Response to Antidepressant Medications in Late-Life Depression Across the Spectrum of Cognitive Functioning

Aaron M. Koenig, MD; Meryl A. Butters, PhD; Amy Begley, MA; Semhar Ogbagaber, MS; Abdus S. Wahed, PhD; and Charles F. Reynolds III, MD

ABSTRACT

Objective: Late-life depression frequently co-occurs with cognitive impairment. To inform clinical management of these conditions, we examined the hypotheses that, relative to cognitively normal elders meeting *DSM-IV* criteria for major depressive disorder, those with cognitive impairment would require greater intensity of pharmacotherapy to reach criteria for antidepressant response and would take longer to respond.

Method: Using data from the MTLD-3 study, we conducted a series of secondary analyses examining the implications of cognitive impairment for short-term, open-trial pharmacotherapy of late-life depression (major depressive disorder in individuals 65 years and older). The treatment algorithm consisted of 3 steps: initial treatment with a selective serotonin reuptake inhibitor (SSRI), a switch to a serotonin-norepinephrine reuptake inhibitor (SNRI) if the patient did not respond, and addition of an atypical antipsychotic if the patient did not respond to the SNRI. The first subject entered the protocol in April 2004, and the last subject exited in September 2009. We examined data for participants who completed the acute phase of MTLD-3 as responders and received a cognitive diagnosis (N = 153) based on National Alzheimer's Coordinating Center (NACC) Uniform Data Set criteria. We divided participants into 3 groups on the basis of NACC cognitive diagnosis: no cognitive disorder (n = 74), mild cognitive impairment (n = 60), and dementia (n = 19). For each group, we calculated the proportion of participants requiring first- (SSRI), second- (SNRI), or third-step (add-on atypical antipsychotic) treatment to meet criteria for response (17-Item Hamilton Depression Rating Scale score ≤ 10 for 3 consecutive weeks). We compared time to response across groups and correlates of nonresponse.

Results: The 3 groups did not differ in intensity of pharmacotherapy ($P = .68$) or time to response ($P = .84$). Nonresponse was more strongly correlated with longer major depressive episode duration ($P = .0015$), presence of recurrent depression ($P = .002$), and younger current age ($P = .047$), rather than cognitive status ($P = .61$).

Conclusions: Cognitive status does not appear to impact short-term pharmacotherapy response variability in individuals whose depression responds to treatment with open-trial antidepressants delivered in a supportive, university-based medication clinic.

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Corresponding author: *Meryl A. Butters, PhD, Western Psychiatric Institute and Clinic, 3811 O'Hara St, Room 462, Pittsburgh, PA 15213 (buttersma@upmc.edu).*

Late-life depression frequently coexists with cognitive impairment,[1–3] and growing evidence suggests that these disease processes are "linked" in multiple ways.[2] For some individuals, late-life depression may be a recurrence of a long-standing depressive illness. For others, it may be the leading symptom of a developing neuropathologic disorder.[2–5]

While understanding the management of depression in the setting of cognitive impairment is a clinical priority, the evidence base for doing so is limited. In clinical practice, medications such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are used to treat individuals with co-occurring depression and cognitive impairment. However, recent studies have given pause to this approach. Banerjee and colleagues,[6] for example, found that standard antidepressant medications for treatment of depression in Alzheimer's disease showed no benefit over placebo. Such findings present a challenge for clinicians who treat an aging population in which co-occurring mood and cognitive disorders are becoming more prevalent. This is particularly true in the growing population of individuals with mild cognitive impairment (MCI). MCI is a clinical label that describes a cognitive decline from a previously higher level of functioning, but one that does not cause significant disability. Different criteria for MCI exist, but in general they include a deficit in at least 1 domain of cognition, in the absence of dementia or impairment in activities of daily living.[7]

Neuropsychiatric symptoms affect many individuals with MCI[8] and nearly all dementia patients at some point, and among these symptoms depression is the most common.[9] While previous studies have examined depression treatment in dementia,[6,10] we are unaware of any studies that have examined depression treatment in individuals with MCI or, more broadly, "across the cognitive spectrum." Understanding the management of depression across this spectrum, and how it differs from that in the "cognitively normal" population, is thus an important but relatively neglected area of research.

To enhance our understanding of this topic, we performed analyses designed to examine whether there is an association between degree of cognitive impairment and antidepressant treatment response. Given that cognitive decline is often observed in the setting of underlying neuropathologic processes (vascular, inflammatory, neurodegenerative), we predicted that greater cognitive impairment would be associated with greater difficulty in treating depression to clinical response (17-Item Hamilton Depression Rating Scale [HDRS-17] score ≤ 10 for 3 consecutive weeks). We hypothesized that participants with MCI or dementia who responded to antidepressant treatment would require a greater scope and quantity of interventions to respond,

Clinical Points

- Late-life depression frequently presents with cognitive impairment in the clinical setting.
- This study suggests that cognitive status does not impact antidepressant pharmacotherapy response variability in individuals who respond to short-term, open-trial treatment provided in a supportive clinical environment.
- Depression severity at the start of treatment and longer depressive episode duration seem to correlate more strongly with antidepressant response variability, rather than with cognitive functioning.

compared with cognitively normal participants who responded. To study this, we examined participants enrolled in a late-life depression intervention trial who, after reaching criteria for clinical response, received a formal cognitive diagnosis from the University of Pittsburgh Alzheimer's Disease Research Center (ADRC). We examined differences in treatment received and response characteristics across the continuum of cognitive functioning, as well as correlates of nonresponse.

METHOD

Overview

This secondary analysis utilized data from the Maintenance Therapies in Late-Life Depression 3 (MTLD-3)[1] study, a randomized, double-blind, placebo-controlled maintenance trial designed to test the efficacy of adjunctive donepezil as part of maintenance treatment for late-life depression. To qualify for randomization to donepezil or placebo in MTLD-3, full antidepressant response was required (defined by HDRS-17[11] score ≤ 10 for 3 consecutive weeks) and was achieved through an open-label antidepressant treatment protocol. This "acute phase" protocol involved a 3-step treatment algorithm. Participants were initially treated with an SSRI (escitalopram, up to 20 mg/d), and those who did not respond were switched to an SNRI (venlafaxine, up to 300 mg/d, or duloxetine, up to 120 mg/d). Treatment with add-on atypical antipsychotic (aripiprazole, up to 15 mg/d) was allowed for participants who did not respond with SNRI monotherapy. The goal of this algorithm was to maximize the number of participants available to participate in the maintenance phase of MTLD-3, a precondition of which was HDRS-17 score ≤ 10 for 3 consecutive weeks. Throughout the study, participants were also allowed low to moderate doses of benzodiazepines, for anxiolytic or hypnotic purposes. The current analyses utilized data from the open-label "acute phase" of MTLD-3, prior to participant randomization to maintenance donepezil or placebo.

Participants

We screened 299 adults, 65 years and older, recruited from primary care practices, mental health clinics, other federally sponsored clinical research projects, and advertisements. To qualify, participants had to meet the following criteria: (1) be 65 years or older; (2) be in a nonbipolar, nonpsychotic major depressive episode (MDE); (3) have a score of 15 or higher on the HDRS-17; and (4) not have a preexisting clinical diagnosis of dementia. Subjects with a clinical diagnosis of dementia were excluded from the MTLD-3 protocol, given the study's focus on examining the efficacy of add-on donepezil as part of maintenance treatment for depression in nondemented elders. In the maintenance phase of MTLD-3, cognitively normal subjects were included to determine if donepezil protects these individuals from developing MCI, and individuals with MCI were included to test for cognitive improvement while receiving donepezil. The protocol was approved by the institutional review board of the University of Pittsburgh, and all participants provided written informed consent. Of the 220 participants who qualified for participation and consented for the study, 203 began open-label "acute phase" treatment. Of these participants, 158 completed the acute phase and responded to antidepressant medications. For the current analyses, we examined data from participants who completed the acute phase protocol and received a "cognitive diagnosis" (N = 153) from the University of Pittsburgh ADRC (Figure 1). The first subject entered the MTLD-3 protocol in April 2004, and the last subject exited the protocol in September 2009.

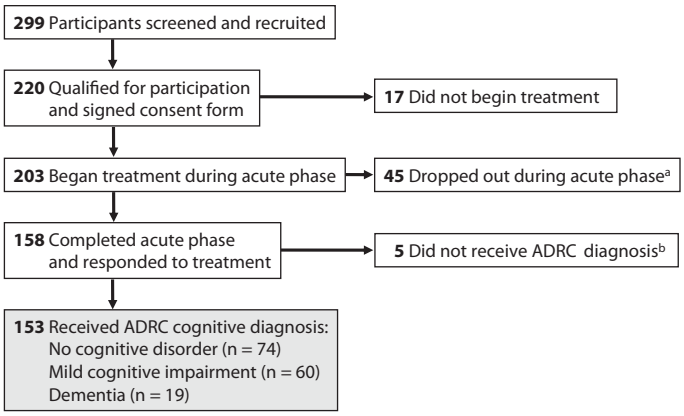
Measures

Diagnostic measures. The Structured Clinical Interview for *DSM-IV*[12] was administered as part of the diagnostic evaluation. Details of past MDEs and other *DSM-IV* diagnoses were ascertained. Upon completion of the acute intervention phase, the ADRC consensus conference reviewed post–depression response neuropsychological data, clinical history, magnetic resonance imaging (MRI) data, and performance-based activities of daily living/instrumental activities of daily living measures. The following diagnoses were conferred according to National Alzheimer's Coordinating Center Uniform Data Set criteria[13]: no cognitive disorder, MCI, and dementia. MCI was subtyped into amnestic MCI or non-amnestic MCI, depending on whether memory was impaired, as well as single-domain or multiple-domain, depending on how many cognitive domains were impaired.[7] Five participants who responded to open-label antidepressant treatment did not receive an ADRC diagnosis of dementia, MCI, or no cognitive disorder and were excluded from the analyses.

Depression severity measure. Depression symptom severity was measured using the HDRS-17.[11] Clinicians administered the HDRS-17 at diagnostic evaluation and weekly during acute phase treatment. Antidepressant response was defined as achieving HDRS-17 scores less than or equal to 10 for 3 consecutive weeks.

Cognitive measurement. Neuropsychological functioning was assessed with 17 well-validated tests measuring multiple domains. We transformed raw scores for individual tests into *Z* scores using the baseline distribution of a nondepressed, cognitively normal, older-adult comparison group. *Z* scores were averaged within each neuropsychological area to produce domain scores and averaged over all 17 tests to

Figure 1. Flowchart of Participants: Acute Phase of MTLD-3 Study



[a]Reasons for termination included comorbid medical problems, noncompliance with study medications or procedures, other treatment-related reasons, and poor response to study medication.
[b]Reasons for not receiving ADRC consensus diagnosis included noncooperation, exited study prior to assessment, and received other (noncognitive) diagnosis.
Abbreviation: ADRC = Alzheimer's Disease Research Center.

calculate a global performance score. We explored 5 domains of neuropsychological functioning: information processing speed, executive functioning, delayed memory, language, and visuospatial functioning. The component tests of each domain are the same as previously reported by Butters et al,[14] with the exception that the modified Rey-Osterrieth figure copy replaced clock drawing. Cognitive functioning was also measured for a subset of participants prior to starting antidepressant medication. These participants, who had been enrolled in a separate but related protocol (N = 115),[15] were administered the Dementia Rating Scale-2 (DRS-2)[16] during diagnostic evaluation. A scaled DRS-2 score ≤ 7 was used to classify participants as cognitively impaired, with a score of 7 representing 1 standard deviation below the test's scaled mean score of 10. We chose to convert raw DRS-2 scores to scaled scores in order to correct for age and educational differences among participants. This process typically increases the sensitivity of the measure, as raw scores may lead to a greater chance of misclassification (for example, older and/or less educated individuals with normal cognition may be misclassified as impaired, while younger and/or more highly educated individuals who are impaired may be misclassified as cognitively normal).

Statistical Analyses

We examined data for all participants who completed the acute phase protocol and received a postintervention ADRC diagnosis (N = 153). We divided participants into 3 groups on the basis of diagnosis: no cognitive disorder (NCD), MCI, and dementia. To maximize statistical power, participants with all MCI subtypes were grouped together. Categorical characteristics of the groups were summarized using means and percentages, and differences across groups were tested using χ^2 tests, or its exact test version when appropriate. Continuous variables were summarized using means and standard deviations or medians and quartiles, and differences across groups were tested using *F* test (for normally distributed data) or Kruskal-Wallis test (for nonnormally distributed data). For each cognitive group, we calculated the proportion of participants who required first-, second-, or third-step treatment to respond and the proportion requiring concurrent benzodiazepines. These proportions were compared using χ^2 tests, or Fisher exact test when appropriate. Length of time to response was summarized using means and standard deviations and compared across the groups using *F* test through an analysis of variance model. Using linear mixed-effect modeling, we analyzed weekly HDRS-17 scores to explore changes over time across the groups.

Next, we built a multivariable ordinal logistic regression model, using backward elimination method, to control for variables (such as baseline demographic factors) that might explain the relationship between cognitive status and level of treatment required to respond; the outcome of the logistic regression model was defined as the level of treatment required to achieve response. Candidate variables were chosen through univariable analyses, and predictors with $P < .25$ were considered for entry into the multivariable model. Variables with higher *P* values were sequentially eliminated until all variables reached a significance cutoff of .05. At this point, interactions between predictors were included, one at a time, and tested for significance.

Finally, to provide additional clinical context, we performed exploratory analyses comparing participants who completed the acute phase protocol with those who did not on demographic and clinical measures. We used *t* tests for continuous variables and χ^2 tests for categorical variables. We further examined the subset of completers with baseline DRS-2 scores, to explore the relationship between baseline cognitive assessment and difficulty in treating depression to clinical response. We divided this group into cognitively normal and cognitively impaired and calculated the proportions requiring first-, second-, or third-step treatment to reach response criteria. To examine whether the groups demonstrated different pathways to response, we plotted mean HDRS-17 scores over time and performed linear mixed-effect model fit. Lastly, we performed κ analyses to examine the level of agreement between pretreatment DRS-2 score and posttreatment ADRC consensus diagnosis.

RESULTS

Examination of Pathways to Response Based on ADRC Diagnosis

Of the 158 participants eligible to receive a consensus diagnosis from the ADRC, 153 participants did so and were included in the analyses (Figure 1). Nineteen (12.4%) were diagnosed with dementia, 60 (39.2%) with MCI, and 74 (48.4%) with NCD. Of note, while individuals with a clinical diagnosis of dementia (at study baseline) were excluded from participating in MTLD-3, 12.4% of responders met criteria for dementia, once their depression had responded to antidepressant treatment.

Table 1. Demographics, Depression History, and MTLD-3 Treatment Response (by ADRC cognitive diagnosis)

	No Cognitive Disorder (n = 74)	Mild Cognitive Impairment (n = 60)	Dementia (n = 19)	Test of Differences	
				Test Result	*P* Value
Demographics					
Age, mean (SD), y	71.95 (5.80)	75.17 (6.08)	78.00 (5.73)	$F_{2,150} = 10.00$	< .001
Gender, female, n (%)	57 (77.03)	45 (75.00)	16 (84.21)	$\chi^2_2 = 0.69$	.71
Race, Caucasian, n (%)	69 (93.24)	50 (83.33)	16 (84.21)	$\chi^2_2 = 3.47$	.18
Education, mean (SD), y	14.07 (2.69)	12.85 (2.15)	13.74 (2.35)	$F_{2,150} = 4.15$	.02
Depression history					
History of recurrent MDD, n (%)	47 (63.51)	29 (48.33)	3 (15.79)	$\chi^2_2 = 14.22$	< .001
Age at first MDE, mean (SD), y	50.45 (21.15)	57.53 (21.54)	68.74 (12.90)	$F_{2,150} = 6.51$	.002
Duration of current MDE, median (25th percentile, 75th percentile), wk[a]	31 (15, 122)	60 (17, 189)	72 (56, 200)	$F_{2,149} = 2.65$	.07
HDRS-17 baseline total score, mean (SD)	18.36 (3.32)	19.07 (3.24)	19.47 (4.69)	$F_{2,150} = 1.10$	.33
DRS-2 scaled baseline total, mean (SD)[b,c]	9.73 (2.03)	7.93 (2.19)	6.00 (2.00)	$F_{2,108} = 21.00$	< .001
Treatment response during acute phase of MTLD-3 study					
Time to response, mean (SD), wk	21.67 (11.02)	22.81 (11.37)	22.41 (10.32)	$F_{2,150} = 0.18$	.84
Response to first-step treatment (SSRI), n (%)	43 (58.1)	34 (56.7)	14 (73.7)	$\chi^2_4 = 2.31$	.68[d]
Response to second-step treatment (SNRI), n (%)	26 (35.1)	20 (33.3)	4 (21.1)		
Response to third-step treatment (SNRI + atypical antipsychotic), n (%)	5 (6.8)	6 (10)	1 (5.3)		
Received benzodiazepine, n (%)	33 (44.6)	29 (48.3)	10 (52.6)	$\chi^2_2 = 0.456$	.79
Benzodiazepine exposure, median (25th percentile, 75th percentile), mg/d[e,f]	1.40 (0.77, 2.2)	1.77 (1.4, 5.2)	1.78 (1.4, 3.5)	$\chi^2_2 = 3.71$	.156

[a]No cognitive disorder: n = 73.
[b]Only those participants (n = 111) who participated in a separate but related protocol[14] had the DRS-2 administered at baseline.
[c]No cognitive disorder: n = 55, mild cognitive impairment: n = 42, dementia: n = 14.
[d]We did not have sufficient power to detect pairwise differences between these groups.
[e]Benzodiazepines used during study included alprazolam, chlordiazepoxide, clonazepam, diazepam, lorazepam, oxazepam, and temazepam. Medications were converted to diazepam equivalent doses[16] and averaged per day in the acute phase of MTLD-3.
[f]Among benzodiazepine recipients.
Abbreviations: ADRC = Alzheimer's Disease Research Center, DRS-2 = Dementia Rating Scale-2, HDRS-17 = 17-Item Hamilton Depression Rating Scale, MDD = major depressive disorder, MDE = major depressive episode, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

As summarized in Table 1, the 3 cognitive groups differed significantly in age ($P < .001$) and years of education ($P = .02$), but not in race or gender. The NCD group was younger than the other groups, and the MCI group had the fewest years of education. The 3 groups did not differ on baseline HDRS-17 score but did differ significantly on baseline DRS-2 score ($P < .001$). As expected, the MCI and dementia groups had lower baseline DRS-2 scores than the NCD group, indicating greater cognitive impairment. Participants with later-onset depression were more common in the dementia and MCI groups, as evidenced by lower rates of participants with a history of recurrent major depressive disorder ($P < .001$) and greater mean age at onset of first MDE ($P = .002$) (Table 1).

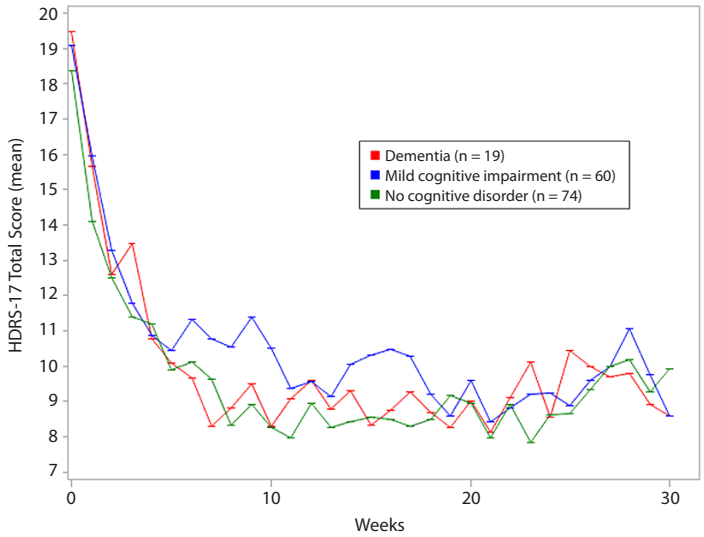
To examine our hypothesis that greater cognitive impairment would impart greater difficulty in responding to antidepressant medications, we quantified the antidepressant interventions required for the NCD, MCI, and dementia groups. First, we calculated the proportion of participants in each group who required first- (SSRI), second- (SNRI), or third-step (add-on atypical antipsychotic) treatment to respond. These proportions did not differ significantly across the 3 groups ($P = .68$) (Table 1). Notably, 73.7% of participants with dementia responded to first-line treatment, compared to 56.7% in the MCI and 58.1% in the NCD groups (Table 1). In addition to antidepressant medications, participants were allowed treatment with concurrent benzodiazepines (primarily lorazepam) for anxiolytic or hypnotic purposes. The proportion of participants requiring benzodiazepines did not differ significantly across the groups ($P = .79$) (Table 1). To more precisely measure benzodiazepine exposure, we calculated average daily benzodiazepine dose for each participant[17] and compared mean values across the 3 groups. Mean dose per day of diazepam equivalents did not differ significantly across the groups ($P = .156$), and overall benzodiazepine exposure was low.

Mean times to response did not differ significantly across the 3 groups ($P = .84$) (Table 1). To examine whether the groups demonstrated different temporal pathways to response, we plotted weekly mean HDRS-17 scores over time for each cognitive diagnosis (Figure 2). Linear mixed-effect model fit demonstrated that all longitudinal HDRS-17 scores followed a quadratic pattern of decline over time. While mean HDRS-17 scores were similar at baseline ($P = .65$), the NCD group showed a slightly larger decline ($P < .04$) over time compared to the other groups, although the absolute difference was small and clinically insignificant (Figure 2).

Multivariate Analyses of Relative Treatment Resistance

In multivariable analyses, longer duration of current MDE ($P = .0015$), presence of recurrent depression ($P = .002$), and younger current age ($P = .047$) were significantly associated with requiring a higher level of treatment to respond. However, after adjusting for these variables, cognitive status was not significantly associated with level of treatment required to respond ($P = .61$). Length of MDE was positively

Figure 2. HDRS-17 Score Trajectories by ADRC Consensus Diagnosis[a]



[a]Linear mixed-effect model fit demonstrated that all longitudinal HDRS-17 scores followed a quadratic pattern of decline over time. While mean HDRS-17 scores were similar at baseline ($P = .65$), the group with no cognitive disorder showed a slightly larger decline ($P < .04$) over time compared to the mild cognitive impairment and dementia groups. From the linear mixed-model fit, the estimated minimum HDRS-17 score (6.3) for the dementia group was achieved at week 24.8, while the estimated minimums for the mild cognitive impairment (5.6) and no cognitive disorder (5.5) groups were achieved at approximately 23 weeks. After reaching a minimum, scores in the group with no cognitive disorder increased slightly more ($P < .04$) than those in the mild cognitive impairment and dementia groups.

Abbreviations: ADRC = Alzheimer's Disease Research Center, HDRS-17 = 17-Item Hamilton Depression Rating Scale.

correlated with odds of requiring third-step treatment to respond: a 1-week increase in current MDE duration increased the odds of requiring third-step treatment by 1.54 times (54%). Similarly, having a diagnosis of recurrent depression was positively correlated with odds of requiring third-step treatment: participants with recurrent depression were 3.62 times more likely to require third-step treatment, compared to participants with nonrecurrent depression. Age was negatively correlated with odds of requiring third-step treatment: the odds of needing third-step treatment were reduced by 6% for each year increase in current age.

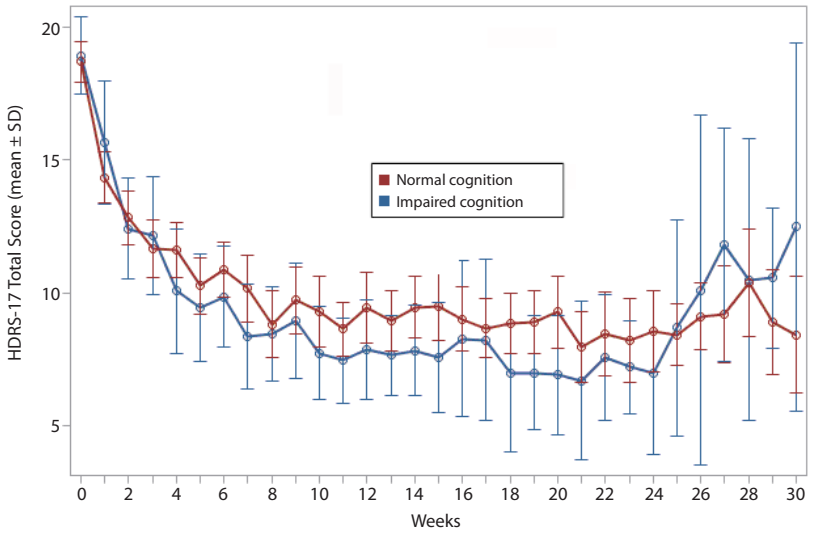
Comparison of Completers and Noncompleters

To provide additional clinical relevance, we undertook analyses to compare the acute-phase completers (N = 153) with participants who dropped out of MTLD-3 prior to completing the acute phase. We analyzed available demographic and clinical data for the 62 noncompleters who dropped out during the acute phase and were ineligible to receive an ADRC cognitive diagnosis. The completers and noncompleters differed significantly in age ($P = .0019$), gender composition ($P = .012$), duration of current MDE ($P = .031$), and baseline HDRS-17 score ($P = .001$), but not in years of education, race, history of recurrent major depressive disorder, or age at first MDE. The noncompleter group had a higher proportion of male participants and was slightly older. The noncompleters were also slightly more depressed at baseline, as indicated by HDRS-17 score, and had longer MDEs at study onset. For a subgroup of participants, we were also able to examine cognitive status (during the MDE) prior to starting treatment in MTLD-3. Scaled baseline DRS-2 scores were available for 69% (149/215) of participants, all of whom had been enrolled in a separate but related protocol.[15] The proportion of participants with DRS-2 scores did not differ significantly between completers and noncompleters ($P = .11$), and mean scaled DRS-2 scores did not differ significantly between the 2 groups ($P = .082$).

Baseline Cognitive Status and Relative Treatment Resistance

We further examined the group of completers with baseline DRS-2 scores (n = 111) to explore the relationship between baseline cognitive assessment and difficulty achieving response. We divided these participants into cognitively normal (baseline DRS-2 ≥ 8) and cognitively impaired (baseline DRS-2 ≤ 7)[16] and calculated the proportion in each group requiring first- (SSRI), second- (SNRI), or third-step (add-on atypical antipsychotic) treatment to respond. The proportions did not differ significantly between the groups ($P = .13$). To examine whether the groups demonstrated different temporal pathways to response, we plotted weekly mean HDRS-17 scores over time (Figure 3). Linear mixed-effect model fit demonstrated that all longitudinal HDRS-17 scores followed a quadratic pattern of decline over time. While both groups declined significantly, the cognitively

Figure 3. HDRS-17 Score Trajectories by Baseline Cognitive Status (DRS-2 score)[a]



[a]For a subgroup of participants, we were able to examine cognitive status prior to the start of antidepressant treatment. Scaled baseline DRS-2 scores were available for 72% of acute phase completers (111/153). Thirty-two subjects had a baseline DRS-2 score within the impaired range (≤7) of cognition, and 79 participants had a baseline DRS-2 score within the normal range (≥8). Using linear mixed-effect modeling, we found that longitudinal HDRS-17 scores followed a quadratic pattern of decline over time. While both groups declined significantly, the cognitively normal group demonstrated a larger decline ($P < .01$) compared to the cognitively impaired group. The estimated minimum HDRS-17 score for the impaired group was achieved at 22.3 weeks and was followed by a minimal increase. The estimated minimum HDRS-17 score for the normal group was achieved at 21.6 weeks and was followed by an increase that was significantly larger than that of the impaired group ($P < .01$).

Abbreviations: DRS-2 = Dementia Rating Scale-2, HDRS-17 = 17-Item Hamilton Depression Rating Scale.

normal group demonstrated a larger decline ($P < .01$) compared to the cognitively impaired group.

Correlation of Pretreatment and Posttreatment Cognitive Assessments

To examine the level of agreement between pretreatment DRS-2 score and posttreatment ADRC diagnosis, we performed 2 κ analyses. When we divided baseline DRS-2 scores into 2 groups (baseline DRS-2 score ≥ 8 corresponding to cognitively normal, and DRS-2 score ≤ 7 corresponding to cognitively impaired [ie, MCI or dementia]), we found κ = 0.39 (95% CI, 0.24–0.54). After dividing baseline DRS-2 scores into 3 groups (DRS-2 score ≥ 8 corresponding to cognitively normal, DRS-2 score of 5–7 corresponding to MCI, and DRS-2 score ≤ 4 corresponding to dementia),[16] we found κ = 0.36 (95% CI, 0.23–0.49). Both analyses suggest a fair level of agreement between pretreatment DRS-2 score (collected during MDE) and ADRC diagnosis (conferred once patient had responded to antidepressant medication). Of note, small cell size in the dementia group (n = 5) prevented 3-way comparisons (NCD, MCI, dementia) of level of treatment required to respond and longitudinal HDRS-17 scores over time.

DISCUSSION

Contrary to our hypothesis, we found that older adults with MCI or dementia who responded to antidepressant treatment did not require a greater level or scope of pharmacotherapy, or take longer to respond, relative to participants with no cognitive disorder. Many participants, including those with dementia, responded to first-line (SSRI) monotherapy. Participants with dementia, MCI, and no cognitive disorder also demonstrated similar response trajectories, based on weekly HDRS-17 scores. It is noteworthy that the average time to response (about 22 weeks) for all 3 cognitive groups was longer than a typical acute treatment trial of 12 weeks. In the MTLD-3 protocol, efforts were focused on maximizing the number of participants available to participate in the randomized, double-blinded maintenance phase of the study, in order to test the primary study hypothesis with maximal power. In many instances, this required additional time in the acute treatment phase, in order to allow participants to receive second- or third-step antidepressant interventions. We also observed a fair amount of variability in response times, with some participants responding within a typical 12-week treatment course and others requiring several months of treatment prior to reaching criteria for stable response. Of note, findings from an ongoing study[18] by our group suggest that it may be possible to shorten time to response by examining early indicators of response probability.

The 3 cognitive groups differed with respect to history of recurrent major depressive disorder and age at first MDE, similar to observations reported by others. For example,

Barnes et al[19] found that onset of depressive symptoms in later life is associated with an increased risk of developing dementia, consistent with our finding that participants in the dementia group had a lower rate of recurrent depression and a later age at onset of first MDE. For these individuals, it is possible that the onset of depressive symptoms in later life represented a "prodrome" of their developing neurodegenerative disorder.

While individuals with a clinical diagnosis of dementia (at study baseline) were excluded from participating in MTLD-3, we were able to identify a number of responders who met criteria for dementia once their depression was adequately treated. Cognitive status was assessed at posttreatment in order to minimize "noise" due to the depressive illness itself. Furthermore, it has become apparent in recent years that dementia—especially in the early stage—is underdiagnosed in the community.[20] Therefore, it is not surprising that while we excluded individuals who had received a clinical diagnosis of dementia prior to entering the study, there were a number of participants with previously undiagnosed dementia who entered and participated in the acute treatment phase of the trial. Our ADRC diagnostic process identified these individuals prior to their entering the maintenance phase of the protocol.

Although participants in the dementia group responded similarly to open-trial antidepressant medication (compared to MCI and NCD groups), the lack of a placebo control is critical to note. For example, Banerjee and colleagues[6] found that monotherapy with antidepressant medication had no benefit over placebo for treatment of depression in Alzheimer's disease. Recent studies have also found central nervous system structural evidence for differential responses to antidepressant treatment among older individuals with depression (though without cognitive impairment). Sheline et al[21] showed that smaller hippocampal volumes on MRI predicted a slower response to antidepressant treatment. These findings have added to the challenge of understanding the interrelationship between hippocampal plasticity, depression, and treatment outcome.

Our analysis of noncompleters found several differences from completers, including older age, greater proportion of men, longer index MDE, and greater severity of depressive symptoms among noncompleters. In contrast, noncompleters did not differ significantly in a pretreatment measure of cognition. This pattern replicates findings that we recently reported in an independent sample of older patients with major depressive disorder—namely, that depression severity at start of treatment and longer index MDE correlate more strongly with response variability than cognitive function.[18] The current analyses were limited by incomplete data on noncompleters, however, and we cannot discount that outcomes may have been influenced by selection bias, such that individuals who would not respond to treatment may have had greater propensity to drop out of the study prior to completion.

Several points should be carried forward. First, among older adults with depression who responded to open-label treatment, there was no detectable association between cognitive diagnosis and intensity of pharmacotherapy or time to or temporal pattern of depressive symptom resolution. However, cognitive status does appear to affect patterns of long-term response during maintenance treatment, as evidenced by greater rates of recurrence among those with MCI (especially among those randomly assigned to donepezil) during 2-year maintenance pharmacotherapy who participated in MTLD-3.[1] In future reports, we aim to more closely examine differences in the "clinical phenotype" of late-life depression among individuals "across the cognitive spectrum," as well as more closely examine differences in cognitive status among study responders and nonresponders. By doing so, we hope to more rigorously answer the question, "How does cognitive status affect the successful treatment of late-life depression?" Collectively, these findings have the potential to significantly impact clinical practice, by allowing practitioners to understand important variables that must be considered when selecting antidepressant treatments for this challenging clinical population.

Drug names: alprazolam (Xanax, Niravam, and others), aripiprazole (Abilify), chlordiazepoxide (Librium and others), clonazepam (Klonopin and others), diazepam (Diastat, Valium, and others), donepezil (Aricept and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), lorazepam (Ativan and others), temazepam (Restoril and others), venlafaxine (Effexor and others).

Author affiliations: Department of Psychiatry, University of Pittsburgh School of Medicine (Drs Koenig, Butters, and Reynolds and Ms Begley); and the Department of Biostatistics (Mr Ogbagaber and Dr Wahed) and Department of Behavioral and Community Health Sciences (Dr Reynolds), Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania.

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