Pretreatment Brain States Identify Likely Nonresponse to Standard Treatments for Depression

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Background: Treatment approaches for major depressive disorder (MDD) result in approximately one third of patients achieving remission after a first treatment. Added treatment generally improves remission rates, but approximately one third of all patients fail to respond after several treatments (sequential monotherapies or combined treatment). A pretreatment biomarker could help identify these patients. Overactivity of the subcallosal cingulate has been associated with failure of response to treatment in MDD, and it is a potential candidate for such a biomarker.

Methods: Investigators enrolled 82 patients with MDD currently not receiving treatment in a two-phase treatment study. Patients underwent a fluorodeoxyglucose positron emission tomography scan. After scanning, patients were randomly assigned to 12 weeks of treatment with either escitalopram or cognitive-behavioral therapy (CBT). Patients not achieving remission after 12 weeks of initial treatment were treated with an additional 12 weeks of escitalopram plus CBT. Subcallosal cingulate metabolism was compared between patients who failed to achieve a response and patients who achieved remission as a result of either phase one or phase two treatment. This analysis was followed by a whole-brain analysis making the same comparison.

Results: After two phases of treatment (24 weeks), 36 patients were identified as remitters, 6 patients were responders, and 9 patients were nonresponders. Subcallosal cingulate metabolism was significantly higher in nonresponders than remitters. In the follow-up whole-brain analysis, increased superior temporal sulcus activity was also associated with nonresponse to two treatments.

Conclusions: Patients with MDD who fail to achieve remission as a result of CBT or escitalopram, either alone or in combination, have a distinct brain metabolic pattern compared with patients who achieve remission as a result of CBT, escitalopram, or their combination.

Key Words: Antidepressant medication, biomarker, depression, psychotherapy, subcallosal cingulate, superior temporal sulcus

After >40 years of research on treatment outcomes in major depressive disorder (MDD), current standards for treatment selection remain imprecise and nonpersonalized. This imprecision has significant clinical repercussions; published remission rates are consistently <40% in depressed patients treated with first-line monotherapies such as antidepressant medications (e.g., selective serotonin reuptake inhibitors [SSRIs]) or evidence-based psychotherapies (e.g., cognitive-behavioral therapy [CBT], interpersonal therapy) (1–6). After an initial treatment failure, subsequent steps generally involve switching between or combining first-line treatments. Common second-step treatment strategies include moving between psychotherapy and antidepressant medication, switching among antidepressant medications, or augmenting antidepressant medication treatment with psychotherapy or a second medication. However, such strategies result in additional remission rates of only 15%–20% (5,7–9). Critically, the lack of response to initial treatments increases the vulnerability of nonremitting patients to ongoing suicidal ideation, social dysfunction, and treatment dropout (10).

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Initial choice of treatment for MDD is typically based on the judgment of the mental health professional delivering the intervention, patient preference, consideration of potential side effects, and drug interactions. Treatment guidelines have suggested that severity of the disorder should guide the choice of intervention, with antidepressant medications or the combination of medications and CBT as the first-line treatment for severely depressed patients (3,11); however, data to support this recommendation are limited and inconsistent (12).

This lack of evidence-based guidance for optimizing treatment for depression has encouraged clinical researchers to evaluate various predictive markers that could be applied at the level of the individual patient. Working toward such a "stratified medicine" approach, numerous strategies have been tested, including clinical (13), imaging (14–17), genetic (18,19), electroencephalographic (20), and immune-related metrics (21). However, many of these strategies focus on a single treatment and can identify only factors predicting good or poor outcome to one treatment modality. Such predictors of single-treatment response have limited clinical application because the key clinical decision is to pick which of several treatment modalities is likely to be most successful for a given patient. Addressing this issue, our group reported recently that metabolic activity in the right anterior insula (among several identified candidates measured using fluorodeoxyglucose positron emission tomography [FDG-PET]) best predicted differential remission and nonresponse to randomized initial treatment with either an antidepressant medication (escitalopram [sCIT]) or CBT (22). However, a more complex combination of regional patterns may be needed to characterize fully patients who require alternative treatments or who may be treatment resistant.

The next step from this data set was to examine potential predictors of patients who are unlikely to show meaningful

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improvement to either of these first-line treatments. Defining neural activity patterns predictive of failure to both a standard antidepressant medication and an evidence-based course of psychotherapy could help "fast-track" such patients to alternative treatments, partially circumventing the protracted trial-and-error process of current clinical care. Toward these goals, we examined regional cerebral glucose metabolism that characterized nonresponse to two MDD recommended treatments: evidence-based psychotherapy and a selective serotonin reuptake inhibitor (P+SSRI) (1). Nonresponders to P+SSRI treatment are defined as patients who fail to respond over 6 months of treatment—the first 3 months randomly assigned to either CBT or sCIT, and the second 3 months receiving combined sCIT and CBT.

Based on previous investigations of treatment failure in MDD (16,23–25), we hypothesized that P+SSRI treatment nonresponders would show increased subcallosal cingulate (SCC) metabolism before treatment as indexed by FDG-PET. Previous studies have shown hyperactivity in the SCC at baseline in patients who fail to respond to various treatments (16), especially in patients who have already failed at least one treatment (23–25). Many of the prior studies included patients receiving active treatment or patients who previously demonstrated treatment resistance. We explored the pretreatment neural patterns associated with nonresponse in depressed patients after randomized, controlled, stepwise treatment with two antidepressant interventions with different presumed mechanisms of action.

Methods and Materials

Participants

Study enrollment has been previously described (22,26). Briefly, a primary diagnosis of MDD was assessed by the Structural Clinical Interview for DSM-IV Axis I Disorders (27) and confirmed through psychiatric evaluation by a study psychiatrist. The Mood and Anxiety Disorders Program at Emory University recruited adult outpatients (18–60 years old) through clinician referrals and advertisement. Severity of depression was defined by the Hamilton Depression Rating Scale (HDRS) (28); cutoffs for inclusions were a 17-item score $\geq$18 at screening and $\geq$15 at the baseline randomization visit. Exclusion criteria included a primary psychiatric condition other than MDD, a medical or neurologic condition potentially contributing to depression or interfering with response to treatment, psychotic features, current suicidal ideation requiring urgent clinical intervention, current substance abuse (past 3 months) or dependence (past 12 months), current obsessive-compulsive disorder or eating disorder, current or intended pregnancy or breastfeeding, current treatment with antidepressant medication, or receipt of electroconvulsive therapy within 6 months of the screening visit. Additional exclusion criteria included lifetime history of failure to respond to adequate treatment with the treatments offered in the current study (minimum four sessions CBT; minimum 10 mg/day sCIT for 6 weeks).

Written informed consent was obtained from all participants with the protocol conducted as approved by the Emory Institutional Review Board and as registered at clinicaltrials.gov (NCT00367341). For interpretation of identified differences in regional metabolism, a comparison group of 24 healthy volunteers was similarly screened with the additional exclusion criterion of no current or past MDD.

Treatment Protocol

Treatment consisted of two phases: monotherapy treatment (phase one) followed by combination treatment (phase two) (Figure 1) (22). In phase one, patients were randomly assigned (1:1) to receive 12 weeks of either sCIT or manual-based, depression-focused CBT. PET and magnetic resonance imaging (MRI) scans were performed before treatment randomization. Patients were subsequently randomly assigned to sCIT or CBT if they continued to meet eligibility criteria. sCIT was started at 10 mg/day and increased to 20 mg/day at or after week 3 if the patient was not in remission and was tolerating the medication. If side effects were intolerable at the higher dose, dosage could be reduced to 10 mg/day. There were 16 CBT sessions scheduled—twice weekly for the first 4 weeks and weekly for the subsequent 8 weeks. Raters who were blinded to treatment group assessed changes in symptom severity using the HDRS. Ratings were performed weekly for the first 6 weeks, then biweekly through week 12. On completion of phase one treatment, patients not showing remission (patients with HDRS score $>$7 at either week 10 or week 12) were offered enrollment in phase two. Phase two treatment included an additional 12 weeks of treatment with combination sCIT and CBT. In phase two, patients initially randomly assigned to sCIT continued on their current dosage with CBT sessions added twice weekly for the first 4 weeks, then weekly for the subsequent 8 weeks. Patients initially randomly assigned to CBT received three booster sessions of CBT at monthly intervals, and sCIT was added using the same dosage as in phase 1. Raters assessed changes in symptom severity using the HDRS: weekly for the first 6 weeks of phase two, then biweekly until week 24.

Clinical Metrics

Clinical outcomes were defined using the HDRS with remission as the target endpoint. Phase one remission was defined as HDRS score $\leq$7 at both week 10 and week 12 of treatment. Similarly, phase two remission was defined as HDRS score $\leq$7 at both week 22 and week 24 of treatment. Patients in remission at the end of phase one or phase two treatments were included in the remitter group. Nonresponse to P+SSRI was defined by HDRS score change of $<$50% from baseline to the end of phase two (week 24). To avoid potential dilution of either the remission or the P+SSRI nonresponse groups, dropouts and patients who achieved response but not remission (change in HDRS score $\geq$50% but with HDRS score $>$7) by the end of phase two were not included in these main outcome groups but were examined post-hoc. Other clinical measures included Beck Depression Inventory (29), Hamilton Anxiety Scale (30), age, gender, age of MDD onset, duration of current episode, number of previous episodes, previous treatment, MDD type, family history of mood disorder, education, marital status, race, employment status, and Childhood Trauma Questionnaire (31). *t* tests were performed to compare P+SSRI nonresponders with remitters on these variables as well as comorbid psychiatric disorders (current anxiety disorder, lifetime posttraumatic stress disorder, and lifetime substance abuse) independent of the primary imaging analyses described subsequently.

Imaging Acquisition

Before treatment randomization, brain glucose metabolism was measured using standard PET methods (Siemens HRRT; Siemens, Nashville, Tennessee) as previously described (22). A 10-mCi dose of FDG was administered intravenously for each scan. A 40-min uptake period during which patients remained