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

Aaron M. Koenig, MD¹, Meryl A. Butters, PhD¹, Amy Begley, MA¹, Semhar Ogbagaber, MS², Abdus S. Wahed, PhD², and Charles F. Reynolds III, MD^{1,3}

¹Department of Psychiatry, University of Pittsburgh School of Medicine (Pittsburgh, PA, USA)

²Department of Biostatistics, Graduate School of Public Health, University of Pittsburgh (Pittsburgh, PA, USA)

³Department of Behavioral and Community Health Sciences, Graduate School of Public Health, University of Pittsburgh (Pittsburgh, PA, USA)

Abstract

Objective—Depression in later life frequently coexists with cognitive impairment. To inform clinical management of these co-occurring conditions, we examined the hypotheses that, relative to cognitively normal elders meeting DSM-IV criteria for major depression, those with cognitive impairment would require greater intensity of pharmacotherapy to reach criteria for response, and take longer to respond.

Method—Using data from the recent Maintenance Therapies in Late Life Depression (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 depression in individuals aged 65 years and older). This short-term treatment trial consisted of three steps: initial treatment with an SSRI, subsequent switch to an SNRI if patient did not meet criteria for response, and addition of an atypical antipsychotic (AAP) for non-response to SNRI monotherapy. The first subject entered the MTLD-3 protocol in April 2004, and the last subject exited the protocol in September 2009. We examined data for participants who completed the acute phase of MTLD-3 as responders and received a consensus cognitive diagnosis (N=153) from the University of Pittsburgh Alzheimer's Disease Research Center, based on National Alzheimer Coordinating Center Uniformed Data Set criteria. We divided participants into three groups, based on cognitive diagnosis: normal cognitive function (N=74), Mild Cognitive Impairment (N=60), and dementia (N=19). For each group, we calculated the proportion of participants who required first (SSRI), second (SNRI), or third-step (add-on AAP) treatment to meet criteria for clinical response (HRSD-17 score ≤ 10 for three consecutive weeks). We compared time to response across groups, and examined patterns of response by inspection of weekly HRSD-17 scores. Finally, we examined correlates of non-response.

Corresponding Author: Meryl A. Butters, PhD, Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Room 462, Pittsburgh, PA 15213, Phone: (412) 246-5280, Fax: (412) 586-9111, ButtersMA@upmc.edu.

Additional information:

The Maintenance Therapies in Late Life Depression (MTLD-3) study is registered at ClinicalTrials.gov: NCT00177671.

Results—The three groups did not differ significantly with respect to time to response ($p=0.84$), trajectories to response, or intensity of antidepressant pharmacotherapy ($p=0.68$). Non-response was more strongly correlated with longer index MDE duration ($p=0.0015$), presence of recurrent depression ($p=0.002$), and younger current age ($p=0.047$), rather than with cognitive status ($p=0.61$).

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

Keywords

late life depression; mild cognitive impairment; dementia; treatment response variability

Introduction

Late life depression (LLD) frequently coexists with cognitive impairment¹⁻³, and growing evidence suggests that these disease processes are “linked” in multiple ways². For some individuals, LLD may be a recurrence of a long-standing depressive illness. For others, it may be the leading symptom of a developing neuropathologic disorder²⁻⁵.

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 SSRIs (selective serotonin reuptake inhibitors) and SNRIs (serotonin-norepinephrine reuptake inhibitors) are used to treat individuals with co-occurring depression and cognitive impairment. However, recent studies have given pause to this approach. Banerjee and colleagues⁶, for example, found that standard antidepressant medications for treatment of depression in Alzheimer’s Disease showed no benefit over placebo. This presents a challenge for clinicians who treat an aging population in which co-occurring mood and cognitive disorders is 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 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 include a deficit in at least one domain of cognition, in the absence of dementia or impairment in activities of daily living⁷.

Neuropsychiatric symptoms affect many individuals with MCI⁸ and nearly all dementia patients at some point, and among these symptoms depression is the most common⁹. 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 (HRSD-17 score ≤ 10 for three 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, compared with cognitively normal participants who responded. To study this, we examined participants enrolled in a LLD 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 non-response.

Method

Overview

These analyses utilized data from the MTLTD-3¹ study, a randomized, double-blind, placebo-controlled maintenance trial designed to test the efficacy of adjunctive donepezil as part of maintenance treatment for LLD. To qualify for randomization to donepezil or placebo in MTLTD-3, full antidepressant response was required (defined by Hamilton Rating Scale for Depression (HRSD-17) score ≤ 10 for three 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/day), and those who did not respond were switched to an SNRI (venlafaxine, up to 300 mg/day, or duloxetine, up to 120 mg/day). Treatment with add-on atypical antipsychotic (aripiprazole, up to 15 mg/day) 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 MTLTD-3, a precondition of which was HRSD-17 ≤ 10 for three 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 MTLTD-3, prior to participant randomization to maintenance donepezil or placebo.

Participants

We screened 299 adults, aged 65 years and older, recruited from primary care practices, mental health clinics, other federally sponsored clinical research projects, and advertisements. To qualify, participants needed to meet the following criteria: (1) age 65 or older; (2) be in a non-bipolar, non-psychotic major depressive episode (MDE); (3) score 15 or higher on the HRSD-17; and (4) not have a pre-existing clinical diagnosis of dementia. Subjects with a clinical diagnosis of dementia were excluded from the MTLTD-3 protocol, given the study's focus on examining the efficacy of add-on donepezil as part of maintenance treatment for depression in non-demented elders. In the maintenance phase of MTLTD-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 IRB 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 MTLTD-3 protocol in April 2004, and the last subject exited the protocol in September 2009.

Measures

Diagnostic measures—The Structured Clinical Interview for DSM-IV¹¹ was administered as part of the diagnostic evaluation. Details of past MDEs and other DSM-IV diagnoses were ascertained. Upon completing the acute intervention phase, the ADRC consensus conference reviewed post-depression response neuropsychological data, clinical history, MRI data, and performance based ADL/IADL measures. The following diagnoses were conferred according to National Alzheimer Coordinating Center criteria: no cognitive disorder, MCI, and dementia. MCI was subtyped into amnesic MCI (aMCI) or non-amnesic MCI (naMCI), depending on whether or not memory was impaired, as well as single-domain or multiple-domain, depending on how many cognitive domains were impaired⁷. Five participants who responded to open-label antidepressant treatment did not receive an ADRC diagnosis of dementia, MCI, or normal cognition, and were excluded from the analyses.

Depression severity measure—Depression symptom severity was measured using the HRSD-17¹². Clinicians administered the HRSD-17 at diagnostic evaluation and weekly during acute phase treatment. Antidepressant response was defined as achieving HRSD-17 scores of less than or equal to 10 for three 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 non-depressed, 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 calculate a global performance score. We explored five 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 al¹³, 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)¹⁴, were administered the Dementia Rating Scale-2 (DRS-2)¹⁵ during diagnostic evaluation. A scaled DRS-2 score⁷ was used to classify participants as cognitively impaired, with a score of 7 representing one 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 an ADRC diagnosis (N=153) post-intervention. We divided participants into three groups, based on diagnosis: no cognitive disorder, 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 chi-square tests, or its exact 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 non-normally 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 chi-square tests, or Fisher's 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 HRSD-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 $p < 0.25$ were considered for entry into the multivariable model. Variables with higher p -values were sequentially eliminated, until all variables reached a significance cut-off of 0.05. 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 chi-square 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 HRSD-17 scores over time, and performed linear mixed effect model fit. Lastly, we performed kappa analyses to examine the level of agreement between pre-treatment DRS-2 score and post-treatment 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 (DEM), 60 (39.2%) with MCI, and 74 (48.4%) with no cognitive disorder (NC). Of note, while individuals with a clinical diagnosis of dementia (at study baseline) were excluded from participating in MTL-D-3, 12.4% of responders met criteria for dementia, once their depression had responded to antidepressant treatment.

As summarized in Table I, the three cognitive groups differed significantly in age ($p < 0.001$) and years of education ($p = 0.02$), but not in race or gender. The NC group was younger than the other groups, and the MCI group had the fewest years of education. The three groups did not differ on baseline HRSD-17 score, but did differ significantly on baseline DRS-2 score ($p < 0.001$). As expected, the MCI and dementia groups had lower baseline DRS-2 scores than the normal cognition 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 MDD ($p < 0.001$) and greater mean age at onset of first MDE ($p = 0.002$) (Table I).

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 NC, MCI, and DEM groups. First, we calculated the proportion of participants in each group who required first (SSRI), second (SNRI), or third step (+AAP) treatment to respond. These proportions did not differ significantly across the three groups ($p = 0.68$) (Table I). Notably, 73.7% of participants with dementia responded to first-line treatment, compared to 56.7% in the MCI and 58.1% in the NC groups (Table I). 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 ($p = 0.79$) (Table I). To more precisely measure benzodiazepine exposure, we calculated average daily benzodiazepine dose for each participant¹⁶, and compared mean values across the three groups. Mean dose per day of diazepam-equivalents did not differ significantly across the groups ($p = 0.156$), and overall benzodiazepine exposure was low.

Mean times to response did not differ significantly across the three groups ($p = 0.84$) (Table I). To examine whether the groups demonstrated different temporal pathways to response, we plotted weekly mean HRSD-17 scores over time for each cognitive diagnosis (Figure 2). Linear mixed effect model fit demonstrated that all longitudinal HRSD-17 scores followed a quadratic pattern of decline over time. While mean HRSD-17 scores were similar at baseline ($p = 0.65$), the NC group showed a slightly larger decline ($p < 0.04$) over time compared to the other groups, though the absolute difference was small and clinically insignificant (Figure 2).

Multivariate analyses of relative treatment resistance

In multivariable analyses, longer duration of current MDE ($p=0.0015$), presence of recurrent depression ($p=0.002$), and younger current age ($p=0.047$) 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 ($p=0.61$). Length of MDE was positively correlated with odds of requiring third-step treatment to respond: a one-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 non-recurrent 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 non-completers

To provide additional clinical relevance, we undertook analyses to compare the acute phase completers ($N=153$) with participants who dropped out of MTLTD-3 prior to completing the acute phase. We analyzed available demographic and clinical data for the 62 non-completers who dropped out during the acute phase and were ineligible to receive an ADRC cognitive diagnosis. The completers and non-completers differed significantly in age ($p=0.0019$), gender composition ($p=0.012$), duration of current MDE ($p=0.031$), and baseline HRSD-17 score ($p=0.001$), but not in years of education, race, history of recurrent MDD, or age of first MDE. The non-completer group had a higher proportion of male participants and was slightly older. The non-completers were also slightly more depressed at baseline, as indicated by HRSD-17 score, and had longer MDE's at study onset. For a subgroup of participants, we were also able to examine cognitive status (during the MDE) prior to starting treatment in MTLTD-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 protocol¹⁴. The proportion of participants with DRS-2 scores did not differ significantly between completers and non-completers ($p=0.11$), and mean scaled DRS-2 scores did not differ significantly between the two groups ($p=0.082$).

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)¹⁵, and calculated the proportion in each group requiring first (SSRI), second (SNRI), or third step (+AAP) treatment to respond. The proportions did not differ significantly between the groups ($p = 0.13$). To examine whether the groups demonstrated different temporal pathways to response, we plotted weekly mean HRSD-17 scores over time (Figure 3). Linear mixed effect model fit demonstrated that all longitudinal HRSD-17 scores followed a quadratic pattern of decline over time. While both groups declined significantly, the cognitively normal group demonstrated a larger decline ($p < 0.01$) compared to the cognitively impaired group.

Correlation of pre-and post-treatment cognitive assessments

To examine the level of agreement between pre-treatment DRS-2 score and post-treatment ADRC diagnosis, we performed two kappa analyses. Dividing baseline DRS-2 scores into two groups (baseline DRS-2 > 8 corresponding to cognitively normal, and DRS-2 ≤ 7 corresponding to cognitively impaired [i.e. MCI or dementia]), we found Kappa=0.39 (95%CI: 24-54). Dividing baseline DRS-2 scores into three groups (DRS-2 > 8 corresponding to cognitively normal, 7 > DRS-2 > 5 corresponding to MCI, and DRS-2 ≤ 4 corresponding to dementia)¹⁵, we found Kappa=0.36 (95%CI: 23-49). Both analyses suggest a fair level of agreement between pre-treatment 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 three-way comparisons (NC, MCI, DEM) of level of treatment required to respond and longitudinal HRSD-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 cognitively normal participants. Many participants, including those with dementia, responded to first-line (SSRI) monotherapy. Participants with normal cognition, MCI, and dementia also demonstrated similar response trajectories, based on weekly HRSD-17 scores. It is noteworthy that average time to response (about 22 weeks) for all three cognitive groups was longer than a typical acute treatment trial of 12 weeks. In the MTLTD-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 study¹⁷ by our group suggest that it may be possible to shorten time to response by examining early indicators of response probability.

The three cognitive groups differed with respect to history of recurrent MDD and age of first MDE, similar to observations reported by others. For example, Barnes et al¹⁸ 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 of 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 MTLTD-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 post-treatment 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 under-diagnosed in the community¹⁹. 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 entering the maintenance phase of the protocol.

Although participants in the dementia group responded similarly to open-trial antidepressant medication (compared to MCI and NC groups), the lack of a placebo control is critical to note. For example, Banerjee and colleagues⁶ found that monotherapy with antidepressant medication had no benefit over placebo for treatment of depression in Alzheimer's disease. Recent studies have also found CNS structural evidence for differential responses to antidepressant treatment among older individuals with depression (though without cognitive impairment). Sheline et al²⁰ 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 non-completers found several differences from completers, including older age, greater proportion of men, longer index MDE, and greater severity of depressive symptoms among non-completers. In contrast, non-completers did not differ significantly in a pre-treatment measure of cognition. This pattern replicates findings that we recently reported in an independent sample of older patients with MDD—namely, that depression severity at start of treatment and longer index MDE correlate more strongly with response variability than cognitive function¹⁷. The current analyses were limited by incomplete data on non-completers, 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, 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 two-year maintenance pharmacotherapy who participated in MTLT-3¹. In future reports, we aim to more closely examine differences in the “clinical phenotype” of LLD among individuals “across the cognitive spectrum,” as well as more closely examine differences in cognitive status among study responders and non-responders. 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.

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Clinical Points

- Late life depression frequently presents with cognitive impairment in the clinical setting.
- The current 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.

Podcast Summary

Late life depression – or major depression in adults age 65 and older - is a growing concern for our aging population. Patients with late life depression frequently report cognitive complaints, and evidence from a number of studies suggests that depression and cognitive impairment in later life may be linked by a number of neurobiological mechanisms. From a clinical perspective, it's important to understand how to effectively treat these individuals, and despite mixed results from recent trials, medications such as SSRIs and SNRIs are typically used to treat patients with co-occurring depression and cognitive dysfunction. In this secondary analysis of data from the recent MTL-D-3 study, Koenig and colleagues examined the relationship between cognitive diagnosis and response to open-label antidepressant medications. Among individuals who completed the acute treatment phase of the study, Koenig and colleagues found that participants with normal cognition, mild cognitive impairment, and dementia were similar in the time and intensity of treatment they required to meet criteria for response, which was defined as achieving a Hamilton score of ten or less for three consecutive weeks. In addition, non-response to medication was more strongly correlated with longer depression duration, a positive history of recurrent depression, and younger age, rather than with cognitive diagnosis. One limitation of the study was the open-label nature of the protocol, which prevented the researchers from concluding if it was the medications that allowed these patients to respond, or if instead it was the supportive environment of the clinic, with very close follow-up, that helped them get better over the course of the study.

Figure 1. Flowchart of Participants – Acute Phase of MTLD-3

^aReasons for termination included: co-morbid medical problems, non-compliance with study medications or procedures, other treatment-related reasons, or poor response to study medication. ^bReasons for not receiving ADRC consensus diagnosis included: non-cooperative, exited study prior to assessment, received other (non-cognitive) diagnosis.

Figure 2. HRSD-17 score trajectories by ADRC consensus diagnosis

Linear mixed effect model fit demonstrated that all longitudinal HRSD-17 scores followed a quadratic pattern of decline over time. While mean HRSD-17 scores were similar at baseline ($p = 0.65$), the cognitively normal group showed a slightly larger decline ($p < 0.04$) over time compared to the MCI and dementia groups. The estimated minimum HRSD-17 score (6.3) for the dementia group was achieved at week 24.8, while the estimated minimums for the MCI (5.6) and cognitively normal (5.5) groups were achieved at approximately 23 weeks. After reaching its minimum, the cognitively normal group increased slightly more ($p < 0.04$) than the MCI and dementia groups.

Figure 3. HRSD-17 score trajectories by baseline cognitive status (DRS-2 score)

For a subgroup of participants, we were able to examine cognitive status prior to starting antidepressant treatment. Scaled baseline DRS-2 scores were available for 72% (111/153) of acute phase completers. Thirty-two subjects had a baseline DRS-2 score that fell within the impaired range (< 7) of cognition, and 79 participants had a baseline DRS-2 score that fell within the normal range (≥ 8). Using linear mixed effect modeling, we found that longitudinal HRSD-17 scores followed a quadratic pattern of decline over time. While both groups declined significantly, the cognitively normal group demonstrated a larger decline ($p < 0.01$) compared to the cognitively impaired group. The estimated minimum HRSD-17 score for the impaired group was achieved at 22.3 weeks, and was followed by a minimal increase. The estimated minimum HRSD-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 ($p < 0.01$).

Table 1
Demographics, Depression History, and MTL-D-3 Treatment Response (By ADRC Cognitive Diagnosis)

	Normal Cognition (NC) (N=74)		Mild Cognitive Impairment (MCI) (N=60)		Dementia (DEM) (N=19)		
Item	N (%)	Mean (SD)	N (%)	Mean (SD)	N (%)	Mean (SD)	Test of Differences
Demographics							
Age (Years)	74	71.95 (5.80)	60	75.17 (6.08)	19	78.00 (5.73)	F(2,150)=10.00, p<0.001
Gender (Female)	57 (77.03)		45 (75.00)		16 (84.21)		$\chi^2=0.69$, df=2, p=0.71
Race (Caucasian)	69 (93.24)		50 (83.33)		16 (84.21)		$\chi^2=3.47$, df=2, p=0.18
Education (Years)	74	14.07 (2.69)	60	12.85 (2.15)	19	13.74 (2.35)	F(2,150)=4.15, p=0.02
Depression History							
History of Recurrent MDD	47 (63.51)		29 (48.33)		3 (15.79)		$\chi^2=14.22$, df=2, p<0.001
Age of First MDE	74	50.45 (21.15)	60	57.53 (21.54)	19	68.74 (12.90)	F(2,150)=6.51, p=0.002
Duration Current MDE (Weeks)	73	31 (15,122) ^a	60	60 (17,189) ^a	19	72 (56,200) ^a	F(2,149)=2.65, p=0.07
HRSD-17 (Baseline total)	74	18.36 (3.32)	60	19.07 (3.24)	19	19.47 (4.69)	F(2,150)=1.10, p=0.33
DRS-2 (Scaled baseline total) ^b	55	9.73 (2.03)	42	7.93 (2.19)	14	6.00 (2.00)	F(2,108)=21.00, p<0.001
Treatment Response During Acute Phase of MTL-D-3							
Time to response (Weeks)	74	21.67 (11.02)	60	22.81 (11.37)	19	22.41 (10.32)	F(2,150)=0.18, p=0.84
Respond to first-step (SSRI)	43 (58.1)		34 (56.7)		14 (73.7)		
Respond to second-step (SNRI)	26 (35.1)		20 (33.3)		4 (21.1)		$\chi^2=2.31$, df=4, p=0.68 ^c
Respond to third-step (SNRI+AAP)	5 (6.8)		6 (10)		1 (5.3)		
Received Benzo? (%Yes)	33 (44.6)		29 (48.3)		10 (52.6)		$\chi^2=0.456$, df=2, p=0.79
Benzo exposure (mg/day) ^d	33	1.40 (0.77,2.2) ^a	29	1.77 (1.4,5.2) ^a	10	1.78 (1.4,3.5) ^a	$\chi^2=3.71$, df=2, p=0.156

^aMedian (25th percentile, 75th percentile)

^bOnly those participants (N=111) who participated in a separate but related protocol¹⁴ had the DRS-2 administered at baseline.

^cWe did not have sufficient power to detect pairwise differences between these groups.

^dBenzodiazepines used during study included alprazolam, clonazepam, clordiazepoxide, clonazepam, diazepam, lorazepam, oxazepam, and temazepam. Medications were converted to diazepam-equivalent doses¹⁶ and averaged per day in the acute phase of MTL-D-3. Abbreviations: MDE (Major Depressive Episode), DRS-2 (Dementia Rating Scale-2), Benzo (Benzodiazepine), SSRI (Selective Serotonin Reuptake Inhibitor), SNRI (Serotonin-Norepinephrine Reuptake Inhibitor), AAP (Atypical Antipsychotic).