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Predictors of response in depression

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Advances in the treatment of depression have resulted in estimates that 80% to 90% of depressed patients can be treated successfully [1]. Antidepressant medications and some psychotherapies have demonstrated efficacy in clinical trials. Recent focus on remission rather than response in clinical trials has emphasized that depression can, in fact, be cured [2]. Yet, the economic burden of depressive disorders in the United States was estimated in 1990 at nearly $44 billion annually [3]. Depression remains underrecognized and undertreated [1]. Even when appropriate treatment is initiated, patients are often plagued with partial responses, recurrent episodes, and treatment intolerance.

The lack of well-defined predictors to guide treatment choices is frustrating to both patient and psychiatrist. For the patient, suffering is often extended through a 3- to 4-week trial of a medication before the choice to escalate dose or alter treatment strategy can be adequately made. With any particular treatment strategy, a patient may obtain a partial response but never reach full remission of symptoms. Multiple medications or combinations of medications may be tried over a period of months until maximum benefit is reached. Further confusing the issue, some patients do well with a medication even if they have failed another medication in the same class. Treatment guidelines and awareness of side effect profiles and medication interactions can help guide clinical choices, but the clinician is most often left with multiple choices and no way of predicting which medication might be beneficial for an individual patient. Interest in clinical trials is shifting from merely reporting "response," often defined as a 50% reduction in a rating scale, which can still leave significant residual symptoms, to "remission," equated with wellness or absence of a disorder [2,4].

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Ideally, one would like to be able to predict the response of a patient to one antidepressant versus another to achieve remission.

This article reviews publications relevant to predictors of response in clinical depression. Post hoc analysis of many clinical studies can shed light in this area and add to an overall body of data. Other studies are specifically designed to test theories of response prediction. Data are often conflicting, and effect sizes can be quite small. Many different types of potential predictors have been sought and grouped into various categories, including clinical, demographic, physiologic, biochemical, psychologic, and neuroanatomic factors. Selected studies relevant to these areas are reviewed.

Clinical predictors

Great strides have been made in the past decades in one significant area that aids in predicting response to treatment: diagnostic specificity. With each revision of the *Diagnostic and Statistical Manual, 4th edition* [5], diagnoses have become more specific and more useful in guiding treatment choices. Depression is no longer thought of as one illness but as a syndrome appearing in many contexts: major depression, dysthymia, bipolar disorder, schizoaffective disorder, substance-induced mood disorder, seasonal affective disorder, premenstrual dysphoric disorder, and postpartum depression. Consideration of comorbidity is also critical to response. Anxiety disorders, such as panic disorder, posttraumatic stress disorder, and social phobia, cooccur frequently with depression. Personality disorders often have coexisting depressive features. Although first-line treatment for many of these may include use of an antidepressant, considerations of dosing, concomitant medications, and appropriate psychotherapeutic interventions may be very different from treatment of a major depressive. Expert consensus and treatment guidelines have been published for many of these syndromes. Inaccurate diagnosis can be a major determinant of poor outcome.

In part to assist in the search for predictors of outcome, the diagnosis of major depression itself has been divided into subtypes, each with a unique clinical presentation. The *Diagnostic and Statistical Manual, 4th edition* includes specifiers for melancholic features (anhedonia, lack of mood reactivity, distinct quality of mood, AM worsening, early morning wakening, marked psychomotor retardation or agitation, significant anorexia, excessive guilt) and for atypical features (mood reactivity, increased appetite, hypersomnia, leaden paralysis, pattern of interpersonal rejection sensitivity) [5]. Now less commonly used, such distinctions as ''endogenous'' and ''exogenous'' depression, and ''agitated'' or ''restrictive'' subtypes, have also been made to define subgroups with particular characteristics and treatment responses.

Available data examining depressive subtypes as predictors of response are often conflicting. For example, studies of fluoxetine reviewed by

Goodnick [6] sometimes show a relative benefit in patients with retarded depressive symptoms, sometimes show a benefit in patients with anxious-agitated depressive symptoms, and sometimes show equal response regardless of type of symptoms. Goodnick and Extein [7] conducted an open trial comparing fluoxetine with bupropion during 8 weeks of treatment in patients with typical, atypical, or bipolar characteristics. Twenty-three patients received fluoxetine (40 mg/d) and 34 patients received bupropion (450 mg/d). A significant response to fluoxetine was seen in typical (54% of patients) but not atypical (22% of patients) depression. A significant response to bupropion was seen in patients with atypical (64%) or bipolar (89%) features, but not in those with typical (11%) depression. In an 8-week study with 41 patients taking slow-release bupropion, patients with bipolar and atypical depression responded better than those with typical depression (mean change in Hamilton Depression Rating Scale 15.6, 17.1, and 7.6, respectively) [8].

Several studies have demonstrated the relative usefulness of the monoamine oxidase inhibitor (MAOI) phenelzine versus imipramine in the treatment of atypical depression [9,10]. McGrath et al [9] conducted a double-blind, placebo-controlled trial of imipramine versus phenelzine in 401 patients with atypical depressive features; most met criteria for ''definite'' or ''probable'' atypical depression, whereas some had only mood reactivity and none of the other four atypical features analyzed. The study found a relatively low rate of response to imipramine compared with phenelzine in patients with even one atypical feature.

Tricyclic antidepressants (TCAs) have been shown in several studies to be particularly useful in melancholic depression [11]. Clinical lore suggesting that anxious patients with insomnia respond better to sedating antidepressants, whereas lethargic patients respond better to more stimulating antidepressants, however, has not been confirmed by controlled studies and may not be relevant to eventual antidepressant response [12].

In a 12-month, prospective effectiveness study, Parker et al [13] suggest that, for melancholic depression, electroconvulsive therapy (ECT), TCAs, and MAOIs were most effective, whereas for nonmelancholic subtypes selective serotonin reuptake inhibitors (SSRIs) were equally effective.

McGrath et al [14] found that symptoms characteristic of atypical depression were predictive of poor outcome during continuation-maintenance treatment with fluoxetine. Fluoxetine was most advantageous for subjects with endogenous vegetative symptoms, chronic depression, and early treatment response. Patients with melancholic depression and psychomotor agitation were found to be more likely to respond to sertraline than fluoxetine (59% versus 44% and 62% versus 39%, respectively) in a randomized, double-blind, 6-week study of 286 outpatients [15].

Severity of depression has been found in some studies to be a predictor of good and in others of poor response. For example, in an open, retrospective study of 71 tricyclic antidepressant–resistant depressed inpatients, those

who responded to lithium augmentation (52%) within 4 weeks were more severely depressed, had a shorter index episode of depression, had lower triiodothyronine serum levels, were less likely to have personality disorders, and were less likely to have required neuroleptics than those who failed to respond [16]. Dose and type of TCA and lithium level were not related to outcome. A meta-analysis of studies in which SSRIs were compared with TCAs indicated that, although both types of medication were effective, certain subsets of depressed patients might respond better to TCAs [17]. There was a slight advantage to TCAs in patients with more severe depressive illness.

As part of the Fluoxetine Collaborative Study Group, Small et al [18] evaluated 266 potential predictors of response in a 6-week, double-blind study of geriatric depression. Only 13 variables showed prognostic value; for fluoxetine response, these included somatic complaints, history of accidental injury, and lack of agitation. Absence of somatic complaints and insomnia and feelings of emptiness were predictive of a placebo response. More stringent statistical analysis failed to confirm the predictive value of any of these predictors. The authors consider that heterogeneity of subjects, which included 671 outpatients from 30 sites, may have confounded the results.

Duration of treatment can be critical in predicting treatment success. Treatment phases of a single episode of major depression have been divided into acute and continuations phases, with the acute treatment phase lasting from initiation of treatment until remission (often thought of as 12 weeks) and the continuation phase lasting until recovery (often thought of as 1 year), when the danger of relapse after discontinuation of treatment is reduced [19]. In the NCQA Health Plans Employer Data and Information Set [20], representing over 120,000 lives in 230 health care plans, 41% of patients did not receive even 3 months of treatment, and 58% of patients did not receive 6 months of treatment. Inadequate duration of treatment has been shown to increase risk of relapse [4] and risk of development of treatment resistance [1]. Patients with residual symptoms have been found to have poorer outcome than those who achieve remission, as have those with greater than three prior episodes of depression, those with dysthymia and major depression, and those with depressive episodes lasting more than 2 years [21]. In a review of studies on depressive breakthrough, Nierenberg and Alpert [22] point out that both controlled and observational studies demonstrate a significant benefit of maintaining antidepressant treatment but recognize the substantial rate of relapse despite treatment.

In a review of predictors of response to TCAs, Bielski and Friedel [23] found that insidious onset, anorexia, insomnia, and psychomotor retardation predicted response; a later review by Joyce and Paykel [24] emphasized insidious onset and psychomotor retardation and endogenicity, with less value to sleep and appetite disturbance. The suggestion that pervasive anhedonia predicted TCA response [25] has not been replicated

consistently [11]. Aliapoulous and Zisook [11] reviewed TCA predictors in specific subtypes of depression and concluded that both melancholic and nonmelancholic subtypes respond but that the greatest response is in patients with melancholic features.

Past history of a lack of response and greater length of depression were predictive of a better response to fluoxetine than to imipramine in one study of 110 patients treated for 4 weeks [26]. In a 5-week study comparing fluoxetine with amitriptyline, the greatest response to fluoxetine was seen in patients with endogenous depression; those with agitated depression did marginally better than those with retarded depression [27]. Another study, albeit with fewer patients, revealed better response to fluoxetine in retarded depression [28]. In a large study published by Eli Lilly, 698 patients were divided into subgroups of agitation, retardation, or neither; improvement was similar in the three groups. Two reports on a large patient base found no difference in rate of response to fluoxetine based on severity of depression or on anxious subtype [29,30].

Demographic predictors

In a study of lithium augmentation of TCA-resistant depressed patients, age and sex were not related to treatment outcome [16]. In a study of 60 depressed outpatients who received 4 months of antidepressant treatment, those who remitted (60% of subjects) were significantly older and more likely to be married.

Men and women have been found in some studies to respond differently to antidepressants, suggesting that gender might be predictive of response in some cases. In some studies, men have responded better to TCAs [31–33], whereas women have responded better to MAOIs [31] and SSRIs [32,34]. In a study of maintenance treatment with fluoxetine, however, age and gender were not predictive of survival to relapse [14].

Casper et al [35], in a study of 501 women and 375 men with major depressive disorder who received placebo in seven clinical trials, found that gender was not predictive of placebo response. At 4 weeks, 20.8% of men and 17.5% of women were considered to have remitted.

Tuma [36] found age to be a predictor of poorer outcome in depression. Duggan et al [37] report on family history data for 89 depressive patients; a family history of severe psychiatric illness in a first-degree relative was associated with poor long-term outcome in the probands.

Socioeconomic factors have also been examined as predictors of response in depression. As part of the Hampshire Depression Project, Ostler et al [38] examined the influence of underprivileged areas on the prevalence and outcome of depression in a primary care population. They found that socioeconomic deprivation was a powerful predictor of the persistence of depressive symptoms.

Pyne et al [39] undertook a study of health-related quality-of-life measures in inpatients with major depression. Acute treatment response was predicted to 86% accuracy with a model that included age at first depression, admission BDI score, melancholic symptoms, and subscales for physical and social activity from the Quality of Well-Being Scale. Bielski and Friedel's [23] review of predictive studies of TCA response indicated upper socioeconomic status as a positive predictor of response in depression.

Physiologic predictors

Physiologic correlates of serotonergic or noradrenergic abnormalities have been postulated to predict response to agents affecting these neurotransmitter systems. In a study by Gallinat et al [40], the pattern of auditory evoked potentials was found to be correlated to response to serotonergic agonists. Measuring the loudness dependency of late auditory evoked potentials, the researchers found that a strong response at baseline was related to significantly greater decrease in depressive symptoms after 4 weeks of treatment. Significantly more responders fell into the group with a strong response (9 of 12); 11 of 17 nonresponders had a weak auditory evoked potential.

Pretreatment systolic blood pressure drop with positional challenge was found to correlate positively with a response to tricyclics [11,41], as did reduced pretreatment rapid eye movement latency [11,42].

In a study examining ECT schedules, size of the postseizure fractal dimension after first ECT, determined by a geometric analysis of EEG amplitude, was predictive of response [43]. Forty patients with melancholic depression received once- or thrice-weekly ECT for 6 treatments and were further subdivided into three levels of dose stimuli. Raters of depression and fractal dimension were blind to treatment group. Smaller postseizure fractal dimension predicted recovery, and those patients who received thrice weekly ECT did better than those who received once-weekly treatment. All of these subjects were predicted to have a good response to ECT by the Newcastle ECT prognostic index. Reviewing studies of predictors in ECT, Nobler and Sackheim [44] found that assessment of treatment adequacy with changes in seizure threshold, degree of change in cerebral blood flow, and the ictal EEG, and several biologic markers, could help adjust treatment appropriately.

Considering the predictive possibilities of response to total sleep deprivation, Fritzsche et al [45] examined the treatment option of light therapy, generally thought of as first-line only in the treatment of seasonal affective disorder. The study found that response to one night of total sleep deprivation predicted response to light therapy in a group of 40 depressed patients. The study was limited by a lack of controls and the inclusion of subjects with seasonal patterns.

Event-related brain potentials in response to auditory stimuli were examined by Paige et al [46] as potential predictors of antidepressant treatment response. The authors had postulated that the P2 component amplitude as a function of stimulus intensity might be related to central serotonergic neurotransmission. In 17 subjects treated with a variety of antidepressants, responders (11 subjects) had significantly larger baseline P2 slopes than nonresponders. Nondepressed controls were not included in this study.

Biochemical and endocrinologic predictors

Historically, the dexamethasone suppression test was developed to assist in the diagnosis of depression. In the presence of exogenous glucocorticoid, serum cortisol normally is suppressed by a negative feedback mechanism of the hypothalamic-pituitary-adrenal axis; depressed patients have been described as nonsuppressors because their cortisol levels fail to suppress after administration of dexamethasone. The dexamethasone suppression test has also been studied as a predictor of treatment response. Ribeiro et al [47] conducted a meta-analysis of the dexamethasone suppression test as a predictor of outcome in depression and concluded the following: baseline dexamethasone suppression test results were not associated with treatment outcome; baseline nonsuppressors were less likely to respond to placebo; and nonsuppression of cortisol in dexamethasone suppression tests conducted after treatment was associated with early relapse and poorer outcome, possibly identifying a subgroup of sicker patients. Major confounding variables in the studies reviewed included such factors as heterogeneity in type and stage of illness and categorization of intermediate cortisol levels as ''suppressive'' or ''nonsuppressive.'' Zobel et al [48] found that a combined dexamethasone–corticotropin-releasing hormone test had value in predicting relapse in 74 remitted patients within 6 months of hospital discharge.

Not only glucocorticoids but also their receptors have been the object of study in the search for predictors of response. Sallee et al [49] examined lymphocyte glucocorticoid type II receptor levels in adolescents with major depressive disorder in an open-label study with sertraline. The 20 patients in the study had significantly lower baseline receptor sites than matched controls. Furthermore, there was a bimodal distribution of receptor sites in the treatment group; responders had significantly fewer sites than nonresponders, and sites were up-regulated after 6 weeks of treatment only in the responder group. These authors postulate that glucocorticoid receptors in lymphocytes might be a marker for changes at the hippocampal level.

Basal levels of a neuroactive steroid, dehydroepiandrosterone sulfate, were shown to predict response to ECT in 17 psychiatric inpatients [50].

Patients exhibited higher levels of cortisol, dehydroepiandrosterone, and dehydroepiandrosterone sulfate than controls both pre- and post-ECT; however, those who failed to respond to ECT had markedly higher baseline dehydroepiandrosterone sulfate levels.

Schatzberg [51] summarizes a study from his group in which urinary levels of the norepinephrine metabolite methyl-hydroxy-phenyl-glycol (MHPG) as predictors of response to relatively serotonergic (fluoxetine) versus relatively noradrenergic (desipramine) medications were examined. Medications showed similar efficacy. Low pretreatment levels of urinary MHPG predicted a response to either antidepressant. Levels of MHPG continued to decrease over 6 weeks of treatment; however, in the desipramine group only, urinary levels of norepinephrine increased over time, suggesting different effects on noradrenergic metabolism. Aliapoulous and Zisook [11], reviewing studies of MHPG with various tricyclic antidepressants, found several studies suggesting that low urinary MHPG predicted response to imipramine, and also suggest that depression with low MHPG levels in general respond well to TCAs. In a study of slow-release bupropion, improvement in patients with bipolar depression was related to an increase in MHPG and homovanillic acid [8].

Biochemical predictors related to serotonin have also been investigated. In an uncontrolled study of eight patients, Alvarez et al [52] reported a change in plasma serotonin after 1 day of treatment with fluoxetine, which differentiated between responders and nonresponders after 28 days of treatment. As had been observed previously, plasma serotonin levels decreased after 28 days of treatment in both responders and nonresponders. Not only did responders have lower serotonin levels after 1 day of treatment than nonresponders, but they had a decrease from their own baseline values, whereas three of four nonresponders had an increase from baseline after 1 day of treatment.

In a study of patients with depression who had responded to treatment, the emergence of temporary depressive symptoms after dietary depletion of tryptophan, a precursor of serotonin, was predictive of future major depressive episodes [53]. Twelve subjects in remission who had been off medication for at least 3 months were compared with 12 matched controls; mood response to tryptophan depletion had a positive predictive value of 70% and a negative predictive value of 86% to identify future depressive episodes. The authors suggest that patients subject to future episodes of depression are exquisitely sensitive to fluctuations in the availability of tryptophan.

Peripheral platelets have been used as an easily accessible model of central serotonergic neurons. Notably, platelets are involved in serotonin uptake and are able to bind antidepressants, such as imipramine. Castrogiovanni et al [54] reported a preliminary study in which patients who responded to fluoxetine had a lower density of imipramine binding sites at baseline than those who did not respond. Goodnick et al [55] reported on 14

patients treated with paroxetine for 8 weeks; patients who responded to treatment had significantly higher baseline platelet serotonin content than those who did not. Goodnick et al [56], in a study of adolescent depressed patients, saw a trend toward those with greater baseline platelet 5HT showing a greater change in Hamilton Depression Rating Scale. Looking at sertraline treatment of depression in patients with diabetes, Goodnick et al [57] reported that response may be predictable by higher baseline platelet 5HT. Lower baseline plasma tryptophan was found to be significantly correlated with response to paroxetine in another study [58].

Metabolites of serotonin, such as 5-hydroxyindoleacetic acid, have been found to be low in suicide victims. Again reviewing TCAs, Aliapoulous and Zisook [11] describe studies in which high 5-hydroxyindoleacetic acid predicted better response to amitriptyline, imipramine, or nortriptyline, whereas low 5-hydroxyindoleacetic acid predicted response to the more serotonergic clomipramine. DeBellis et al [59] found no relationship between baseline 5-hydroxyindoleacetic acid and response to fluoxetine in a small study with nine patients.

Another potential biochemical predictor, prolactin response to tryptophan or to the serotonin-releaser fenfluramine, is reviewed by Goodnick [6]. Higher levels of platelet serotonin, lower plasma tryptophan, and exaggerated prolactin response may be candidates for predictors of response to the most serotonergic medications.

Psychologic predictors

Various factors, such as temperament, character, and perceived parental care, have been examined as potential risk factors for depression; more recently, studies have also investigated the role of such factors in predicting the outcome of depression with adequate treatment. Using Cloninger's theory of personality to study 86 consecutive patients with major depression in a 16-week open trial of maprotiline, Sato et al [60] suggest that character dimensions, such as cooperativeness and self-directedness, may be predictors of response to antidepressants. Tome et al [61] found temperament dimensions to be associated with outcome in a study of patients taking paroxetine, some of whom received augmentation with pindolol.

Noting that a number of studies have examined parenting as a risk factor in the development of depression, Sakado et al [62] investigated the relationship between dysfunctional parenting and treatment outcome in depression. The Parental Bonding Instrument, a self-report questionnaire, was administered to 60 patients who completed 4 months of antidepressant treatment. The researchers observed that low perceived levels of paternal care and a high isolation tendency predicted poor response to antidepressants [62].

Neuroanatomic predictors

Advances in neuroimaging and recent neurobiologic models of depression are being applied to predicting treatment response. Studies using methodologies, such as multichannel EEG and positron emission tomography, have indicated that baseline activity in the rostral region of the anterior cingulate cortex predicts response to depression [63,64]. Pizzagalli et al [64] recorded 28-channel EEGs from depressed patients and controls; patients were then treated with nortriptyline and after 4 to 6 months of treatment dichotomized as "better" or "worse" responders according to degree of change from baseline. Those who responded better had higher baseline theta activity in the rostral anterior cingulate than those who did not do as well and also had higher activity than comparison subjects. Mayberg et al [63] used positron emission tomography to measure pretreatment regional cerebral glucose metabolism and correlate this with antidepressant response. Eighteen depressed patients were studied and followed 6 weeks later; 15 control subjects were also studied. Eight patients were considered responders; compared with controls, responders showed hypermetabolism and nonresponders showed hypometabolism in the rostral anterior cingulate. Other brain areas also differentiated responders from nonresponders but not from controls. Clinical factors, such as number of prior depressive episodes, duration and severity of current episode, and medication type, did not account for the observed differences. Pizzagalli et al [64] note that "[t]aken together, these results suggest that hyperactivation of the rostral anterior cingulate cortex may represent an adaptive, compensatory reaction to the state of being depressed that increases the likelihood of remission and then normalizes after recovery." In a model of depression integrating information about the anterior cingulate, the dorsal compartment is postulated to regulate attention and cognition and the ventral compartment is postulated to regulate vegetative and somatic symptoms; the rostral anterior cingulate may have a role in integrating the two.

Summary

Conflicting or sparse data on predictors of treatment response in depression have resulted in lack of clear guidelines in choosing antidepressant treatment. Critical to treatment outcome are accurate diagnosis and adequate treatment. Other data easy to obtain, such as age, gender, and marital status, have failed to be consistent predictors; more elaborate studies, such as receptor analysis or neuroimaging, are not yet accessible to most clinicians or economically feasible; however, they offer hope for the future, when more biologically based diagnostic distinctions may come to guide treatment choices.

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