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EXPERT REVIEW SUPPLEMENT

CURRENT EVIDENCE AND FUTURE DIRECTIONS: *AUGMENTATION AND DOSING STRATEGIES FOR MAJOR DEPRESSIVE DISORDER*

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ABSTRACT

Despite the availability of a large number of antidepressants, treatment nonresponse in major depressive disorder (MDD) persists. As highlighted by findings from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, the first few months of treatment may be the most critical for treatment success. When the first antidepressant is not effective, a common dilemma is whether to use an adjunctive treatment or to switch medications completely. A substantial proportion of patients with MDD do not achieve remission from sequential courses of treatment with currently available strategies. Many who do improve are left with significant residual symptoms. Adjunctive treatments in MDD have the capacity to reduce relapse rates during the process of switching medication, provide neurotransmitter effects, or cause intended therapeutic side effects. However, they can also cause pharmacokinetic interactions, additive side effects, regimen complexity, and poorer compliance. Second-generation antipsychotics (SGAs) have a much larger evidence base than other adjunctive strategies for MDD, although they are associated with extrapyramidal side effects. While antidepressant monotherapy is the standard first-line treatment, psychotherapy still represents an important treatment pathway. Cognitive-behavioral therapy, interpersonal therapy, and several more basic forms of behavior therapy have been shown to have antidepressant efficacy comparable to antidepressant medication.

In this Expert Review Supplement, Michael E. Thase, MD, provides an overview of unmet needs in the management of MDD. Highlighting findings from STAR*D, Dr. Thase discusses expected first-line treatment outcomes, augmentation/switch strategies, and the role of psychotherapy. Next, Michael Gitlin, MD, provides an overview of several first-line adjunctive treatments, focusing on lithium, triiodothyronine, and stimulants. Finally, J. Craig Nelson, MD, reviews the role of adjunctive SGAs in treatment-resistant depression.

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Accreditation Statement

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Credit Designation

The Mount Sinai School of Medicine designates this educational activity for a maximum of 2 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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Statement of Need and Purpose

Effective management of major depressive disorder (MDD) continues to be a challenging task. No single treatment is uniformly effective for MDD and more than one treatment is often required to reach symptom remission. Despite the availability of different classes of drugs for the treatment of MDD, there remains a high prevalence of drug resistance, partial response, subsyndromal symptomatology, recurrence, and relapse. It is critical to treat MDD early since the disorder becomes more difficult to treat over time. Results from the Sequenced Treatment Alternatives to Relieve Depression study shows that remission rates tend to decrease dramatically after the second phase of treatment. Residual symptoms are common among patients receiving MDD treatment and are associated with an increased risk of relapse and poor psychosocial functioning. Consequently, interest has increased in treatment augmentation with medications that can improve core depressive symptoms such as sadness, lack of energy/fatigue, lack of interest, sleep problems, suicidality, and inability to enjoy daily activities. There is a range of potential augmenting agents in MDD, each with varying available evidence regarding efficacy and tolerability; these agents include multiple antidepressants, lithium, thyroid hormone, buspirone, stimulants, and atypical antipsychotics. New data continue to emerge regarding the efficacy and safety of these novel treatment strategies. Each atypical antipsychotic has a unique mechanism of action, which may result in different benefits and limitations in the treatment of depression. The safety and tolerability of augmenting with atypical antipsychotics versus other augmentation or switching strategies for treatment-resistant depression also warrants educational coverage to ensure that the benefits and risks of therapy are known.

Learning Objectives

At the completion of this activity, participants should be better able to:

- Identify the need for expanded treatment options for patients with treatment-resistant depression.
- Assess current evidence on augmentation strategies, including the use of atypical antipsychotics, in the treatment of major depressive disorder for patients who do not achieve full remission or recovery.
- Design treatment plans that address functional outcomes and motivate patients to make relevant lifestyle and behavior changes.

Target Audience

This activity is designed to meet the educational needs of psychiatrists.

Faculty Affiliations and Disclosures

Michael E. Thase, MD, is professor of psychiatry in the Department of Psychiatry and chief of the Mood and Anxiety Disorders Treatment and Research Program at the University of Pennsylvania in Philadelphia. He is also a member of the medical staff of the Philadelphia Veterans Affairs Medical Center and adjunct professor of psychiatry at the University of Pittsburgh Medical Center. Dr. Thase has provided scientific consultation to AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Forest Pharmaceuticals, GlaxoSmithKline, Lundbeck, MedAvante, Neuronetics, Otsuka, Ortho-McNeil, Pfizer, Merck, Shire, Supernus, Takeda, and Transcept; has been a member of the speaker's bureaus for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, and Pfizer; receives grant funding from Eli Lilly, Forest Pharmaceuticals, GlaxoSmithKline, the National Institute of Mental Health, Otsuka, and Sepracor; has equity holdings in MedAvante; and receives royalty income from American Psychiatric Publishing, Guilford Publications, Herald House, Oxford University Press, and W.W. Norton & Company. His wife is senior medical director for Advogent (which does business with BMS and Pfizer/Wyeth).

Michael Gitlin, MD, is professor of clinical psychiatry at the Geffen School of Medicine at the University of California, Los Angeles. He is also director of the Mood Disorders Clinic and of the Adult Division of Psychiatry at the Resnick Neuropsychiatric Hospital at UCLA. Dr. Gitlin has received honoraria from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, and Servier. Dr. Gitlin's article includes discussion of off-label use of lithium, T_3, stimulants, and transcranial magnetic stimulation.

J. Craig Nelson, MD, is Leon J. Epstein profession of psychiatry in the Department of Psychiatry at the University of California, San Francisco. Dr. Nelson is a consultant to Bristol-Myers Squibb, Corcept, Covidien, Eli Lilly, Forest, Lundbeck, Medtronic, Merck, Orexigen, Otsuka, and sanofi-aventis; is on the advisory boards of Bristol-Myers Squibb, Eli Lilly, Labopharm, and Otsuka; has received lecture honoraria from Eli Lilly Global, Otsuka Asia, and Schering Plough/Merck Asia; has received research support from the National Institutes of Mental health and the Health Resources and Services Administration; and owns stock in Atossa. Dr. Nelson's article includes off-label discussion of lithium, risperidone, ziprasidone, paliperidone, asenapine, and iloperidone in major depression.

CME Course Director **James C.-Y. Chou, MD**, is associate professor of psychiatry at Mount Sinai School of Medicine in New York City. Dr. Chou has received honoraria from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Merck, Novartis, and Pfizer.

Activity Review Information

The activity content has been peer-reviewed by Eran Chemerinski, MD, assistant professor of psychiatry at Mount Sinai School of Medicine. Dr. Chemerinski reports no financial, academic, or other interest in any organization that may pose a conflict of interest.

Review Date: April 26, 2010.

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To Receive Credit for this Activity

Read this Expert Review Supplement, reflect on the information presented, and complete the CME posttest and evaluation on pages 15 and 16. To obtain credit, you should score 70% or better. Early submission of this posttest is encouraged. Please submit this posttest by June 1, 2012 to be eligible for credit.

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CME Podcast Version

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