Quantitative Electroencephalogram Biomarkers for Predicting Likelihood and Speed of Achieving Sustained Remission in Major Depression: A Report From the Biomarkers for Rapid Identification of Treatment Effectiveness in Major Depression (BRITE-MD) Trial

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ABSTRACT

Objective: Clinical trials in major depressive disorder (MDD) commonly assess remission at a single endpoint. Complementary, clinically relevant metrics include the likelihood and speed of achieving sustained remission. A neurophysiologic measure, the Antidepressant Treatment Response (ATR) index, previously predicted 8-week outcomes of pharmacotherapy. We retrospectively examined data from the Biomarkers for Rapid Identification of Treatment Effectiveness in Major Depression (BRITE-MD) trial to evaluate this biomarker's properties in predicting sustained remission and time to achieve sustained remission.

Method: In the BRITE-MD trial, 67 adults with *DSM-IV* MDD received escitalopram continuously for 13 weeks. The 17-item Hamilton Depression Rating Scale ($HDRS_{17}$) was used to define sustained remission as achieving remission ($HDRS_{17}$ score ≤ 7) at a series of consecutive assessments, including week 13. The onset of sustained remission was defined as the earliest time from which all subsequent $HDRS_{17}$ assessments were ≤ 7. The ATR was evaluated by using frontal quantitative electroencephalogram recordings at baseline and week 1. Subjects were stratified based on ATR status (ie, ATR+/ATR–). Kaplan-Meier survival analysis evaluated group differences in time to sustained remission. Higher ATR was hypothesized to predict sustained remission and time to sustained remission. Subjects participated between January 2006 and July 2007.

Results: Of 67 subjects, 36 achieved remission by week 13, and ATR predicted this single endpoint in receiver operating characteristic analyses ($P = .016$; sensitivity, 52.8%; positive predictive value, 76.0%). Remitters had a higher mean (SD) ATR value than those who did not remit (57.9 [10.0] vs 51.9 [8.7], $P = .012$). Sixteen of the 31 individuals with sustained remission had ATR+ status, while 28 of the 36 who were not sustained remitters had ATR– status ($P = .012$). The mean time to reach sustained remission was significantly shorter among ATR+ subjects than ATR– individuals (38 vs 53 days, $P = .038$).

Conclusions: The ATR index predicted remission at 13 weeks as well as the speed of achieving sustained remission with antidepressant monotherapy. This finding suggests that the ATR biomarker may predict stable longer-term outcomes.

Trial Registration: ClinicalTrials.gov identifier: NCT00289523

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Major depressive disorder (MDD) is a common and disabling illness, accounting for considerable disability[1] and cost to both individuals and society.[2] Investigations into treatment efficacy or effectiveness commonly employ assessments made at a single point at the end of the trial, using measures of symptom severity such as the 17-item Hamilton Depression Rating Scale ($HDRS_{17}$) or the 16-item Quick Inventory of Depressive Symptomatology.[3] For many patients, monotonic improvement in symptom severity may occur over successive assessments, but for other individuals, severity waxes and wanes from visit to visit and benefits of treatment may fade over time.[4–7] In the clinical setting, durability of mood improvement is among the most salient of outcomes. One indicator of such durability is achievement of sustained remission, ie, persistence of low symptom severity continuously at multiple evaluations prior to the final evaluation.[8–10]

A neurophysiologic biomarker, the Antidepressant Treatment Response (ATR) index, has been studied as a predictor of antidepressant treatment outcome.[11,12] The ATR combines electroencephalogram (EEG) features recorded from frontal brain regions prior to and after 1 week of antidepressant treatment; this numerical index previously has been shown to be predictive of outcome.[13–15] The use of ATR in characterizing final outcomes to widely used antidepressants was studied in the Biomarkers for Rapid Identification of Treatment Effectiveness in Major Depression (BRITE-MD) trial (ClinicalTrials.gov identifier: NCT00289523).[11,12]

In the BRITE-MD trial, adults with MDD received 1 week of escitalopram and underwent EEG recording both before and after this period in order to calculate ATR values. After 1 week, subjects were randomized to continue escitalopram, switch to bupropion, or combine escitalopram with bupropion added (see Method section below). In previous reports,[11,12] the presence of a high ATR value assessed on escitalopram (ATR+ status) was significantly associated with week 7 response and remission outcomes of treatment with escitalopram, while low values (ATR–) were associated with poor outcome. Conversely, for subjects randomized to treatment with bupropion, ATR– status (on escitalopram) was significantly associated with better outcome. The relationship of ATR score to outcome has

Clinical Points

- Treatment selection in major depressive disorder could be improved if a biomarker could predict the likelihood and speed of achieving sustained remission with a particular agent for an individual patient.
- A novel biomarker, based on prefrontal brain electrical activity in the first week of treatment, appears able to predict these clinically relevant aspects of response to treatment in a personalized medicine paradigm.

been independently confirmed in a naturalistic study with antidepressants selected by clinicians' choice.[16]

While prior BRITE-MD reports have focused on an $HDRS_{17}$ score at week 7 as the primary outcome, data also were collected from frequent assessments throughout the entire 13 weeks of the trial. In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial,[17] approximately half of the subjects who entered remission in level 1 treatment did so by week 6, but half entered remission between weeks 6 and 14, indicating that 13 weeks may be a particularly salient timeframe. In addition, because of the clinical relevance of *sustained remission* as opposed to remission at a single endpoint, for this analysis, we examined clinical outcome at successive time points through 13 weeks to determine whether each subject did or did not attain sustained remission. Finally, we examined *time to sustained remission* as a complementary measure of clinical interest. We hypothesized that in subjects receiving the same medication continuously during and after biomarker measurement, high ATR values would be associated with sustained remission and with shorter times to achieving it.

METHOD

Overview

The BRITE-MD study was conducted at 9 sites by using methods that are described in more detail elsewhere[11,12] and are described briefly below.

Subjects

A total of 375 adults 18–75 years of age and meeting *DSM-IV* criteria for MDD based on the Mini-International Neuropsychiatric Interview (MINI)[18] were enrolled in this protocol. Subjects had a score of >12 on the Quick Inventory of Depressive Symptomatology, Self-Rated version, at enrollment and had no medical illnesses of sufficient severity to affect brain function. Subjects were excluded if they were pregnant or refused to use medically acceptable means of birth control; met criteria for another primary mood, cognitive, psychotic, substance dependence, or abuse disorder within the past 6 months; or had an Axis II disorder severe enough to interfere with completion of the protocol. Subjects also were excluded for having electroconvulsive therapy (ECT) within the previous 6 months; intolerance to, contraindication for, or failure of treatment with either study drug in the current episode; received fluoxetine or a monoamine oxidase inhibitor within the past 4 weeks; started psychotherapy for depression (ie, cognitive-behavioral therapy, interpersonal therapy) within the previous 2 months; or current successful and stable treatment with antidepressant medication(s). Use of any medications known to affect central nervous system function significantly was disallowed during the study period, and urine toxicology was used to confirm the absence of these medications as well as illicit substances. Medications acceptable for occasional use (not within 48 hours prior to an EEG recording) included nonsedating antihistamines, codeine- or oxycodone-containing compounds, over-the-counter cold remedies, cough suppressants, and nonprescription sleep aids. After complete description of the study to the subjects, written informed consent was obtained and documented in accordance with institutional review board procedures at each institution. Subjects participated between January 2006 (first subject enrollment) and July 2007 (final follow-up visit). As previously reported,[11] the mean (SD) age for subjects receiving escitalopram was 20.6 (4.4) years, with 65.8% female subjects (61.6% white, 21.9% Hispanic/Latino, 12.3% black/African American, 4.1% Asian).

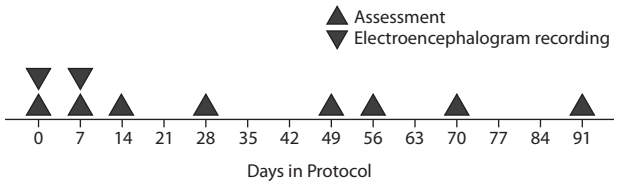
Intervention

All subjects received escitalopram 10 mg daily for 1 week and then were randomized to open-label treatment for the trial in 1 of 3 arms: (1) continue escitalopram 10 mg (group 1), (2) switch to bupropion extended release (XL) 300 mg (group 2), or (3) combine escitalopram 10 mg with bupropion XL 300 mg (group 3).[11] Electroencephalogram biomarker data were acquired before subjects started treatment and again 1 week later, before they were sent home with their randomized treatment agent. We report here only the subjects who continued taking escitalopram for the entire 13-week study period because these are the only subjects who received the same medication continuously during and after the biomarker measurement. Per protocol, if a subject achieved remission by the week 7 visit, the starting escitalopram dosage was continued, while dosage could be increased to 20 mg by week 8 for subjects not in remission. Medication was continued as tolerated through the end of the project at week 13 of treatment.

Assessments and Determination of Sustained Remission

$HDRS_{17}$ scores were assessed at baseline and weeks 1, 2, 4, 7, 8, 10, and 13. Study events are shown in Figure 1. The onset of sustained remission was operationalized for this report as the time at which remission ($HDRS_{17}$ score ≤7) was achieved for that visit and *all* subsequent visits. Therefore, a subject achieving remission only at day 91 would not be counted as a sustained remitter, while a subject first achieving remission at the penultimate visit (ie, week 10) and still in remission at the last visit (ie, week 13) would be counted. Any visits without scores were treated as not in remission, so the onset points in this analysis represent a conservative estimate. Sustained remission could begin at any time after the start of treatment.

Figure 1. Timeline for the Biomarkers for Rapid Identification of Treatment Effectiveness in Major Depression Trial[a]



[a]Clinical assessments and electroencephalogram recordings over the 13 weeks of the project are indicated with upward- and downward-pointing triangles, respectively.

EEG Biomarker Methods

Electroencephalogram data were collected by using the Aspect Medical Systems' NS-5000 system. This system consisted of a laptop computer connected to a 4-channel EEG amplifier unit, as has been previously described.[11] Self-prepping electrodes (Zipprep [Aspect Medical Systems; Norwood, Massachusetts]) were placed at 4 sites on the forehead (Fpz, FT7, FT8, ground) and 2 on the earlobes (A1, A2). Electroencephalogram data were recorded while subjects rested in a reclining chair during two 6-minute segments with eyes closed, separated by a 2-minute eyes-open segment.

Following automated rejection of artifact and drowsy EEG, power spectra were calculated for each channel by using 2-second epochs recorded while subjects reclined with eyes closed. The development and details of the ATR algorithm (revision 4.1) have been reported previously[11,12] and are summarized here. Briefly, the ATR index is a nonlinear combination of 3 features from the power spectra measured at 2 time points (baseline and week 1). These features are relative power for a combined theta and alpha band (3–12 Hz), alpha absolute power (8.5–12 Hz) at baseline, and alpha absolute power (9–11.5 Hz) at week 1. Specifically, relative combined theta and alpha power (3–12 Hz) is calculated as the ratio of the total absolute power in theta and alpha band ranges (3–12 Hz) divided by total power (2–20 Hz). The ATR is a weighted combination of these elements and ranges from 0 (low probability of response to medication received during week 1) to 100 (high probability of response). We evaluated ATR with a threshold of 58.6, the same cutoff used in prior BRITE-MD reports.[11,12]

Data Analysis

Kaplan-Meier survival analysis, Cox regression analysis, receiver operating characteristic (ROC) analysis, χ^2, and *t* tests were performed by using Predictive Analytics SoftWare (SPSS Inc, Chicago, Illinois). To be included in our present analyses, subjects were required to have artifact-free EEGs for computing ATR and, for completer analyses, to have $HDRS_{17}$ scores at the 13-week visit at the end of the trial. For analyses with the full intent-to-treat (ITT) sample, any subject with an ATR value was considered, and outcomes were classified according to the last recorded $HDRS_{17}$ score by using the last-observation-carried-forward (LOCF) imputation method. Two-tailed tests are reported.

RESULTS

Final 13-Week Clinical Outcomes

Of the 73 subjects who received escitalopram, 67 had $HDRS_{17}$ scores at week 13 (mean [SD] age = 43.3 [13.0] years old; 22 men, 45 women; mean [SD] baseline $HDRS_{17}$ score, 20.8 [4.5]). Thirty-six of these 67 subjects (53.7%) were in remission at week 13, and 31 (46.3%) exhibited sustained remission (ie, in remission at week 13 and continuously from week 10 or earlier). In the ITT sample, in which LOCF imputation was used for subjects who dropped out, 36 of 73 (49.3%) were in remission at week 13 (mean [SD] age = 42.7 [12.7] years; 25 men, 48 women; mean [SD] baseline $HDRS_{17}$ score, 20.6 [4.4]).

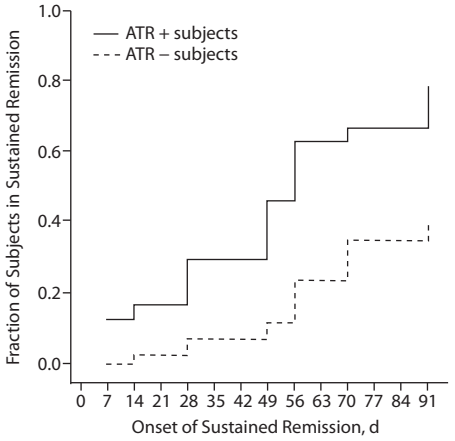
Comparison of ATR+ and ATR– Subject Characteristics

Considering the 67 subjects with scores at week 13, ATR+ (n = 24) and ATR– (n = 43) groups did not differ in mean (SD) age (44.2 [10.3] vs 42.8 [14.4] years, $t = -0.42$, 2-tailed $P = .67$), initial $HDRS_{17}$ depression severity score (21.8 [4.1] vs 20.3 [4.7] $t = -1.3$, 2-tailed $P = .19$), or sex (8 men and 16 women vs 14 men and 29 women, $\chi^2 = 0.004$, 2-tailed $P = .95$). For the full ITT sample, ATR+ (n = 25) and ATR– (n = 48) groups did not differ on mean (SD) age (43.6 [10.4] vs 42.2 [13.8] years, $t = -0.46$, 2-tailed $P = .64$), entry $HDRS_{17}$ score (21.7 [4.1] vs 20.0 [4.5], $t = -1.48$, 2-tailed $P = .14$), or sex (9 men and 16 women vs 16 men and 32 women, $\chi^2 = 0.05$, 2-tailed $P = .82$).

ATR Prediction of 13-Week Outcome

Higher ATR values were significantly correlated with lower $HDRS_{17}$ scores at week 13 (completer analysis: $r = -0.32$, 2-tailed $P = .008$; full ITT: $r = -0.30$, 2-tailed $P = .01$), and remitters had significantly higher mean (SD) ATR values than nonremitters (57.9 [10.0] vs 51.9 [8.7], $t_{71} = -2.57$, 2-tailed $P = .012$; ITT: 57.9 [10.0] vs 51.3 [9.4], $t = -2.88$, 2-tailed $P = .005$). Of the 67 subjects receiving escitalopram continuously for 13 weeks, 24 (35.8%) exhibited an ATR+ biomarker status, while 43 (64.2%) showed ATR– status. Of these, 19 of the 36 subjects in remission at week 13 showed ATR+ status, while 26 of the 31 nonremitters at that visit had ATR– status ($\chi^2_1 = 9.73$, 2-tailed $P = .002$; sensitivity, 52.8%; specificity, 83.9%; positive predictive value [PPV], 79.2%; negative predictive value [NPV], 60.5%); when examining the ITT sample with LOCF imputation, 19 of the 36 subjects in remission showed ATR+ status and 31 of the 37 nonremitters showed ATR– status ($\chi^2_1 = 10.83$, 2-tailed $P = .001$; sensitivity, 52.8%; specificity, 83.8%; PPV, 76.0%; NPV, 64.6%). By ROC analysis of these 67 completers, ATR was a significant predictor of categorical outcome of week 13 remission, with an area under the curve (AUC) of 0.67 ($P = .016$) and 67% overall correct classification of remitters. Considering the full ITT sample with values imputed with LOCF for noncompleters, the AUC was 0.68 ($P = .008$), with 50 subjects (69%) correctly predicted by ATR. In both analyses, we evaluated ATR with a threshold of 58.6, the same cutoff used in prior BRITE-MD reports.[11,12]

Figure 2. Speed of Sustained Remission via Kaplan-Meier Curves[a]



[a]The proportions of subjects in sustained remission for ATR+ subjects (n = 24) and ATR– subjects (n = 43) are plotted over 13 weeks. Once a subject enters sustained remission, he or she is included in all subsequent time points. The mean (SD) time to reach sustained remission was significantly shorter for ATR+ individuals than ATR– subjects (31.8 [20.9] days vs 53.2 [17.5] days, $t = 2.18$, 2-tailed $P = .038$).
Abbreviation: ATR = Antidepressant Treatment Response.

ATR and Likelihood of Achieving Sustained Remission

The ATR prediction of achieving sustained remission over the 13-week period was accurate in 44 of 67 completer subjects (66%). Sixteen of the 31 individuals with sustained remission had ATR+ status, while 28 of the 36 who were not sustained remitters had ATR– status ($\chi^2_1 = 6.26$, 2-tailed $P = .012$; sensitivity, 51.6%; specificity, 77.8%; PPV, 66.7%; NPV, 65.1%). In ITT analysis, 16 of the 31 sustained remission subjects exhibited ATR+ status, while 33 of the 42 not in sustained remission had ATR– status ($\chi^2 = 7.22$, 2-tailed $P = .007$; sensitivity, 51.6%; specificity, 78.6%; PPV, 64.0%; NPV, 68.8%).

ATR and Time to Sustained Remission

Among those 31 completer subjects who exhibited sustained remission, the mean (SD) time to reach that state was significantly shorter for ATR+ individuals than for ATR– subjects (38.1 [20.9] days vs 53.2 [17.5] days; $t = 2.18$, 2-tailed $P = .038$). Considering all 67 completers, Kaplan-Meier survival curves for ATR+ and ATR– completer groups are shown in Figure 2, yielding a significant overall difference (Breslow $\chi^2_1 = 13.7$, $P < .001$). With ITT analyses employed to include subjects who did not complete the trial, the Breslow χ^2 of 15.0 was significant, with $P < .001$.

To evaluate the potential for other subject-related features to influence time to sustained remission, a Cox regression analysis was performed, offering age, sex, and initial depression severity as independent variables along with ATR status. Only ATR status entered the model ($\beta = .99$, Wald = 5.5, $P = .019$).

Remission Status at Weeks 7 and 13

In the initial reports from the BRITE-MD trial,[11,12] 73 subjects received escitalopram for the first 7-week period. Of these 73 subjects, 67 completed the entire 13-week protocol. Among the 73 subjects in the ITT sample, 28 (38%) were in remission at week 7[11] and 36 (49%) were in remission at week 13. Of the subjects in sustained remission at week thirteen, 16 (44%) had been in sustained remission starting at week 7 or earlier.

DISCUSSION

The ATR biomarker predicted the likelihood of remission and time to onset of sustained remission during 13 weeks of treatment with escitalopram. To our knowledge, this is the first report of a biomarker predictive of the speed of reaching sustained remission in unipolar major depression. These findings extend the potential usefulness of the ATR biomarker. This index could be used to guide patient management decisions about not only the likelihood of achieving remission but also the rapidity with which sustained remission might be attained. In clinical application, patients could be advised at 1 week whether remission is likely with the agent being used and how soon it is likely to be achieved; this information could be useful in clinical decision making and could reassure individuals who are ambivalent about use of medication that adherence to treatment will most likely lead to remission in a certain time frame. This shift in approach would represent a clear departure from the historical paradigm of monitoring symptoms to decide whether to modify the treatment plan after weeks to months of trying.[19–21]

Sustained remission, or stable improvement over time, is an important indication of successful antidepressant treatment. One recent study[22] examining STAR*D clinical outcomes demonstrated that a subgroup of patients who showed response to treatment by 6 weeks lost the benefits of treatment within a 12-week timeframe. Other subjects show a more complex pattern of "symptom volatility," in which periods of improvement may alternate with periods of symptom worsening.[7] While both the unsustained and volatile patterns of symptom improvement indicate that the subjects derived some benefit from treatment, these patterns of symptom change may place the subjects at greater risk of poor long-term outcomes. The present results, along with those from previous studies, suggest that neurophysiologic monitoring may help to identify subjects who will experience these unstable responses[7] and who, therefore, should be monitored more closely or receive more aggressive treatment.

Clinical, demographic, biological, and other markers predictive of long-range outcomes and of achieving sustained remission are not yet well established in MDD. In a prospective examination of clinical features and acute treatment outcomes in MDD with a variety of medications, Holma and colleagues[23] identified 3 factors associated with longer times to achieving full remission: comorbid dysthymic disorder, presence of a cluster C personality disorder, or longer duration of the depressive episode prior to starting treatment. None of these factors can be easily altered to improve outcomes or to guide treatment selection. It is unclear whether any of these

clinical features are indicators of overall poor prognosis or can be used a priori to select treatments that will be more effective for subgroups of patients, a question that should be the subject of future studies. Katz and colleagues[24] reported that a decrease in score of 20% or more on the $HDRS_{17}$ scale after 2 weeks of treatment was predictive of remission that was sustained over 8 months of follow-up, while the absence of that early symptomatic decrease predicted unsuccessful treatment. In a study of major depression with psychotic features, Craig et al[25] reported that the absence of substance use history and presence of a higher Global Assessment of Functioning score in the first 6 months of treatment were the only clinical or demographic factors predictive of sustained remission (defined for that work as remission in at least 19 of the 24 months of follow-up after inpatient admission). Some of these reports considered observations over a longer time frame than possible with our dataset, so the relationship between early treatment biomarkers and questions of relapse or recurrence (as operationalized by Kupfer[26]) will require additional research.

Dotoli and colleagues[27] examined genetic factors as predictors of sustained remission, but none of the polymorphisms they examined were significantly related to outcome. Scharnholz and colleagues[28] examined nighttime cortisol and reported that subjects in remission at all visits over a 20-week period did not differ from subjects without sustained remission in terms of cortisol excretion. Taylor and colleagues[29] reported that the presence of white matter hyperintensities was predictive of lower likelihood of achieving sustained remission in late-life depression. Coryell and Zimmerman[30] reported that, following a course of ECT, those individuals who had shown normalization of the dexamethasone suppression test (DST) with treatment were *less* likely to have sustained remission during 6-month follow-up than those individuals who still had abnormal DST findings after ECT, a finding contrary to the investigators' expectations.

As a complement to these observations about prediction of sustained remission, Phillips and colleagues[31] recently reported on its consequences. In their study, individuals with sustained remission exhibited greater increases in gray matter volume over a 12-month observational period, in comparison with nonremitters; in contrast, the nonremitters showed a decrease in white matter volume (left anterior limb of the internal capsule). These findings suggest that achieving sustained remission may have important consequences for treatment-related neuroplasticity.

In comparing our 13-week observations with the previous 7-week findings from BRITE-MD,[11,12] it is noteworthy that, of the 73 subjects in the ITT analyses, 38% were in remission at week 7, with the proportion growing to 49% at week 13. Additionally, 56% of those in sustained remission at week 13 had entered remission after week 7. One reason for the accrual of remitters with time may be that escitalopram dosing was fixed at 10 mg/d through week 7, with dose increases allowable after that visit. It is also useful to note that the predictive accuracy of ATR for week 7 outcomes on escitalopram was 74%,[11] while for week 13 remission, we found ATR was accurate in 66% of subjects. In examining the relationship of biomarker to sustained remission, one must therefore consider that the biomarker was ascertained on a different dosage than was ultimately used for treatment of some subjects, ie, those who chose to continue through week 13 but were not in remission at week 7. Under naturalistic treatment conditions, Iosifescu and colleagues[16] also had found that ATR predictions were superior in subjects treated without dose increase than in subjects who received dose titration. Future work with ATR may explicitly address whether the biomarker is best measured on the dose used for treatment.

Although results of the present study are encouraging regarding the ability of ATR to predict durable remission, the findings are subject to limitations similar to those of the original reports from the BRITE-MD study. First, subjects with some psychiatric or medical comorbidities were excluded, with implications for the generalizability of the findings. Second, some individuals had EEG data that could not be used because of excessive artifact. Future implementations of the EEG system may employ improved artifact-rejection algorithms or channels that are less prone to electrocardiogram artifact. Finally, treatments were administered under open-label conditions, and there was no placebo control group. Future studies may examine ATR with designs that incorporate blinding, placebo controls, or both to parse out the effects of treatment factors that are not specific to the medications used.

The systematic application of biomarker-guided treatment has potential to dramatically shorten the time for patients to reach remission and thus reduce both their personal symptomatic suffering and the societal economic burden of depression. As noted previously, the current paradigm of "watchful waiting" for antidepressant treatment response may be contrary to the interests of most patients who will not respond to the first antidepressant selected.[32] A paradigm in which antidepressant treatment was changed early in the course of treatment if sustained remission was unlikely could improve health outcomes for many patients. Additional efforts to replicate the associations between early neurophysiologic changes emerging with treatment and later clinical outcome will help delineate the utility of this approach in clinical care.

Drug names: bupropion (Aplenzin, Wellbutrin, and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), oxycodone (OxyContin, Oxecta, and others).

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