The Relationship Between Cerebrovascular Risk, Cognition and Treatment Outcome in Late-Life Psychotic Depression

Kathleen S. Bingham, M.D., Ellen M. Whyte, M.D., Barnett S. Meyers M.D., Benoit H. Mulsant, M.D., Anthony J. Rothschild, M.D., Samprit Banerjee, Ph.D., Alastair J. Flint, M.B., on behalf of the STOP-PD Study Group

From the Department of Psychiatry (KSB, AJF, BHM), University of Toronto, Canada; Western Psychiatric Institute and Clinic, Department of Psychiatry (EMW), University of Pittsburgh School of Medicine, Pittsburgh, PA; Department of Psychiatry (BSM), Weill Medical College of Cornell University and New York Presbyterian Hospital, Westchester Division, NY; Centre for Addiction and Mental Health (BHM), Toronto, Canada; University of Massachusetts Medical School and UMass Memorial Health Care (AJR), Worcester, MA; Department of Healthcare Policy and Research (SB), Weill Cornell Medical College, New York, NY; Department of Psychiatry (AJF), University Health Network, Toronto, Canada; Toronto General and Toronto Rehab Research Institutes (AJF), Toronto, Canada.

Send correspondence and reprint requests to Alastair J. Flint, M.B., Toronto General Hospital, 200 Elizabeth St., 8 Eaton North Room 238, Toronto, Ontario, M5G 2C4, Canada. E-mail: alastair.flint@uhn.ca

Key words: vascular risk; executive function; processing speed; treatment outcome; major depressive disorder; psychotic depression

Running title: Cerebrovascular risk, cognition, and psychotic depression outcome

Trial Registration and URL: Clinicaltrials.gov. Registry ID: NCT00056472.

Disclosures

E.M. Whyte has received research support from the National Institute of Mental Health (NIMH), the National Institute of Child Health and Human Development (NICHD), the Department of Defense (DOD) and through a Small Business Innovation Research (SBIR) grant from Fox Learning Systems/ National Institute of Neurological Disorders and Stroke (NINDS).

B.S. Meyers receives research support from the National Institute of Mental Health.

B.H. Mulsant currently receives research funding from Brain Canada, the CAMH Foundation, the Canadian Institutes of Health Research, and the US National Institutes of Health (NIH). During the last five years, he also received research support from Bristol-Myers Squibb (medications for a NIH-funded clinical trial), Eli-Lilly (medications for a NIH-funded clinical trial), and Pfizer (medications for a NIH-funded clinical trial). He directly own stocks of General Electric (less than \$5,000).

A.J. Rothschild receives grant or research support from Alkermes, AssureRx, Cyberonics, Janssen, the National Institute of Mental Health, St Jude Medical, and Takeda and is a consultant to Eli Lilly and Company, GlaxoSmithKline, Omnicare, and Pfizer Inc. Dr. Rothschild has received royalties for the Rothschild Scale for Antidepressant Tachyphylaxis (RSAT)®; Clinical Manual for the Diagnosis and Treatment of Psychotic Depression, American Psychiatric Press, 2009; The Evidence-Based Guide to Antipsychotic Medications, American Psychiatric Press, 2010; and The Evidence-Based Guide to Antidepressant Medications, American Psychiatric Press, 2012.

A.J. Flint currently receives grant support from the U.S. National Institutes of Health, the Canadian Institutes of Health Research, Brain Canada, the Ontario Brain Institute, and Lundbeck, and within the past three years has received honoraria from Pfizer Canada.

S. Banerjee has no disclosures.

K.S. Bingham has no disclosures.

The STOP-PD clinical trial was funded by USPHS grants MH 62446, MH 62518, MH 62565, and MH 62624 from the National Institute of Mental Health. Eli-Lilly did not provide funding for this study but provided olanzapine; Pfizer did not provide funding for this study but provided sertraline and matching placebo pills.

ABSTRACT

Objective: To examine whether cerebrovascular risk, executive function, and processing speed are associated with acute treatment outcome of psychotic depression in older adults.

Methods: The authors analyzed data from 142 persons aged 60 years or older with major depression with psychotic features who participated in a 12-week randomized controlled trial (RCT) comparing olanzapine plus sertraline with olanzapine plus placebo. The independent variables were baseline cerebrovascular risk (Framingham Stroke Risk Score), baseline executive function (Stroop interference score and the initiation/perseveration subscale of the Mattis Dementia Rating Scale), and baseline processing speed (color and word reading components of the Stroop). The outcome variable was change in severity of depression, measured by the 17-item Hamilton Rating Scale for Depression total score, during the course of the RCT.

Results: Greater baseline cerebrovascular risk was significantly associated with less improvement in depression severity over time, after controlling for pertinent covariates. Neither executive function nor processing speed predicted outcome.

Conclusion: This study suggests an association of cerebrovascular risk, but not executive function or processing speed, with treatment outcome of major depression with psychotic features in older adults.

INTRODUCTION

There is a complex relationship between late-life depression (LLD), cerebrovascular disease (CVD) and cognition(1).The “depression executive dysfunction syndrome” describes a subgroup of patients with LLD and executive dysfunction, along with other signs of frontostriatal impairment(2). Several studies have found that executive dysfunction in LLD predicts poorer antidepressant response(3,4). Executive dysfunction can persist following remission(5), suggesting that it is not simply a state phenomenon of acute depression. The specificity of the depression executive dysfunction syndrome has, however, been questioned, given that tests of non-executive cognitive domains have also been found to predict treatment outcome, suggesting LLD prognosis is related to cognitive impairment more globally(6). Some authors have proposed that slow information processing speed is the core cognitive deficit in LLD that underlies executive dysfunction and other neuropsychological abnormalities(7) and that it may be more strongly predictive of antidepressant treatment outcome than executive dysfunction(8).

Clinical and neuroimaging data suggest CVD as an etiology of frontostriatal impairment(1). CVD can contribute to both LLD and cognitive impairment by damaging frontostriatal circuits involved in both mood regulation and cognition(9). Hypothetically, as stated by the “vascular depression hypothesis”, this damage results in a subtype of depression that is less responsive to pharmacological treatment(9). Although vascular risk factors have been consistently linked to vascular disease of the brain(10), there is inconsistent evidence linking vascular risk factors to executive dysfunction(7,8) and to outcome of late-life depression(8,11,12).

As a large, well-characterized sample, the Study of the Pharmacotherapy of Psychotic Depression (STOP-PD)(13) data set provides an excellent opportunity to further investigate the relationship among cerebrovascular risk, cognitive dysfunction, and depression outcome in non-demented older persons with major depression. The focus on vascular risk, as opposed to magnetic resonance imaging (MRI) of vascular disease in the brain, is clinically relevant, given that cerebrovascular risk can be readily estimated for

every patient, whereas MRI is an expensive and limited resource. Thus, STOP-PD provides an opportunity to explore the association among executive dysfunction, processing speed, cerebrovascular risk, and treatment outcome in a group of older adults with psychotic depression, an illness characterized by more severe frontostriatal dysfunction and cognitive impairment than major depression without psychotic features(14,15). Since the goal of the current study is to contribute to the body of knowledge pertaining to the relationship of cerebrovascular risk and executive dysfunction to outcome of depression, we confined our analyses to outcome of depression, as measured by the 17-item Hamilton Rating Scale for Depression (HAM-D)(16).

We hypothesized that cerebrovascular risk, executive function, and processing speed are associated with poorer outcome of depression, in older adults receiving pharmacotherapy for an episode of major depression with psychotic features. Furthermore, we hypothesized that if both cerebrovascular risk and cognitive function predicted outcome, cerebrovascular risk would partially mediate the association between both executive function and processing speed and outcome.

.

METHODS

This study is a secondary analysis of data from STOP-PD. The design, methods, and main findings of STOP-PD have been previously reported(13). One of the aims of STOP-PD was to compare outcomes in younger and older adults; as a result randomization to study medications was stratified by age group (18-59 years versus 60 years or older). One hundred seventeen participants aged 18-59 years and 142 participants aged 60 years or older with an episode of major depressive disorder and at least one associated delusion and a 17-item HAM-D total score greater than or equal to 21 were randomized to 12 weeks of double-blind treatment with either olanzapine plus sertraline or olanzapine plus placebo. Among the exclusion criteria were another Axis 1 mood disorder or psychotic disorder; DSM-IV(17) defined dementia preceding the index episode of depression;

substance abuse or dependence within the preceding 3 months; neurologic disease that might affect neuromuscular function such as Parkinson's disease; and unstable physical illness, although many of the study participants had stable chronic physical problems. Using procedures approved by local institutional review boards, written informed consent was obtained from all participants or their substitute decision maker prior to the initiation of any research assessments or treatment.

In this analysis, we included only data pertaining to participants aged 60 years or older. Table 1 reports pertinent baseline characteristics of these older participants. Our primary outcome measure was the 17-item HAM-D total score at each study visit during the 12-week treatment trial: the HAM-D was obtained weekly for the first 6 weeks and every second week for the remainder of the trial. The independent variables were: (i) baseline cerebrovascular risk, measured by the Framingham Stroke Risk Score(18); (ii) baseline executive function, measured by a) the color-word interference score on the Stroop(19) and b) the initiation/perseveration subscale of the Mattis Dementia Rating Scale (DRS I/P)(20); and (iii) baseline information processing speed, measured by each of the color and word reading components of the Stroop. The color-word interference score from the Stroop task was calculated using the method proposed by Chafetz and Matthews(21) and converted to T-scores.

The Framingham Stroke Risk Score (FSRS) is an algorithm based on clinical and demographic information, specifically age, gender, treatment with antihypertensive medication, systolic blood pressure, cigarette smoking, diabetes mellitus, history of cardiovascular disease, atrial fibrillation, and left ventricular hypertrophy on electrocardiogram. It provides a score whereby higher scores are associated with increased stroke risk. The FSRS correlates with measures of CVD, including white matter hyperintensities on MRI(10), and has been used in outcome studies in LLD(8,11).

Data Analysis

The outcome (17-item HAM-D) measurements for all assessments were analyzed in a series of linear mixed effects regression models for the three predictor categories

mentioned above. Each of the five predictor variables was analyzed separately. The mixed model had a patient-level random intercept and fixed effects for time trend parameters, predictor, and predictor $\times$ time interaction. In addition, each model included fixed effects for the following covariates known to affect depression outcome or cognitive performance: age, gender, level of education, age at onset of lifetime major depressive disorder, duration of index depressive episode, treatment non-response during the index depressive episode rated with the Antidepressant Treatment History Form (ATHF)(22), and cumulative medical burden rated with the Cumulative Illness Rating Scale for Geriatrics(23). In a previous analysis of the effect of treatment non-response on outcome in STOP-PD, Blumberger et al.(24) found that failure to respond to either an adequate trial of antidepressant monotherapy or to an adequate trial of combination therapy (combined antidepressant and antipsychotic medications) during the index episode of depression before entry to STOP-PD were associated with similar outcomes in STOP-PD. Therefore, in the current analyses, treatment non-response was defined by an ATHF score of 3 or more for an antidepressant monotherapy trial (i.e., at least 4 weeks of an adequate dose of antidepressant) or an ATHF score of 2 or more for a combination treatment trial (i.e., at least 4 weeks of an adequate dose of antidepressant combined with at least 3 weeks of an adequate dose of antipsychotic) during the index episode of depression prior to study entry.

In addition to the mixed effects models, we calculated Spearman's rank correlation coefficients between FSRS score and each of the four neuropsychological test scores at baseline to examine the association between cerebrovascular risk and cognition.

All analyses were carried out using SAS 9.3 (©SAS Institute, Cary, NC) and performed with two-tailed alpha set at 0.05.

RESULTS

After controlling for covariates, baseline FSRS score was significantly associated with change in HAM-D profiles over time based on the time $\times$ predictor interaction ($F_{1,791}=$

9.91, $p = 0.002$): the greater the baseline cerebrovascular risk, the less improvement in depression severity. Neither the measures of executive function nor the measures of processing speed were significant predictors of depression outcome (time $\times$ predictor interactions for Stroop color-word interference score: $F_{1,728} = 2.12$, $p = 0.15$; DRS I/P score: $F_{1,739} = 2.37$, $p = 0.13$; Stroop color score: $F_{1,745} = 3.06$, $p = 0.08$; and Stroop word score: $F_{1,732} = 0.03$, $p = 0.86$). Because we did not find a relationship between cognition and outcome, we were not able to test the mediator hypothesis.

A statistically significant but weak correlation was found between FSRS score and DRS I/P score ($r = -0.20$; $p = 0.03$; $n = 124$). FSRS score was not significantly correlated with Stroop color-word interference score ($r = -0.14$; $p = 0.12$; $n = 119$), Stroop color score ($r = -0.18$; $p = 0.06$; $n = 122$), or Stroop word score ($r = -0.15$; $p = 0.11$; $n = 120$).

DISCUSSION

The principal finding of this study is that cerebrovascular risk predicts poorer treatment response in older adults with psychotic depression after controlling for pertinent covariates. This finding is consistent with studies suggesting that cerebrovascular risk is associated with poorer treatment outcome of LLD. Building on research in non-psychotic depression in older adults(8), our finding supports the utility of the FSRS as a simple clinical measure of cerebrovascular risk in predicting treatment outcome of LLD.

We did not find that measures of executive function and processing speed predicted treatment outcome in STOP-PD participants. This finding is in contrast with other studies of cognitive predictors of treatment outcome in LLD that used the Stroop and DRS I/P as measures of executive function(3,8). However, not all measures of executive function predict LLD outcome(6,25,26). Secondly, while processing speed has been found to be a robust predictor of LLD treatment outcome(8), this has not been a consistent finding in all studies(27). We suggest several possible explanations for our findings. First and foremost, participants in STOP-PD had a more severe depressive illness (as evidenced by the presence of psychosis, a high mean HAM-D score, and more than two thirds of

patients requiring hospitalization) than typical participants in other studies that have examined the relation of cognitive dysfunction and antidepressant response(3,8,12,28). The presence of psychosis and the severity of depression may have compromised some STOP-PD participants' ability to engage in neuropsychological testing, thereby confounding the test results. Second, because of the secondary nature of the analyses in this report, we relied on Stroop color and word scores as post-hoc measures of processing speed. These measures are not ideal: the digit symbol substitution test, which was not part of the STOP-PD design, is fairly specific to processing speed(29) and may have been a more discriminating measure of this cognitive domain. The choice of neuropsychological measure would not, however, explain our negative findings regarding executive function and treatment outcome, since the Stroop interference task and the Mattis I/P have been used in several studies with positive findings(3,8,12). Our study participants had very low scores on tests of executive function: the mean Stroop color-word interference T score of 24.7 was more than two standard deviations below the population mean(19) and the mean DRS I/P score of 30.5 falls in the 6th-10th percentile for community-based persons aged 69-80 years and the 11th-18th percentile for those aged 81-86 years(30). Moreover, these mean scores fall within the range considered to represent executive dysfunction in older depressed patients(31). The executive function scores in our participants were highly skewed towards the low end of functioning: this lack of range across the study group may have contributed to our negative finding regarding the association between neuropsychological performance and treatment outcome. Finally, it is possible that psychotic LLD represents a subtype of major depression for which, in contrast with non-psychotic LLD, cognitive function and treatment outcome are not associated. To further clarify this question without the potential confound of depression severity and psychosis on neuropsychological testing, future studies could examine the effect of cognitive dysfunction on risk of relapse and recurrence of remitted psychotic depression.

We did not find statistically significant correlations between FSRS score and the neuropsychological measures, with the exception of a weak correlation between FSRS score and DRS I/P score. Sheline et al.(8) reported statistically significant correlations between higher FSRS scores and both executive dysfunction and slower processing

speed, but the strength of the correlation with executive dysfunction was modest ($r = -0.28$). As noted by Sheline et al.(8) and others(7), the etiology of executive dysfunction in LLD is likely not limited to cerebrovascular disease: age-related changes, neurodegenerative changes, and medical burden may also contribute. Alexopoulos et al.(12) found that while executive dysfunction and heart disease burden each contributed to lower remission rates of geriatric depression, the relationship between heart disease and depression outcome was not mediated by executive dysfunction, suggesting independent pathways. Given the potential etiologic heterogeneity of cognitive dysfunction in LLD, it is not surprising that studies may not find a strong correlation between cerebrovascular risk and cognitive impairment.

In conclusion, this study suggests an association of cerebrovascular risk, but not executive function or processing speed, with treatment outcome of major depression with psychotic features in older adults.

References

1. Taylor WD, Aizenstein HJ, Alexopoulos GS. The vascular depression hypothesis: mechanisms linking vascular disease with depression. *Mol Psychiatry* 2013; 18:963–74
2. Alexopoulos GS. “The depression-executive dysfunction syndrome of late life”: a specific target for D3 agonists? *Am J Geriatr Psychiatry* 2001; 9:22–9
3. Kalayam B, Alexopoulos GS. Prefrontal dysfunction and treatment response in geriatric depression. *Arch Gen Psychiatry* 1999; 56:713–8
4. Sneed JR, Roose SP, Keilp JG, et al. Response inhibition predicts poor antidepressant treatment response in very old depressed patients. *Am J Geriatr Psychiatry* 2007; 15:553–63
5. Bora E, Harrison BJ, Yücel M, et al. Cognitive impairment in euthymic major depressive disorder: a meta-analysis. *Psychol Med* 2013; 43:2017–26
6. McLennan SN, Mathias JL. The depression-executive dysfunction (DED) syndrome and response to antidepressants: a meta-analytic review. *Int J Geriatr Psychiatry* 2010; 25:933–44

7. Butters MA, Whyte EM, Nebes RD, et al. The nature and determinants of neuropsychological functioning in late-life depression. *Arch Gen Psychiatry* 2004; 61:587–95
8. Sheline YI, Pieper CF, Barch DM, et al. Support for the vascular depression hypothesis in late-life depression: results of a 2-site, prospective, antidepressant treatment trial. *Arch Gen Psychiatry* 2010; 67:277–85
9. Alexopoulos GS, Meyers BS, Young RC, et al. “Vascular depression” hypothesis. *Arch Gen Psychiatry* 1997; 54:915–22
10. Jeerakathil T, Wolf PA, Beiser A, et al. Stroke risk profile predicts white matter hyperintensity volume: the Framingham Study. *Stroke* 2004; 35:1857–61
11. Miller MD, Lenze EJ, Dew MA, et al. Effect of cerebrovascular risk factors on depression treatment outcome in later life. *Am J Geriatr Psychiatry* 2002; 10:592–8
12. Alexopoulos GS, Kiosses DN, Murphy C, et al. Executive dysfunction, heart disease burden, and remission of geriatric depression. *Neuropsychopharmacol* 2004; 29:2278–84
13. Meyers BS, Flint AJ, Rothschild AJ, et al. A double-blind randomized controlled trial of olanzapine plus sertraline vs olanzapine plus placebo for psychotic depression: the Study of Pharmacotherapy of Psychotic Depression (STOP-PD). *Arch Gen Psychiatry* 2009; 66:838–47
14. Schatzberg AF, Rothschild AJ. Psychotic (delusional) major depression: should it be included as a distinct syndrome in DSM-IV? *Am J Psychiatry* 1992; 149:733–45
15. Schatzberg AF, Posener JA, DeBattista C, et al. Neuropsychological deficits in psychotic versus nonpsychotic major depression and no mental illness. *Am J Psychiatry* 2000; 157:1095–100
16. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960; 23:56–62
17. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Washington, DC: American Psychiatric Association, 1994
18. D’Agostino RB, Wolf PA, Belanger AJ, et al. Stroke risk profile: adjustment for antihypertensive medication. The Framingham Study. *Stroke* 1994; 25:40–3
19. Trennery M, Crosson B, DeBoe J, et al. *The Stroop Neuropsychological Test*. Odessa, Fla: Psychological Assessment Resources, 1989
20. Mattis S. *Dementia Rating Scale*. Odessa, Fla: Psychological Assessment Resources, 1989

21. Chafetz MD, Matthews LH. A new interference score for the Stroop test. *Arch Clin Neuropsychol* 2004; 19:555–67
22. Oquendo MA, Baca-Garcia E, Kartachov A, et al. A computer algorithm for calculating the adequacy of antidepressant treatment in unipolar and bipolar depression. *J Clin Psychiatry* 2003; 64:825–33
23. Miller MD, Paradis CF, Houck PR, et al. Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale. *Psychiatry Res* 19; 41:237–48
24. Blumberger DM, Mulsant BH, Emeremni C, et al. Impact of prior pharmacotherapy on remission of psychotic depression in a randomized controlled trial. *J Psychiatr Res* 2011; 45:896–901
25. Majer M, Ising M, Künzel H, et al. Impaired divided attention predicts delayed response and risk to relapse in subjects with depressive disorders. *Psychol Med* 2004; 34:1453–63
26. Potter GG, Kittinger JD, Wagner HR, et al. Prefrontal neuropsychological predictors of treatment remission in late-life depression. *Neuropsychopharmacol* 2004; 29:2266–71
27. Story TJ, Potter GG, Attix DK, et al. Neurocognitive correlates of response to treatment in late-life depression. *Am J Geriatr Psychiatry* 2008; 16:752–9
28. Taylor BP, Bruder GE, Stewart JW, et al. Psychomotor slowing as a predictor of fluoxetine nonresponse in depressed outpatients. *Am J Psychiatry* 2006; 163:73–8
29. Joy S, Kaplan E, Fein D. Speed and memory in the WAIS-III Digit Symbol--Coding subtest across the adult lifespan. *Arch Clin Neuropsychol* 2004; 19:759–67
30. Lucas JA, Ivnik RJ, Smith GE, et al. Normative data for the Mattis Dementia Rating Scale. *J Clin Exp Neuropsychol* 1998; 20:536–47
31. Areán PA, Raue P, Mackin RS, et al. Problem-solving therapy and supportive therapy in older adults with major depression and executive dysfunction. *Am J Psychiatry* 2010; 167:1391–8

Table 1. Baseline Characteristics of Participants Aged 60 Years or Older in STOP-PD (N=142)

Characteristic	Mean (SD)
Age, mean (years)	71.7 (7.8)
Education (years)	12.2 (3.6)
Duration of index episode (months)	9.1 (13.0)
Age at onset of MDD (years)	54.5 (20.1)
HAM-D total score	30.1 (5.4)
CIRS-G total score	6.8 (3.8)
MMSE total score	26.3 (3.4)
Stroop color-word interference score ^a	24.7 (6.3)
Stroop color score ^a	49.5 (16.0)
Stroop word score ^a	17.9 (4.9)
DRS I/P score	30.5 (5.7)
FSRS score	12.1 (4.7)
Characteristic	N (%)
Female	91 (64.1)
Race	
White	129 (90.1)
Black	10 (7.0)
Asian	3 (2.1)
Ethnicity	
Hispanic	6 (4.2)
Non-Hispanic	136 (95.8)
Inpatient	102 (71.8)
Single depressive episode	42 (29.6)
Late-onset MDD (age $\geq$ 60 years) ^b	67 (51.9)
Treatment non-response during current episode ^c	60 (42.3)

HAM-D =17-item Hamilton Depression Rating Scale; CIRS-G = Cumulative Illness Rating Scale for Geriatrics; MMSE = Mini Mental State Examination; DRS I/P = Mattis Dementia Rating Scale Initiation/Perseveration subscale; FSRS = Framingham Stroke

Risk Score; MDD = Major Depressive Disorder; ATHF = Antidepressant Treatment History Form

^aReported as T-scores

^bData available in N = 129 participants

^cSee text for definition of treatment non-response