57 (131.02)	712.62 (109.08)	837.25 (168.63)	838.25 (148.94)

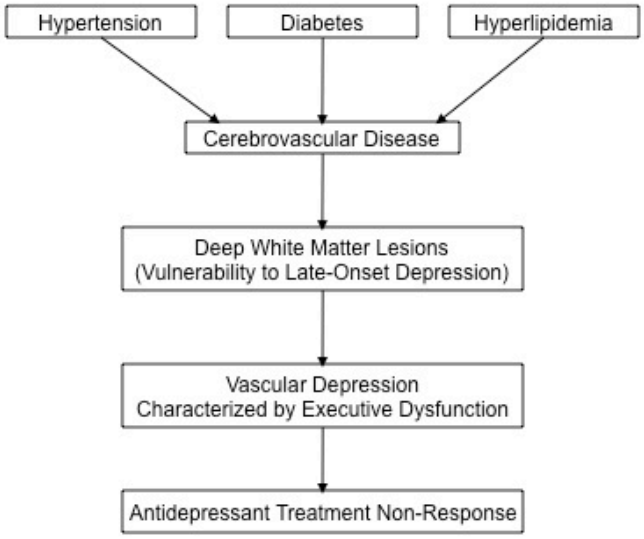

Figure 3. A schematic diagram of the vascular depression hypothesis based on Krishnan and McDonald (1995)

GENERAL DISCUSSION

The purpose of this series of studies was to examine the impact of antidepressant medication on the cognitive functioning of depressed older adults. We explored the following questions within three treatment trials: 1) what impact does medication have on cognitive functioning; 2) is there a differential impact of antidepressant medication on cognitive functioning depending on medication class; 3) is there a differential impact of antidepressant medication on cognitive functioning depending on diagnostic subtype? Finally, across all three studies, we examined whether change in cognitive functioning following antidepressant treatment depended on medication response.

In Study 1, we examined the impact of SSRIs on the cognitive functioning of depressed older adults (age>75) using data from an 8-week, randomized, placebo-controlled trial of citalopram. We found that the placebo condition demonstrated a clear practice effect across the neuropsychological test battery whereas the citalopram condition improved on some tests and declined on others; the pattern of cognitive change from pre- to post-treatment in the medication group, however, depended on responder status. Specifically, medication non-response was associated with a decline in verbal learning and psychomotor speed. Although medication responders demonstrated significant improvement in visuospatial functioning and psychomotor speed when compared to non-responders, this improvement did not exceed that of placebo responders suggesting that the observed change was no more than a practice effect due to repeat testing.

We considered a number of possible explanations for these findings. Specifically, we thought the citalopram group may have had a disproportionately high number of cognitive

impaired patients and/or risk factors for cognitive decline (e.g., cerebrovascular disease), but this was not the case. We also considered that the decline in verbal learning was due to the anticholinergic effects of SSRIs, as the impact of citalopram on the cognitive functioning of older adults remains unclear. Regardless of the mechanism, the findings indicate that SSRIs may have a deleterious effect on some aspects of cognition among patients aged 75 and suggest that depressed older adults should not be maintained on citalopram if they have not responded to an adequate trial in terms of dose and duration.

In study 2, we examined the differential impact of medication class on cognitive functioning using data from a 12-week, randomized, double-blind, parallel-group design comparing sertraline and nortriptyline in the treatment of depressed older adults. We found that patients treated with sertraline showed significantly more improvement in verbal learning compared to patients treated with nortriptyline. When looking at change in cognitive functioning by treatment condition and responder status, we found that sertraline responders showed significantly more improvement in verbal learning compared to nortriptyline responders but no more than sertraline non-responders or nortriptyline non-responders. Unexpectedly, nortriptyline responders were the only treatment by responder status group to show no improvement in verbal learning from baseline to endpoint.

We discussed several potential explanations that could account for this paradoxical finding. We first thought that the improvement in memory among nortriptyline responders may have been blocked by the anticholinergic effect of nortriptyline; however, plasma drug levels of nortriptyline were blood-controlled in this study, and it is unlikely that the anticholinergic effect differentially impacted the cognitive functioning of responders and non-responders on

nortriptyline. Another possibility we considered was that the nortriptyline responder group was older, less educated, more cognitively impaired at baseline, or had greater medical comorbidities, all factors that could have a negative influence on cognitive functioning. However, this was also not the case as there were no significant differences on these variables between the patient groups.

In Study 3, we examined the impact of diagnostic subtype on change in cognitive functioning following acute antidepressant treatment using data from an 8-week open treatment trial of antidepressant medication. Consistent with our hypothesis, we found that vascular depressed non-responders declined on one measure of executive functioning (TMT B) relative to the improvement seen across the other patient groups. Although this suggests that patients with vascular depression may decline in some aspects of cognitive functioning following antidepressant treatment, the findings remain promising in that response to treatment appears to counteract the potential impact of white matter progression on cognition (at least in the acute phase of treatment).

METHODOLOGICAL ISSUES

This dissertation highlighted several important methodological issues that were relevant to all three studies. First, there was missing data, as is typically the case in clinical trials. Aside from multiple imputation, we considered several alternative approaches to accommodate for missing data including mean substitution, regression estimation, listwise deletion and pairwise deletion. However, many of the traditional imputation methods may produce biased results; they ignore the uncertainty of missing data by treating imputed values no different than observed values resulting in underestimated standard errors and overestimated test statistics (Allison,

2001). Last observation carried forward, for example, makes assumptions (e.g., patient response is constant from the last observation to the end of the trial) that can lead to biased results (Mallinckrodt, Kaiser, Watkin, Molenberghs, & Carroll, 2004). Complete case analysis or deletion methods are also problematic as they result in discarded data and a significant loss of power. Ultimately, we found that multiple imputation (Schafer & Olsen, 1998) was the most effective method that gave us the flexibility to perform the statistical analyses that we felt were most appropriate to address our aims. Unlike many other imputation methods, multiple imputation accounts for uncertainty by obtaining several imputed datasets, analyzing each dataset using standard statistical analyses, and combining the results to generate valid statistical inferences with greater accuracy than traditional methods (Schafer, 1999; Schafer & Graham, 2002; Schafer & Olsen, 1998).

The second issue we encountered was how to analyze two-time-point neuropsychological test data. We considered a number of analytic approaches including the analysis of simple change scores and the analysis of regressed change. Analyzing two-time-points using simple change scores (i.e., T2-T1) can be problematic because they do not take unreliability of measurement into account (J. Cohen, et al., 2003). Therefore, change scores tend to overcorrect the endpoint score by the baseline score; this results in the overestimation of a treatment effect when baseline scores are low because of regression to the mean (Bland & Altman, 1994). These problems can be averted by adopting a regressed change procedure, which treats the baseline test score as a covariate thereby removing all correlation of the endpoint score from the baseline score (J. Cohen, et al., 2003). Consequently, generated results are unaffected by baseline differences between groups. Because of these advantages, we used the regressed change

approach in studies 1 and 3. Although an analysis of change scores was used in Study 2 so as to be consistent throughout the study, conducting the analyses using both strategies did not yield substantively different findings.

The third methodological issue is the impact of study design on antidepressant response and cognitive change. Each of the three clinical trials utilized a different study design (i.e., randomized placebo controlled trial, comparator trial, and open treatment trial), which may have influenced affective and cognitive outcomes. For instance, response rates are often higher in open treatment trials than placebo-controlled randomized clinical trials (S. Y. Kim & Holloway, 2003). Similarly, in a comparison of placebo-controlled and comparator trials in LLD, one study found that the odds of medication response in comparator trials were nearly 2 times the odds in placebo-controlled trials (Sneed et al., 2008); comparable results were found in a population of depressed adults aged 18-65 (B. R. Rutherford, Sneed, & Roose, 2009). The most salient difference between study designs is that patients enrolled in open and comparator trials (versus placebo-controlled trials) know that they are receiving an active agent, which may cause them to have greater expectancies of improvement during the course of the study (B. Rutherford, Sneed, Devanand, Eisenstadt, & Roose, 2010). The influence of expectancy on affective outcomes and, potentially, cognitive outcomes may have contributed to the observed inconsistencies in the findings across studies.

SUBSTANTIVE ISSUES

Based on the three studies, we can draw several tentative yet interesting conclusions. First, SSRI administration may result in a decline in verbal learning and psychomotor speed among non-responders. However, this finding may only pertain to the depressed 'old-old' (Study

1) as there was no objective evidence of any cognitive decline among medication non-responders within a 'young-old' sample (Study 2). In fact, treatment with an SSRI among the young-old in Study 2 led to an *improvement* in verbal learning, regardless of whether the patient responded to the medication. The most cogent explanation for this discrepancy is that the old-old are at greater risk for cognitive decline and are thus more vulnerable to the cognitive effects of medication. For instance, older age is associated with greater medical burden, cerebrovascular risk factors, and white-matter hyperintensities, all of which have an established relationship with baseline cognitive dysfunction and subsequent decline (Boone, et al., 1995; Butters, et al., 2004; King, et al., 1993; Lesser, et al., 1996; Lesser, et al., 1991; Potter, et al., 2009). Of course, age itself is a risk factor for cognitive decline and conversion to dementia (M. D. Kim et al., 2012). Another critical consideration is that older adults generally have a number of medical problems that may require several medications. This increases the risk for drug-drug interactions, which could interfere with antidepressant response and cognitive performance. Although citalopram is thought to have minimal drug interaction potential, it is possible that the measurement of cognitive change in Study 1 was complicated by these issues given that the mean age of the sample (M=79.6) was substantially higher than that in Study 2 (M=64.2) and 3 (M=62.3).

The second conclusion we can draw is that treatment with an SSRI may result in greater improvement in verbal learning than treatment with a TCA. This is consistent with previous reports comparing the impact of SSRIs to TCAs on the cognitive functioning of older adults (Doraiswamy, et al., 2003). This is not surprising given that TCAs have greater anticholinergic properties than SSRIs (Pollock, et al., 1998), which in turn are negatively associated with endpoint cognitive improvement among depressed older adults (Doraiswamy, et al., 2003). In

our study, however, this finding depended on responder status as we found that nortriptyline responders were the only treatment condition by responder status group to show no improvement in verbal learning. Although this paradoxical finding may represent a type 1 error, if replicated it may indicate that the therapeutic and cognitive effects of nortriptyline have different mechanisms. This idea would be consistent with another study that found higher plasma nortriptyline concentration over 6 weeks of treatment to be associated with poorer free recall but better affective outcome (Young, et al., 1991).

The third conclusion we can draw is that the cognitive functioning of patients with relatively extensive cerebrovascular disease differentially changes following acute antidepressant treatment when compared to patients with relatively low levels of cerebrovascular disease, though cognitive change by diagnostic status (i.e., level of cerebrovascular disease) depends on responder status. Overall, the literature on vascular depression seems to conclude that patients with vascular depression, or relatively extensive cerebrovascular disease, are cognitively vulnerable (Culang-Reinlieb et al., 2010). This is generally consistent with our findings, which suggest there may be a deleterious interaction between medication non-response and the cognitive impact of white matter disease progression over time. Taken together with the observed response rates among patients with vascular depression (44%), which were less robust that than of patients with nonvascular depression, the results of Study 3 suggest that future research may want to examine the effectiveness of augmentation of antidepressant medication with a non-pharmacological approach that targets cognitive deficits and potentially reduces the risk of cognitive decline.

Our fourth and final conclusion is that it is nearly impossible to disentangle the cognitive effects of medication from that of symptom remission. In fact, across all three studies, we found that the impact of medication on cognitive functioning depended on responder status. Examining the impact of medication on cognition without considering the influence of medication response may actually produce misleading results. In Study 1, for instance, if we only examined the cognitive effect of treatment condition (i.e., placebo versus citalopram) we would have concluded that citalopram had a negative impact on verbal learning and psychomotor speed. However, when looking at the interaction between medication administration and responder status on cognition, we observed that the effect was largely driven by non-responders; the "whole picture" was much more valuable clinically than the main effect. Therefore, future studies that examine the cognitive impact of antidepressant medication in LLD should consider the influence of both symptom remission and medication administration.

In summary, given these results, one could argue that antidepressant medication may be cognitively benign among 'young-old' depressed patients, particularly in the absence of significant cerebrovascular disease. The presence of relatively extensive cerebrovascular disease may negatively interact with medication non-response to influence cognitive outcomes. Among 'old-old' patients, medication may have a deleterious effect on cognition, but only among those who do not respond to treatment. This supports the contention that 'old-old' patients, or depressed older adults with extensive cerebrovascular disease, should not be maintained on a medication if they have not responded following an adequate trial as it may negatively impact some aspects of cognition.

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