Differential Response to Antidepressants in Melancholic and Severe Depression

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With the introduction of the selective serotonin reuptake inhibitors (SSRIs) approximately one decade ago, the clinical practice of antidepressant pharmacotherapy has undergone a steady shift away from the use of tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). In addition, primary care physicians, who were once less comfortable prescribing antidepressants due to concerns over side effects, are now increasingly likely to begin a patient on SSRIs. These new trends have no doubt benefitted many patients, and the more widespread treatment of depression has helped reduce social stigma about mental illness. However, questions have been raised as to the appropriateness of reflexively considering the SSRIs as broad-spectrum antidepressants to be given as the first treatment for all depressed patients. This concern is specifically germane to the treatment of severe and/or melancholic depression.

This article reviews the issue of whether the SSRIs are clinically effective in patients with severe and/or melancholic depression, and the related issue of whether tricyclics offer any advantage over the newer medications in this patient population. However, to critically review the available data, it is necessary to first consider some of the important methodological questions that are inherent in this type of clinical research.

METHODOLOGICAL ISSUES
Subtype of Mood Disorder

There is a long tradition of distinguishing phenomenological subtypes of depressive disorder; perhaps the most well-established and well-accepted example of this is the separation between the unipolar and bipolar forms of illness. However, even within the unipolar spectrum, contemporary diagnostic systems differentiate among several depressive subtypes, including dysthymia, major depression, major depression with psychotic features (delusional depression), major depression with atypical features, and major depression with melancholic features. Therefore, simply calling a patient depressed is no longer an adequate diagnosis.

Furthermore, whereas for 30 years electroconvulsive therapy (ECT), lithium, TCAs, and MAOIs were the only treatments for depression, the past 10 years have seen the introduction of several new groups of medications used for the treatment of affective disorders including the SSRIs, bupropion, venlafaxine, valproic acid, and carbamazepine. Therefore, to consider the "antidepressants" as a single pharmacotherapeutic class is as much an oversimplification as considering that all "depressed" patients have the same illness.

One important consequence of distinguishing among diagnostic subtypes is that studies have established that certain types or combinations of antidepressants are specifically effective for some subtypes and ineffective for others. The prototypic example of this is the observation that patients with delusional depression do not respond to tricyclics at the same rate as...
patients with non-delusional depression. However, this syndrome is quite responsive to either a combination of a TCA and an antipsychotic, or ECT. Subsequent to this observation, a series of studies established that patients with atypical depression respond at a higher rate to MAOIs compared to tricyclics.

With respect to the melancholic subtype of depressive disorders, early studies demonstrated that this clinical syndrome appeared to be associated with a favorable response to TCAs among inpatient. Gibbons and colleagues later replicated this finding, and Abou-Saleh and Copper found that response to a TCA was predicted by an endogenous score on the Newcastle I Scale. Despite the consistency of these inpatient studies, the finding that melancholic features predict a response to a TCA has not been replicated in outpatient studies.

Thus, in addition to the long-accepted fact that there are pharmacological treatments specific for the bipolar form of affective disorder, it has been demonstrated that certain subtypes of unipolar depression respond preferentially to different forms of pharmacological treatment. This knowledge has changed our expectations of newly released medications because we no longer necessarily expect a single antidepressant to be equally effective in all depressive subtypes. However, when a new antidepressant is first released, it is unlikely that we will have the information available to know in what type of depressed patient the medication will work most effectively, and in what type it may be relatively ineffective.

Symptom Severity Versus Melancholic Subtype

Although the terms "severe" and "melancholic" are often used interchangeably, it should be emphasized that symptom severity and the presence or absence of melancholic features are two separate, although related, parameters. In the research setting, symptom severity is generally established by a validated depression rating scale such as the well-known Hamilton Rating Scale for Depression (HRSD). However, although the HRSD has well-established interrater reliability and construct validity, there are no validated cut-off points to classify scores as mild, moderate, or severe. For example, a number of studies consider patients with a baseline HRSD of >25 as severe, but this is an arbitrary decision. To complicate matters further, there are at least three versions of the HRSD commonly in use, so what constitutes a "severe" HRSD score is not only arbitrary but variable.

In contrast to the lack of accepted criteria for classifying a patient as severe, the melancholic subtype of depression can be reliably diagnosed according to standardized criteria, and there are data regarding the internal consistency and the validity of the diagnosis. Although there are many diagnostic systems that include melancholic subtype, such as the Newcastle scales and CORE in the United States, the DSM-IV is the most widely used in both clinical and research settings.

Practically speaking, most patients with melancholic depression will have high levels of symptom severity. However, not all patients with severe depression have melancholic symptoms. A patient may have a high overall HRSD score resulting from high scores on individual items other than those reflecting the neurovegetative symptoms central to the melancholic subtype diagnosis. From a research standpoint, collecting a patient sample according to diagnostic subtype criteria rather than severity score will provide a more homogeneous group of patients. Such a patient sample will be more suitable for a randomized controlled trial comparing two treatments in which the only variable to be studied is the medication condition.

Adequacy of Pharmacological Treatment

The definition of what constitutes an adequate pharmacological trial generally involves at least two dimensions, namely, the dose of medication and the duration of treatment. For the TCAs, specifically for imipramine, desipramine, and nortriptyline, studies have established the relationship between plasma level of medication and clinical outcome, so that it is reasonable to define adequate dose of drug as that dose necessary to achieve a therapeutic plasma level of medication. The use of monitoring to ensure that a patient is at a therapeutic plasma level of drug has had a profound impact on optimizing the efficacy of these medications. In studies where patients received a fixed dose of medication, the overall response rate reported has been in the 60% to 65% range. However, studies in which all patients receive a therapeutic plasma level of tricyclic report response rates in the 80% to 85% range. Unfortunately, information on the relationship between plasma level of drug and clinical outcome is not available for antidepressants other than for tricyclics.

When comparing a tricyclic to an SSRI, one is faced with the methodological problem of deciding what are comparable doses of medication. Ironically, the problem has not been that comparison studies have favored the TCA, which would be the case if optimal tricyclic treatment, ie, therapeutic plasma level, was compared to the best guess "optimal" dose of SSRI. Rather, most studies comparing an SSRI to a TCA have been sponsored by the pharmaceutical manufacturers of the SSRI and, not surprisingly, have compared an adequate dose of an SSRI to an inadequate dose of a tricyclic, ie, a study design that favors the SSRI.

In addition to dosage of medication, another parameter influencing response rate to antidepressant medication is the length of the treatment trial. There are some data, albeit incomplete, that suggest that a trial of 3 to 4 weeks at a therapeutic plasma level of tricyclic is adequate duration, although there is a clin-
ical belief that this trial length may have to be extended for elderly patients. With respect to the SSRIs, there are even less data, and consequently much debate, over what constitutes adequate length of treatment. In a comparison of an SSRI to a TCA, a shorter trial duration, eg, 4 weeks, might bias the results in favor of the tricyclic.

Remission Versus Response

Another important issue in the clinical trials literature is the criterion that defines "response" to drug. The most common definition of clinical response in an antidepressant trial is a 50% reduction of the baseline HRSD score. For the majority of outpatients with mild to moderate depression, such a decrease represents significant clinical improvement. However, in the case of melancholic depression, where the baseline HRSD is significantly higher, a patient meeting this criterion for response may still have significant residual symptomatology, and indeed might still satisfy diagnostic criteria for major depression. Thus, classifying a patient as a responder only on the basis of a percentage reduction in the baseline HRSD can be misleading.

To circumvent this problem, a second category has been constructed, "remission," which is defined as an absolute final HRSD of less than a minimum value such as 7 or 10 (depending on which version of the HRSD is used). The category of remission also resonates with the clinical experience of many psychiatrists who were used to depressed patients having a robust response when treated with a therapeutic plasma level of tricyclic or ECT. From a research point of view, if studies include a significant percentage of melancholic patients, the use of the "remission" rather than the "response" criteria is compelling because there may be a significant difference between the percentage of patients who meet criteria for these two categories.

ARE SSRIs EFFECTIVE IN SEVERE AND MELANCHOLIC DEPRESSION?

The first major study to address the efficacy of SSRIs in severe and melancholic depression was carried out by the Danish University Antidepressant Group (DUAG). Patients with endogenous major depression were randomized to either 5 weeks of a TCA (150 mg/day of clomipramine) or an SSRI (up to 60 mg/day of citalopram). Using a remission criterion of final HRSD score of less than 7, only 34% of the patients assigned to citalopram achieved remission compared to 62% of the patients taking clomipramine. In a second study by DUAG, endogenously depressed inpatients were randomly assigned to either 6 weeks of clomipramine (150 mg/day) or paroxetine (40 mg/day). The results paralleled the first study: only 25% of the patients taking paroxetine met remission criteria (HRSD <7) compared with 56% of the patients on clomipramine. Thus, in both DUAG studies, the response rate to SSRIs among inpatients with melancholic depression was disappointing. Furthermore, the difference between the TCA and SSRI may have been minimized because the dose of TCA was low and consequently the efficacy of clomipramine may not have been optimized. On the other hand, 5 or 6 weeks of treatment may not have been long enough to permit full response to the SSRI.

Subsequently, Tignol and colleagues21 conducted a meta-analysis of the worldwide paroxetine database to compare the efficacy of paroxetine versus placebo in outpatients with melancholia. One hundred seventy-eight patients received paroxetine (10 to 40 mg/day) for up to 6 weeks. Response was defined as 50% reduction in HRSD score, and the remission criterion was a final HRSD <10. Forty-six percent of patients taking paroxetine met the response criterion compared with 26% of patients receiving placebo; however, only 31% of patients taking paroxetine met criterion for remission. Although this was significantly greater than the 15% remission rate for patients taking placebo, nonetheless, the paroxetine remission rate is strikingly low and is consistent with the two DUAG studies. This study illustrates the difference between response and remission rates and extends the observation about poor SSRI response in melancholia from inpatients to outpatients.

This finding was also extended to other SSRIs. Beasley and colleagues6 reported on a 6-week multicenter trial of fluoxetine (median dose 80 mg/day) versus imipramine (median dose 200 mg/day) in depressed inpatients with a mean baseline HRSD of 28. Response was defined as 50% reduction in HRSD, and remission was defined as a final HRSD <7. The response rate for fluoxetine in this study was 54%; however, given that the mean baseline HRSD score was 28, patients classified as responders could have a final HRSD score of 14. Such a score indicates clinically significant residual symptomatology. In fact, the remission rate on fluoxetine was only 21%, confirming that a low percentage of patients achieved full symptomatic relief on the SSRI.

There is one study that reports a fairly robust response of melancholic patients to an SSRI. Heiligenstein and colleagues63 compared fluoxetine (20 mg/day for 8 weeks) to placebo in 52 outpatients with melancholic depression and 37 with non-melancholic depression. Forty-eight percent of the melancholic patients on fluoxetine met criteria for remission (final HRSD <8) compared with an 11% remission rate for the placebo-treated group. However, in this study, only 30% of non-melancholic patients achieved remission on fluoxetine, which was not statistically different from the 40% placebo remission rate. This finding is inconsistent with the extensive literature reporting that the SSRIs are especially effective in moderate depressive syndromes. If the result in the non-melancholics is suspect, then one must also be circumspect.
about the data on melancholic response rates reported in this study.

ARE TCAs MORE EFFECTIVE THAN SSRIs IN SEVERE AND MELANCHOLIC DEPRESSION?

There is an extensive literature that in hospitalized depressed patients, the presence of melancholic features predicts good response to TCAs. However, in more recent studies, the predictive significance of the melancholic subtype with respect to TCA response has not been clearly established for outpatients. The reasons for this discrepancy are unclear, but may include the fact that inpatient studies generally used a higher dose of TCA, which is more likely to produce a therapeutic plasma level, and the inpatient setting insured greater patient compliance than can be expected in outpatient studies.

The question is whether the TCAs are superior in efficacy to the SSRIs in severe and/or melancholic depression. The two DUAG studies dealt with this issue most directly. The TCA, clomipramine, was significantly more efficacious than an SSRI, either citalopram or paroxetine. However, clomipramine has significant serotoninergic activity in addition to its blockade of noradrenaline reuptake. Thus, clomipramine pharmacologically mimics a combination of TCA and SSRI. Because a combination of SSRI and TCA may have greater antidepressant effect than TCA alone, it could be argued that the use of clomipramine as the comparison TCA is potentially problematic. However, there is no evidence that clomipramine is a more effective antidepressant than any other TCA. Thus, despite potential methodological problems, the DUAG studies provided the first substantive evidence that SSRIs are less effective than the TCAs in melancholic depression.

In contrast, there are a number of studies that have reported equivalent efficacy of TCAs and SSRIs in this patient population. In the Beasley and colleagues' study, the response and remission rates with imipramine were 60% and 34.3%, respectively, which were not different for those found with fluoxetine. Tignol and colleagues reported on 109 patients receiving paroxetine compared with 107 patients who received amitriptyline, clomipramine, mianserin, or maprotiline (dosages not specified). The response and remission rates on paroxetine were 53% and 32%, respectively, and 55% and 41% for patients receiving the non-SSRIs. However, both the Beasley and colleagues and Tignol and colleagues studies were supported by the pharmaceutical industry, and the conclusion of equivalent efficacy for SSRIs and tricyclics was based on the remission rates for tricyclics, which are much lower than reported in the larger, non-industry-supported literature. This discrepancy is most likely a consequence of the fact that industry-supported studies routinely use a relatively low dose of TCA and never use plasma level monitoring to ensure optimal TCA treatment. In other words, industry-sponsored studies do not compare an SSRI to an adequate trial of a tricyclic.

The only attempt to compare a trial of SSRI to an adequate tricyclic trial in a severe or melancholic sample was reported by Roose and colleagues. In this study, the authors compared the efficacy of fluoxetine in 22 inpatients with cardiac disease and unipolar major depression to that of nortriptyline using an historical comparison group. Thirteen of the patients (59%) met criteria for melancholic depression, and the mean baseline HRSD (21-item) was 26. Patients received fluoxetine 20 mg/day for 2 weeks and then 40 to 60 mg/day of fluoxetine for an additional 5 weeks. The nortriptyline comparison group (N=42) met the same inclusion criteria (both psychiatric and cardiac) as the fluoxetine group. Thirty-two of these patients (76%) met criteria for melancholic depression, and the mean baseline HRSD was 28. The projected nortriptyline dose was calculated to be 1 mg/kg, which was achieved by the fifth day on medication. Steady-state plasma levels were obtained 1 week later, and the dose was adjusted to achieve a level in the range of 50 to 150 ng/mL. The total length of the nortriptyline trial was 4 weeks.

Of the 42 patients who began nortriptyline, 34 completed the trial. Twenty-eight of the 34 completers (82%) met the remission criterion (final HRSD <=8). The intent-to-treat response rate to nortriptyline was 67% (28 of 42). Of the patients with melancholic depression who completed the trial, 30 of 24 (83%) responded to nortriptyline. Of the 22 patients who began fluoxetine, 18 completed the trial. Only 5 of 18 (28%) of the completers met the response criterion, and the intent-to-treat response rate to fluoxetine was 23% (5 of 22). Strikingly, only 10% (1 of 10) of the patients with melancholic depression who received fluoxetine were rated as responders. Nortriptyline was significantly more efficacious than fluoxetine in all three comparisons; however, these differences were not due to a high partial response rate to fluoxetine. In fact, among completers, the mean final HRSD score for fluoxetine non-responders was 21.

The major methodological problem with the study of Roose and colleagues was that the two comparison groups were not created by random assignment, raising the possibility that there may have been differences between the patients receiving the two medications that may have affected treatment outcome. Furthermore, the findings were based on a retrospective analysis of data. Yet, results of this study are consistent with other studies that report that a TCA is more effective than an SSRI in severely depressed, primarily melancholic inpatients.

CONCLUSIONS

The preponderance of data, albeit flawed, suggests that SSRIs are not particularly effective in the treatment of severe and melancholic depression. This is in contrast to an extensive literature indicating robust remission with tri-
cyclics in this population. Further, direct comparison studies have found that tricyclics are superior to SSRIs in melancholia, and the only study comparing SSRIs to a definitely adequate trial of tricyclic also found the tricyclic to be superior in efficacy. Yet, all of the available studies have methodological drawbacks, and, consequently, a randomized clinical trial of adequate duration comparing therapeutic plasma level tricyclic to SSRIs is needed to resolve this controversy.

If the TCAs really are superior to SSRIs in the treatment of severe and melancholic depression, we are still left with the intriguing question as to why. Could the SSRIs be “weaker” in antidepressant activity than the TCAs? Or, alternatively, could patients with higher levels of symptom severity and/or melancholic features have some pathophysiologic disturbance that is preferentially responsive to treatment with a TCA?

One avenue of research may shed some light on these questions. Recently, Prudic and colleagues examined the impact of nonresponse to antidepressant pharmacotherapy (utilizing stringent criteria for treatment adequacy) on predicting short-term response to ECT. The findings indicated that resistance to an adequate trial of TCA predicted poorer outcome with ECT, while resistance to SSRI did not show predictive relations. The authors speculated that these findings suggest a greater overlap between the mechanisms of action of TCAs with ECT than between SSRIs and ECT.

At present, the clearest conclusion to be drawn is that in severe and/or melancholic depression, the tricyclics remain the most efficacious pharmacotherapeutic agent. However, what may be the most effective treatment may not always be the “best” treatment. In terms of a risk/benefit ratio, the tricyclics are not without adverse effects, especially in patients with ischemic heart disease. There are also quality of life considerations, especially among the elderly with melancholia. For instance, in a recent multicenter study of nortriptyline versus sertraline in patients over age 60, the responders to nortriptyline had more difficulty with residual side effects. Therefore, there is no one “first-line” treatment for depressed patients, even for patients with the melancholic subtype. Treatment decisions must be made on a case by case basis, taking into account the nature and severity of the depressive illness and the efficacy and side effects of the different antidepressant treatments.

REFERENCES