Predictors, moderators, and mediators (correlates) of treatment outcome in major depressive disorder

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Definitions

Major Depressive Disorder (MDD) is a prevalent illness that is frequently associated with significant disability, morbidity, and mortality. Results from the 2003 National Comorbidity Replication study found that the lifetime prevalence of MDD among American adults is 16.2%, ranking it among the most common and costly medical illnesses.[1] Despite the development and availability of numerous treatment options for MDD, studies have shown that antidepressant monotherapy yields only modest rates of response and remission. For example, a meta-analysis[2] of all double-blind placebo-controlled studies of

Major Depressive Disorder (MDD) is a prevalent illness that is frequently associated with significant disability, morbidity, and mortality. Despite the development and availability of numerous treatment options for MDD, studies have shown that antidepressant monotherapy yields only modest rates of response and remission. Clearly, there is an urgent need to develop more effective treatment strategies for patients with MDD. One possible approach towards the development of novel pharmacotherapeutic strategies for MDD involves identifying subpopulations of depressed patients who are more likely to experience the benefits of a given (existing) treatment versus placebo, or versus a second treatment. Attempts have been made to identify such "subpopulations," specifically by testing whether a given biological or clinical marker also serves as a moderator, mediator (correlate), or predictor of clinical improvement following the treatment of MDD with standard, first-line antidepressants. In the following article, we will attempt to summarize the literature focusing on several major areas ("leads") where preliminary evidence exists regarding clinical and biologic moderators, mediators, and predictors of symptom improvement in MDD. Such clinical leads will include the presence of hopelessness, anxious symptoms, or medical comorbidity. Biologic leads will include gene polymorphisms, brain metabolism, quantitative electroencephalography, loudness dependence of auditory evoked potentials, and functional brain asymmetry.

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Selected abbreviations and acronyms

5-HT	*serotonin*
DSM	*Diagnostic and Statistical Manual of Mental Disorders*
EEG	*electroencephalogram*
HDRS	*Hamilton Depression Rating Scale*
LDAEP	*loudness dependence of auditory evoked potentials*
MAOI	*monoamine oxidase inhibitor*
MDD	*Major Depressive Disorder*
SSRI	*selective serotonin reuptake inhibitor*
STAR*D	*Sequenced Alternatives to Relieve Depression*
TCA	*tricyclic antidepressant*

antidepressants published since 1980 revealed response rates of 53% for antidepressants and 36% for placebo (absolute difference in response rate of 16.8%). Similarly, Petersen et al[3] report remission rates as low as 20% to 23% following each successive treatment among patients with MDD enrolled in one of two academically affiliated, depression-specialty clinics. In fact, only about 50% of all patients enrolled ultimately achieved full remission of their depression. Similarly, only about one in three patients with MDD experienced a remission of their depression following treatment with the selective serotonin reuptake inhibitor (SSRI) citalopram during the first level of the large, multicenter, Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial.[4] Clearly, there is an urgent need to develop safer, better-tolerated, and more effective treatments for MDD.

There are three major "paths" towards the development of novel pharmacotherapeutic strategies for MDD *(Table I)*.[5] The first approach involves developing new antidepressants to be used as monotherapy. A second approach involves combining pharmacologic agents, including established treatments (ie, established antidepressants), existing but not established agents, and new or novel agents.

- Develop new agents as monotherapy
- Combine two or more pharmacologic treatments
  - o Two or more existing or established agents
  - o A combination of existing, established, and new agents
- Identify subpopulations of MDD patients who are more likely to experience the benefits of a given treatment
  - o Biological markers
  - o Clinical markers

Table I. Common pathways towards the development of more effective pharmacologic strategies for Major Depressive Disorder (MDD).

Finally, a third approach involves identifying subpopulations of depressed patients who are more likely to experience the benefits of a given (existing) treatment versus placebo, or versus a second treatment. Attempts have been made to identify such "subpopulations," specifically by testing whether a given biological clinical marker also serves as a moderator, mediator (correlate), or predictor of clinical improvement following the treatment of MDD with standard, first-line antidepressants. A *predictor* of treatment (efficacy) outcome can involve factors (whether clinical or biologic), the presence or magnitude of which influences the likelihood of a particular outcome occurring during treatment. Efficacy outcomes in MDD commonly include either the resolution of depressive symptoms during treatment (the magnitude of reduction in depressive symptoms), the rapidity of response (the time course of symptom reduction), the attainment of a treatment response, or the attainment of symptom remission.

Differential predictors or *moderators* of efficacy outcome are a special subcategory of outcome predictors. Moderators of outcome involve factors (clinical or biologic), the presence or magnitude of which at baseline (immediately before treatment is initiated) influences the *relative* likelihood of a particular outcome occurring following treatment with one versus another agent. Thus, moderators of response can help predict differential efficacy between two or more treatments for MDD (for example, patients who present with a given moderator are more likely to respond to treatment with one antidepressant versus another than patients who do not present with that given moderator).

Mediators of efficacy outcome (sometimes also referred to as correlates) are measurable *changes* (usually biologic) that occur during treatment and correlate with treatment outcome. These changes can either precede (in which case they may also predict outcome—"predictive mediators"), or temporally coincide with treatment outcome ("simple mediators"). Differential mediators of outcome are also possible (changes that predict or correlate with an event following treatment with one agent but not another). *Figure 1* provides an overview regarding the combinations pertaining to mediators, moderators, and predictors of efficacy outcome in MDD. *Table II* outlines potential clinical, scientific, and treatment-development implications that may derive by identifying mediators, moderators, and predictors of efficacy outcome in MDD.

In the following paragraphs, we will attempt to summarize the literature focusing on several major areas ("leads") where preliminary evidence exists regarding clinical and biologic moderators, mediators, and predictors of symptom improvement in MDD. In the first section, we will focus on clinical variables while, in the second section, on biological variables.

Clinical factors

To date, the overwhelming majority of published studies focusing on identifying predictors of response during the acute-phase of treatment of MDD involve the SSRIs. These studies focus on examining the role of illness characteristics (ie, depressive subtype) or comorbidity (psychiatric (ie, axis I), characterologic (axis II), and medical (axis III), and will be reviewed according to antidepressant class.

SSRI treatment

In general, the presence and/or extent of factors associated with personality or temperament, including the presence of a Diagnostic and Statistical Manual of Mental Disorders (DSM)-defined personality disorder,[6-9] neuroti-

- Identification of factors which are simple predictors of treatment outcome would allow for the stratification of patients according to risk for treatment-resistance, which, in turn, could lead to the development of tailored approaches that would improve overall treatment outcome (ie, choosing a more "aggressive" treatment a priori).
- Identification of moderators (ie, differential predictors) of treatment outcome may lead to the development of tailored treatment approaches (algorithms) for a given subgroup of MDD patients that would improve treatment outcome (ie, matching treatment with MDD subtype).
- Predictive or nonpredictive mediators (correlates) of treatment outcome may provide mechanistic insights into the underlying pathophysiology of MDD, thereby helping identify new molecular targets for drug development or for defining clinically relevant subgroups.
- Predictive or nonpredictive mediators (correlates) of treatment outcome may be used in screening for potential new antidepressants (for example, selecting pharmacologic agents that also result in similar changes in clinical or preclinical models).

Table II. Potential clinical, scientific and treatment development applications of predictors, moderators and mediators of treatment outcome in Major Depressive Disorder.

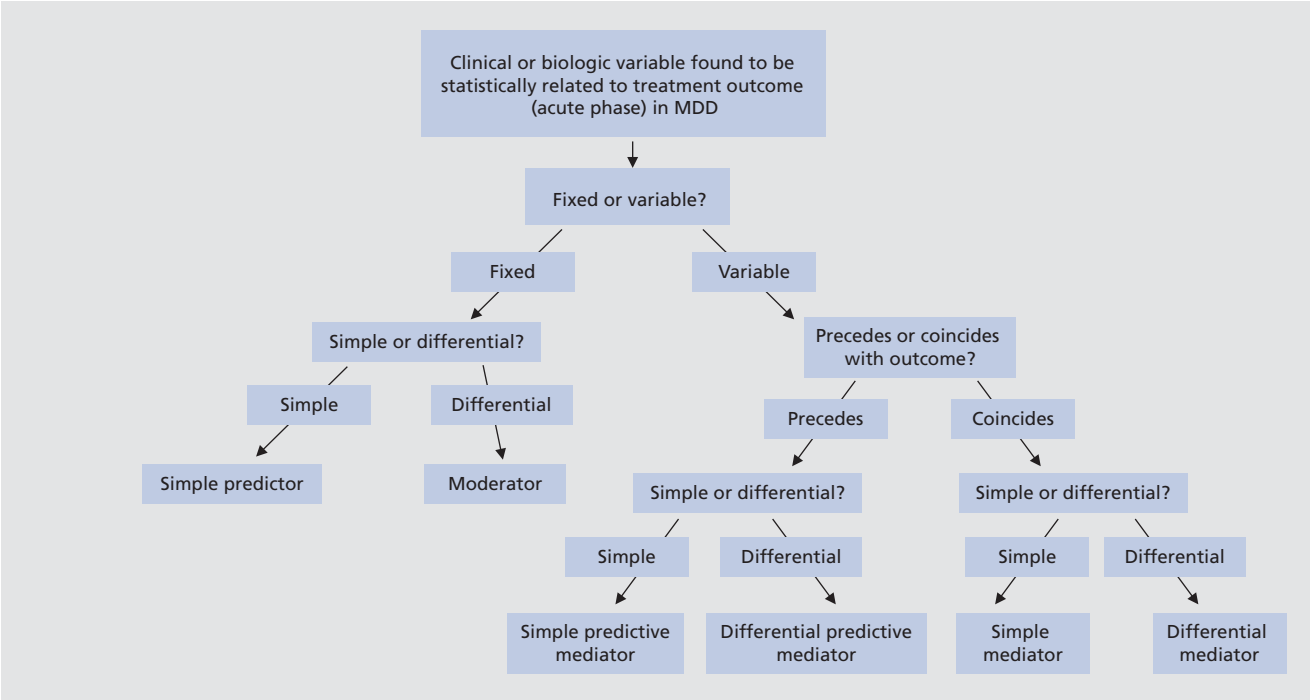

Figure 1. Schematic depiction of definitions. MDD, major depressive disorder

cism,[10] hypochondriacal concerns,[11] dysfunctional attitudes,[12] or temperamental style[13] do not appear to predict response to the SSRIs.

In contrast, the presence and or degree of general[14] as well as specific medical comorbidity, including hypercholesterolemia,[15] greater body weight,[16] other risk factors for vascular disease,[17,18] hypofolatemia,[18-20] and magnetic resonance imaging (MRI) white-matter hyperintensities[18,21,22] consistently appear to predict poorer outcome during the acute phase of treatment of MDD with the SSRIs, although other factors, such as the presence of mild hypothyroidism[23] and anemia,[24] do not.

The presence and severity of several symptoms of depression have also been linked to poorer prognosis, including hopelessness,[25] cognitive symptoms of depression including executive dysfunction,[26] physical symptoms of depression (somatic symptoms including pain, fatigue, physical symptoms of anxiety, and gastrointestinal symptoms),[27-30] and psychomotor retardation.[27] Early improvement in depressive symptoms appears to also predict better outcome during the acute phase of treatment of MDD with fluoxetine, and vice versa.[31,32]

Illness features including greater chronicity,[7,8] atypical depression,[7] depression with anger attacks,[7] or depression with comorbid attention deficity-hyperactivity disorder,[33] or insomnia[8,34,35] do not appear to confer a worse prognosis. However, greater MDD severity was found to predict a greater likelihood of attaining remission of depression following treatment with the SSRI escitalopram than several older SSRIs (fluoxetine, sertraline, paroxetine, citalopram) in MDD (moderator).[36]

The presence of an anxious MDD subtype (defined using the "syndromal" approach as MDD presenting with at least one comorbid DSM anxiety disorder) was found to result in poorer outcome during the acute phase of treatment of MDD with fluoxetine[7] but not sertraline.[8] Until recently, however, several relatively small studies[9,37-40] defining anxious MDD using the "dimensional" approach (most commonly defined as a score of 7 or more on the anxiety-somatization subscale (HDRS-AS)[41] of the Hamilton Depression Rating Scale (HDRS),[42] and have not confirmed earlier findings by Fava et al.[7] The HDRS-AS subscale is comprised of the following HDRS items: psychic anxiety, somatic anxiety, somatic symptoms-gastrointestinal, somatic symptoms-general, hypochondriasis, and insight. Other studies[37,43,44] which employ a scale different than the HDRS-AS to define anxious MDD (dimensional approach) have also not confirmed the findings of the earlier work by Fava et al.[7] However, recently, evidence stemming from Levels 1 and 2 of STAR*D do suggest significantly lower remission rates following the treatment of MDD with either first-line (citalopram) or second-line treatment strategies (switching to antidepressants versus augmentation or combination strategies).[45]

Most of the studies described above examining the potential role of several factors as possible predictors of outcome following the acute phase of treatment of MDD with an SSRI share two major limitations: (i) most involve a relatively small sample size, resulting in limited statistical power to detect an effect of a factor on treatment outcome; and (ii) most involve analyses conducted in either univariate or bivariate fashion (ie, simply controlling for overall depression severity at baseline). More recently, Trivedi et al[4] conducted multivariate analyses in STAR*D, examining potential predictors of response to open-label citalopram (up to 60 mg, up to 14 weeks of treatment) in MDD utilizing a dataset of unprecedented statistical power (n=2876). Variables examined as potential predictors of outcome included several demographic (ie, age, gender, race, sociodemographic variables) and clinical (age of onset of MDD, duration of episode, the presence of psychiatric and medical comorbidity) factors. Participants who were Caucasian, female, employed, or had higher levels of education or income had higher chances of success. Longer depressive episodes, more concurrent psychiatric disorders (especially anxiety disorders and or drug abuse) and general medical disorders, and lower baseline psychosocial functioning and quality of life were associated with poorer chances of success.

Treatment with older agents (TCAs and MAOIs)

In general, results of these studies parallel those focusing on the use of SSRIs in MDD.

While the results of two studies suggest that the presence of a comorbid personality disorder confers an increased risk of poor outcome during the treatment of MDD with the tricyclic antidepressants (TCAs),[46,47] the majority of studies do not support this relationship.[8,48-55] However, two studies do report poorer outcome among MDD patients with than without a comorbid cluster C personality disorder during TCA treatment.[53,56]

Several studies do not report the presence of neuroticism to predict antidepressant response following TCA treatment in MDD.[50-52,55] The interactions of certain elements of temperament (novelty seeking, harm avoidance, and

reward dependence) were found to help predict response to TCAs in one,[50] but not a subsequent study.[57]
Symptom chronicity was found to result in poor outcome during treatment of MDD with the TCAs in one,[52] but not a second study.[8] Finally, specific symptoms including insomnia[8,35] and suicidal ideation[58] do not appear to predict response to TCA treatment. However, the presence of somatic symptoms of depression,[59] elevated cholesterol levels,[60] but not the presence and/or extent of medical comorbidity[61] have been linked to lower chances of responding to the TCA nortriptyline in MDD.
Although earlier studies had suggested that patients with anxious MDD may respond more poorly to treatment with the TCAs and/or monamine oxidase inhibitors (MAOIs),[62-64] a number of studies did not find a significant relationship between the presence of an anxious MDD subtype and poorer outcome following treatment with an MAOI[65-70] or TCA.[9,38,40,48,65-70] Finally, the presence of atypical MDD has been shown to predict a greater likelihood of clinical response to treatment with the MAOI phenelzine than the TCA imipramine.[69,71]

Treatment with newer agents

Only a handful of studies specifically focus on identifying predictors of acute-phase outcome (efficacy) during the treatment of MDD with newer agents. Nelson and Cloninger[72] reported the interaction of several temperamental factors, including reward dependence and harm avoidance, to predict response to the serotonin (5HT-2–receptor antagonist nefazodone in MDD (n=18). This was confirmed shortly thereafter using a larger database (n=1119).[73] However, the predictive power of neuroticism in the latter study accounted for a trivial 1.1% of the total variance in outcome, raising questions regarding the clinical relevance of this finding.
Rush et al[43,44,74] did not find the presence of pretreatment anxiety or insomnia to confer a better or poorer prognosis during treatment with the noradrenaline-dopamine reuptake inhibitor (NDRI) bupropion. However, a more recent analysis involving 10 randomized, double-blind clinical trials comparing bupropion with an SSRI for MDD did reveal a greater likelihood of clinical response following treatment with an SSRI than bupropion among patients with anxious MDD (moderator).[75]
Sir et al[39] and Davidson et al[76] did not find that the presence of an anxious subtype of MDD or anxious symptoms in MDD had influenced the likelihood of responding to venlafaxine in MDD, although Silverstone and Salinas[77] found a slower onset of antidepressant effects among venlafaxine-treated patients with MDD and comorbid generalized anxiety disorder (GAD) than those without comorbid GAD, and patients with anxious depression, as defined by elevated scores on the HDRS-AS scale, were significantly less likely to remit following venlafaxine treatment in Level 2 of STAR*D.[45] However, postmenopausal women with MDD who were not on hormone-replacement therapy were found to be much more likely to attain remission of MDD following treatment with the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine than an SSRI than either premenopausal women or postmenopausal women on hormone replacement therapy in one study.[78]
Kornstein et al[79] did not find either age nor gender to influence efficacy outcome following treatment with the SNRI duloxetine. Mallinckrodt et al[80] did not find the presence of a melancholic subtype to influence efficacy outcome following treatment with duloxetine. However, greater MDD severity was found to predict a greater likelihood of attaining remission of depression following treatment with the SNRI duloxetine than the SSRIs fluoxetine and paroxetine in MDD (moderator).[81]

Biologic factors

To date, numerous studies have explored several potential genetic markers of outcome during the acute phase of treatment of MDD. The majority of these studies stem from one of two fields: genetics and neurophysiology. Due to the paucity of reports focusing on non-SSRI agents, biologic factors will be reviewed according to field (ie, genetics versus neurophysiology) rather than class (ie, SSRI versus non-SSRI treatment).

Genetic markers

A number of reports explore various genetic markers as predictors of clinical response to antidepressants in MDD. The vast majority of these focus on genes coding for proteins directly involved in the monoaminergic system, including tryptophan hydroxylase (TPH—the rate-limiting step in serotonin synthesis), the serotonin transporter (5-HTT), the serotonin 5-HT-2 receptors, the monoamine oxidase enzyme (MAO), and the catechol-O-methyltransferase enzyme (COMT). The overwhelming majority of these studies involve treatment with the SSRIs.

SSRIs

Three studies suggest that patients with a specific polymorphism (A218C) in the gene coding for the TPH enzyme may respond more poorly to SSRIs than those without such a polymorphism,[82-84] although this was not confirmed in three other studies.[85-88] Early on, the results of some[88-98] but not all[99-103] studies also suggested that depressed patients with a certain (insertion/deletion) polymorphism located in the promoter region of the gene coding for the serotonin transporter *(5HTTPR)* have a relatively poorer response to the SSRIs than those without. Several pooled analyses and meta-analyses have subsequently confirmed a predictive role for *5HTTPR* genotype with regards to SSRI response in MDD, more so for Caucasian than Asian patients.[104-106] More recently, however, Kraft et al[107] and, subsequently, Hu et al[108] did not find an association between response to the SSRI citalopram and *5HTTPR* genotype among 1914 subjects who participated in the first level of the STAR*D trial. This report provides the strongest evidence to date against a role for variation at this gene as a factor predicting clinical response to the SSRIs.

Similarly, there have been conflicting reports regarding the role of 5-HT_2-receptor genotype as a predictor of SSRI response. Specifically, two studies have identified a specific single nucleotide polymorphism (SNP) in the promoter region of the 5-HT_2 receptor (A1438G) that appears to predict response to the SSRIs in MDD.[91,109] However, this finding was not confirmed in a third report.[110] More recently, however, McMahon et al[111] conducted an analysis of numerous candidate genes as potential predictors of response to open-label citalopram in MDD utilizing the STAR*D level-1 dataset (n=1953). Of 68 candidate genes investigated, only genetic variation at the locus coding for the 5-HT_2 receptor gene was found to consistently predict clinical outcome,[111] with differences in genotype (comparison of two homozygous groups) accounting for an 18% difference in the absolute risk of having no response to treatment.

Relatively fewer studies have focused on genes coding for proteins not directly related to the monoaminergic system. Using a STAR*D-based dataset, Perlis et al[112] demonstrated a relationship between the presence of a variant (KCNK2) in a gene *(TREK1)* coding for a potassium channel and the likelihood of experiencing symptom improvement following treatment of MDD with the SSRI citalopram. In a separate study, Paddock et al[113] reported that genetic variation in a kainic acid-type glutamate receptor was associated with response to the antidepressant citalopram (marker (rs1954787) in the GRIK4 gene, which codes for the kainic acid-type glutamate receptor KA1). There is also a STAR*D-based report suggesting a relationship between the likelihood of achieving remission of symptoms during treatment with the SSRI citalopram and genotype at one of the markers (rs4713916) in the FKBP5 gene, a protein of the hypothalamic-pituitary adrenal (HPA) system modulating the glucocorticoid receptor.[114]

Other agents

Studies looking at genetic markers as predictors of response to other antidepressants are few. The results of one study report 5HTTPR genotype to influence the likelihood of responding to the tricyclic antidepressant (TCA) nortriptyline in MDD[115] although this could not be replicated in a separate study.[99] Two separate studies report 5HTTPR genotype to predict response to the SNRI venlafaxine,[116] and the 5-HT_2 alpha-2 adrenergic receptor inhibitor mirtazapine.[117] Finally, there is also a single study examining the role of MAO-A genotype as a predictor of clinical response to the MAOI moclobemide; no relationship was found.[118]

Reports from studies comparing agents of different classes

Reports examining for genetic predictors of response from randomized, double-blind clinical trials comparing two antidepressants of different classes are few. Although preliminary, such studies can be useful in genetic markers that may serve as moderators of treatment efficacy. Joyce et al[119] studied 169 MDD patients randomized to treatment with either fluoxetine or nortriptyline, and examined whether 5HTTPR or G-protein beta3-subunit (C825T) genotype influenced symptom improvement following treatment with either of these two agents. For patients younger than 25 years of age, the T allele of the G protein beta3 subunit was associated with a poorer response to nortriptyline. There was no relationship between 5HTTPR genotype and response to treatment with either antidepressant among this age group, nor was there any relationship between G protein beta3 subunit genotype status and response to paroxetine. Among patients 25 years of age or older, however, 5HTTPR

genotype predicted response to both fluoxetine and nortriptyline. Findings stemming from this report have yet to be replicated. Similarly, Szegedi et al[120] studied the relationship between the COMT (val158met) polymorphism status and antidepressant response following treatment with paroxetine versus mirtazapine (5-HT_2-alpha-2 adrenergic receptor antagonist) in MDD. Patients homozygous for COMT-met showed a poorer response to mirtazapine than patients with other genotypes. A similar finding was not observed during paroxetine treatment. Preliminary findings from these two trials have yet to be prospectively confirmed.

Neurophysiology

Brain functioning and metabolism

A number of studies have examined the potential relationship between functional changes, including changes in regional blood glucose metabolism as measured by positron emission tomography (PET), and clinical response following the treatment of MDD with standard antidepressants. Mayberg,[121,122] for instance, studied the relationship between regional metabolic changes in the central nervous system (CNS) and clinical response following a 6-week trial of the SSRI fluoxetine for MDD. The results of her work suggest that metabolism in certain brain areas, as measured by PET, may serve as a mediator of response to the SSRIs. Specifically, she found an increase in brain stem and dorsal cortical metabolism (prefrontal, parietal, anterior cingulate, and posterior cingulate), and a decrease in limbic and striatum metabolism (subgenual cingulate, hippocampus, insula, and palladium) from week 1 to week 6 of treatment among fluoxetine responders. Fluoxetine nonresponders did not demonstrate changes in these areas during the same treatment period (weeks 1-6). Similarly, Iosifescu et al[123] established a relationship between normalization in measures of brain bioenergetic metabolism among patients with SSRI-resistant MDD who experienced symptom improvement (clinical response) following T3 augmentation of their SSRI treatment regimen.

In a recent work, Mayberg et al[121] reviewed earlier studies examining the relationship between regional metabolic changes and symptom improvement during the treatment of MDD with antidepressants, and concluded that a significant correlation between normalization of frontal hypometabolism and clinical improvement was the best-replicated finding. However, a similar relationship (ie, between an increase in frontal metabolism and symptom improvement) was also reported during placebo treatment.[121] The results of the latter study suggest that such changes, at least as detected by the technology available at the time, appear to be related to nonspecific (placebo) rather than specific (drug) treatment effects and, therefore, may not serve as robust differential treatment mediators. Little et al,[124] for instance, examined whether there are differences in the relationship between brain metabolism at baseline (predictor or moderator) and symptom improvement between two antidepressants of different class (the NDRI bupropion versus the SNRI venlafaxine). For the most part, similar findings predicted symptom improvement for both agents (frontal and left temporal hypometabolism), although some differences emerged (compared with control subjects, bupropion responders (n = 6) also had cerebellar hypermetabolism, whereas venlafaxine responders showed bilateral temporal and basal ganglia hypometabolism). This study has yet to be replicated, either with regards to baseline brain metabolism (ie, moderator of response), or changes in baseline brain metabolism (ie, mediator of response).

Quantitative EEG

Quantitative electroencephalography (QEEG) involves the use of computer software analysis to deconstruct electroencephalographic (EEG) tracings and quantify parameters including frequency and amplitudes (traditional EEG involves manual readings). A relevant measurement generated by the software traditionally employed by QEEG is called cordance, which involves a combination of absolute power (the power of a frequency band) and relative power (the percentage of power in a frequency band compared with the total power across all frequency bands).[125,126] Cordance of frontal EEG measurements in the theta band (4 to 8Hz) has consistently been found to correlate with antidepressant response in MDD. Specifically, the result of several studies suggest a decrease in theta cordance from prefrontal EEG leads during the first week of treatment with either an SSRI, an SNRI, or a variety of antidepressants, to predict greater symptom improvement following 4 to 10 weeks of treatment.[127-129] In contrast, an increase in prefrontal theta cordance during the first week of treatment was demonstrated among placebo-

responders, suggesting that prefrontal theta cordance may serve as a differential (predictive) mediator of response to antidepressants versus placebo.[130] Interestingly enough, a report by Hunter et al[131] suggests that the decrease in prefrontal EEG theta cordance during the week immediately preceding the initiation of treatment of MDD with antidepressants (fluoxetine, venlafaxine) or placebo (placebo lead-in period) is related to the likelihood of responding to antidepressants but not placebo following 9 weeks of treatment (moderator of response). Thus, the sum of the evidence reviewed above suggests a potential role for the change in prefrontal theta EEG cordance during the first week of treatment in MDD as a mediator and predictor of response to antidepressants but not placebo (differential mediator). Although the exact physiologic relevance of this probable treatment mediator is, at present, unclear, several lines of evidence suggest it may serve as a proxy for changes in underlying prefrontal cortex metabolism (see ref 127 for further details).

Loudness dependence of auditory evoked potentials

Much less is known regarding the potential predictive ability of other EEG-related biomarkers. Loudness dependence of auditory evoked potentials (LDAEP) is one such measurement, derived from EEG recordings thought to correspond to the primary auditory cortex following the administration of an auditory stimulus.[125] A "strong" LDAEP suggests that the characteristics of evoked potentials following an auditory stimulus are highly dependent on the intensity (loudness) of the auditory stimulus.[134] In contrast, a "weak" LDAEP suggests that evoked potentials following an auditory stimulus do not vary much as a function of how loud the sound is.[132] To date, a variety of clinical studies have demonstrated that patients with "strong" LDAEP at baseline are more likely to respond to treatment with SSRIs than those with "weak" LDEAP.[133-137] However, in a small (n=35) randomized, open-label trial comparing the SSRI citalopram with the norepinephrine reuptake inhibitor (NRI) reboxetine for MDD, patients with "strong" LDAEP were more likely to respond to citalopram than reboxetine while patients with "weak" LDAEP were more likely to response to reboxetine than citalopram[138] (differential predictor or moderator of response). Double-blind, randomized clinical trials involving treatment with antidepressants of different class (ie, SSRI versus NRI) which are specifically designed to examine any potential moderating effects of LDAEP (ie, randomization based on LDAEP status would also need to occur) have yet to be conducted.

Brain functional asymmetry (dichotic listening)

Dichotic listening tasks involve auditory stimuli being presented to both the left and the right ear. Potential differences in perception (perceptual asymmetry) are then used as a proxy for brain functional asymmetry. Bruder et al[140] first studied the relationship between the presence of perceptual asymmetry following dichotic listening tasks at baseline and symptom improvement following treatment with the TCAs. A left-ear (right hemisphere) advantage was significantly more common among nonresponders than responders. This was replicated for fluoxetine (SSRI) treatment in two different studies[140,141] and bupropion (NDRI) treatment in a separate study.[142]

Conclusion

A number of potential clinical predictors of symptom improvement during the pharmacologic treatment of MDD have been identified to date, mostly from studies focusing on the acute phase of treatment of MDD with the SSRIs. These include the presence of a greater number of concurrent psychiatric disorders (especially anxiety disorders), or general medical disorders (ie, cardiovascular illness, hypofolatemia). The presence of or more of these factors should alert clinicians to alter their treatment approach in order to help optimize the chances of patients recovering from depression. For instance, clinicians may chose to initiate therapy with two treatments, ie, pharmacotherapy and psychotherapy, schedule more frequent follow-up visits, increase the dose sooner in treatment nonresponders, or resort to various switching, augmentation, or combination strategies sooner for patients who do not experience a sufficient improvement in symptoms. Several potential clinical mediators of response have also been identified including the presence of severe MDD (escitalopram and duloxetine versus "older" SSRIs), anxious MDD (bupropion versus SSRIs), atypical MDD (MAOIs versus TCAs), and hormonal status among women (venlafaxine versus "older" SSRIs). However, at the present time, such "leads" are preliminary and have not been prospectively confirmed in randomized, double-blind clinical trials. Finally, pre-

liminary studies have identified a number of putative "biomarkers," relating to genetic or neurophysiologic (particularly quantitative EEG (QEEG)-based measurements as well as measures of prefrontal cortical metabolism), which appear to correlate with symptom improvement during the treatment of MDD with standard antidepressants (mediators of response). Conducting further studies designed to establish reliable, replicable, and robust biological factors which function as predictors, mediators, or moderators of clinical improvement in MDD could benefit the field in several ways, from enhancing our ability to develop more effective treatments to improving our ability to choose an individualized pharmacotherapeutic regimen for patients with MDD which would result in a more rapid and robust resolution of depressive symptoms. ❑

Predictores, moderadores y mediadores (correlatos) de la evolución del tratamiento en el trastorno depresivo mayor

El trastorno depresivo mayor (TDM) es una enfermedad prevalente que está asociada frecuentemente con incapacidad, morbilidad y mortalidad significativas. A pesar del desarrollo y de la disponibilidad de numerosas opciones terapéuticas para el TDM, los estudios han mostrado que la monoterapia antidepresiva sólo produce bajas frecuencias de respuesta y remisión. Es claro que hay una urgente necesidad de desarrollar estrategias terapéuticas más efectivas para los pacientes con TDM. Una posible aproximación para el desarrollo de novedosas estrategias farmacoterapéuticas para el TDM implica identificar subpoblaciones de pacientes depresivos que con mayor probabilidad experimenten los beneficios de un tratamiento dado (existente) versus placebo, o versus un segundo tratamiento. Se han realizado intentos para identificar tales "subpoblaciones", específicamente analizando si un determinado marcador biológico o clínico también sirve como un moderador, mediador (correlato) o predictor de la mejoría clínica en el tratamiento del TDM con antidepresivos estándar de primera línea. En este artículo se intentará resumir la literatura focalizada en algunas áreas principales ("pistas") donde existe evidencia preliminar relacionada con moderadores, mediadores y predictores clínicos y biológicos de mejoría de síntomas en el TDM. Las pistas clínicas incluirán la presencia de desesperanza, síntomas ansiosos o comorbilidad médica. Las pistas biológicas incluirán polimorfismo genético, metabolismo cerebral, electroencefalografía cuantitativa, dependencia a la intensidad del volumen de los potenciales evocados auditivos y asimetría cerebral funcional.

Facteurs prédictifs, modérateurs et médiateurs (corrélats) des effets thérapeutiques dans le trouble dépressif majeur

Le trouble dépressif majeur (TDM) est une pathologie prévalente fréquemment associée à une invalidité, une morbidité et une mortalité significatives. Malgré le développement et l'existence de nombreux traitements pour le TDM, des études ont montré que les monothérapies antidépressives ne donnaient que de modestes taux de réponse et de rémission. Il devient vraiment urgent de développer des stratégies thérapeutiques efficaces pour les patients atteints de TDM. Une approche éventuelle pour un tel développement serait d'identifier des sous-populations de patients déprimés plus susceptibles de bénéficier d'un traitement donné (existant) versus placebo ou versus un second traitement. Des tentatives ont été menées afin d'identifier de telles « sous-populations », en vérifiant en particulier si un marqueur biologique ou clinique donné pouvaitt aussi servir de modérateur, médiateur (corrélat) ou prédicteur de l'amélioration clinique consécutive au traitement du TDM avec des antidépresseurs standard de première intention. Dans cet article, nous allons essayer de résumer la littérature dirigée vers plusieurs axes importants (« directeurs ») et pour lesquels il existe des arguments préliminaires en ce qui concerne les prédicteurs, médiateurs et modérateurs cliniques et biologiques de l'amélioration des symptômes du TDM. Ces symptômes cliniques « directeurs » incluront les symptômes de désespoir,d'anxiété ou de comorbidité médicale. Le polymorphisme génétique, le métabolisme cérébral, l'électroencéphalographie quantitative, la dépendance à l'intensité du son des potentiels évoqués auditifs et l'asymétrie cérébrale fonctionnelle feront partie des critères biologiques directeurs exposés.

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