Introduction

The Multiple Facets of Treatment-Resistant Depression

By Daniel Souery, MD, PhD, and Karel Van der Auwera, MD

Depression remains a highly prevalent disorder in the general population with significant personal and socioeconomic implications. Several European studies estimated the 6-month prevalence of depression to be ~17% for depressive disorders as a whole and 6.9% for major depression. Recently, the World Health Organization World Mental Health Survey Consortium estimated the 12-month prevalence of mood disorders in Europe to range from 3.6% in Germany to 9.1% in Ukraine compared with 9.6% in the United States. However, depression still remains under-diagnosed and, consequently, under-treated.

When adequately treated, up to half of all patients do not respond adequately to first-line monotherapy and 60% to 70% of depressed patients fail to reach complete remission despite rapid development in the therapeutic armamentarium of mood disorders since the late 1980s. Selective serotonin reuptake inhibitors (SSRIs), reboxetine (a selective norepinephrine reuptake inhibitor), and newer dual action antidepressants, such as venlafaxine, mirtazapine, and milnacipran, have been proposed as replacements to the older tricyclic antidepressants (TCAs). Although they are safer and better tolerated, they have not significantly altered the rate of improvement in depressive symptoms.

In the past, nonresponse and resistance in depression, which incorporates more than a third of depressed patients, had not received much attention. This has resulted in unsystematic research and uncontrolled clinical trials, which in turn have led to a degree of confusion. However, recent research has provided substantial progress on more fundamental aspects of nonresponse in depression. These aspects mainly include methodological considerations and predictive factors of response to antidepressants.

The key parameters characterizing and defining treatment-resistant depression (TRD) include basic criteria used to specify diagnosis, treatment adequacy, response to treatment, and several previous trials. Diagnostic issues include the need for accurate diagnosis, different treatment modalities according to the different depressive disorders (eg, psychotic, metabolic, chronic), and comorbidity with other psychiatric or personality disorders. Treatment adequacy is to be considered in terms of dosage, duration, and compliance. Standardization of these criteria is essential. Unfortunately, a lack of consensus on most items persists. Assessment of treatment response raises the problem of evaluating remission and the minimal duration of remission required. Previous failed trials remain a controversial subject referring to the type (different classes, including electroconvulsive therapy [ECT]) and number of adequate antidepressant trials required for considering resistance. Such a foundation is essential and will hopefully lead to more systematic research in clinical trials for evaluating specific strategies and new drugs. Interpretation of research findings and their translation to clinical applications are only possible through comparison of results obtained with consistency in the definitions used.

Response or resistance to acute treatment and relapse or maintenance after recovery also indicate that some patients will present different degrees of resistance to therapeutic strategies or agents in the different phases of their treatment history. This observation should be taken into consideration and may be useful to differentiate acute versus long-term resistance.

The difficulties of defining therapy resistance are clearly different considering clinical and research perspectives. Research objectives mainly include validation of the concept, suggesting operational criteria for identification of predictive factors, biological investigations, or drug trials. In the clinical perspective, defining therapy resistance is more focused on recognition, diagnosis, and treatment alternatives.

This month's issue of CNS Spectrums presents articles on multiple aspects of treatment resistance, from therapeutic options to diagnostic diversity.

Michael E. Thase, MD, has, for many years, contributed to clarifying the role of the different therapeutic approaches in refractory depression. In his review, a simple five-stage system for categorizing TRD is described and the evidence pertaining to the major strategies is summarized. Based upon the weight of this evidence, an attempt is also made to provide treatment algorithms for TRD patients. This approach represents a helpful tool for the clinician regarding the most commonly used strategies in difficult-to-treat patients. An initial strategy consists of switching within a class of antidepressants. The evidence level for SSRIs with a response of 50% to 60% to a second SSRI is considered B, whereas switching between TCAs has not been found to be a useful strategy.
A second strategy is switching across medication classes. In this approach, venlafaxine, being extensively investigated and showing a response rate of 30% to 60% in SSRI nonresponders, warrants an A level of evidence.4 A B level is given to mirtazapine, as it is better tolerated and produces an earlier relief of symptoms. Augmentation strategy is also covered, where there is no need to taper the ineffective antidepressant nor cross-titrate. Taking into account the presumed complementary mechanism of action on the primary antidepressant, this has become quite a popular strategy among clinicians.5 Because of the relative safety of SSRIs, a fourth option is to combine antidepressants with complementary receptor profiles in order to broaden the spectrum. However, these widely used combinations have not been subjected to rigorous investigation and, as weighted by evidence, only warrant a C level (although a combination of SSRIs with either mianserine or mirtazapine favors an additive antidepressant effect in some double-blind studies).

Good evidence has been supplied for cognitive-behavioral therapy (CBT) to have an additive effect in treating TRD by dealing with nonbiological factors such as persistent psychosocial difficulties that maintain a depressive mental state. Reduction of residual symptoms and relapse rates are the main benefits of CBT.

ECT has the highest chance of response in TRD. Nevertheless, relapse remains a substantial limitation and ECT should be followed by maintenance therapy encompassing a potent antidepressant and lithium. Continuation therapy by means of less-frequent ECT and other somatic treatments, such as vagal nerve stimulation (VNS) and repetitive transcranial magnetic stimulation (rTMS), are promising but still in an experimental phase.

In the second article, Nikolas Klein, MD, and colleagues focus on the role of atypical antipsychotics in resistant depression. They remind us that the use of antipsychotics in depression is not new in specific clinical situations like psychotic depression. The role of antipsychotics in TRD is reevaluated in light of the available studies with the new atypical antipsychotics, well known for their low rate of extrapyramidal symptoms (EPS), lifetime tardive dyskinesia, and cognitive impairment. Encouraging data are already available for olanzapine, quetiapine, risperidone, and ziprasidone in adjunct to antidepressants.

Next, David S. Husted, MD, and Nathan A. Shapiro, MD, PhD, address the specific area of treatment resistance in obsessive-compulsive disorder (OCD) and its management with deep brain stimulation (DBS). Blockade of dopamine receptors in the cortico-striatal-thalamic-cortical system, has proven effective as an augmentation strategy in OCD patients who are treatment resistant (ie, failure to respond to at least two adequate SSRI trials). Blind placebo-controlled studies have confirmed such augmentation effects with risperidone and quetiapine, giving them more weight when compared with other antipsychotics, for which positive effects are reported as well (eg, olanzapine). In the case of refractory OCD, neurosurgery, VNS, DBS, and transcranial magnetic stimulation (TMS) are considerable options, with TMS being the least invasive and reversible technique.

DBS requires implantation of quadripolar electrodes in the anterior limbs of both internal capsules, which are then connected to two pulse generators. The intensity of stimulation can be adjusted to the individual's needs and side-effect profile. In this technique, neuronal firing is electrophysiologically altered showing significant reduction in frontal lobe metabolism. DBS has been found to be very effective in reported cases and in one blind crossover study (>35% decrease in postoperative Yale-Brown Obsessive-Compulsive Scale scores) with sustained efficacy during follow-up. Intracerebral hemorrhage is the most severe adverse outcome from surgery. Although transient and not particularly debilitating, confusion, speed disturbance, paraesthesia, oculomotor abnormalities, and muscle contractions encompass other common side effects.

In addition to the important topics covered in this issue of CNS Spectrums, the problem of treatment resistance in bipolar disorders should be addressed. The concept of resistance to the treatment is particularly complex in bipolar disorders.

The natural course of bipolar disorder is characterized by marked severity of acute affective episodes, followed by high rates of relapse and recurrence. The primary goals of treatment in bipolar disorder are to treat both acute phases of the illness and to prevent recurrence. Treatment may be required for acute mania, acute depression, or to prevent recurrence of such states. The type of treatment also depends on the subtype of bipolar disorder considered, such as rapid cycling or mixed states. In order to prevent recurrence, long-term or lifetime prophylactic strategies may be necessary. Lithium has been considered to be the effective reference prophylactic treatment but newer medications offer promising advantages in the management of acute and long-term management of this disorder.

While consensus definitions have been well established for treatment phases in unipolar recurrent depression,6 such advances remain lacking for bipo-
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The clinical heterogeneity of bipolar disorder makes it difficult to generalize about treatment strategies. The bipolar disorder spectrum includes bipolar I, bipolar II, and cyclothymic disorder, as enumerated by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. A patient with bipolar I may present with only one manic episode or a combination of manic and depressive episodes where the most recent episode is either manic, hypomanic, mixed, or depressed. Patients with bipolar II may present with either hypomanic or depressive episodes. The clinician is faced with a heterogeneous group of patients who represent the spectrum of bipolar disorder yet exhibit different features and degrees of severity. Moreover, these patients may be seen at different moments in their illness, presenting with different acute episodes that require different treatment strategies. Even among a group of patients receiving a bipolar I diagnosis, there are a variety of clinically relevant features that may predict treatment choice, outcome, and the overall course of illness. Such clinical features include psychosis, catatonia, a seasonal pattern, and rapid cycling. Other episode specifiers include melancholic features, atypical features, postpartum onset, and length of episode. These clinical manifestations may imply different treatment modalities.

Working clinical definitions for treatment-refractory bipolar illness have been suggested. These definitions are proposed as a starting point and need validation through controlled studies. Treatment-refractory bipolar depression is defined by the lack of remission of a depressive state despite two adequate trials of standard antidepressant agents (6 weeks each), with or without augmentation strategies. This last definition suffers the same limitations as the definition proposed for TRD. Moreover, an adequate antidepressant trial for bipolar depression is not well defined, particularly concerning the role of mood stabilizers.

Treatment-refractory mania is defined as a manic episode without remission despite 6 weeks of adequate therapy with at least two antimanic agents (lithium, neuroleptic, anticonvulsant) in the absence of antidepressant or other mood-elevating agents. The Young Mania Rating Scale (YMRS) is widely used in clinical trials to evaluate treatment response. A YMRS total score of 12.5 has been described as reflecting the median euthymic rating, 15 as the lower limits of mania, 20 as mania of moderate severity, and 25 as the lower limit of mania of sufficient severity to require hospitalization. Treatment-refractory mood cycling may be defined as continued cycling despite maximal tolerated lithium in combination with valproate or carbamazepine for a period of three times the average cycle length or 6 months, whichever is longer, in the absence of antidepressants or other cycle-promoting agents. The definitions of treatment-refractory mania and mood cycling should also be examined regarding all methodological considerations discussed above for TRD. Lastly, resistance to long-term treatment or "maintenance resistance" can be of particular relevance in bipolar affective disorder.

The growing number of therapeutic strategies available in bipolar disorders increases the chances of response to the treatment in the various phases of the disease. Beyond the traditional treatments like lithium, the antiepileptics and the typical neuroleptics, new antiepileptics, and atypical antipsychotics must be considered in particular clinical situations.

The treatment of choice for classic euphoric mania is lithium, while valproate is preferred for mixed episodes, mania with dysphoric mood or mania in rapid cycling bipolar disorder. For rapid stabilization of severe mania, valproate is recommended because therapeutic blood levels can be attained quickly through a loading dose strategy of 20 mg/kg/day. Valproate may also be used to treat classic mania due to its side-effect profile or a previous nonresponse to lithium. Similarly, carbamazepine may be effective for mixed episodes or for rapid cycling as opposed to valproate due to its side-effect profile or the patient's previous treatment history. Combinations of antimanic agents may also be necessary, particularly in treatment-resistant manic, mixed, and hypomanic episodes.

New molecules, and lamotrigine, in particular, have been tested in bipolar disorder. The effectiveness of lamotrigine is now established in the depressive phases and maintenance in placebo-
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controlled studies among patients with bipolar I and II disorders, fast cycles or not. Calabrese and colleagues and Calabrese showed antidepressant effectiveness compared with placebo among depressive bipolar patients. Lamotrigine is particularly tempting because of its strong long-term tolerance. Nevertheless, cutaneous rash has been reported at the beginning of treatment, with increased risk of Stevens-Johnson syndrome. To avoid this adverse effect, a diagram of progressive administration is recommended. Indeed, valproate inhibits the metabolism of lamotrigine, while carbamazepine accelerates it. Lamotrigine does not seem to induce manic or hypomanic states nor increase the frequency of cycles. On the other hand, studies in bipolar disorders could not confirm antimanic effectiveness.

Recent data obtained with lamotrigine suggest that this is a treatment of choice in bipolar patients for whom the burden of disease is mainly explained by their depressive episodes or symptomatology. It may also become a first-line treatment for acute bipolar depression. Lamotrigine was superior to placebo in a 7-week blinded, randomized trial on most analyses, although the Hamilton Rating Scale for Depression, which was the primary rating instrument, did not indicate a significant difference from placebo. Lamotrigine has also been studied in three placebo-controlled maintenance trials in bipolar disorder. In rapid cycling bipolar II disorder patients, lamotrigine was significantly superior to placebo in delaying time to intervention, with most benefit seen in the delay in intervention for emerging depression. Lamotrigine was not significantly different than placebo among bipolar I patients. The study suggests that the prophylactic effect of lamotrigine is seen when depression, not mania, is the primary illness characteristic. Lamotrigine was also studied in two 18-month trials, one that enrolled currently or recently manic patients, another that enrolled recently depressed patients. In both studies, lamotrigine monotherapy, but not lithium, delayed time to intervention for depression. Lamotrigine also reduced average depressive symptomatology in comparison with placebo. Among the >1,000 patients studied in blind, randomized, placebo-controlled trials, there was no evidence that lamotrigine destabilized mood or precipitated mania or hypomania. If confirmed, those data may offer new therapeutic strategies in resistant bipolar disorders, in the acute phase of treating depressive episodes, and in maintenance resistance, preventing depressive phases when the burden of the disease is explained by the high rate of depressive recurrences.

Just like traditional neuroleptics, atypical antipsychotics are effective in the control of agitation and psychotic symptoms associated with the manic state. More recent studies have highlighted the fact that antipsychotics would have a specific antimanic effect independent of the antipsychotic action. This observation explains why the main target of clinical trials with atypical antipsychotics used to be pure mania. Data are available in this direction for olanzapine, risperidone, ziprasidone, quetiapine, and clozapine. Olanzapine has been recognized by the Food and Drug Administration for the indication of "acute mania" on the basis of a randomized, placebo-controlled study, showing an acute effectiveness within 3–4 weeks among manic or mixed bipolar patients. Other studies show the effectiveness of olanzapine in combination with lithium or valproate among patients not responding to these treatments. A controlled study has shown the comparable effectiveness of risperidone 6 mg compared with haloperidol 10 mg and lithium 900–1,200 mg in mania. For risperidone, the majority of studies relate to effectiveness in combination with conventional mood stabilizers (add-on therapy). Although it may be less relevant for registration purposes, as far as clinical needs are concerned it is of importance that most atypical antipsychotics have also been tested in combination treatments. Finally, data are now available on long-term prophylactic efficacy of atypical antipsychotics. These combined efficacy data definitely support the use of atypical antipsychotics in bipolar disorder, and offer new possibilities in resistant bipolar disorder patients.

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