

*The following abstracts, from peer reviewed journals containing literature on the treatment of depression, were selected for their relevance to this Special Report supplement.*

### **Study Examines Recurrence of Major Depressive Disorder After Recovery**

*Longitudinal prospective follow-up data from the National Institute of Mental Health Collaborative Program on the Psychobiology of Depression-Clinical Studies were used to characterize the recurrence of an affective disorder in patients who initially recover from major depressive disorder (MDD). Up to 15 years of prospective follow-up data on the course of MDD disorder were available on 380 patients who recovered from an index episode of MDD and on 105 patients who subsequently remained well for at least 5 years after recovery. Baseline demographic and clinical characteristics were evaluated as predictors of recurrence of an affective disorder, and naturalistically applied antidepressant therapy was examined. Based on Kaplan-Meier estimates, a cumulative proportion of 85% of the 380 patients who recovered experienced a recurrence, as did 58% of those who remained well for at least 5 years. Being female, experiencing a more lengthy depressive episode before intake, more previous episodes, and never marrying significantly predicted a recurrence. Neither these characteristics nor any others persisted as predictors of recurrence in those who recovered and were subsequently well for at least 5 years. Patients reported being given low levels of antidepressant treatment during the index episode, which further decreased in amount and extent during the period they were well. It was concluded that few baseline demographic or clinical characteristics are predictive of who will or will not experience a recurrence of an affective disorder after recovery from an index episode of MDD even among those who remain well for extended periods of time. Naturalistically applied levels of antidepressant treatment are well below levels shown to be effective in maintenance pharmacotherapy studies.*

Mueller TI, Leon AC, Keller MB, et al. Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. *Am J Psychiatry* 1999;156:1000-1006.

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### **Categorizing Depression**

*Much debate centers on the dividing of persistent depression into meaningful and useful subcategories, including major depression, dysthymia, recurrent brief depression, and depressive personality disorder. Depression can be grouped according to its type and the severity of symptoms, cause, clinical course, or its association with other psychiatric illnesses. Epidemiologic and family studies have been conducted to assess the prevalence of depressive disorders, their diagnostic stability over time, and the amount of overlap that exists between them. Despite progress toward a better understanding of the various disorders, not enough evidence exists to support the hypothesis that such disorders are separate and distinct from one another. Nonetheless, preliminary data suggest that depressive personality disorder is separate from other disorders, and several questions have been raised as to the extent to which differentiating between depressive disorders, especially major depression and dysthymia, affects treatment decisions.*

Hirschfeld RM. Major depression, dysthymia, and depressive personality disorder. *Br J Psychiatry* 1994;December(suppl 26):23-30.

### Evolution of Antidepressant Action

Over time, an understanding has evolved regarding the mechanisms of antidepressant action. The potent antidepressant activity of the tricyclic antidepressants (TCAs) has provided support for the use of both norepinephrine and serotonin (5-HT) in depression and the dynamics involved in the action of such drugs. The succeeding generation of antidepressants included the selective serotonin reuptake inhibitors (SSRIs), which reinforced the role of serotonin, whereas the selective norepinephrine reuptake inhibitors, such as maprotiline and reboxetine, underscored the relevance of norepinephrine. Such developments suggest that facilitation of serotonin or norepinephrine or both might eventuate in an antidepressant response. The next step was the development of the mixed serotonin-norepinephrine reuptake inhibitors, such as venlafaxine and milnacipran. Like the TCAs, the antidepressant activity of selective norepinephrine reuptake inhibitors is founded on the inhibition of norepinephrine and serotonin reuptake, but unlike TCAs such drugs do not possess anticholinergic, antihistaminergic, and cardiotoxic effects. Although norepinephrine can stimulate the serotonin cell firing rate by the  $\alpha_1$ -adrenoceptors, norepinephrine and serotonin possess independent antidepressant action. The most recent development has been the introduction of the noradrenergic and specific serotonergic antidepressant mirtazapine, whose antidepressant effect seems to be related to the dual enhancement of central noradrenergic and serotonergic neurotransmission through blockade of the  $\alpha_2$ -adrenoceptors. Mirtazapine also directly blocks 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptors, which may account for its anxiolytic and sleep-improving properties as well as its lack of the adverse events typical of SSRIs.

Westenberg HGM. Pharmacology of antidepressants: Selectivity or multiplicity? *J Clin Psychiatry* 1999;60(suppl 17):4-8.

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### Medication Algorithms Developed by Consensus Conference Panel

The development of consensual medication algorithms for treatment of patients with major depressive disorder (MDD) in the Texas public mental health system is discussed in what is believed by panelists to be the first attempt to develop and prospectively evaluate consensus-based medication algorithms for the treatment of those with severe and persistent mental illnesses. The goal of the Texas Medication Algorithm Project is to improve the consistency of appropriate treatment for MDD and the clinical outcomes of patients with the disorder. Conference participants included academic clinicians and researchers, practicing clinicians, administrators, consumers, and families. The conference was convened to develop evidence-based consensual algorithms for the pharmacotherapy of MDD in the Texas mental health system. The algorithms were drafted after a series of presentations and panel discussions. There was consensus among panel members on the algorithms for both nonpsychotic and psychotic depression, which consist of systematic strategies to define appropriate treatment interventions and ways to assess optimal implementation of the strategies. After the consensus process, the algorithms were further modified and expanded to aid in their implementation on a local basis. The algorithms serve as the basis for development and implementation of medical treatment algorithms for patients who are treated in public mental health systems. Future articles will describe specific issues related to adaptation, implementation, feasibility testing, and evaluation of outcomes using the pharmacotherapeutic algorithms.

Crison ML, Trivedi M, Pigott TA, et al. The Texas Medication Algorithm Project: Report of the Texas Consensus Conference Panel on Medication Treatment of Major Depressive Disorder. *J Clin Psychiatry* 1999;60:142-156.

### **A Long-Term Approach to the Treatment of Depression**

*Although the concept that depression is a recurrent and chronic disorder is generally well accepted, the condition often goes underrecognized and undertreated. Current guidelines recommend that treatment of depression with antidepressants be continued for at least 4 to 6 months after the initial response and that long-term prophylactic treatment be administered to patients who have had 2 or more depressive episodes. Nevertheless, there is little agreement on the length of time continuation or maintenance treatment should be given. The long-term strategy for the treatment of unipolar major depression, especially in terms of length of treatment and the types of patients who would benefit from maintenance treatment, is reviewed.*

Keller MB. The long-term treatment of depression. *J Clin Psychiatry* 1999;60(suppl 17):41-45.

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### **Response to Maintenance Nortriptyline Treatment in Late-Life Depression**

*The long-term efficacy of 2 fixed plasma levels of nortriptyline—80 to 120 ng/mL and 40 to 60 ng/mL—in the prevention or delay of recurrence of major depression and in the minimization of residual depressive symptoms and somatic complaints was compared in 41 elderly patients who had a history of recurrent major depression. The patients were randomly assigned to 3-year, double-blind maintenance pharmacotherapy using nortriptyline with controlled plasma concentrations of 80 to 120 ng/mL compared with 40 to 60 ng/mL. Times to and rates of recurrence of major depression were compared, as well as the frequencies of side effects, non-compliance episodes, and subsyndromal symptomatic flareups. Major depressive episodes recurred in 6 (29%) of 21 patients in the 80- to 120-ng/mL group and in 8 (40%) of the 20 patients in the 40- to 60-ng/mL group, a nonsignificant difference. Most recurrences occurred during year 1 of maintenance treatment. Hamilton depression scores that were in the subsyndromal range, that is, higher than either 10 or 7, occurred markedly more often at the 40- to 60-ng/mL range, whereas constipation occurred markedly more often at the 80- to 120-ng/mL range. The proportions of patients who reported missed doses did not differ. Maintenance pharmacotherapy with nortriptyline 80 to 120 ng/mL demonstrates fewer residual depressive symptoms, that is, a less variable long-term response, than pharmacotherapy at the 40- to 60-ng/mL level; however, reports of constipation are more frequent, and no marked difference exists in the recurrence of syndromal major depressive episodes. As a result, treatment at the 80- to 120-ng/mL level may be preferable because of fewer residual symptoms and a less variable response, as long as the burden of side effects can be successfully managed.*

Reynolds CF III, Perel JM, Frank E, et al. Three-year outcomes of maintenance nortriptyline treatment in late-life depression: A study of two fixed plasma levels. *Am J Psychiatry* 1999;156:1177-1181.