Psychosocial and clinical predictors of response to pharmacotherapy for depression

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A more complete understanding of the psychosocial and clinical predictors of response to pharmacotherapy would be of great value to both patients and physicians. Most demographic and clinical factors have not been found to be useful predictors of response. Although comorbid illness affects quality of life, there is confounding evidence about its importance when predicting response to antidepressant therapy. Some social support factors appear to be positive predictors of outcome in most trials. There is evidence to suggest that comorbid anxiety disorders and panic–agoraphobic spectrum symptoms are negative predictors of response to treatment. Substance abuse has been associated with a poorer response to antidepressant therapy, and recovery from substance abuse problems has been shown to be poorer among patients with comorbid depression. Assessment of personality dimensions may be a useful predictor of clinical course and outcome, but personality disorders present a complicated picture, with significant interaction among variables. A number of variables are significantly related to clinical course, but few factors have been clearly linked to treatment response. The challenge is to determine if any of these factors are indeed independent predictors of response and whether it is possible to match choice of antidepressant therapy and patient type.

Il serait très utile tant pour les patients que pour les médecins de comprendre entièrement les prédicteurs psychosociaux et cliniques de la réponse à la pharmacothérapie. La plupart des facteurs démographiques et cliniques ne sont pas des prédicteurs utiles de réponse. Même si une comorbidité a des répercussions sur la qualité de vie, il existe des données confusionnelles sur son importance lorsque l'on prédit la réponse à une thérapie aux antidépresseurs. On a constaté que certains facteurs d'appui social sont des prédicteurs positifs des résultats dans le cadre de la plupart des études. Tout semple indiquer que les troubles comorbides de l'anxiété ou les symptômes de la gamme panique-agoraphobie sont des prédicteurs négatifs de réponse au traitement. On a établi un lien entre la toxicomanie et une moins bonne réponse à la thérapie aux antidépresseurs, et l'on a démontré que le rétablissement à la suite d'une toxicomanie est moins bon chez les patients atteints d'une dépression comorbide. L'évaluation des aspects de la personnalité peut constituer un prédicteur utile de l'évolution et du résultat clinique, mais les troubles de la personnalité présentent un tableau compliqué où l'interaction entre les variables est importante. De nombreuses variables ont un lien important avec les résultats, mais les facteurs reliés

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clairement à la réponse au traitement sont peu nombreux. Le défi consiste à déterminer si certains de ces facteurs sont vraiment des prédicteurs indépendants de réponse et s'il est possible de jumeler le choix de la thérapie aux antidépresseurs et le type de patient.

Introduction

Despite the introduction of a variety of antidepressant medications over the past 10–15 years, an unfavourable response to pharmacological intervention in the treatment of depression is not uncommon. As a result, there have been many attempts to determine the characteristics of depressed patients who will or will not respond to treatment. Both sociodemographic and clinical factors have been examined, but the potential predictors of nonresponse are most often inconsistent or not strong enough to be useful clinically. More often, antidepressants are chosen on the basis of side-effect profile an not the predicted efficacy for individual patients or patient groups.[1] The ability to select the most successful treatment and to predict the outcome of therapy for a patient would be of great value to both patients and physicians.[2] The purpose of this paper is to systematically review the association between treatment outcome and a number of psychosocial variables as identified in the published literature. Articles were retrieved using MEDLINE searches, and further key references were then identified from the initial review papers.

Demographic and clinical factors

Demographics

Most demographic factors have not been found to be useful predictors of response to antidepressant therapy. With few exceptions, age and sex do not affect response rates (Table 1).[1–5] In the 2 studies that did show an age–response relation, one reported a poorer response in older subjects[6] and the other, a poorer response in younger subjects.[7] It has also been suggested that antidepressants are less effective in children and adolescents.[8,9] This idea is based mainly on earlier small studies using tricyclic antidepressants (TCAs). More recent placebo-controlled trials with selective serotonin reuptake inhibitors (SSRIs), fluoxetine and paroxetine have demonstrated significant efficacy in this patient population.[9,10] Race or ethnicity does not appear to be associated with treatment response either.[4] In one study, a better than average treatment response reported for a subgroup of African–Americans was determined to be associated with less aggressive pretreatment of the index episode, which resulted in fewer treatment-resistant cases in this patient population.[3]

Clinical factors

Duration of illness, number of prior episodes and age of onset do not appear to be predictors of response.[1,3,4,5,7,11]

Severity of illness may predict response in patients with primary depressive episodes,[6,7,11] but not in patients with recurrent depression.[1,3,5,12] However, in a study by Hirschfeld and colleagues,[2] of 623 patients with chronic major or double depression, those who responded to antidepressant therapy had significantly lower baseline depression severity scores as measured by the Montgomery–Asberg Depression Rating Scale (MADRS) than nonresponders; however, the Hamilton Rating Scale for Depression (HAM-D) scores did not differ between responders and nonresponders.[2]

Age of onset of depression may be an important source of heterogeneity in both chronic and nonchronic mood disorders. In a study examining this variable as a potential predictor of response in 289 outpatients, early-onset chronic major depression had a more malignant course and was associated with more comorbid disorders than late-onset chronic major depression.[13] However, the early–late onset distinction was not associated with differences in symptom severity, functional impairment or treatment response. This supports several other studies that also reported no impact of age of onset on response to therapy.[1,3,5,12]

Greater degree of cognitive impairment (as measured by the KDS Self-rating Scale or the Mini-Mental State Examination) at admission was an independent predictor of nonresponse to therapy in middle-aged and elderly inpatients with major depression.[3,5]

Results indicate that an early nonresponse to medication (i.e., 1–2 wk) may predict a poor outcome overall.[14] No response to fluoxetine as early as week 2 of therapy predicted a negative outcome at 8 weeks.[15] Moreover, the opposite was found to be true — of those patients who experienced a robust improvement by weeks 2 or 4, 80%–90% went on respond well, suggesting that

Table I: Psychosocial and clinical variables that have been investigated as possible predictors of response to antidepressant treatment

Study	Sample	Age	Sex	Race	≤ High school education	Age of onset	Duration of illness	Illness severity	Recurrent depression	Personality disorders / traits	Lack of social support	Lower functioning	Initial cognitive performance	Life events	Melancholia subtype	Dysthymia	Panic or anxiety	Substance abuse	Comorbid Axis I or Axis II disorder	Medical illness
Primary episode																				
Weissman et al[4]	*n* = 150 women, ≤ 1 previous episode	↔		↔				↕	↕	X	↕			↕						
Bromberger et al[24]	*n* = 18 postnatal women, not chronic							↕			X									
Paykel et al[11]	*n* = 60 in- or outpatients with primary depression						↕	X		↕ X						↕				
Ezquiaga et al[6]	*n* = 87, not chronic	X older						X	X	X	X	X		↕	↕	↕				
O'Leary et al[7]	*n* = 100, 74% first episode	X younger	↔			X	X	X	↕		↕ X			↕			X			↕
Chronic or recurrent																				
Kupfer, Spiker[5]	*n* = 76 refractory inpatients	↔	↔			↕		↕	↕				X		↕		X			
Joyce et al[1]	*n* = 84, 58% recurrent	↔			↕			↕	↕	↕ X					↕	↕	↕			
Zubenko et al[3]	*n* = 205 inpatients, 60% recurrent	↔	↔	X		↕		↕	↕		↕		X						↕	X
Hirschfeld et al[2]	*n* = 623, chronic	↔			X			X		↕ X	X	X					↕	↕	↕	

X = predictor of negative response; ↔ = no effect on outcome. Space left blank if variable was not assessed in the study.

responsiveness can at least be determined relatively quickly. Similar results have been also been demonstrated with TCAs.[16]

Comorbid physical illness

In elderly patients in community, outpatient and inpatient samples, physical illness emerges consistently as the most common clinical feature associated with depressive symptoms and diagnosis.[17–19] In addition, some studies indicate that physical illness is associated with a poor prognosis for depression.[20,21] However, in a study assessing the impact of comorbid illness on functional status and treatment outcome in 671 older depressed outpatients, Small et al[22] found those with chronic physical illness responded to antidepressants as well as those without such illness. Interestingly though, the burden of prior (historical) physical illness was associated with a greater fluoxetine response and a lower placebo response. In contrast, another study of 205 consecutively admitted elderly inpatients with major depression demonstrated that the number of medical problems and length of hospital stay independently contributed to the prediction of response to treatment.[3]

Social support

Some researchers have suggested that social support has an important impact on recovery from depression.[2,6,23] For example, elderly patients who were impaired in social interaction and subjective social support at baseline were less likely to recover from their depressive episode.[23] Living with a spouse or partner, longer duration of personal relationships, higher educational level and higher

quality of life have been found to be significant predictors of positive response.[2] Other studies have also found that lack of everyday psychological support provided by a spouse was associated with incomplete recovery.[6] In a sample of 18 married mothers who underwent 12-week antidepressant treatment for major depressive disorder, high disaffection toward their husband was a predictor of incomplete recovery, independent of symptom severity.[24]

A naturalistic study of 100 inpatients found that a longer time to remission was associated with not owning a house, residing in an urban residence and single marital status.[7] None of these variables were significant predictors in the multivariate analysis, however. Several other studies have failed to find a relation between response to antidepressant therapy and social factors such as social class, marital status, widowhood or prior residential setting.[3,4]

Religion

There has been increasing interest in the effects of religious belief and activity on mental health and depression.[25] Despite evidence suggesting its potential importance, the effects of religion on recovery from depression have been largely ignored.[26] Studies show a significant inverse relation between religiosity and depression.[27–29] In a study of 87 depressed elderly patients, which controlled for many potential predictors of outcome, greater intrinsic religiosity independently predicted shorter time to remission.[30] This was not attributable to the social aspects of organized religious functions and church going, as these activities were not associated with time to remission. Less than half of the patients in this study received antidepressants or psychotherapy.

Predicting remission versus predicting response

Many studies chose either remission or response as endpoints. The few that have examined both have found that, in general, the predictors of remission and those of response are similar. In a study assessing the factors associated with full remission (defined as HAM-D < 8), response and nonresponse, the univariate analysis indicated that greater age was a significant predictor of remission but not of response, and initial higher HAM-D score was a negative predictor of response but not of recovery.[6] In the multivariate analysis, initial functioning and partner social support were predictors of remission, initial HAM-D was predictive of response and personality disorders were associated with both response and remission. In another study, significantly lower levels of self-rated cognitive disorganization, depression and anxiety were seen in the complete responders (HAM-D ≤ 12) than in the partial (HAM-D 13–19) or nonresponders.[5] In elderly patients, predictors of remission were found to be the same when the HAM-D cutoff was 10 or less and when it was below 7.[3] Although there appear to be some variations, insufficient data are available to draw conclusions about whether various factors have different predictive value for remission or response.

Comorbid DSM-IV Axis I conditions

Anxiety disorders

Converging evidence indicates that patients with major depression and comorbid anxiety disorders experience less favourable treatment outcomes than patients who have major depression alone.[31–39] There are relatively few studies in which the existence of a comorbid anxiety disorder was not predictive of nonresponse.[1,2]

In a recent study, a lifetime burden of panic–agoraphobic spectrum symptoms (including core and severe symptoms and more subtle features related to the core condition) predicted a poorer response to interpersonal psychotherapy (IPT) and an 8-week delay in response to sequential treatment (adding an SSRI to IPT) among 61 women with recurrent depression.[40] Even after controlling for lifetime panic history, patients with high panic scores differed significantly in treatment outcome for depressive symptoms than those with low scores. In another study of 312 patients fulfilling criteria for treatment-resistant depression, response to treatment with venlafaxine was significantly higher in patients with an absence (58%) compared with the presence (31%) of any comorbid psychiatric disorder ($p < 0.001$).[41]

Substance abuse

An estimated 14% of the general population in the United States have a history of alcohol abuse or dependence, and alcoholism exists as a comorbid diagnosis in 20% of depressed men and 10% of depressed women.[42,43] The prevalence of smoking is also higher

among patients with depression than it is in normal control groups (49% v. 30%).[44] "Self-medication," both with legal and illegal drugs of various kinds, is common among depressed patients.[44–46]

Consumption of alcohol has been shown to be a predictor of poorer response to antidepressant therapy even in those who are not considered to be abusers (i.e., avg. intake < 30 mL [1 oz] per day).[47] The degree of alcohol consumption at baseline was a significant predictor of poorer response in 94 patients treated with fluoxetine, even after adjusting for severity of depression at baseline. Patients with depression secondary to anxiety and substance abuse were less improved after treatment and more likely to have suicidal thoughts and relapses than patients with comorbid medical but not psychiatric conditions.[48] Other studies, however, have found that a comorbid Axis I diagnoses, including substance abuse, does not influence antidepressant response rates.[2,3]

The alternative — recovery from comorbid conditions in patients with depression — has also been shown to be poorer. For example, recovery from substance abuse was poorer when patients had comorbid anxiety or depressive disorders.[49] Comorbid patients had comparable substance abuse outcomes but fared worse on psychological symptoms and employment outcomes. Similarly, recovery from bulimia nervosa was poorer when there was comorbidity with depression.[50]

Comorbid DSM-IV Axis II disorders and personality dimensions

There has long been interest in the connection between personality and depression. The presence of a DSM-IV Axis II personality disorder has been linked to increased severity of depression and a poorer response to pharmacotherapy.[6,11,51,52] Nevertheless, studies in which Axis II personality disorders have been specifically recorded do not consistently show a link.[51,53,54] Personality traits, or specific dimensions of personality, appear to be more important predictors of outcome in patients with major depressive disorder.[1,54,55]

In a study designed to examine predictors of short-term response, Joyce and colleagues[1] reported that personality traits, rather than clinical variables or Axis II personality disorder diagnoses, were the main predictors of response to TCAs. Eighty-four patients with a current major depressive episode completed a 6-week double-blind trial of either clomipramine or desipramine. No specific personality disorder diagnosis was predictive, but borderline personality did show a trend toward poorer treatment outcome ($p = 0.09$). The personality dimensions neuroticism, psychoticism and extraversion also did not predict outcome. Three temperament types in Cloninger's biosocial model of personality — novelty seeking, harm avoidance and reward dependence — accounted for 35% of the variance in treatment outcome, compared with less than 5% predicted by clinical variables. In the more severely depressed patients, these temperaments predicted nearly 50% of the variance in treatment outcome. Schizoid, passive–aggressive and passive–dependent personalities were associated with better outcomes, whereas antisocial and cyclothymic personalities fared poorly.

Hirschfeld et al[2] reported that, in patients with chronic or double depression, the presence of a concurrent personality disorder did not predict response to medication. When specific diagnoses were examined, an Axis II passive–aggressive personality disorder was found to be significantly associated with a favorable response to 12 weeks of acute-phase treatment. Although the measurement of overall "depressive temperament" (as determined by the Diagnostic Interview for Depressive Personality) was not predictive of nonresponse to pharmacotherapy, certain characteristics of depressive personality, specifically low self-esteem, introversion and quietness, were.

In Paykel's landmark paper on residual symptoms after partial remission of depression, patients with residual symptoms had higher rates of personality abnormalities.[11] Passive–dependent, but not schizoid, sociopathic or anankastic personality traits were associated with a poorer response.

Similarly, in a study in 83 depressed outpatients treated with fluoxetine for 8 weeks, there were no differences in outcome between patients who had and did not have a comorbid personality disorder diagnosis at baseline (as assessed with a self-rating score on the Personality Diagnostic Questionnaire-Revised).[52] However, when diagnoses were grouped into clusters, the presence of a pretreatment cluster B diagnosis (i.e., histrionic, narcissistic, borderline and antisocial diagnosis) was predictive of a better response to antidepressant treatment than the absence of pretreatment cluster B diagnosis. No differences in response were apparent in patients with or without Cluster A (i.e., paranoid, schizoid, schizotypal) or Cluster C (i.e., avoidant, dependent, obsessive–compulsive, passive–aggressive) diagnoses.

In another prospective study specifically designed to identify predictors of recovery, the presence of Axis II personality disorder was the strongest predictor of poor outcome.[6] Having suffered a previous episode, lower level of functioning and some aspects of social support were also associated with not achieving full remission. Only personality disorder and high initial HAM-D score were related to nonresponse. This study also examined self-esteem; a poorer response was observed in patients with a high negative evaluation of self.

Two other studies have also looked at the personality dimensions neuroticism and extraversion. In one study,[4] neuroticism but not extraversion was an important predictor of chronic poor outcome with both psychotherapy and drug treatment. In contrast, the other study reported that neuroticism may be a predisposing factor for major depression but was not a predictor of response when severity of illness was considered.[56] Moreover, extraversion was the best predictor of treatment outcome, with the gregariousness facet accounting for the reduction in depressive symptoms.

Several other studies have reported on the effects of specific personality traits on response to treatment. A better response has been shown in low angry-hostile, than in high angry-hostile depressive patients.[57] In addition, distraction but not rumination was demonstrated to predict response.[58] Rector et al[59] reported that neither pretreatment self-criticism nor dependency scores were predictors of response to pharmacotherapy, but self-criticism scores were predictive of response to cognitive therapy.[59]

These findings demonstrate that personality assessment may be useful to help predict the clinical course and outcome of treatment for depressed patients. Dimensions of personality may prove to be more helpful than formal personality disorder diagnoses, but, at present, this idea requires further study.

Antidepressant therapy and personality

Some of the variability in the results of studies assessing personality may be related to the specific medication patients were taking. In women, temperament type predicted a variable response to different tricyclic antidepressants, with high reward dependence associated with a good response to clomipramine, and high harm avoidance associated with a good response to desipramine.[1] This phenomenon was not observed in the men.

Some researchers have suggested that different antidepressant agents may have different effects on particular personality disorders or traits. One trial showed a reduction in anger attacks with fluoxetine treatment and suggested that patients with depression and anger attacks may respond better to SSRIs.[60] In a study testing this hypothesis, in which 2 SSRIs, sertraline and paroxetine, as well as a tricyclic and a serotonin and norepinephrine reuptake inhibitor were used, there was no likelihood that high angry-hostile patients would respond better to SSRIs than to the other classes of medications.[57] A comparison of the effectiveness of sertraline and citalopram in depressed patients with comorbid personality disorders showed equal reductions in paranoid, borderline, avoidant and dependent personality disorder diagnoses.[61] Note, however, that both of these medications are SSRIs.

Conclusion

Despite finding a number of variables that were significantly related to outcome, few have been clearly linked to treatment response at this time.[2] Clinical and sociodemographic variables are not particularly helpful, with age, sex, age of onset, duration of illness and number of recurrences having no effect on response to treatment. Severity of illness may predict response in patients with first-onset depression. Social support has been shown to be a predictor, particularly living with a spouse or partner, as has religiosity. Concurrent medical illness, although it appears to negatively affect quality of life, does not appear to be associated with treatment response.

Comorbid anxiety disorders as well as substance abuse appear to be negative predictors of response. Comorbid personality disorder diagnoses may not be predictive, as such, but personality dimensions or traits may be. Passive–aggressive personality, extraversion and lower hostility levels contribute to a positive response to therapy. Personality disorders present a complicated picture, with significant interaction between variables. A patient with more comorbid personality problems may have more severe illness and less social support. It is difficult to determine whether any of these variables are truly independent predictors of response or if they all are intertwined, combining to create a situation where the patient is unlikely to achieve a positive response. There is also the additional confound that many Axis II traits appear as symptoms for many Axis I conditions.[62] This calls into question

whether one can use Axis II traits as a stable independent predictor of changes in Axis I conditions.

Finally, it is important to reiterate that none of the reviewed variables are particularly powerful or consistent predictors of response. Moreover, most, if not all, of the studies reviewed fail to make inference regarding the causal relation between the predictor and outcome variables. For example, it was unclear if the predictor variables were moderators of outcome (i.e., when or under what conditions effects will occur) or mediators of outcome (i.e., how or why effects occur). Future studies might benefit by clarifying the nature of their predictors.

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