Executive Function Predicts Antidepressant Treatment Noncompletion in Late-Life Depression

Pilar Cristancho, MD[a,*]; Eric J. Lenze, MD[a]; David Dixon, PhD[a]; J. Philip Miller, AB[b]; Benoit H. Mulsant, MD[c]; Charles F. Reynolds, III, MD[d]; and Meryl A. Butters, PhD[d]

ABSTRACT

Objective: To examine whether executive function (EF) is associated with nonremission and noncompletion of antidepressant pharmacotherapy in older adults with depression.

Design: In this prospective study (July 2009 to May 2014), older adults (aged ≥ 60 years; n = 468) with a *DSM-IV*–defined major depressive episode diagnosed via structured interview received 12 weeks of venlafaxine extended release with the goal of achieving remission. A hypothesis was made that worse baseline EF would predict both nonremission and noncompletion (primary outcomes). Treatment-related factors, including side effects and nonadherence, were also studied.

Methods: Baseline EF, including response inhibition and set-shifting, was assessed with subtests of the Delis-Kaplan Executive Function System and the semantic fluency subtest of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Attention, immediate memory, delayed memory, visuospatial ability, and global cognition were also assessed with the RBANS.

Results: Of 468 participants, 96 (21%) failed to complete the treatment trial, 191 (41%) completed and remitted, and 181 (39%) completed and did not remit. Univariate analyses indicated that some EFs (set-shifting and semantic fluency) and other cognitive variables (attention, immediate memory, visuospatial ability, and global cognition) predicted treatment noncompletion, whereas no cognitive variables predicted nonremission. In a multivariate logistic regression model, semantic fluency ($P = .003$), comorbid medical burden ($P < .001$), and early nonadherence ($P < .001$) were significant predictors of treatment noncompletion.

Conclusions: Poorer EF predicted treatment noncompletion. These findings suggest that EFs of initiation and set maintenance (examined by the semantic fluency task) may allow depressed elderly individuals to engage and stay in treatment. Identification of those at risk for noncompletion may help implementation strategies for personalized care.

Trial Registration: ClinicalTrials.gov identifier: NCT00892047

J Clin Psychiatry 2018;79(3):16m11371

To cite: Cristancho P, Lenze EJ, Dixon D, et al. Executive function predicts antidepressant treatment noncompletion in late-life depression. *J Clin Psychiatry.* 2018;79(3):16m11371.

To share: https://doi.org/10.4088/JCP.16m11371

[a]Department of Psychiatry, Healthy Mind Laboratory, School of Medicine, Washington University in St Louis, St Louis, Missouri

[b]Division of Biostatistics, School of Medicine, Washington University in St Louis, St Louis, Missouri

[c]Centre for Addiction and Mental Health, Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada

[d]Department of Psychiatry, University of Pittsburgh, Pittsburgh, Pennsylvania

**Corresponding author:* Pilar Cristancho, MD, Department of Psychiatry, Healthy Mind Laboratory, School of Medicine, Washington University in St Louis, Campus Box 8134, 660 S. Euclid Ave, St Louis, MO 63110 (cristanp@psychiatry.wustl.edu).

Executive functions (EFs) are specific cognitive processes involved in directing behavior toward a goal.[1,2] They impact everyday function, including activities involved in medical care and self-care.[3–5] Core EFs include response inhibition, set-shifting (cognitive flexibility), and working memory.[6] EF processes also include initiation, goal maintenance, updating, planning, and sequencing.[2,7] EFs are often related and governed by anatomically distinct but connected brain regions within the prefrontal cortex (PFC), including the dorsolateral PFC, ventrolateral PFC, and anterior cingulate,[2,8] as indicated by neuroimaging and neurophysiologic studies showing recruitment of these regions during EF tasks.[9,10]

Executive function impairment often coexists with depression in older adults (late-life depression).[2,11] Co-occurrence of these problems was initially termed the *depression executive dysfunction syndrome*[12] and was posited as the phenotype of microvascular lesions affecting white matter tracts connecting prefrontal and subcortical structures.[13] Recently, altered resting state connectivity in the cognitive control network and the default mode network[14] have been found to be associated with EF deficits in late-life depression.

The clinical relevance of EF impairments in late-life depression lies with its prediction of treatment outcomes. In several,[13,15–18] but not all[19,20] studies, EF deficits were associated with poorer antidepressant response. However, no consensus exists on which EFs are most predictive of response. For example, only planning and organization were associated with antidepressant response in a recent meta-analysis.[21] On the other hand, some research groups[22,23] have reported a wider range of cognitive functions (besides EF) such as episodic memory, language, and processing speed in association with antidepressant response. McLennan and Mathias[24] suggested that executive impairment should not be viewed as an exclusive marker of antidepressant response. They examined 17 studies and found that the Initiation/Perseveration subscale of the Dementia Rating Scale (IP-DRS) was the only EF test that distinguished antidepressant response from nonresponse; in addition, non-EF measures of reaction time, construction, attention, working memory, and delayed recall were also associated with antidepressant response.[24] Overall, the field has not reached agreement on whether impaired EF decreases antidepressant response and, if so, whether it

Clinical Points

- Although executive function has been associated with response to antidepressants in late-life depression, little is known about its impact on antidepressant treatment noncompletion.
- Executive dysfunction, nonadherence early in treatment, and comorbid medical problems predicted antidepressant treatment noncompletion in older adults with depression.

is linked to "global" cognitive dysfunction or to specific EF processes. Therefore, in this large study sample, we examined the impact of EF and other broad cognitive variables on treatment remission.

In addition, we examined whether EF impairment contributes to antidepressant treatment completion. We posit that EFs are important for treatment completion because every treatment step requires executive control. For example: depressed patients should seek and engage in treatment (initiation); they have to determine steps to attain their treatment goal (planning and sequencing); they must "stay on task" by attending visits and taking medications on schedule (goal maintenance or task set); if side effects or changes occur (eg, dosage increases), they should flexibly adapt (set-shifting); and, finally, if unexpected stressors occur, they must continue to attend to their treatment and inhibit impulses to focus solely on the stressor (inhibition).

Treatment completion is an important factor in differentiating between true treatment resistance and pseudoresistance. Likewise, treatment dropout is higher among those receiving inadequate treatment.[25] Treatment resistance has been defined as a failure to respond to at least 1 antidepressant trial of adequate dose and duration.[26] Pseudoresistance is a misperception of treatment resistance due to undertreatment.[27] Differentiating treatment resistance from pseudoresistance has important implications. Treatment resistance requires alternative treatments, whereas pseudoresistance requires addressing reasons for undertreatment: inadequate antidepressant dosage, short trial duration, or failure to complete treatment.

We analyzed data from the open-label phase of the National Institute of Mental Health–sponsored Incomplete Response in Late-Life Depression: Getting to Remission (IRL-GRey) study.[28] IRL-GRey's large sample (N = 468), careful characterization of EF at baseline, and protocolized treatment with venlafaxine extended release (XR) allowed us to examine whether EF was associated with poor treatment outcomes. We hypothesized that worse baseline EF performance would predict both nonremission and treatment noncompletion. Additionally, we examined whether other treatment factors, including side effects and nonadherence, contributed to treatment noncompletion.

METHODS

Participants

This analysis included 468 IRL-GRey participants who started open-label venlafaxine XR (for details, see Lenze et al[28]). Briefly, this 3-site study (ClinicalTrials.gov identifier: NCT00892047) recruited adults aged ≥ 60 years between July 2009 and May 2014. All participants provided informed consent, and Institutional Review Board approval was obtained from the 3 sites.

Inclusion criteria included a diagnosis of current major depressive disorder (MDD) based on the Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID-I)[29] and a Montgomery-Asberg Depression Rating Scale (MADRS)[30] score ≥ 15. Exclusion criteria included lifetime diagnosis of bipolar disorder, schizophrenia, schizoaffective disorder, delusional disorder, or current psychotic symptoms as diagnosed by the SCID-I and unstable physical illness and abuse or dependence of alcohol or other substances within the past 3 months as determined by SCID-I and confirmed by study physician interview.

Subjects with dementia or cognitive impairment were excluded. Evidence of dementia was based on review of medical records and formal review of *DSM-IV* diagnostic criteria for dementia by the study team. In addition, Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)[31] scores and Mini-Mental Status Examination (MMSE) scores were reviewed. A score of ≤ 20 on the MMSE, indicative of significant cognitive impairment, excluded subjects.[32] Additionally, the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)[33] was performed in subjects who scored 21–26 on the MMSE, subjects who scored 1 standard deviation or more below the mean (ie, < 85) on more than 1 index score on the RBANS, and subjects in whom the study team was concerned about cognitive impairment. We used a cutoff of 3.6 on the IQCODE for detecting dementia.

Assessments and Intervention

EF assessment. We assessed response inhibition and set-shifting using measures from the Delis-Kaplan Executive Function System (D-KEFS).[34] Response inhibition was assessed with the D-KEFS Color-Word Interference Condition 3 and Condition 4 measures, and a set-shifting scaled score was calculated by subtracting the motor speed component of the Trail Making test from the number/letter switching motor speed component of the Trail Making test. Removing the motor speed component allows determination of cognitive flexibility.[35] The D-KEFS provides normed scaled scores with a mean of 10 and standard deviation of 3. Semantic fluency was measured using the semantic fluency task of the RBANS.[31] This task requires not only language integrity and semantic knowledge but also executive function[36] (ie, initiating and maintaining the search of one's lexicon and semantic store to retrieve the names of fruits and vegetables). Thus, because our depressed participants typically have intact language, we used this task as an EF measure of set initiation and maintenance.

Nonexecutive function assessment. We also used the RBANS standardized subtest scores to evaluate attention, immediate memory, delayed memory, and visuospatial ability and the RBANS total score to evaluate global cognition. The mean for RBANS Index Scores and the semantic fluency

Table 1. Baseline Demographic and Clinical Characteristics for the Whole Sample and for Completers Versus Noncompleters[a]

Characteristic	All (N = 468)	Completers (n = 372)	Noncompleters (n = 96)	Statistic	*P*
Demographic					
Age	69.0 (7.2)	68.6 (7.0)	70.8 (7.8)	2.65	.008
Female, n (%)	304 (65)	241 (65)	63 (66)	0.02	.88
Race, n (%)				0.63	.89
White	412 (88)	329 (88)	83 (86)		
African American	47 (10)	36 (10)	11 (11)		
Other	9 (2)	7 (2)	2 (2)		
Education, y	14.4 (2.8)	14.4 (2.8)	14.2 (2.8)	−0.75	.46
Depression					
MADRS score at baseline	26.7 (5.7)	26.7 (5.6)	26.6 (6.2)	−0.18	.85
Duration of current episode, wk	290.0 (609.0)	316.6 (661.6)	187.1 (318.5)	21,130.0	.27
Anxiety (PSWQ-A score)	59.4 (13.1)	59.5 (13.1)	59.0 (13.1)	−0.32	.75
Medical variables					
Comorbid medical burden (CIRS-G score)	9.9 (4.5)	9.6 (4.3)	11.0 (4.8)	2.77	.006
Early nonadherence, n/total n (%)[b]	41/451 (9)	24/371 (6)	17/80 (21)	17.40	< .001
Early side effects, n/total n (%)[b]	279/453 (62)	225/373 (60)	54/80 (68)	1.43	.23

[a]Values shown as mean (SD) unless otherwise noted. *t* Test was used for continuous variables, and χ^2 test was used for categorical variables. Wilcoxon rank test was used for duration of episode.
[b]Total n values differ from total n values listed at the top of the column for each group due to missing data for these variables.
Abbreviations: CIRS-G = Cumulative Illness Rating Scale for Geriatrics, MADRS = Montgomery-Asberg Depression Rating Scale, PSWQ-A = Penn State Worry Questionnaire, Abbreviated version.

subscale score is 100 in each instance, and the standard deviation for each is 15.

Depression was assessed with the MADRS; anxiety with the Penn State Worry Questionnaire, Abbreviated version[37]; and burden of comorbid physical illness with the Cumulative Illness Rating Scale for Geriatrics (CIRS-G).[38]

Venlafaxine was started at 37.5 mg/d and increased to 150 mg/d during 2 weeks. After 6 weeks, if the MADRS score was > 10, the dosage was further increased to 300 mg/d. Participants were queried about side effects at every visit, and the dosage could be lowered. To measure adherence, participants were also asked at each visit how many doses they missed since their last visit. We focused on adherence during the first 2 weeks of treatment, as early adherence has been associated with depression outcomes, including treatment dropout.

In addition to medication and monitoring of symptoms and side effects, the study implemented general measures of depression care management including psychoeducation, assessment of suicidality, and encouragement to continue treatment.[39] Participants were allowed to continue outside psychotherapy and preexisting antianxiety and sleep medications (ie, low-dose benzodiazepines, zolpidem, eszopiclone, trazodone, or very low dose tricyclic antidepressant).

Outcomes

The MADRS was performed at baseline (pretreatment) and weekly or every other week until the last study visit. Remission was defined as a MADRS score ≤ 10 for the last 2 consecutive visits. Study noncompletion was defined as failure to complete treatment for any reason.

Analysis

Data were tested for normality using histograms and the Shapiro-Wilk test. Baseline EF and other cognitive measures were compared among treatment remitters, nonremitters, and noncompleters using 1-way analysis of variance (ANOVA) and post hoc contrasts. This analysis allowed us to further characterize 2 groups: completers and noncompleters. Among these groups, we examined baseline differences in demographics, depression severity, anxiety, and medical burden using *t* test for continuous variables and χ^2 test for categorical variables. We also compared side effects and adherence in completers and noncompleters using χ^2 tests. We evaluated whether side effects or adherence was related to cognitive function using *t* tests. We used logistic regression to determine predictors of side effects or nonadherence. A stepwise logistic regression was used to determine predictors of noncompletion. A final parsimonious logistic regression model was built using the significant predictors from the previous analyses. Predictive value of the model was assessed with the C-statistic and the Hosmer and Lemeshow test. Analyses were computed on SAS 9.1.3 (SAS Institute, Cary, North Carolina), and α levels were set at .05 with 2-tailed test.

RESULTS

Table 1 shows demographic and clinical characteristics for the sample. Of 468 participants who started venlafaxine XR treatment, 20% (n = 96) did not complete the 12-week treatment trial, 41% (n = 191) completed and remitted, and 39% (n = 181) completed and did not remit. Reasons for noncompletion included preference for other treatment:

Table 2. One-Way ANOVA for Baseline Executive Function and Nonexecutive Measures Between Treatment Outcomes Groups[a]

Cognitive Task	All (N = 468)	Remitters (n = 191)	Nonremitters (n = 181)	Noncompleters (n = 96)	*F*	*P*	Contrast 1: Noncompleters vs Completers (remitters + nonremitters) (*F* statistic)	*P*	Contrast 2: Remitters vs Nonremitters (*F* statistic)	*P*
Executive										
Set-shifting[b,c]	8.2 (3.7)	8.2 (3.7)	8.5 (3.6)	7.5 (3.7)	2.21	.11	4.03	.045	0.41	.52
Color-Word Interference Condition 3[b]	10.1 (3.2)	10.0 (3.2)	10.2 (3.1)	10.1 (3.3)	0.28	.76	0.03	.87	0.53	.47
Color-Word Interference Condition 4[b]	9.9 (3.6)	10.1 (3.8)	10.0 (3.4)	9.3 (3.8)	1.65	.19	3.12	.08	0.17	.68
Semantic fluency										
Raw[d]	19.3 (5.2)	19.8 (5.3)	19.6 (5.1)	17.6 (4.8)	6.45	.002	12.76	< .001	0.12	.73
Scaled[e]	9.3 (3.2)	9.7 (3.3)	9.4 (3.2)	8.4 (3.1)	5.28	.005	9.58	.002	.92	.34
Nonexecutive										
Attention	98.4 (17.2)	100 (16.4)	99.3 (17.7)	93.4 (16.8)	5.03	.007	9.87	.002	0.16	.69
Immediate memory[f]	96.6 (18.2)	98.7 (17.9)	96.5 (17.9)	92.5 (19.0)	3.64	.03	5.85	.02	1.37	.24
Delayed memory[g]	96.2 (15.7)	97.7 (15.8)	96.0 (16.2)	93.8 (14.1)	1.94	.11	2.80	.09	1.05	.31
Visuospatial[h]	91.8 (17.4)	91.7 (17.1)	93.6 (17.9)	88.4 (16.7)	2.86	.06	4.55	.03	1.20	.27
Total score[i]	94.7 (16.0)	96.5 (15.6)	95.5 (16.8)	89.8 (14.0)	5.74	.004	11.06	.001	0.39	.53

[a]All values except statistics shown as mean (SD). Contrast analysis showed that set-shifting, semantic fluency, attention, immediate memory, visuospatial ability, and global cognition (RBANS total score) were associated with noncompletion outcome but not with nonremission.
[b]Delis-Kaplan Executive Function System scaled score.
[c]Calculated by subtracting the motor speed component from the number/letter switching component of the Trail Making test from the Delis-Kaplan Executive Function System.
[d]Raw score from the subtest semantic fluency index from the RBANS.
[e]Normed values obtained by transforming the variable raw score to a *Z* score and then converting to a scaled score using the following formulas: raw score variable mean – mean from corresponding age group from the RBANS standardization sample/standard deviation from corresponding age group from RBANS standardization sample = *Z* score. The *Z* scores were then converted to scaled scores using the formula 10 + 3(*Z*).
[f]RBANS Index score.
[g]RBANS Modified Delayed Memory Index score.
[h]Modified Visuospatial score.
[i]Modified Total Index score.
Abbreviations: ANOVA = analysis of variance, RBANS = Repeatable Battery for the Assessment of Neuropsychological Status.

28% (27/96); side effects or adverse events: 33% (32/96); nonadherence: 11% (11/96); intercurrent medical problems: 10% (10/96); and miscellaneous issues (drug or alcohol use, depression worsening, cognitive impairment/dementia, death, and administrative reason): 17% (16/96).

EF as a Predictor of Treatment Remission and Treatment Completion

As shown in Table 2, 1 EF measure, semantic fluency, and several nonexecutive cognitive measures, including attention, immediate memory, and global cognition, were associated with treatment outcome (remission, nonremission, or noncompletion), with the noncompleters exhibiting the lowest scores. To test whether these differences were related to noncompletion, we compared EF and non-EF scores between completers and noncompleters (contrast 1 in Table 2): the noncompleters had significantly lower scores than completers for 2 EF measures (set-shifting and semantic fluency). Similarly, noncompleters had significantly lower scores than completers for non-EF measures, including attention, immediate memory, visuospatial ability, and global cognition. Similarly, to test whether group differences from the ANOVA test were related to treatment efficacy, we compared EF and non-EF measures between remitters and nonremitters; no statistical differences were found between these 2 groups (contrast 2 in Table 2). Analysis to examine whether baseline EF and other cognitive variables were associated with treatment response (≥ 50% improvement in MADRS score) did not change these results (Supplementary eTable 1).

Table 1 shows baseline differences that might explain the lower cognitive scores in noncompleters. Noncompleters were older than completers and had higher mean (SD) CIRS-G scores than the completers (11.0 [4.8] vs 9.6 [4.3]; $t_{465} = 2.77$, $P = .006$).

Side Effects and Adherence to the Antidepressant as Predictors of Treatment Noncompletion

In a stepwise fashion, we explored whether having side effects in the first 2 weeks of treatment predicted treatment noncompletion. First, the proportion of completers and noncompleters who experienced side effects did not differ significantly (225/373 [60%] vs 54/80 [68%]; $\chi^2_1 = 1.43$, $P = .23$). Next, we examined differences in EF and other cognitive measures between those reporting side effects during the first 2 weeks of treatment and those who did not (in the whole sample). Only 1 cognitive measure (nonexecutive) differed significantly between the 2 groups: participants reporting early side effects had lower mean (SD) delayed memory scores than those who did not (95.13 [15.98] vs 98.49 [15.02]; $t_{431} = 2.17$, $P = .03$) (see Supplementary eTable 2). However, in a logistic regression model controlling for age

Table 3. Levels of Predictor Variables in Groups at Low Versus High Risk for Treatment Noncompletion

Group[a]	Total n[b]	Noncompleters, n (%)	Medical Burden Score, Mean (SD)	Semantic Fluency Score, Mean (SD)	Adherence, n (%)	
					Yes	No
Low risk, deciles 1–5	264	21 (8)	8.1 (3.7)	21.7 (4.3)[c]	264 (100)	0 (0)
High risk, deciles 6–10	169	50 (30)	12.3 (4.2)	15.8 (4.3)[c]	131 (78)	38 (22)

[a]Groups were classified according to deciles of risk for noncompletion from the Hosmer and Lemeshow test.
[b]The total n for this analysis was 433 subjects rather than the study sample of 468 subjects because of missing values for the covariates that were entered in this final analysis.
[c]By comparison, normative mean (SD) Repeatable Battery for the Assessment of Neuropsychological Status score for semantic fluency in individuals aged 60–69 years is 21.0 (4.6).

and medical burden, delayed memory was not a significant predictor of side effects. The overall fit of the model was poor (results not shown).

In a similar fashion, we examined whether nonadherence in the first 2 weeks of treatment predicted noncompletion. A higher proportion of noncompleters than completers had early nonadherence (17/80 [21%] vs 24/371 [6%]; $\chi^2_1 = 17.40$, $P < .001$). Only 1 cognitive measure (nonexecutive) differed significantly in the 2 groups: participants who were nonadherent early in treatment had lower mean (SD) visuospatial scores than those who were adherent (84.82 [17.76] vs 92.56 [17.14]; $t_{440} = -2.69$, $P = .007$) (see Supplementary eTable 3). A logistic regression model controlling for age and medical burden indicated a minimal contribution from the visuospatial variable (odds ratio [OR] = 0.98; 95% CI, 0.96–0.99; $P = .003$).

Model of Predictors of Treatment Noncompletion

We conducted a diagnostic stepwise logistic regression model using the 4 baseline EF measures (set-shifting, color word interference condition 3 and condition 4, and semantic fluency), nonexecutive measures (attention, immediate memory, delayed memory, visuospatial ability, and global cognition), and demographic and clinical characteristics (age, medical burden [per the CIRS-G], report of side effects early in treatment, and early nonadherence). There were 3 significant predictors of treatment noncompletion ($P < .05$): medical burden, semantic fluency, and adherence. These variables were entered into a logistic regression to yield the most parsimonious model: in this model, every unit increase in semantic fluency score was associated with decreased likelihood of treatment noncompletion (OR = 0.92; 95% CI, 0.88–0.97; $P = .003$), every unit increase in comorbid medical burden was associated with increased likelihood of treatment noncompletion (OR = 1.09; 95% CI, 1.02–1.16; $P < .001$), and early nonadherence was associated with increased likelihood of treatment noncompletion (OR = 5.41; 95% CI, 2.62–11.16; $P < .001$). The model was robust with a moderate predictive value for noncompletion as indicated by a C-statistic = 0.72 (0.5 = nonpredictive value and 1 = 100% predictive value). Additionally, the Hosmer and Lemeshow goodness-of-fit test indicated a good fit: $\chi^2_8 = 13.16$, $P = .11$. This test grouped subjects into deciles of risk for noncompletion (Supplementary eTable 4). Using this model, we classified participants at low or high risk for treatment noncompletion based on their levels of predictor variables (Table 3).

DISCUSSION

In this large sample of depressed older adults receiving protocolized treatment with venlafaxine XR, our univariate analysis indicated that EFs (set-shifting and semantic fluency) and broader cognitive function measures were associated with treatment noncompletion. Adherence, but not side effects, was also associated with treatment noncompletion. In a multivariate model, only 1 EF measure (semantic fluency) and 2 clinical variables (early medication nonadherence and medical burden) were independent predictors of treatment noncompletion. None of the EF or other cognitive measures were associated with treatment nonremission.

Among the predictors of treatment noncompletion, semantic fluency was the only EF variable contributing to this outcome. Other cognitive variables were not significant contributors in the multivariate model. This finding suggests that initiation and set maintenance (examined by the semantic fluency task) allowed patients to engage and stay in treatment. This finding adds to the importance and clinical relevance of EF in antidepressant treatment outcomes.[21] The role of semantic fluency during antidepressant treatment in late-life depression has been previously examined in a study[40] that demonstrated that patients who employed a "semantic strategy" when approaching a semantic fluency task had better treatment outcome. Our findings suggest that those patients with better performance on this task overall, possibly because they used such a strategy, were more likely to stay in treatment.

We also observed that comorbid medical burden was a significant predictor of noncompletion. The relationship between disease burden and depression is bidirectional: disease burden increases depressive symptomatology in older adults,[41,42] and depressed elderly individuals report more medical complaints.[43] Our findings add another dimension to this relationship by indicating that medical burden also interferes with older patients' likelihood of completing antidepressant treatment.

Finally, lack of adherence early in treatment was the strongest predictor of noncompletion. Several factors may influence adherence in older adults: using more than 3 medications, prescriptions by multiple doctors, living

alone, and global cognitive impairment (MMSE score < 24) have been shown to be associated with nonadherence.[44] In addition, we found that participants with lower performance on visuospatial function measures were more likely to be nonadherent early in treatment. Although this contribution was small, this finding may reflect an effect of mental decline on adherence in depressed elderly individuals. By contrast, we did not find an association between EF and adherence, unlike a prior study in which EFs involving planning, organizing, and adjusting to changes (cognitive flexibility) were hypothesized as being necessary for medication adherence in mixed-age adults.[45] Nonetheless, our data suggest that early nonadherence and EF are independent risk factors for treatment noncompletion.

Treatment noncompletion is an undesirable outcome typically associated with treatment failure. Patients who do not complete treatment are unlikely to benefit from it. These patients will add to the pool of individuals who do not improve because of inadequate treatment (ie, are pseudoresistant) rather than being treatment resistant. Our predictors may be helpful for identifying depressed older adults at high risk of noncompletion. In our study, patients at high risk for treatment noncompletion have several (on average, 6) medical comorbidities (eg, cardiac, respiratory, gastrointestinal), have lower semantic fluency scores (on average, ≥ 1 SD below normative scores), and will report missing at least 1 dose of the antidepressant during the first 2 weeks of treatment (see Table 3). Clinicians should address comorbidities, monitor for further decline in EF, and keep these patients engaged in treatment. Early nonadherence is a modifiable risk amenable to interventions. For example, the Treatment Initiation and Participation (TIP) program proposed by Sirey et al[46] offers a model in which provider and patient work collaboratively on addressing barriers to adherence.

Last, contrary to previous reports,[16–18,40] we did not find statistical associations between EF and treatment remission. Possible reasons for this discrepancy include differences between our EF measures and those used in previous studies. Also, our sample was largely cognitively intact; the higher degree of executive dysfunction seen with mild cognitive impairment or early dementia (an exclusion criterion in this study) could reduce treatment response.

The following study limitations should be considered. First, we did not include psychosocial variables that could have impacted treatment adherence and completion such as participants' beliefs about their illness,[3] burden associated with medication and treatment procedures, participants' satisfaction with study physician,[47] or social support. Second, adherence was determined with a self-report measure, which could have overestimated adherence rates, as opposed to more objective measures such as pill counts or use of electronic monitoring devices.[3,48] Last, further studies and replication of these findings will allow for a better understanding of factors that lead to treatment noncompletion.

In summary, a semantic fluency task—measuring initiation and set maintenance—predicted treatment noncompletion but not treatment nonremission in older depressed patients treated with venlafaxine XR. Executive function should be assessed as part of a multidimensional strategy for identifying older depressed patients who are at high risk for early dropout from antidepressant treatment. Other robust predictors of treatment noncompletion included burden of comorbid medical illness and nonadherence early in treatment. These patient variables could allow clinicians to personalize care by enhancing engagement of those at high risk for dropout to ensure they have the opportunity to benefit from treatment.

Submitted: November 30, 2016; accepted August 31, 2017.

Published online: April 3, 2018.

Potential conflicts of interest: **Dr Mulsant** currently receives research support from Brain Canada, the Canadian Institutes of Health Research, the Centre for Addiction and Mental Health (CAMH) Foundation, the Patient-Centered Outcomes Research Institute (PCORI), the US National Institutes of Health (NIH), Eli Lilly (medications for a NIH-funded clinical trial), Pfizer (medications for a NIH-funded clinical trial), Capital Solution Design LLC (software used in a study founded by CAMH Foundation), and HAPPYneuron (software used in a study founded by Brain Canada); within the past 5 years, he has also received research support from Bristol-Myers Squibb (medications for a NIH-funded clinical trial) and Pfizer/Wyeth (medications for a NIH-funded clinical trial), and he owns stocks of General Electric (less than $5,000). **Drs Cristancho**, **Lenze**, **Dixon**, **Reynolds**, and **Butters** and **Mr Miller** have no conflicts of interest to disclose.

Funding/support: Research reported in this publication was supported by National Institute of Mental Health grants P30MH090333, P50 AG005133, and R01 MH083660 to the University of Pittsburgh, R01 MH083648 and R34MH101433 to Washington University; and R01 MH083643 to the University of Toronto. Additional funding was provided by the University of Pittsburgh Medical Center Endowment in Geriatric Psychiatry, Taylor Family Institute for Innovative Psychiatric Research, Center for Brain Research in Mood Disorders, National Center for Advancing Translational Sciences, and the Campbell Family Mental Health Research Institute. Pfizer provided venlafaxine XR for the study.

Role of the sponsor: Funding agencies did not participate in study design; conduct, collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

Supplementary material: See accompanying pages.

REFERENCES

1. Alvarez JA, Emory E. Executive function and the frontal lobes: a meta-analytic review. *Neuropsychol Rev*. 2006;16(1):17–42.
2. Snyder HR. Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: a meta-analysis and review. *Psychol Bull*. 2013;139(1):81–132.
3. Morrell RW, Park DC, Kidder DP, et al. Adherence to antihypertensive medications across the life span. *Gerontologist*. 1997;37(5):609–619.
4. Hildebrand C, Taylor M, Bradway C. Elder self-neglect: the failure of coping because of cognitive and functional impairments. *J Am Assoc Nurse Pract*. 2014;26(8):452–462.
5. Kavanagh NT, Schiller B, Saxena AB, et al. Prevalence and correlates of functional dependence among maintenance dialysis patients. *Hemodial Int*. 2015;19(4):593–600.
6. Diamond A. Executive functions. *Annu Rev Psychol*. 2013;64(1):135–168.
7. Banich MT, Compton RJ. *Cognitive Neuroscience*. 3rd edition. Belmont, California: Wadworth; 2011.
8. Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. *Annu Rev Neurosci*. 2001;24(1):167–202.
9. Duncan J, Owen AM. Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends Neurosci*. 2000;23(10):475–483.
10. Rajji TK, Sun Y, Zomorrodi-Moghaddam R, et al. PAS-induced potentiation of cortical-evoked activity in the dorsolateral prefrontal cortex. *Neuropsychopharmacology*. 2013;38(12):2545–2552.
11. Mulsant BH, Ganguli M. Epidemiology and diagnosis of depression in late life. *J Clin*

Psychiatry. 1999;60(suppl 20):9–15.
12. Alexopoulos GS. Role of executive function in late-life depression. *J Clin Psychiatry*. 2003;64(suppl 14):18–23.
13. Alexopoulos GS, Murphy CF, Gunning-Dixon FM, et al. Microstructural white matter abnormalities and remission of geriatric depression. *Am J Psychiatry*. 2008;165(2):238–244.
14. Alexopoulos GS, Hoptman MJ, Kanellopoulos D, et al. Functional connectivity in the cognitive control network and the default mode network in late-life depression. *J Affect Disord*. 2012;139(1):56–65.
15. Kalayam B, Alexopoulos GS. Prefrontal dysfunction and treatment response in geriatric depression. *Arch Gen Psychiatry*. 1999;56(8):713–718.
16. Alexopoulos GS, Kiosses DN, Heo M, et al. Executive dysfunction and the course of geriatric depression. *Biol Psychiatry*. 2005;58(3):204–210.
17. Sneed JR, Culang ME, Keilp JG, et al. Antidepressant medication and executive dysfunction: a deleterious interaction in late-life depression. *Am J Geriatr Psychiatry*. 2010;18(2):128–135.
18. Potter GG, Kittinger JD, Wagner HR, et al. Prefrontal neuropsychological predictors of treatment remission in late-life depression. *Neuropsychopharmacology*. 2004;29(12):2266–2271.
19. Butters MA, Bhalla RK, Mulsant BH, et al. Executive functioning, illness course, and relapse/recurrence in continuation and maintenance treatment of late-life depression: is there a relationship? *Am J Geriatr Psychiatry*. 2004:12(4):387–394.
20. Saghafi R, Brown C, Butters MA, et al. Predicting 6-week treatment response to escitalopram pharmacotherapy in late-life major depressive disorder. *Int J Geriatr Psychiatry*. 2007;22(11):1141–1146.
21. Pimontel MA, Rindskopf D, Rutherford BR, et al. A meta-analysis of executive dysfunction and antidepressant treatment response in late-life depression. *Am J Geriatr Psychiatry*. 2016;24(1):31–41.
22. 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(3):277–285.
23. Story TJ, Potter GG, Attix DK, et al. Neurocognitive correlates of response to treatment in late-life depression. *Am J Geriatr Psychiatry*. 2008;16(9):752–759.
24. McLennan SN, Mathias JL. The depression-executive dysfunction (DED) syndrome and response to antidepressants: a meta-analytic review. *Int J Geriatr Psychiatry*. 2010;25(10):933–944.
25. Tew JD Jr, Mulsant BH, Houck PR, et al. Impact of prior treatment exposure on response to antidepressant treatment in late life. *Am J Geriatr Psychiatry*. 2006;14(11):957–965.
26. Sackeim HA. The definition and meaning of treatment-resistant depression. *J Clin Psychiatry*. 2001;62(suppl 16):10–17.
27. Thase ME. New approaches to managing difficult-to-treat depressions. *J Clin Psychiatry*. 2003;64(suppl 1):3–4.
28. Lenze EJ, Mulsant BH, Blumberger DM, et al. Efficacy, safety, and tolerability of augmentation pharmacotherapy with aripiprazole for treatment-resistant depression in late life: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2015;386(10011):2404–2412.
29. First MB, Spitzer RL, Gibbon M, et al. *User's Guide for the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) Clinician Version*. Washington, DC: American Psychiatric Press; 1997.
30. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134(4):382–389.
31. Randolph C, Tierney MC, Mohr E, et al. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. *J Clin Exp Neuropsychol*. 1998;20(3):310–319.
32. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189–198.
33. Jorm AF, Jacomb PA. The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): socio-demographic correlates, reliability, validity and some norms. *Psychol Med*. 1989;19(4):1015–1022.
34. Delis DC, Kaplan E, Kramer JH. *Delis-Kaplan Executive Function System (D-KEFS)*. San Antonio, TX: The Psychological Corporation; 2001.
35. Lezak MD, Howieson DB, Bigler ED, et al. *Neuropsychological Assessment*. 5th edition. New York, NY: Oxford University Press; 2012.
36. Reverberi C, Laiacona M, Capitani E. Qualitative features of semantic fluency performance in mesial and lateral frontal patients. *Neuropsychologia*. 2006;44(3):469–478.
37. Meyer TJ, Miller ML, Metzger RL, et al. Development and validation of the Penn State Worry Questionnaire. *Behav Res Ther*. 1990;28(6):487–495.
38. 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*. 1992;41(3):237–248.
39. Reynolds CF 3rd, Dew MA, Martire LM, et al. Treating depression to remission in older adults: a controlled evaluation of combined escitalopram with interpersonal psychotherapy versus escitalopram with depression care management. *Int J Geriatr Psychiatry*. 2010;25(11):1134–1141.
40. Morimoto SS, Gunning FM, Murphy CF, et al. Executive function and short-term remission of geriatric depression: the role of semantic strategy. *Am J Geriatr Psychiatry*. 2011;19(2):115–122.
41. Sutin AR, Terracciano A, Milaneschi Y, et al. The trajectory of depressive symptoms across the adult life span. *JAMA Psychiatry*. 2013;70(8):803–811.
42. Cristancho P, Lenze EJ, Avidan MS, et al. Trajectories of depressive symptoms after hip fracture. *Psychol Med*. 2016;46(7):1413–1425.
43. Drayer RA, Mulsant BH, Lenze EJ, et al. Somatic symptoms of depression in elderly patients with medical comorbidities. *Int J Geriatr Psychiatry*. 2005;20(10):973–982.
44. Barat I, Andreasen F, Damsgaard EM. Drug therapy in the elderly: what doctors believe and patients actually do. *Br J Clin Pharmacol*. 2001;51(6):615–622.
45. Stilley CS, Bender CM, Dunbar-Jacob J, et al. The impact of cognitive function on medication management: three studies. *Health Psychol*. 2010;29(1):50–55.
46. Sirey JA, Bruce ML, Kales HC. Improving antidepressant adherence and depression outcomes in primary care: the treatment initiation and participation (TIP) program. *Am J Geriatr Psychiatry*. 2010;18(6):554–562.
47. Wolf MH, Putnam SM, James SA, et al. The Medical Interview Satisfaction Scale: development of a scale to measure patient perceptions of physician behavior. *J Behav Med*. 1978;1(4):391–401.
48. Hinkin CH, Castellon SA, Durvasula RS, et al. Medication adherence among HIV+ adults: effects of cognitive dysfunction and regimen complexity. *Neurology*. 2002;59(12):1944–1950.

Editor's Note: We encourage authors to submit papers for consideration as a part of our Early Career Psychiatrists section. Please contact Erika F. H. Saunders, MD, at esaunders@psychiatrist.com.

Supplementary material follows this article.

THE JOURNAL OF CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

Supplementary Material

Article Title: Executive Function Predicts Antidepressant Treatment Non-Completion in Late-Life Depression

Author(s): Pilar Cristancho, MD[a,*]; Eric J. Lenze, MD[a]; David Dixon, PhD[a]; J. Philip Miller, AB[b]; Benoit H. Mulsant, MD[c]; Charles F. Reynolds, III, MD[d]; and Meryl A. Butters, PhD[d]

DOI Number: https://doi.org/10.4088/JCP.16m11371

List of Supplementary Material for the article

1. **eTable 1** One-Way ANOVA baseline executive function and non- executive measures between responders (≥50% improvement in MADRS score) and non- responders
2. **eTable 2** Differences in executive and non-executive indices among subjects with and without early side effects
3. **eTable 3** Differences in executive and non – executive indices among medication adherent and non-adherent subjects early in the treatment course
4. **eTable 4** Hosmer and Lemeshow goodness -of-fit test: grouping of subjects into deciles of risk for non-completion based on their levels of predictor variables

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary eTable 1. One-Way ANOVA baseline executive function and non- executive measures between responders (≥50% improvement in MADRS score) and non- responders.

Cognitive task	All (n= 468)	Responders (n = 198)	Non-responders (n = 174)	Non-completers (n= 96)	Statistic *F*	*p*	Contrast 1 Non completers vs. completers (responders + non responders) *(F statistic)*	*p*	Contrast 2 Responders vs. non responders (*F* statistic)	*p*
Executive	*M (SD)*	*M (SD)*	*M (SD)*							
Set shifting[ab]	8.2 (3.6)	8.3 (3.7)	8.5 (3.6)	7.6 (3.6)	2.02	.13	3.80	0.05	0.30	0.59
Color word interference 3[a]	10.2 (3.0)	10.2 (2.8)	10.3 (3.1)	10.2 (3.2)	0.06	.94	0.07	0.79	0.06	0.81
Color word interference 4[a]	9.9 (3.6)	10.2 (3.7)	10.0 (3.3)	9.4 (3.6)	1.40	.25	2.57	0.11	0.19	0.66
Semantic fluency Scaled[c]	9.3 (3.2)	9.7 (3.3)	9.5 (3.2)	8.4 (3.1)	4.95	.008	9.53	.002	0.28	0.6
Non – executive										
Attention[e]	98.4 (17.2)	99.7 (16.6)	99.6 (17.7)	93.4 (16.8)	4.90	.008	9.79	0.002	0.00	0.96
Immediate Memory[d]	96.5 (18.2)	98.8 (17.7)	96.1 (18.0)	92.5 (19.0)	3.94	.02	5.64	0.02	2.05	0.15
Delayed Memory[e]	96.3(15.5)	97.5 (15.6)	96.2 (16.2)	94.1 (13.9)	1.47	.23	2.23	0.14	0.64	0.43
Visuospatial[e]	92.0 (17.2)	91.5 (16.9)	94.2 (17.8)	88.8 (16.3)	3.08	.05	4.14	0.04	2.17	0.14
Total score[e]	94.9 (15.8)	96.3 (15.5)	95.8 (16.9)	90.3 (13.4)	4.97	.007	9.82	0.002	0.08	0.78

Contrast analysis showed that set shifting, semantic fluency, attention, inmmediate memory, visuospatial ability and global cognition (Repeatable Battery for the Assessment of Neuropsychological Status [RBANS] total score) were associated with non-completion outcome but not with non- response.

[a]Delis Kaplan Executive Function System scaled score

[b] Calculated by subtracting the motor speed component from the number/letter switching component of the Trail Making test from the Delis Kaplan Executive Function System.

c RBANS index score normed value. This value was obtained by transforming the variable raw score to Z score and then converting to a scaled score using the following formulas: Raw score variable mean - mean from corresponding age group from the RBANS' standardization sample / standard deviation from corresponding age group from RBANS standardization sample = Z score. Then the Z scores were converted to scaled scores using the formula: 10 + 3 (Z).

[d] RBANS Index score

[e] RBANS Modified Delayed Memory Index score, Modified Visuospatial, Modified Total Index Score

Supplementary eTable 2. Differences in executive and non-executive indices among subjects with and without early side effects.[a]

Variable	Side effects *Mean (SD)* n	No side effects *Mean (SD)* n	*t* statistic	*P Value*
Executive measures				
Set shifting	8.01 (3.70) [n = 262]	8.56 (3.51) [n = 159]	-1.51	.13
Color word interference 3	10.06 (3.07) [n = 264]	10.06 (3.22) [n = 160]	-0.00	.10
Color word interference 4	9.85 (3.58) [n= 262]	9.96 (3.75) [n =160]	0.30	.77
Semantic fluency	19.32 (5.12) [n= 269]	19.57 (5.33) [n = 165]	0.49	.62
Non executive measures				
Attention	98.66 (17.01) [n=269]	98.70 (17.05) [n = 164]	0.03	.98
Delayed Memory	95.13 (15.98) [n = 269]	98.49 (15.01) [n = 164]	2.17	.03
Immediate memory	96.59 (18.19) [n =274]	97.55 (17.67) [n=172]	0.55	.58
Visuospatial	91.65 (17.40) [n = 271]	92.25 (17.21) [n= 171]	0.35	.72
Total score	94.44 (15.94) [n =265]	96.23 (15.69) [n = 164]	1.13	.26

[a] Side effects reported by subjects during in the first two weeks of treatment

Supplementary eTable 3: Differences in executive and non – executive indices among medication adherent and non- adherent subjects early in the treatment course[a].

Variable	Adherent *Mean (SD)* n	Non-adherent *Mean (SD)* n	*t* statistic	*p* Value
Executive measures				
Set Shifting	8.28 (3.64) [n = 385]	7.56 (3.54) [n = 36]	-1.14	.25
Color word interference 3	10.09 (3.14) [n = 389]	9.66 (2.97) [n = 35]	-0.79	.43
Color word interference 4	9.89 (3.63) [n= 387]	9.83 (3.76) [n =35]	-0.10	.92
Semantic fluency	19.5 (5.25) [n= 396]	18.5 (4.54) [n = 38]	-1.13	.26
Non- executive measures				
Attention	99.09 (16.96) [n=395]	94.32 (17.07) [n = 38]	-1.66	.09
Delayed Memory	96.63 (15.79) [n = 395]	94.05 (14.53) [n = 38]	-0.97	.33
Immediate memory	97.13(18.02) [n = 406]	95.15 (17.56) [n = 40]	-0.67	.51
Visuospatial	92.56 (17.14) [n = 403]	84.82 (17.76) [n= 39]	-2.69	.007
Total score	95.53 (15.86) [n =392]	90.81 (15.21) [n = 37]	-1.74	.08

[a]Early in the treatment course refers to the first two weeks of treatment.

Supplementary eTable 4: Hosmer and Lemeshow goodness -of-fit test: grouping of subjects into deciles of risk for non-completion based on their levels of predictor variables.

Group	Sample size per decile	Non completers		Completers	
		observed	expected	observed	expected
Low Risk					
1	43	0	2.35	43	40.65
2	44	5	3.33	39	40.67
3	45	6	4.01	39	40.99
4	43	4	4.48	39	38.52
5	43	5	5.21	38	37.39
High Risk					
6	46	1	6.4	45	39.6
7	43	9	7.24	34	35.76
8	45	10	9.28	35	35.72
9	44	16	11.6	28	32.4
10	37	15	17.1	22	19.9
All 10 groups	433	71	71	362	362

The Hosmer and Lemeshow goodness-of fit test indicated the model was a good fit: $\chi^2 = 13.16$ (8), $p = 0.11$.