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Using biomarkers to predict treatment response in major depressive disorder: evidence from past and present studies

Michael E. Thase, MD

Major depressive disorder (MDD) is a heterogeneous condition with a variable response to a wide range of treatments. Despite intensive efforts, no biomarker has been identified to date that can reliably predict response or nonresponse to any form of treatment, nor has one been identified that can be used to identify those at high risk of developing treatment-resistant depression (ie, nonresponse to a sequence of treatments delivered for adequate duration and intensity). This manuscript reviews some past areas of research that have proved informative, such as studies using indexes of hypercortisolism or sleep disturbance, and more recent research findings using measures of inflammation and different indicators of regional cortical activation to predict treatment response. It is concluded that, although no method has yet been demonstrated to be sufficiently accurate to be applied in clinical practice, progress has been made. It thus seems likely that—at some point in the not-too-distant future—it will be possible to prospectively identify, at least for some MDD patients, the likelihood of response or nonresponse to cognitive therapy or various antidepressant medications.

Introduction

Major depressive disorder (MDD) is one of the world's greatest public health problems; beyond the subjective suffering associated with depression, it is a significant contributor to early mortality (especially from suicide), absenteeism and diminished productivity in the workplace, and dysfunctional parenting.[1] Effective treatments have been available for MDD since the introduction of electroconvulsive therapy (ECT) in the late 1940s and 1950s, and the tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) in the late 1950s and early 1960s. However, the response to treatment is slow and hard to predict, and a significant proportion of people will develop treatment-resistant depression (TRD) despite receiving adequate courses of therapy. Part of the problem has been the heterogeneity of MDD, although attempts to identify more treatment-responsive subtypes based on clinical characteristics did not tangibly improve outcomes. Another problem was tied to the clinical pharmacology of the

Author affiliations: Department of Psychiatry, Perelman School of Medicine of the University of Pennsylvania, Philadelphia Veterans Affairs Medical Center, Philadelphia, Pennsylvania, USA; University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA

Address for correspondence: Michael E. Thase, MD, Chief, Mood and Anxiety Disorders Section, Department of Psychiatry, 3535 Market St, Suite 670, Philadelphia, PA 19104, USA
(e-mail: thase@mail.med.upenn.edu)

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first generation of antidepressants, although introduction of large number of more tolerable and easier to prescribe antidepressants likewise did not solve the problem of TRD.[2] The search for biomarkers of antidepressant response has thus become the best hope for improving the ability to match a particular patient with a specific form of treatment. Indeed, as reviewed by Smith,[3] the amount of literature on putative biomarkers for MDD has skyrocketed over the past decade.

Early biomarker studies: selected examples

The 1980s and early 1990s were a time of therapeutic optimism and there were a number of reasonably well-replicated biological assessment strategies that were evaluated as potential biomarkers, including various measures of hypercortisolism and EEG sleep profiles.

Measures of hypercortisolism

By far the best studied indicator of hypercortisolism was the dexamethasone suppression test (DST), which is a test of the integrity of feedback inhibition of the hypothalamic-pituitary-adrenocortical axis. A "positive" DST result, reflected by an elevated plasma cortisol level for at least 18 hours after attempted suppression with 1 or 2 mg of the potent synthetic glucocorticoid dexamethasone, was thought to be indicative of a kind of autonomous dysfunction of brain stress-responsiveness associated with more severe endogenous or melancholic depression. Research documented that patients who were DST nonsuppressors were typically older, more symptomatically severe, and more likely to manifest psychotic features; they were also significantly less likely to respond to placebo as compared with DST suppressors (ie, depressed patients with a normal feedback inhibition response to dexamethasone).[4,5] DST nonsuppressors were not, however, more likely to respond to tricyclic antidepressants or electroconvulsive therapy, so the abnormality appeared to simply reflect a greater need for active treatment, a conclusion similarly supported by the clinical correlates of cortisol nonsuppression.[4,5] Moreover, the test performance of the DST did not support its routine use in clinical practice: too many people with "real" depressive episodes had normal DST results (ie, low sensitivity) and in ambulatory settings the proportion of "true-positive" to "false-positive" cases was too low to permit high diagnostic con-

fidence in test results.[4] Nevertheless, hypercortisolism remains relevant to the pathophysiology of depression as a severity-linked, state-dependent illness marker and, as suggested by the results of one recent study of adolescent boys, may be associated with the risk of developing depression.[6] Consistent with reports that DST nonsuppression was associated with lower placebo response rates, our group found that response to an intensive inpatient cognitive behavior therapy protocol was significantly poorer among patients with elevated urinary free cortisol levels than those with more normal cortisol profiles.[7] Again, the clinical utility of this observation is tempered by the relatively low rate of hypercortisolism in depressed outpatients.

Polysomnographic studies

In an era before functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) were available, polysomnographic studies were arguably the best tool to visualize brain function at rest and in response to various challenges. Moreover, the "architecture" of brain activity during sleep was known to be regulated by monoamines, acetylcholine, and other neurotransmitters relevant to the pathophysiology of depression. However, when compared with the DST, polysomnographic studies required a specialized laboratory and were both time-consuming and expensive, and, because of the manifold effects that antidepressants can have on EEG sleep profiles, valid studies could only be performed on people who were either unmedicated in the current depressive episode or who had been carefully withdrawn from pharmacotherapy. Thus, the literature on EEG sleep studies as a biomarker of antidepressant treatment response was less voluminous than that for the DST. Nevertheless, a number of studies did document associations between selected sleep characteristics—such as reduced latency to the onset of rapid eye movement (REM) sleep—and depression, and there was some evidence of an association between antidepressant-induced suppression of REM sleep and subsequent clinical response (see, for example, ref 8 for a comprehensive review of early studies). However, the strength of such associations only accounted for a small proportion of the variance in outcome and, like the DST, the diagnostic performance of EEG sleep studies did not justify routine use in clinical practice.[9]

Subsequently, a series of studies by our group at the University of Pittsburgh[10-13] examined whether a constellation of sleep abnormalities, including reduced REM latency, increased REM density, and poor sleep continuity, might be used as a biomarker for depressive episodes that might respond preferentially to pharmacotherapy rather than psychotherapy. This sleep profile, which was evident in about 40% to 50% of unmedicated adults seeking ambulatory treatment for MDD,[10-13] was found to be associated with poorer response to both interpersonal psychotherapy[10] and cognitive behavioral therapy (CBT),[11] but was not predictive of response to fluoxetine or imipramine.[10] Interestingly, even when patients with this sleep biosignature responded to CBT, they were at high risk for subsequent recurrent episodes of depression,[11] perhaps because successful treatment with CBT did not normalize sleep abnormalities.[13]

Contemporary studies

Immune mechanisms

Although it is now widely recognized that depression is a proinflammatory state[14] and a number of contemporary studies have examined immune status in relation to antidepressant response, no consistent pattern of immune dysfunction as a biomarker of antidepressant response has been observed to date.[3] Cytokines and other markers of inflammatory response nevertheless are relevant to central nervous system stress responses[14] and may contribute to the host of illness processes that may render some individuals more treatment-resistant.[14,15] In this regard, the findings of the recent study by Raison and colleagues[16] are most interesting. In this trial, 60 outpatients with MDD and a history of nonresponse to two or more antidepressants were randomized to receive either three infusions of infliximab (5 mg/kg), a tumor necrosis factor (TNF) antagonist (n=30) or placebo (n=30); infusions were given at baseline and repeated at weeks 2 and 6; outcomes were evaluated across 12 weeks. On the primary analysis, they found that patients who received active, inflammation-suppressing therapy were no more likely to respond to treatment than were those receiving placebo.

The potential differential therapeutic implications of an elevated C-reactive protein (CRP) level were likewise studied by Uher and colleagues.[17] In this sec-ondary analysis of a large-scale study primarily aimed at investigating genetic correlates of depression and treatment response, inflammatory markers were assessed in 241 patients with MDD prior to being randomized to 12 weeks of open-label therapy with either escitalopram or nortriptyline. Although the two antidepressants were comparably effective overall, patients with low pretreatment CRP levels were significantly more responsive to escitalopram, whereas those with high CRP levels were significantly more responsive to nortriptyline. Although replication is necessary, these findings do suggest that patients with high baseline inflammatory markers, while less responsive to selective serotonin reuptake inhibitors, may benefit from treatment with alternate approaches to therapy.

Transcriptomics

The potential importance of transcriptomics has been suggested by the results of a pair of recent, small studies.[18,19] Pajer and colleagues ascertained genome-wide transcriptomic (RNA) profiles in blood of animals using two well-replicated animal models of depression, one hereditary and the other related to chronic stress.[18] They identified a combined set of 26 transcripts and then searched for these putative biomarkers in the blood of 14 unmedicated adolescents with MDD and matched healthy controls. They found that a group of 11 transcriptomic markers differentiated the MDD patients from the healthy control group. Despite low statistical power for subgroup analyses, they found that a partly overlapping set of 18 transcripts separated the MDD subjects with high levels of anxiety from those who did not have comorbid anxiety. Four transcripts that were detected only in the chronic stress model also were found in the depressed youths with a history of maltreatment (but not in the youths with no history of maltreatment). In the second study, blood RNA was examined in 32 adult outpatients with MDD and matched controls, focusing on 20 of the transcripts identified in the earlier study.[19] They found that nine transcripts (ADCY3, DGKA, FAM46A, IGSF4A/CADM1, KIAA1539, MARCKS, PSME1, RAPH1, and TLR7) differentiated between groups at the nominal level of statistical significance, with effect sizes (Cohen's *d*) ranging between 0.47 and 0.79. A total of 28 of the depressed subjects were reassessed 18 weeks later after completing a course of cognitive behavior therapy (CBT). At post-treatment, three transcripts (DGKA,

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KIAA1539, and RAPH1) continued to differentiate between groups but remained significantly different between subjects with MDD and ND controls, suggesting that some elements of this transcriptomic "biosignature" may be state-independent. Interestingly, the pattern of co-occurrence of transcripts at pretreatment appeared to be different among the patients who responded to CBT versus those who did not, which might point to a particular pattern of dysregulation or desynchronization of stress response that might be more responsive to a more biologically active approach to treatment, such as pharmacotherapy. These preliminary findings, which require replication in much larger samples, suffer from the empiric or atheoretical nature of their discovery. There is also some risk of confusing an epiphenomenal finding, such as a change in gene activity that might be caused by weight loss or poor sleep, with an observation that is intimately related to the pathophysiology of the illness in question. It will of course also be informative to study how these transcriptomic variables might perform if the outcome of interest was response to specific types of antidepressant drugs or placebo.

Neuroimaging studies

Neuroimaging studies using both PET and fMRI have suggested characteristic abnormalities that are both associated with depression and may be targets for therapeutic intervention.[20-23] Recent work suggests that some changes in neural correlates of information processing may be evident within hours of first treatment exposure.[24] Our own work suggests that CBT may capitalize on depressed patients' ability to suppress or distract their negative cognitive and emotional responses to stimuli; this feature is evident in the subgenual cingulate (sgACC; BA25).[25,26] Such an adaptive decrease in processing of negative information is also evident in parallel studies using the pupil as the indicator of cerebral activation.[27]

The findings linking psychotherapy response to the capacity to dampen emotional responses to negative stimuli reinforce the intuitive view that CBT works by enhancing "top-down" control of negative emotions. The converse notion, namely that pharmacotherapy or rTMS target different aspects of emotional information processing networks, are supported by parallel studies.[21-23] The findings of McGrath and colleagues,[28] who used PET to study patterns of cerebral activation in 80 MDD patients randomized to 12 weeks' treatment with either CBT or escitalopram, are therefore of interest. Among study completers who either unequivocally remitted or failed to benefit from treatment (n=38), regional cerebral activity in the right insula strongly predicted differential response to CBT and pharmacotherapy. Whereas patients with relatively high levels of cerebral glucose activity in this region responded well to pharmacotherapy and not CBT, those with relatively low levels of glucose metabolism in this region showed a preferential response to CBT over pharmacotherapy. Assuming that increased resting-state glucose activity in the right anterior insular region is a marker of increased or sustained negative information processing bias, ie, a particular kind of severe disturbance of adaptive affective processing, these findings dovetail nicely with those from the fMRI studies of predictors of CBT response. Moreover, as the biomarkers studied in the 1980s and 1990s were similarly associated with more severe depressive states, it may be that the older and newer research models are pointing to the same core pathophysiological process.

Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care for Depression

Perhaps the most ambitious systematic effort to develop biomarkers to guide the treatment of MDD is the project known as Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care for Depression (EMBARC). Led by Madhukar Trivedi[29] and colleagues at both the University of Texas Southwestern Medical Center in Dallas, Texas and Columbia University in New York City, this large-scale study (n=400 patients with early-onset, recurrent MDD) was funded in 2010 by the National Institute of Mental Health. The study is built around an 8-week, placebo-controlled, randomized controlled trial, with patients who do not respond to the first course of active treatment (sertraline) switched to a second course of therapy with a dissimilar medication (bupropion) and patients not responding to placebo switched to active sertraline. Potential clinical moderators of treatment response include symptom severity, anxiety, a history of early trauma, chronicity, personality pathology, and depressive subtypes (atypical depression and melancholia). Potential biomarkers of treatment response include structural (cerebral cortical thickness) and functional (reward and emotion conflict tasks) magnetic

resonance imaging (MRI), resting state connectivity, and cortical evoked potentials. Moderating effects are tested using pretreatment studies and potentially mediating effects are tested by repeating selected studies after 1 week on therapy. In addition, biological samples (eg, DNA, RNA, and plasma) will be collected before and during treatment and stored for future studies. One important feature of the EMBARC study is that a healthy control group is being recruited to ensure that "abnormalities" are indeed abnormal and to help confirm test-retest stability of selected measures. Another extremely important aspect of the EMBARC study is the effort taken to standardize the assessment battery across the multiple participating sites. Although results of EMBARC are not yet available, the study has completed enrollment and it can be anticipated that findings will begin to be presented at scientific meetings in 2015.

Future directions and conclusions

It is fair to say that no biological marker or biosignature of depression exists, nor that any particular constellation of neurobiological abnormalities has been definitively shown to have value for predicting differential response to antidepressant therapies. However, it is evident that progress is being made and several novel findings warrant further careful study. In this regard, studies utilizing neuroimaging methods appear to be pointing to

factors that predispose to differential response to psychotherapy and pharmacotherapy, which in turn might also lead to a better means of predicting who might benefit from the two therapies together or in combination. Moreover, whereas a meta-analysis of three larger-scale studies failed to identify any replicable genetic markers of antidepressant response,[30] this does not preclude the possibility that specific genes involved in drug metabolism[31] or neurotransmitter synthesis[32] might have specific therapeutic implications. The specific impact of genes may of course be modified or shaped by life experiences and other epigenetic factors, which makes the transcriptomic approach of Redei and colleagues[18,19] not only all the more interesting but also in the most acute need of larger-scale replication. ❏

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El empleo de biomarcadores para predecir la respuesta terapéutica en el Trastorno Depresivo Mayor: evidencias del pasado y estudios actuales

El Trastorno Depresivo Mayor (TDM) es una condición heterogénea con una respuesta variable a una diversidad de tratamientos. A pesar de grandes esfuerzos, a la fecha no se ha identificado ningún biomarcador confiable que pueda predecir la respuesta o falta de ella para alguna forma de tratamiento, ni se ha encontrado alguno que pueda ser empleado para identificar a los pacientes con alto riesgo de desarrollar una depresión resistente al tratamiento (por ejemplo, falta de respuesta a una secuencia de tratamientos aplicados con una duración e intensidad adecuadas). Este artículo revisa algunas investigaciones antiguas que aportaron información, como los estudios que emplearon indicadores de hipercortisolismo o alteraciones del sueño, y hallazgos de investigaciones más recientes que han empleado marcadores de la inflamación y diferentes indicadores de activación cortical regional para predecir la respuesta terapéutica. Se concluye que, aunque se han realizado progresos, aun no se ha demostrado que algún método sea totalmente preciso para ser aplicado en la práctica clínica. Parece ser entonces que, en algún momento del futuro cercano, será posible identificar prospectivamente –al menos para algunos pacientes con TDM- la probabilidad de respuesta o falta de ella a la terapia cognitiva o a varios fármacos antidepresivos.

Utilisation des biomarqueurs pour prédire la réponse au traitement dans le trouble dépressif majeur : données issues des études passées et présentes

Le trouble dépressif majeur (TDM) est une pathologie hétérogène dont la réponse à une large gamme de traitement est variable. Malgré des efforts considérables, à ce jour, aucun biomarqueur n'a été identifié pour prédire de façon fiable une réponse ou une non-réponse à un traitement donné, ou pour identifier les patients à risque élevé de développer une dépression résistante au traitement (c'est-à-dire l'absence de réponse après une série de traitements administrés avec une dose et une durée adéquates). Cet article passe en revue d'anciens domaines de recherche intéressants tels que les études sur les marqueurs d'un hypercortisolisme ou sur des anomalies du sommeil, ainsi que des résultats de travaux récents sur la mesure de l'inflammation et sur des indicateurs d'activation corticale régionale pour prédire la réponse au traitement. En conclusion, bien qu'aucun examen biologique précis n'ait été encore validé pour être utilisé en pratique clinique, des progrès ont été faits. Il est donc probable que, dans un futur pas trop éloigné, il sera possible d'identifier de façon prospective, au moins pour certains patients atteints de TDM, la probabilité de réponse ou de non-réponse à un traitement cognitif ou aux différents antidépresseurs..

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