Early Symptom Trajectories as Predictors of Treatment Outcome for Citalopram Versus Placebo

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Objectives: *The high percentage of failed clinical trials for anti-depressant medications, especially in elderly populations, obscures the fact that some patients may benefit greatly from treatment. Early detection of patients who may benefit most from antidepressant medication may improve treatment decisions. We examined whether depressed patients in a large clinical trial exhibit distinct trajectories of early symptom change that predict differential response to medication or placebo.* **Methods:** *We reanalyzed data of 174 patients aged 75 years and older with unipolar depression who were randomly assigned to citalopram or placebo. We used growth mixture modeling to identify trajectories of early change (weeks 1–4) on the Hamilton Rating Scale for Depression in the citalopram and placebo conditions.* **Results:** *In the citalopram condition, two distinct trajectories of early change were detected that were associated with significantly different symptom reduction, but only one trajectory was detected for the placebo condition. One of the early trajectories of patients receiving citalopram (N = 33) showed significantly better symptomatic change than placebo; the other trajectory (N = 51) did not differ significantly from placebo. Poor baseline functional scores predicted trajectory membership, so that individuals with a score below 4.5 on baseline instrumental activities of daily living showed a higher tendency to be in the trajectory that outperformed placebo.* **Conclusions:** *The subgroup of citalopram-treated patients exhibiting better symptom trajectory early in a trial are likely to have beneficial outcomes relative to placebo. Future research should focus on developing reliable pre-treatment clinical and biological measures to identify this subgroup.* (Am J Geriatr Psychiatry 2017; ■■:■■–■■)

Key Words: Placebo, depression, trajectories of early symptom change, personalized treatment

Major depressive disorder (MDD) in the elderly has many negative consequences, including functional decline and a higher risk for other illnesses, such as dementia, and its healthcare costs are high.[1–3] The current gold standard for the treatment of MDD is antidepressant medications,[4] but even with maximal treatment many patients fail to experience sustained remission of their depression.[5] Better

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pharmacological options for treating MDD are urgently needed, but a rise in failed trials of putative antidepressant agents[6,7] has made the development of effective treatments difficult and expensive. This "psychopharmacological crisis"[6] is especially troubling among the elderly population.

It has recently been suggested that aggregated data from many individuals may mask inter-individual variability[8–10] because some patients demonstrate a clear advantage for a given medication over placebo, whereas for others this is not the case.[11] The complex etiology of late-life depression may result in distinct clinical depression subtypes based on their underlying biology, each requiring a different treatment approach.[12] Only some of these subtypes may respond to medication. Indeed, patient cohorts included in current antidepressant trials for the elderly show a heterogeneous response to antidepressants,[13] which may have contributed to treatment failure for the cohort as a whole. Such failures increase the cost of drug development, delay marketing, and eventually limit treatment for patients who could benefit from the medication. Early detection of responsive patients can aid in decision-making, improve response rates, and lower costs by focusing on patients who could benefit most from treatment and referring others to alternative treatment options.

Advanced statistical tools can help identify distinct trajectories of change in different subpopulations within the same cohort. In a re-analysis of the data from a clinical trial of duloxetine, Gueorguieva et al.[14] identified distinct trajectories for responders (76.3% of the sample) and nonresponders (23.7% of the sample) in an antidepressant-treated subsample, whereas placebo-treated patients were characterized by a single response trajectory. Patients in the "responders" trajectory had better treatment outcomes than the placebo group, whereas those in the "non-responders" trajectory had poorer outcomes than the placebo group. Although these findings are promising, they are currently restricted to younger populations, and have not yet been studied in the elderly. Furthermore, trajectories of change were evaluated based on data that is available only at the end of treatment, limiting the clinical usefulness of identifying non-responders. Evaluating early trajectories of change as predictors of treatment outcome is more relevant for practical use.

In the present study we conducted a secondary analysis of a randomized controlled trial (RCT) comparing medication with placebo in patients diagnosed with unipolar depression, aged 75 years and older. This large, well-conducted study failed to find significant outcome differences across the entire sample between participants randomized to citalopram and those receiving placebo. In the current study, however, we were interested in determining whether it is possible to identify a significant medication-responsive subgroup of participants based on distinctive trajectories of early symptomatic change. We chose to focus on the first four symptom assessments, because most previous reports have used between three[15] and five[16] sessions for detecting early change in treatment. We reasoned that choosing the first four sessions can produce clinically meaningful information early enough to affect subsequent treatment, including the possibility of switching to a different treatment when necessary.[17]

METHODS

Sample and Clinical Trial Procedures

The procedures used in this multi-site, placebo-controlled RCT have been previously described.[13] Briefly, 174 community-dwelling men and women aged 75 years or older who met DSM-IV criteria (based on a Structured Clinical Interview for DSM-IV Axis I Disorders interview) for non-psychotic unipolar depression (single or recurrent), with a baseline 24-item Hamilton Rating Scale for Depression (HRSD[18]) score of 20 or higher, participated in this 8-week RCT. All patients began the trial with a one-week, single-blind placebo lead-in, with the baseline visit conducted at the end of the lead-in period. Patients were randomized in 15 centers to citalopram (20 mg/day) or matched placebo at a ratio of 1:1 only if they continued to meet inclusion and exclusion criteria at the end of the placebo lead-in period. At the end of the fourth week, patients with an HRSD score less than 10 had their medication dose increased to two pills per day (i.e., 40 mg of citalopram, or two placebo pills). Clinical assessments were conducted at baseline and at weeks 1, 2, 3, 4, 5, 6, and 8 (final week). For this analysis, baseline and weekly assessments of the HRSD were used, together with the intake assessment of the instrumental activities of daily living (IADL[19]).