# Introduction

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Despite recent advances in the understanding and management of depression and anxiety, these disorders remain a challenge for the practicing clinician. As many as one third of patients with depression do not respond to monotherapy with an antidepressant.[1] The human and economic impact of depression remains high; unipolar depression is expected to become the most common cause of disability in developed countries within the next several years.[2] Treatment resistance confers an additional economic burden, resulting in higher treatment costs than those associated with the care of non–treatment-resistant patients.[3]

Clearly, more effective strategies for managing patients with treatment-resistant depression and anxiety are needed. The development of new drugs and novel modes of treatment is one avenue for achieving higher rates of response and decreasing the personal and societal burden associated with these illnesses. Alternatively, clear evidence-based strategies for using existing agents can be developed. This supplement explores current issues related to treatment-resistant depression and anxiety and reviews the current data that support various treatment approaches.

First, Martin B. Keller, M.D., presents a general overview of the current state of knowledge of treatment-resistant depression and discusses several issues related to its epidemiology, economic impact, and treatment. Lack of consistent definitions of what constitutes treatment resistance, and, further, of what constitutes treatment response and remission, makes determining the true incidence of treatment-resistant depression difficult and compromises understanding of the illness. Strategies used by clinicians in treating patients resistant to first-line therapies include switching to a different drug, combining drugs of different classes, and augmenting an antidepressant with a nonantidepressant drug; each of these strategies has particular advantages and disadvantages. Several emerging nonpharmacologic therapies, including transcranial magnetic stimulation, vagus nerve stimulation, and deep brain stimulation, are currently under investigation.

An understanding of the effect of antidepressants on neurotransmitter systems is helpful in understanding how augmenting antidepressants with nonantidepressant agents, such as atypical antipsychotics, can improve response and remission rates. Pierre Blier, M.D., Ph.D., and Steve T. Szabo, Ph.D., review research that elucidates the reciprocal interactions of the serotonin and norepinephrine systems and the mechanisms by which resistance to antidepressants occurs. An atypical antipsychotic with high 5-$HT_{1A}$ affinity and $\alpha_2$-adrenergic antagonist properties may alleviate treatment resistance by restoring firing of norepinephrine neurons that have been suppressed by treatment with a selective serotonin reuptake inhibitor (SSRI). $\alpha_2$-Adrenergic and 5-$HT_{1D}$ receptor blockade may be the mechanism by which antipsychotics are effective as augmentation therapy in anxiety disorders.

In my section of this supplement, I review the clinical evidence for the efficacy and safety of augmentation of antidepressants with atypical antipsychotics in patients with treatment-refractory depression. Several studies indicate that risperidone, olanzapine, and ziprasidone are safe and effective in combination with a variety of newer antidepressants in treatment-

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resistant unipolar depression. Several large, industry-sponsored trials of patients with treatment-resistant depression are currently under way to further evaluate atypical antipsychotic augmentation in this clinical setting.

An additional treatment challenge is presented by patients who have an anxiety disorder as well as depression. Comorbidity between depression and anxiety disorders is common, and comorbidity is associated with increased morbidity and decreased treatment response. Mark H. Pollack, M.D., reviews relevant diagnostic issues, epidemiology, risk factors, and time-course related to comorbid anxiety and depression. An SSRI is generally considered the treatment of choice in patients with these comorbid disorders; however, using second-line agents or combining therapy with drugs of other classes or psychotherapy may be necessary. Evidence supporting the efficacy of the use of other pharmacologic agents, including benzodiazepines and anticonvulsants, and augmentation with atypical antipsychotics is reviewed.

Clearly, more double-blind, placebo-controlled studies are required before the place of atypical antipsychotics in the management of refractory mood and anxiety disorders can be defined.

## REFERENCES

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