Comorbidity and Depression Treatment

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Comorbidity is common among patients with major depression, but in most instances it may be of little relevance. Nonetheless, it is a complex issue because of its relation to treatment response, and few studies have attempted to address this. Most have examined comorbidity after the fact in secondary analyses. In this article, I focus on whether comorbidity influences depression treatment response among patients who are primarily diagnosed as suffering from major depression. At least three comorbidities are believed to influence treatment response: medical, anxiety, and personality disorders. Whether studies find that these factors predict worse outcomes in patients with major depression appears to depend on the nature and severity of the medical illness, the study setting, and the study design. The best designed studies reported the least effects of these factors on treatment outcome. Clinically, this suggests that these factors should not be seen as impediments to treatment.

Medical Comorbidity

Clinical trials of antidepressants generally exclude patients who have significant medical illness, yet depression with medical comorbidity is the norm rather than the exception among patients who are seen in most clinical settings. The treatment of depression in medically ill patients is challenging. Recognition, compliance, differential diagnosis, side effects, and tolerance of drug regimens can complicate the treatment of depression among patients who are medically ill. Before the introduction of selective serotonin reuptake inhibitors (SSRIs), it was generally believed that medically ill depressed patients did not tolerate or respond well to antidepressant treatment. Koenig et al (1989) reported that nortriptyline was contraindicated in 90% of medically ill depressed patients. He also noted that 80% of potentially eligible patients were unable to complete a trial of nortriptyline. In a retrospective review Popkin et al (1985) reported that only 40% of medically ill depressed patients responded to treatment and that 32% could not tolerate treatment. Both these studies were conducted before the advent of SSRIs and led to a nihilistic perception regarding the use of antidepressants in the medically ill. This perception may not be warranted.

A recent Cochrane report on the use of antidepressants in the medically ill addresses the issue of whether antidepressants are effective in this population (Gill and Hatcher 2000). This review analyzed all relevant randomized trials that compared any antidepressant drug with placebo or no treatment in patients diagnosed with depression and a specified physical disorder. This review included 18 studies, covering 838 patients with a range of medical conditions (cancer in two studies, diabetes in one, head injury in one, heart disease in one, HIV in five, lung disease in one, multiple sclerosis in one, renal disease in one, stroke in three, combined disorders in two). Six studies used SSRIs, three used atypical antidepressants, and the reminder used tricyclic antidepressants (TCA). The key finding was that patients treated with antidepressants were more likely to improve than those who were given placebo or no treatment. The finding that about four patients would need to be treated with antidepressants to produce one recovery from depression that would not have occurred had they been given placebo or no treatment is similar to that seen in trials of depressed patients without medical problems. The other interesting finding was that antidepressants were well tolerated by patients; about 10 patients would need to
be treated with antidepressants to produce one dropout from treatment, which would not have occurred had they been given placebo. (Gill and Hatcher 2002). By inference from this review, one can conclude that medical comorbidity is not a major factor in treatment response. A problem with the studies reviewed in Gill and Hatcher (2002) is that they did not include both healthy and medically ill patients with depression. Thus, it cannot be definitively stated that, under the same trial conditions, medical comorbidity does not influence treatment response. Steffens recently studied this issue in a naturalistic manner (Steffens et al 2002). Thirty-one elderly patients with unipolar major depression (DSM-IV) who were enrolled in Duke’s Mental Health Clinical Research Center for the Study of Depression in Later Life were prescribed bupropion SR or IR, alone or in combination with other antidepressant agents, for 12 weeks. Montgomery–Asberg Depression Rating Scale (MADRS; Montgomery and Asberg 1979) scores and Clinical Global Impression (CGI) severity scores were used to define response. Seventy-four percent of the sample responded to treatment. Fifty-three percent (16 of 30) achieved a partial or complete remission of major depression at week 12. Response rates did not differ between those with high versus low medical comorbidity. Steffens et al (2002) concluded that geriatric patients with high and low medical comorbidity responded well to bupropion and buproprion SR.

We recently evaluated the effect of sertraline in patients with major depression and comorbid vascular disease (Krishnan et al 2001). Patients were divided into one of three groups: 1) patients with a current diagnosis of hypertension only, 2) patients with a current or past history of cardiovascular illness but no hypertension, and 3) patients with no hypertension or comorbid vascular illness. Sertraline treatment yielded similar levels of response in all three groups (response criterion: CGI much or very much improved) at treatment end point on a completer analysis (hypertension: 86%; vascular disease: 89%; no vascular disease: 77%). Both our study and that of Steffens et al (2002) were limited to a single drug treatment, however, and the medical comorbidity evaluated was restricted to vascular disease in our study. We therefore evaluated the role of medical factors in a large sample of elderly patients who were treated using a staged approach. The sample consisted of 259 subjects enrolled in the National Institute of Mental Health–sponsored Mental Health Clinical Research Center for the Study of Depression in Later Life (Conte Center). The subjects were ≥ 60 years and met DSM-IV criteria for major depression at baseline. Exclusions included other major psychiatric illness (e.g., schizophrenia, schizoaffective disorder, bipolar disorder) or major neurologic illness (e.g., Alzheimer’s disease and other forms of dementia, stroke, Parkinson’s disease, and multiple sclerosis); subjects with current or recent histories of substance abuse were also excluded. At baseline, subjects received standardized clinical assessments including the MADRS and Cumulative Illness Rating Scale (CIRS; Linn et al 1968). A trained interviewer administered the Duke Depression Evaluation Schedule (DDES) (George et al 1989; Landerman et al 1989; Robins et al 1981). The DDES is a composite instrument that includes the Centers for Epidemiologic Studies-Depression Scale (CES-D) (Radloff 1977) and portions of the National Institute of Mental Health Diagnostic Interview Schedule (DIS). The interview consists of questions that screen for DSM-IV diagnoses including major depression, bipolar disorder, generalized anxiety disorder, and panic disorder. Clinical assessments were repeated every 3 months and when contact was clinically indicated.

Subjects in the study were treated as clinically indicated, using antidepressant medications, electroconvulsive therapy (ECT), and individual and group cognitive–behavioral psychotherapy as described in Steffens et al (2001).

The results of the study demonstrated that the cumulative remission rate was slightly greater among patients without medical illness than among those with mild medical illness (CIRS > 5; see Figure 1). Remission was defined as MADRS score less than 8; when adjusted for age, however, this variable was not significant. In summary, the results of these three studies, in consonant to the Cochrane review (Gill and Hatcher 2002), indicate that medical comorbidity has only a modest and insignificant effect on antidepressant treatment response; however, this may not be the case for other medical conditions and needs to be further evaluated. Whether studies find that medical disorders predict worse outcome in patients with major depression appears to depend on the nature and severity of
the medical illness, the study setting, and the study design. The best designed studies reported the least effect of medical illness on depression treatment outcome. Clinically, this suggests that medical illness should not be seen as an impediment to treatment.

Anxiety Disorder

Anxiety disorder is also common among patients with major depression. Zimmerman (2002) studied the frequency of diagnostic comorbidity in major depressive disorder (MDD). At the time of the evaluation, 64.1% of the patients met criteria for at least 1 of the 23 Axis I disorders, and more than one third had two or more disorders. Anxiety disorders were the most frequent co-morbid disorders (56.8%), and social phobia was the most frequent individual disorder. Among depressed patients, the more severe the depression, the more likely the presence of anxiety symptoms. It is assumed that anxiety symptoms affect treatment response. This has been evaluated in a number of studies. Paykel (1972) reported that people with depression who were anxious responded poorly to amitriptyline compared with other depressed patients. Another study reported that neurotic symptoms also predicted poor response to TCAs (Bielski 1976).

The data with regard to the SSRIs appears to be different. Tollefson et al (1994) pooled data from 19 randomized, double-blind clinical trials comparing fluoxetine with placebo or TCAs in patients with major depression. On the basis of the anxiety/somatization factor within the 21-item Hamilton Rating Scale for Depression (HAM-D), patients were characterized as anxious (score ≥ 7) or nonanxious (score < 7). Fluoxetine was significantly (p ≤ .05) more effective than placebo in treating both anxious and nonanxious major depression. Fluoxetine was also more effective than placebo in reducing the anxiety/somatization factor score (Tollefson et al 1994).

The effect of anxiety on treatment response to sertraline was evaluated in a study of chronic depression (Russell et al 2001). In this study, patients diagnosed with chronic major or double depression were randomized to 12 weeks of double-blind treatment with either sertraline or imipramine in a 2:1 ratio. A high-anxiety subgroup was operationally defined by a HAM-D anxiety/somatization factor score ≥ 7. Of the total sample, 209 were treated with imipramine and 426 with sertraline. Thirty-six percent of the population met criteria for the high-anxiety subgroup. Patients with significant concurrent anxiety symptoms were more likely to respond by 12 weeks (66.4%) than those without significant anxiety symptoms (54.2%). There was no significant difference in response rates for sertraline versus imipramine. In a comparison of SSRIs among patients with anxious depression classified as described earlier, no difference in treatment response was found among paroxetine, sertraline, and fluoxetine (Fava et al 2000). Rudolph (1998) evaluated the efficacy of venlafaxine in patients with anxiety and depression. A pooled analysis was conducted of six short-term trials of venlafaxine measuring anxiety in anxious-depressed patients using the HAM-D, anxiety/somatization factor and psychic anxiety item scores. Treatment with venlafaxine resulted in a significant improvement in depression scores in patients who were anxious at baseline compared with placebo-treated patients.

Data from eight randomized, double-blind, placebo-controlled clinical trials comparing mirtazapine to placebo in patients with high anxiety and depression were reported by (Fawcett et al 1998). Mirtazapine-treated patients demonstrated a statistically significant reduction in the sum of anxiety and agitation compared with placebo-treated patients. In general, the drug was effective in treating both anxiety and depression, and anxiety did not predict treatment response (Fawcett et al 1998).

All these studies primarily classified patients on the basis of the anxiety subscale of the HAM-D. They did not specifically address the issue of whether the anxiety was part of depression or as part of another anxiety disorder. In general, these studies would have excluded patients with primary anxiety disorders. The data are modest in terms of whether the presence of an anxiety disorder can influence treatment response. Sonawalla (1999) assessed treatment response in patients with major depression and comorbid anxiety disorder who were treated with fluvoxamine. The mean number of comorbid anxiety disorders per patient was 2.1 ± 1.1. Fluvoxamine was shown to be effective in treating outpatients with major depression with comorbid anxiety disorder. This study was limited by the small number of subjects and by the fact that a number of studies have not shown a clear antidepressant effect for fluvoxamine. Silverstone et al (2001) recently reported on the efficacy of venlafaxine on patients with concomitant generalized anxiety disorder and depression. Ninety-two patients meeting DSM-IV criteria for MDD who also had comorbid generalized anxiety disorder were compared with 276 noncomorbid patients. Patients received venlafaxine XR (75–225 mg/day), fluoxetine (20–60 mg/day), or placebo for 12 weeks. Onset of efficacy was slower in comorbid than in noncomorbid patients. Response, defined as ≥ 50% decrease in symptom score on the HAM-D, was achieved in 66% of the noncomorbid patients in the venlafaxine XR group at week 12. This response was higher than that seen with fluoxetine (52%) or placebo (36%).

In contrast to these reports, a study in primary care patients reported that anxiety can predict persistence of depression (Gaynes et al 1999). Of 85 patients with major
depression at baseline, 43 had coexisting anxiety disorder (38 with social phobia). The risk for persistent depression at 12 months was 44% greater among those with coexisting anxiety; this may largely reflect the type of anxiety disorder that coexists with major depression. A recent study (Hoehn-Saric et al 2000) showed that sertraline is more effective than desipramine for depression in the context of obsessive–compulsive disorder. This is consistent with data showing that SSRIs are more effective than drugs that primarily work through a norepinephrine mechanism. Given that SSRIs are effective for posttraumatic stress disorder, social phobia, obsessive–compulsive disorder, panic disorder, and generalized anxiety disorder, it is not surprising that these drugs are effective in treating depression in the context of anxiety disorders. Nonetheless, randomized trials evaluating whether the response rate is altered by the presence of each of these anxiety disorders remain sparse.

The data with psychotherapy may be significantly different. For example, Feske et al (1998) reported that higher levels of anxiety predicted poor response to treatment. Additional studies are needed to evaluate whether treatment response is different with specific comorbid disorders. Additional studies are needed to evaluate whether treatment response is different with specific comorbid disorders or not personality pathology significantly worsens outcome in patients with major depression appears to depend on study design, since the rate of personality pathology varies markedly depending on how it is measured. In addition, depressed patients with personality pathology appear less likely to receive adequate treatment in uncontrolled studies. Finally, studies rarely control for depression characteristics (e.g., chronicity, severity) that may influence outcome and be related to personality pathology. Overall, the best designed studies reported the least effect of personality pathology on depression treatment outcome. Clinically, this suggests that comorbid personality pathology should not be seen as an impediment to good treatment response (Mulder 2002).

### Summary

Comorbidity as generally seen in the context of major depression appears to be only a minor factor determining treatment response. Medical comorbidity has a modest and insignificant effect on short-term treatment response to SSRIs and other, more recently introduced medications. The nihilistic assumption that antidepressants are not effective based on early studies with TCAs is not warranted. In fact, even in patients with significant medical problems, antidepressants are effective. Severity of anxiety symptoms does not appear to have a major differential

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### Personality Traits and Disorders

Personality traits have long been considered important in the treatment outcome of depression. The study of personality traits and disorders is complex, and a variety of methods has been used, including dimensional measures, such as neuroticism and the Tridimensional Personality Questionnaire (TPQ) (Newman et al 2000), and categorical measures such as DSM-based personality disorder scales. Mulder (2002) recently evaluated these studies in an excellent review. To summarize the results based on his review, neuroticism generally predicted poor long-term response. The studies of shorter duration care were more equivocal, with most not showing a relationship to short-term outcome. Studies with the TPQ were done at a later time point and were better designed. The TPQ measures novelty seeking, which reflects differences in the behavioral activation system; harm avoidance, which reflects differences in the behavioral inhibition system; and reward dependence, which reflects differences in the behavioral maintenance system. The largest study, by Nelson and Cloninger (1997), showed that reward dependence predicted less than 1% of variance.

The categorical assessment studies were highly varied in that a variety of methods was used. Seven studies used both a standardized assessment and standardized treatment (sertraline, TCAs, ECT). Of the five studies that used medication treatment, three showed no difference, and two showed worse outcome for patients with personality disorders (one with desipramine and one with maprotiline; Table 1). The largest study (Hirshfield 1998), with more than 600 patients, used sertraline and showed no difference between patients with and without significant personality pathology. Fava (2000) reported that cluster B factors affected treatment response, with patients with high reward dependence responding better to clomipramine than to desipramine. In his review of these studies, Mulder’s appropriate conclusion is as follows: “Whether or not personality pathology significantly worsens outcome in patients with major depression appears to depend on study design, since the rate of personality pathology varies markedly depending on how it is measured. In addition, depressed patients with personality pathology appear less likely to receive adequate treatment in uncontrolled studies. Finally, studies rarely control for depression characteristics (e.g., chronicity, severity) that may influence outcome and be related to personality pathology. Overall, the best designed studies reported the least effect of personality pathology on depression treatment outcome. Clinically, this suggests that comorbid personality pathology should not be seen as an impediment to good treatment response (Mulder 2002).
effect on somatic treatment response, especially for the SSRIs and other newer antidepressants, although it may for psychotherapy. Anxiety disorders are well treated with SSRIs, and thus the findings that these drugs work well for depression in the context of anxiety disorders is not surprising. At least for comorbid generalized anxiety and depression, the presence of comorbidity does not affect treatment response. Personality disorder also does not appear to have a major effect on treatment response. Although intuitively it is likely that severe personality disorder is likely to reduce treatment response, this has yet to be studied. Neuroticism appears to be a predictor of long-term treatment response.

References


