

JCP

V I S U A L S

JOURNAL OF CLINICAL PSYCHIATRY

THIS ISSUE OF JCP VISUALS

DISCUSSES THE MANAGEMENT OF TREATMENT-RESISTANT DEPRESSION AND ANXIETY USING A VARIETY OF PHARMACOTHERAPIES.

To obtain credit, read the material and complete the CME Posttest and Registration Form.

CME OBJECTIVES

After completing this educational activity, you should be able to:

- Review the literature on the use of atypical antipsychotics in treatment-resistant depression and anxiety
- Discuss the neurobiological relationship of depression and anxiety
- Outline the role of atypical antipsychotics in the treatment of depression and anxiety
- Select appropriate treatment for patients with resistant depression and anxiety

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New Therapies for Treatment-Resistant Depression and Anxiety

CHARLES B. NEMEROFF, M.D., PH.D.

Many advances in the treatment of depression and anxiety have been made in recent years. However, improvements are still needed, especially in finding new treatments that will improve both depressive and anxious symptoms and that will alleviate treatment-resistant depression and anxiety. One strategy is to develop new agents that will achieve these goals; another is to look to existing agents to determine whether augmentation will meet these needs.

Issues in Treatment-Resistant Depression and Anxiety

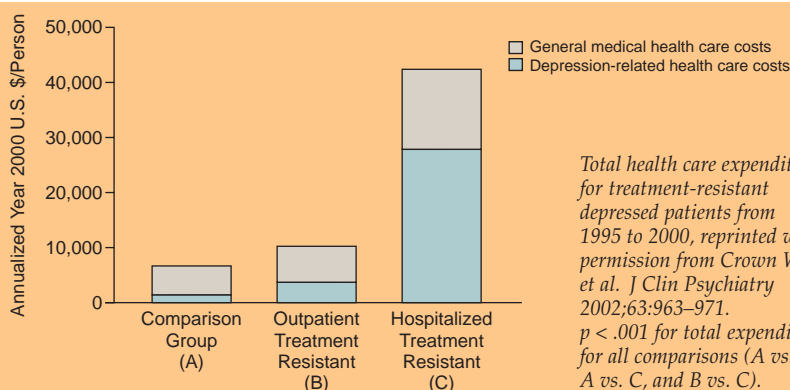
MARTIN B. KELLER, M.D.

Treatment-resistant depression is highly prevalent in the community and is associated with a substantial socioeconomic burden. Approximately 17% of individuals are expected to experience a major depressive episode during their lifetime, with a 1.7 greater risk in women compared with men [Kessler RC, et al. *J Affect Disord* 1994;30:15–26]. However, determining the proportion of those individuals who experience treatment-resistant depression is complicated by the varying definitions of treatment resistance and antidepressant response in the literature. Since remission is the ultimate goal for all depressed patients, a greater understanding of treatment-resistant depression is needed, as are effective management and treatment strategies. However, although the first step in treating depression is obvious—initiate antidepressant therapy—the optimal next step to take if the first fails remains to be determined.

Costs of Depression

Considering that up to one third of patients fail to respond to antidepressant monotherapy [Fava M, Davidson KG. *Psychiatr Clin North Am* 1996;19:179–200] and that depression can cause grave disability, it follows that treatment-resistant depression is a costly disorder. Crown and colleagues examined medical claims data from 1995 to 2000 and categorized patients

as hospitalized patients with treatment-resistant depression, outpatients with treatment-resistant depression, or controls with depression that was not treatment resistant. Total health care expenditures for hospitalized patients were significantly greater than those for outpatients, which in turn were significantly greater than those for controls (see Figure).



Definitions of Treatment Resistance and Response

Treatment-resistant depression has been defined as the failure to respond to only 1 trial of monotherapy with an antidepressant such as a tricyclic antidepressant (TCA) or a selective serotonin reuptake inhibitor (SSRI). Another definition is the failure to respond to ≥ 2 trials of different types of antidepressant monotherapy. Yet another definition is the failure to respond to ≥ 4 trials of different antidepressant therapy, including augmentation and combination therapy as well as electroconvulsive therapy (ECT).

Thase and Rush [*J Clin Psychiatry* 1997;58(suppl 13):23–29] proposed a system for staging resistance to antidepressant therapy. In their system, each stage

builds on the previous one. For example, stage I is the failure of at least 1 adequate trial of antidepressant monotherapy, and stage II consists of stage I plus failure of an adequate trial of an antidepressant from a class other than that used in stage I. This system goes up to stage V, which consists of failure of all 4 stages of pharmacotherapy plus failure of a course of bilateral ECT. However, that system does not take into account augmentation or combination trials, nor does it recognize psychotherapy.

Antidepressant response must also be consistently defined for serious study of treatment-resistant depression to begin. Some operational definitions have been proposed (see Table).

Operational Definitions of Response and Remission

- Nonresponse: no clinically meaningful response
- Partial response: between 25% and 50% improvement on a standardized rating scale
- Response: $\geq 50\%$ improvement on a standardized rating scale
- Remission: return to premorbid function or absence of virtually all psychopathology and dysfunction

From Greden JF. *J Clin Psychiatry* 2001;62(suppl 16)26–31.

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Statement of Need and Purpose

Although treatment-resistant depression and anxiety are serious public health issues, there is little research in the area to guide clinicians. Atypical antipsychotics have been reported useful for treatment-resistant depression and anxiety in a few small studies, but additional clinical trials are necessary. This activity was designed to meet the needs of participants in CME activities provided by Physicians Postgraduate Press, Inc. who have requested information on managing patients with treatment-resistant depression and anxiety. There are no prerequisites for participating in this activity.

Accreditation Statement

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Date of Original Release/Review

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Faculty Disclosure

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Forest, GlaxoSmithKline, Janssen, Merck, Mitsubishi Pharma, Novartis, Organon, Pfizer, Pharmacia, Sanofi-Synthelabo, Scirex, Sepracor, Somerset, Vela, and Wyeth; **Dr. Pollack** is on the advisory boards for Bristol-Myers Squibb, Cephalon, Forest, GlaxoSmithKline, Janssen, Eli Lilly, Novartis, Otsuka, Pfizer, Roche, UCB Pharma, and Wyeth; has received grant/research support from Cephalon, Forest, GlaxoSmithKline, Janssen, Eli Lilly, Pfizer, UCB Pharma, and Wyeth; and is involved with speaker programs for Forest, GlaxoSmithKline, Janssen, Eli Lilly, Pfizer, Solvay, and Wyeth; **Dr. Charney** has no affiliations or other relationships to disclose relevant to the presentation.

Disclosure of Off-Label Usage

The chair has determined that, to the best of his knowledge, ketamine, memantine, olanzapine, riluzole, and risperidone are not approved by the U.S. Food and Drug Administration for the treatment of depression. If you have questions, contact the medical affairs department of the manufacturer for the most recent prescribing information.

Acknowledgment

This *JCP Visuals* was derived from the planning roundtable "New Therapies for Treatment-Resistant Depression and Anxiety" held September 28–29, 2003, in Atlanta, Ga. The roundtable and this *JCP Visuals* were independently developed by the CME Institute of Physicians Postgraduate Press, Inc. pursuant to an unrestricted educational grant from Janssen Pharmaceutica Products, L.P. The opinions expressed herein are those of the authors and do not necessarily reflect the views of the CME provider and publisher or the commercial supporter.

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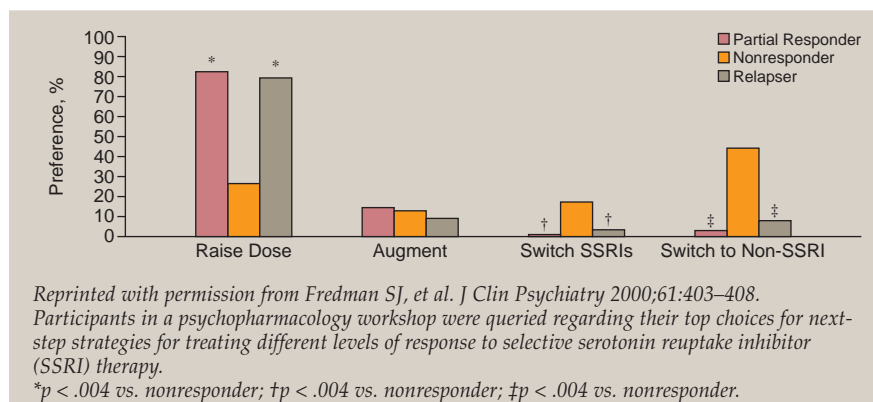
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Strategies Used for Managing Treatment Resistance

Several surveys have reported the course clinicians typically take when presented with a treatment-resistant or partially responding patient. In one study, psychiatrists were asked how they would manage a case of depression with initial TCA treatment failure; most responded that they would raise the dose of the TCA [Shergill SS, Katona CL. *J Affect Disord* 1997;43:19–25]. In another study, psychiatrists were presented with a similar case but chose lithium augmentation as the best strategy [Nierenberg AA. *J Clin Psychiatry* 1991;52:383–385]. A survey of clinicians attending a psychopharmacology workshop found that SSRI partial response was most often handled by raising the dose, whereas nonresponse was managed by switching



to a different type of antidepressant agent (see Figure). Unfortunately, not all of these management strategies are confirmed by the literature. For example, some SSRIs have a flat dose-response curve; after a certain dose

has been reached, raising it will have no further effect on symptoms. In addition, switching from an SSRI to a different type of agent may be effective, but switching from one SSRI to another may be effective as well.

Pharmacotherapy Management Strategies: Benefits and Drawbacks

Each strategy for managing resistance—augmentation, combination, and switching—has benefits and drawbacks. One advantage of either augmentation or combination is that the patient will not experience withdrawal or discontinuation symptoms. Augmentation or combination may be the best choice in patients who have a partial response, since that response will not be lost. Disadvantages of augmentation and combination include increased costs of additional medication, the risk of decreased compliance due to the additional pills to

- Augmentation with another antidepressant
- Combination with an agent other than an antidepressant
- Switching to a different medication

be taken, and the possibility of drug-drug interactions or other adverse effects.

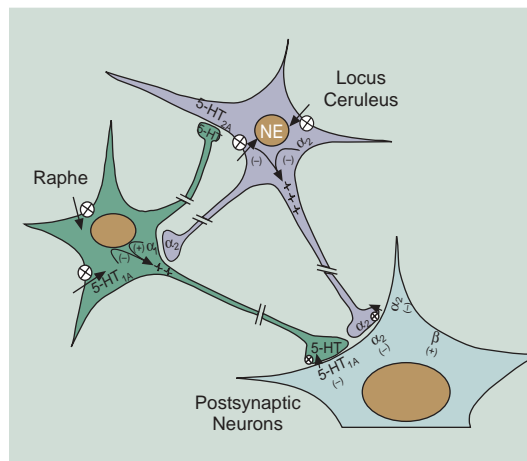
Switching to another antidepressant has its own set of advantages and disadvantages. Switching to a different medi-

cation rather than adding one may maintain or improve compliance, and it may be less expensive for the patient. Switching decreases the possibility for drug-drug interactions. However, switching from one antidepressant to another may induce withdrawal or discontinuation effects, and it may take longer for the patient to respond to a new drug. In addition, the patient may be reluctant to try a new agent out of fear of new side effects or despair that if the current drug did not work, nothing will. ■

Mechanisms of Action of Antidepressants

PIERRE BLIER, M.D., PH.D.

The serotonin (5-HT) and norepinephrine systems have a pivotal role in antidepressant response. However, it is important to remember that these systems do not exist in isolation in the brain. These 2 systems are interconnected on the cell body level and have reciprocal interactions (see Figure). Understanding the mechanisms of action of commonly used antidepressants will enable us to understand the role non-antidepressant medications like the atypical antipsychotics may play as augmenting agents.

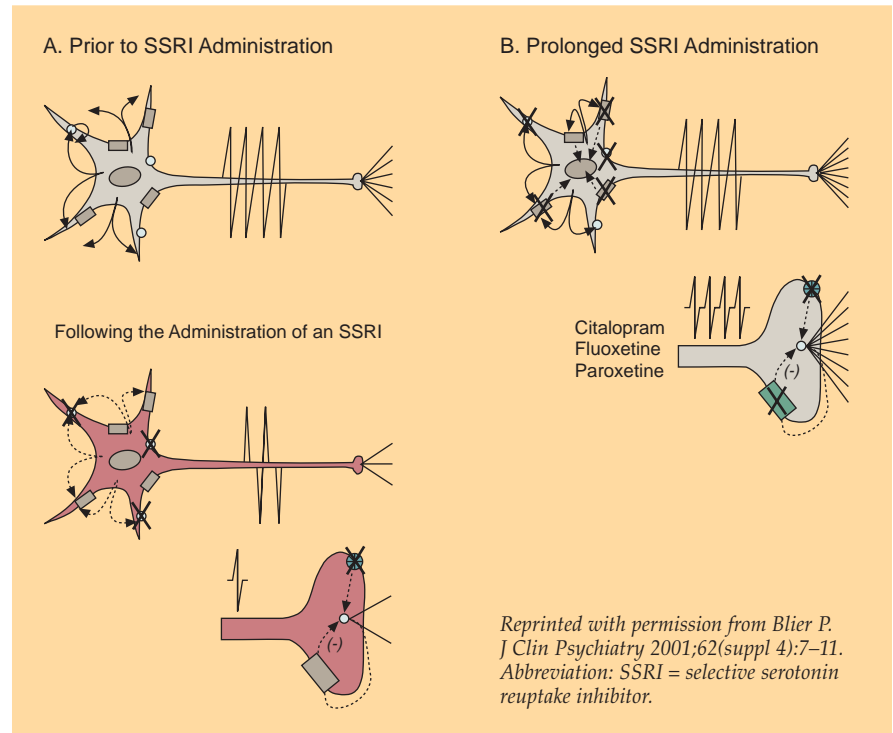


Reprinted with permission from Blier P. *J Clin Psychiatry* 2001;62(suppl 4):7–11. The circles with arrows represent high-affinity reuptake transporters for serotonin (5-HT) and norepinephrine (NE). Plus and minus signs in parentheses indicate excitatory and inhibitory action, respectively, of the various receptor subtypes. There is no direct evidence of 5-HT_{2A} receptors on the cell body of NE neurons, but the activation of this receptor subtype, using a 5-HT_{2A} agonist, suppresses their firing activity. 5-HT exerts an inhibitory tone on NE neuron activity through this receptor subtype.

■ The Effect of Antidepressants on the Firing Activity and Release of 5-HT and NE

In panel A of the figure at right, the squares on the cell body represent the 5-HT_{1A} autoreceptors, which normally exert an inhibitory action on firing activity, represented on the axon by peaks and troughs (i.e., action potentials). The crosses over the circles represent the blockade of the 5-HT transporters by the reuptake inhibitors. These drugs produce a decrease in firing rates and release of 5-HT. The total amount of 5-HT at the level of the terminals is, however, not decreased because the terminal 5-HT_{1B} autoreceptor, represented by a square, compensates for the decreased firing. In panel B, prolonged administration of the SSRIs listed produces a desensitization of the 5-HT_{1A} autoreceptors (represented by an X over them), which permits a normalization of the firing rate. This treatment desensitizes the terminal 5-HT_{1B} autoreceptor as well, which ultimately produces a net increase in 5-HT release.

The SSRIs can also affect norepinephrine receptors, because a change in serotonin levels can decrease the firing of norepinephrine neurons and norepinephrine levels. This effect on noradrenergic neurons may explain why the SSRIs are effective treatments for some anxiety disorders. The decrease in nor-



epinephrine may also explain why some depressed patients do not respond to SSRIs but do respond to dual-action antidepressants or augmentation with an agent such as an atypical antipsychotic.

The norepinephrine reuptake inhibitors (NRIs) affect norepinephrine firing and release. Acute treatment with an NRI increases the amount of norepinephrine

in the synapse, which decreases firing [Szabo ST, Blier P. *J Pharmacol Exp Ther* 2002;302:983-991]. Unlike what is seen with SSRIs, firing rates do not recover with long-term NRI treatment. However, even though the cell body does not become desensitized, the terminal does, which enhances the increased amount of norepinephrine in the synapse.

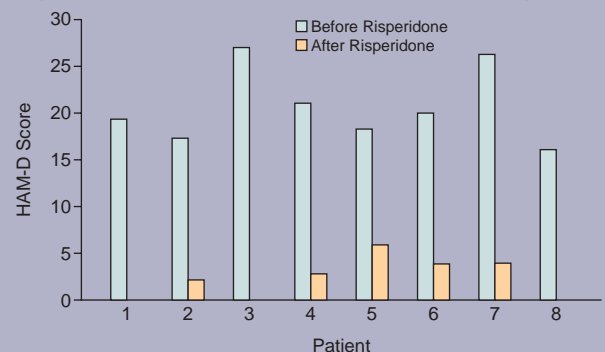
■ Potential Mechanisms for Atypical Antipsychotic Augmentation

Many agents are available with which a clinician can augment antidepressant treatment to try to improve a patient's treatment response. For example, when a small group of depressed patients received risperidone in addition to ongoing antidepressant treatment, all quickly remitted (see Figure).

Atypical antipsychotics may augment the antidepressant action of SSRIs because of their capacity to block 5-HT_{2A} receptors; combining 5-HT reuptake inhibition with 5-HT_{2A} receptor antagonism increases norepinephrine release and desensitizes α_2 adrenoceptors on the cell body of norepinephrine neurons. Another property of atypical antipsychotics, especially risperidone, that may increase norepinephrine activity where an antidepressant has decreased it is α_2 -adrenergic antagonism. The addition of an α_2 -adrenergic antagonist could restore firing activity, thereby increasing norepinephrine activity.

The term *atypical antipsychotic* inadequately describes the potential of these agents to be useful tools in alleviating the symptoms of treatment-resistant depression and anxiety. ■

Risperidone Augmentation of Selective Serotonin Reuptake Inhibitors in Treatment-Resistant Depression



Data from Ostroff RB, Nelson JC. J Clin Psychiatry 1999;60:256-259. Return visit HAM-D score = 0 for patients 1 and 8. No return visit and no HAM-D score obtained for patient 3; patient and referring psychiatrist reported complete remission. Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

■ Use of Atypical Antipsychotics in Refractory Depression and Anxiety

CHARLES B. NEMEROFF, M.D., PH.D.

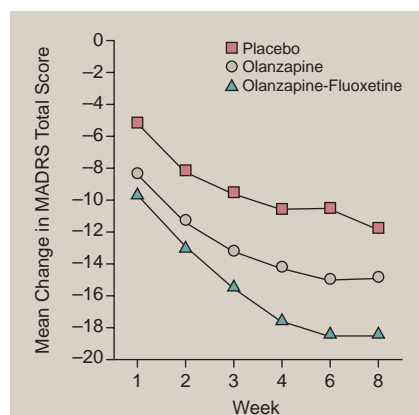
The atypical antipsychotics have been theorized to be effective augmenting agents in the treatment of refractory depression. The available clinical data seem to support this theory in both bipolar and unipolar depression. In addition, these agents have been tried in anxiety disorders such as obsessive-compulsive disorder (OCD).

Larger trials are currently underway that will further examine the effect of augmentation with atypical antipsy-

chotics on treatment-resistant depression and some forms of anxiety such as OCD. Some atypicals, such as risperidone and olanzapine, have recently been approved by the U.S. Food and Drug Administration for use in mood disorders. A paradigm shift may be needed that will allow us to view these agents as something more than simply antipsychotics, since their uses in other types of disorders are being established.

■ Bipolar Depression

Few data are available on the treatment of bipolar depression with atypical antipsychotic augmentation. A recently published 8-week, double-blind, placebo-controlled trial of either olanzapine or olanzapine plus fluoxetine found that the combination was more effective in the treatment of bipolar I depression (see Figure). The primary outcome measure was the Montgomery-Asberg Depression Rating Scale (MADRS). At week 8, almost half (48.8%; 40/82) of the olanzapine-fluoxetine group met criteria for remission, compared with almost one third (32.8%; 115/351) of the olanzapine group and about one fourth (24.5%; 87/355) of the placebo group. Treatment-emergent mania occurred infrequently in all 3 study groups (5.7%–6.7%).



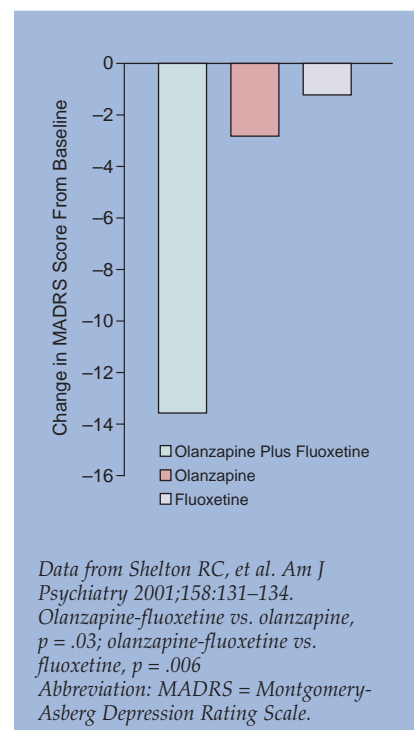
Reprinted with permission from Tohen M, et al. *Arch Gen Psychiatry* 2003;60:1079–1088. According to mixed-effects model repeated-measures analysis, at week 8, olanzapine vs. placebo, $p = .002$; olanzapine-fluoxetine vs. placebo, $p < .001$; olanzapine vs. olanzapine-fluoxetine, $p = .01$. Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.

■ Major Depression

Atypical antipsychotics have also been used as augmenting agents in treatment-resistant major depression. An open study examined the effect of low-dose risperidone in 8 patients with nonpsychotic major depressive disorder who had not responded to SSRI therapy [Ostroff RB, Nelson JC. *J Clin Psychiatry* 1999;60:256–259]. Before risperidone was initiated, Hamilton Rating Scale for Depression (HAM-D) scores ranged from 16 to 27. After ≤ 1 week of risperidone augmentation, all patients experienced remission, with HAM-D scores ranging from 0 to 6. In addition, several patients reported improvement in sexual function and sleep, and the treatment was well tolerated. All patients maintained this improvement for at least 3 months. Of note is that improvement was not limited to a particular type of symptom such as delusions or agitation; all patients benefited quickly from risperidone augmentation.

A 6-week, open-label study included 36 patients who met criteria for major depressive disorder [Hirose S, Ashby CR Jr. *J Clin Psychiatry* 2002;63:733–736]. Patients were given fluvoxamine and risperidone. The primary assessment measure was the HAM-D. Remission was defined as a 75% to 100% reduction in score; response, a 50% to 74% reduction; minimum response, a 25% to 49% reduction; and no response, $< 25\%$ reduction. Of the 30 patients who completed the study, 23 (76%) remitted, 5 (17%) responded, and 2 (7%) had no response. The treatment was well tolerated.

Olanzapine has been reported useful in combination with SSRIs for treatment-

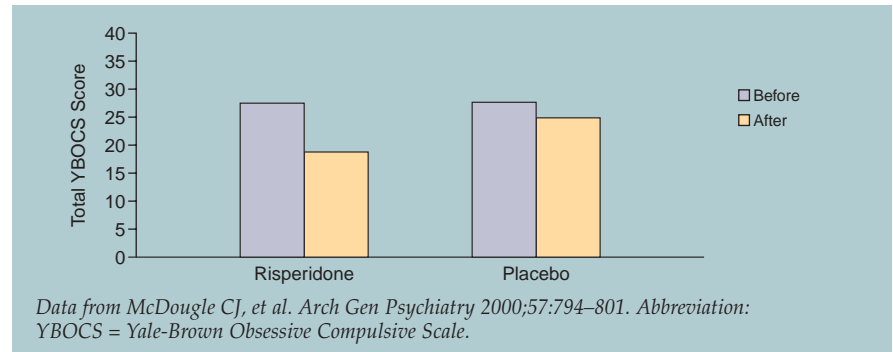


Data from Shelton RC, et al. *Am J Psychiatry* 2001;158:131–134. Olanzapine-fluoxetine vs. olanzapine, $p = .03$; olanzapine-fluoxetine vs. fluoxetine, $p = .006$. Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.

resistant depression as well. Shelton and colleagues reported on 28 patients with nonpsychotic depression and a history of treatment resistance who participated in an 8-week, double-blind study of the combination of olanzapine and fluoxetine. Patients received fluoxetine plus placebo, olanzapine plus placebo, or olanzapine plus fluoxetine for 8 weeks. After 8 weeks of double-blind treatment, patients on combination treatment experienced a significantly greater decrease in symptoms as measured by the MADRS (see Figure). In addition, this decrease was seen as early as week 1 of the study. No significant between-group differences in treatment-emergent adverse events were reported.

■ Obsessive-Compulsive Disorder

Atypical antipsychotics have also been used as augmenting agents in OCD. A 6-week, double-blind, placebo-controlled study examined the benefit of adding risperidone to ongoing SSRI treatment. Patients were randomly assigned to receive either risperidone (N = 20) or placebo (N = 16) as an augmenting agent. Response rates were higher in the risperidone group, in which 50% (9/18) of completers were considered responders, compared with no placebo-treated patients. Risperidone augmentation was significantly more effective than placebo in reducing



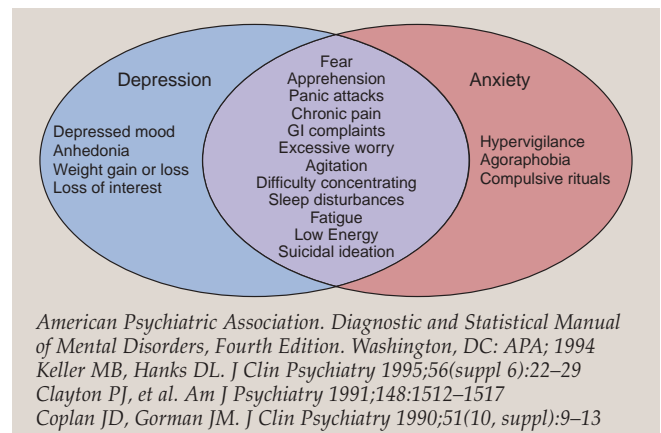
OCD ($p < .001$; see Figure), depressive ($p < .001$), and anxiety ($p = .003$) symptoms, and it was well tolerated, with mild, transient sedation as the most commonly reported side effect.

Larger trials are currently underway that will further examine the effect of augmentation with atypical antipsychotics on anxiety disorders such as OCD. ■

■ Comorbid Anxiety and Depression

MARK H. POLLACK, M.D.

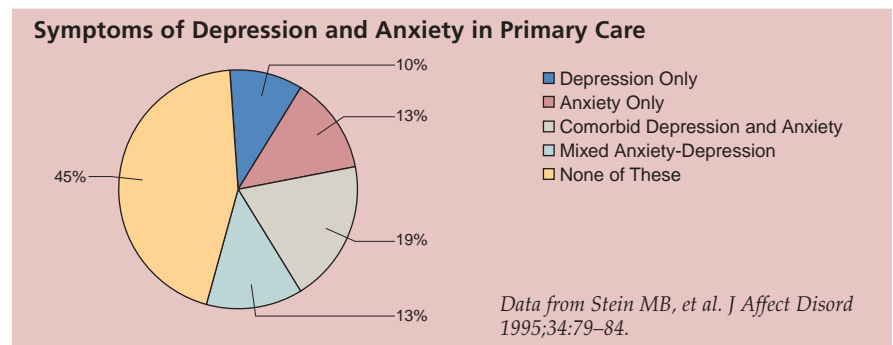
Clinicians see and treat a great deal of comorbidity of anxiety and depressive disorders. Certain symptoms are disorder specific, but there is a significant overlap. Comorbid anxiety and depression is associated with increased morbidity, poorer acute and long-term outcomes, increased suicide risk, and increased treatment resistance [Lydiard RB, Brawman-Mintzer O. *J Clin Psychiatry* 1998;59(suppl 18):10–17]. However, the exact relationship between anxiety and depression, as well as the optimal strategy to properly diagnose and treat these comorbid conditions, has yet to be determined.



■ Prevalence and Diagnosis of Comorbid Anxiety and Depression

According to the lifetime rates established by the National Comorbidity Survey, 58% of individuals with major depression have a secondary anxiety disorder, and 68% of individuals with any primary anxiety disorder have secondary major depression [Kessler RC, et al. *Br J Psychiatry Suppl* 1996;30:17–30]. Multiple anxiety disorders also increase the risk for depression and may be associated with more severe symptoms.

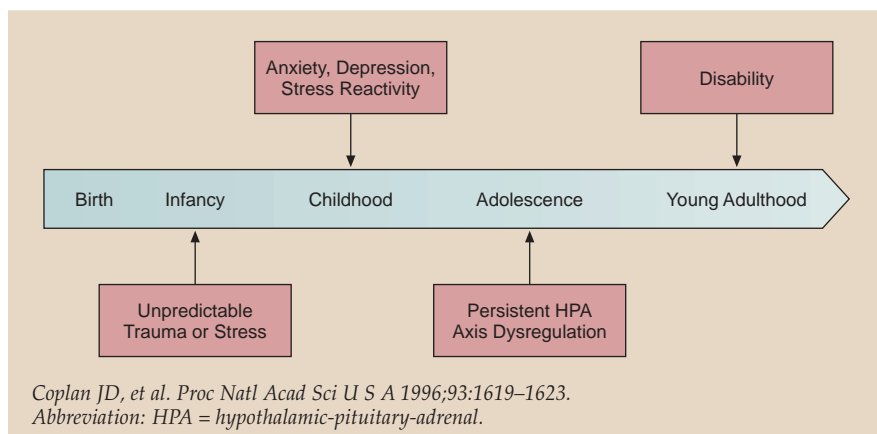
Criteria for “mixed anxiety-depression” were introduced in the appendix of the DSM-IV. Patients with anxiety and affective symptoms who do not meet criteria for a depressive or anxiety disorder can be as likely to seek treatment as those with a disorder that does meet diagnostic criteria. In addition, these subsyndromal disorders



have been associated with significant distress and impairment. Stein and coworkers attempted to determine the prevalence of the mixed anxiety-depression diagnosis in primary care. Seventy-eight primary care patients who had no known psychiatric diagnosis were subjected to a thorough interview

to determine whether a psychiatric diagnosis was applicable (see Figure). Those who fulfilled criteria for mixed anxiety-depression reported a level of disability comparable to that reported by patients who had depression or an anxiety disorder. The validity and stability of this diagnosis need further research.

Model of Susceptibility: Anxiety and Mood Disorders



Coplan and coworkers [*Proc Natl Acad Sci U S A* 1996;93:1619–1623] attempted to determine the impact of environmental stress on the development of affective and anxiety disorders. They measured levels of corticotropin-releasing factor (CRF), which is a regulator of the physiologic stress response and may be implicated in the pathology of mood disorders, in the cerebrospinal fluid of nonhuman primates. Some animals were raised in

a stressful environment—without a predictable food supply—and some were not. Those raised in the unstable environment had higher CRF levels than those raised in a stable environment.

On the basis of these results, it is possible to conceptualize a model of susceptibility to mood disorders in which early-life stress may contribute to the development of mood disorders (see Figure).

Potential Familial and Genetic Factors in Comorbid Anxiety and Depression

Several researchers have proposed that familial or genetic factors may play a role in comorbid anxiety and depression. For example, Leckman and coworkers found that relatives of those with major depression and an anxiety disorder are at higher risk for both types of disorders than are relatives of those with major depression only [*Am J Psychiatry* 1983;140:880–882]. In a twin study, Kendler and colleagues concluded that the vulnerability to depression or generalized anxiety disorder was in part secondary to genetic influences and that environmental factors may determine whether an individual will develop one or both of these disorders [*Arch Gen Psychiatry* 1992;49:716–722]. A family study of posttraumatic stress disorder (PTSD) following rape reported that familial vulnerability to depression was associated with the onset of PTSD in rape survivors [*Davidson JR, et al. J Psychiatr Res* 1998;32:301–309]. ■

The Biology of Depression and the Development of New Medications

DENNIS S. CHARNEY, M.D.

Despite advances in molecular biology, the so-called “pipelines” of drug development have yet to be filled, and the number of new drug applications fell from 131 in 1996 to 78 in 2002 [*Warner S. The Scientist* 2003 May 19;17(10)]. The advances in biology have not been translated into new medications; this lack is evident in psychiatry, where new agents are often refinements of older agents and are not fundamentally different from the older agents. A workgroup that investigated this problem on behalf of the National Institute of Mental Health (NIMH) identified 4 areas of highest priority:

1. Develop better animal models of mood disorders
2. Identify genetic determinants of mood disorders
3. Develop agents with new mechanisms of action and identify biological markers of mood disorders in humans
4. Recruit neuroscientists of diverse backgrounds to the field to enhance basic disease research

With these priorities in mind, the workgroup critiqued animal models currently used in depression research and identified many potential targets for the development of new antidepressants and mood stabilizers [*Nestler EJ, et al. Biol Psychiatry* 2002;52:503–528]. More recently, Manji and coworkers [*Biol Psychiatry* 2003;53:707–742] expanded upon these potential targets with suggestions of their own. Some of these suggestions address monoaminergic targets, while others go beyond the monoamines to explore ways in which agents that enhance neuroplasticity—that is, how the brain perceives and adapts to external and internal stimuli—may be useful in the treatment of depression.

Potential Targets for the Development of New Antidepressants and Mood Stabilizers

Serotonin (5-HT) antagonists
5-HT_{1A/1B}, 5-HT₂, 5-HT₇
α-Adrenergic antagonists
CRF antagonists
NPY receptor agonists
Glutamatergic system:
NMDA antagonists,
AMPA receptor potentiators
PDE4 inhibitors
MAP kinase phosphatase inhibitors
Isozyme selective PKC inhibitors
GSK-3 inhibitors, β-catenin
upregulators
Bcl-2 upregulators

Based on Nestler EJ, et al. *Biol Psychiatry* 2002;52:503–528, and Manji HK, et al. *Biol Psychiatry* 2003;53:707–742. Abbreviations: AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazole propionate, CRF = corticotropin-releasing factor, GSK = glycogen synthase kinase, MAP = mitogen-activated protein, NMDA = N-methyl-D-aspartate, NPY = neuropeptide Y, PDE4 = phosphodiesterase 4, PKC = protein kinase C.

■ Pros and Cons of Animal Models Used in Depression Research

Test	Pros	Cons
Forced swim test	Responds to antidepressant treatment; easy to perform	Responds to acute drug treatment
Tail suspension test	Same as above	Same as above
Learned helplessness	Causes some depression-like symptoms; responds to some antidepressants	Requires extreme stressors; may be better model of posttraumatic stress disorder
Chronic stress	Causes some depression-like symptoms	Difficult to reproduce and to show antidepressant activity
Early life stress	Causes some depression-like symptoms	Changes in social behavior not well-characterized in rodents; effects of antidepressants need to be better established
Selective breeding	Focuses on individual differences in susceptibility to depression	No line has been well-established
Reward models	May measure affective state and model motivational symptoms of depression; responds to some antidepressants	Need validation in more traditional models of depression

Based on Nestler EJ, et al. Biol Psychiatry 2002;52:503–528.

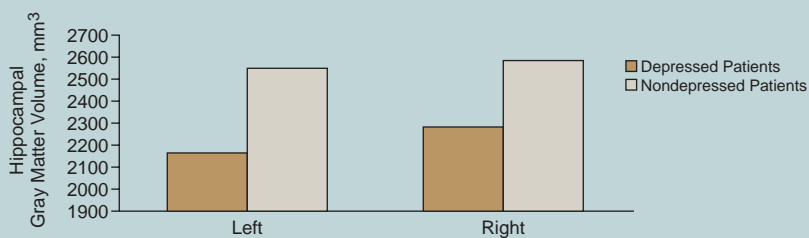
■ Potential Targets for Novel Antidepressants: Current Research

Of the antidepressant targets listed by the NIMH workgroup [Nestler EJ, et al. *Biol Psychiatry* 2002;52:503–528] and Manji et al. [*Biol Psychiatry* 2003;53:707–742], several have been studied in depression. For example, serotonin dysfunction has been implicated in depression, and several types of serotonin antagonists may have effects on depressive symptoms.

α_2 -Adrenergic antagonists have antidepressant effects as well. These agents may regulate serotonin neurons, according to the NIMH workgroup, and therefore may be especially effective in combination with other antidepressants such as the SSRIs. Mirtazapine has α_2 -adrenergic antagonist properties, but it is unclear whether those properties contribute to the agent's antidepressant effect. Corticotropin-releasing factor (CRF) antagonists may also be effective antidepressants, because of evidence implicating increased CRF levels in depression. Neuropeptide Y may also prove to be a fruitful target of study. This substance may be an endogenous anxiolytic, and neuropeptide Y agonists could theoretically alleviate depressive and anxious symptoms.

Another type of agent that could prove to be useful in depression is an N-methyl-D-aspartate (NMDA) antagonist. Current approved uses of NMDA antagonists vary and include anesthetics such as ketamine and Alzheimer's

Mean Hippocampal Volume in Depressed Patients (N = 10) Vs. Nondepressed Controls (N = 10)



Data from Sheline YI, et al. Proc Natl Acad Sci U S A 1996;93:3908–3913

disease treatments such as memantine. A small study examined the effect of a single dose of ketamine (0.5 mg/kg) in 7 participants with major depression [Berman RM, et al. *Biol Psychiatry* 2000;47:351–354]. These participants experienced significant improvement in depressive symptoms lasting 72 hours.

Other agents with actions on the glutamatergic system may also be effective treatments for mood disorders. Lamotrigine, an anticonvulsant that appears to modulate presynaptic release of glutamate, has been approved by the U.S. Food and Drug Administration for the maintenance treatment of bipolar disorder. This agent has a beneficial effect on bipolar depression [Calabrese JR, et al. *J Clin Psychiatry* 1999;60:79–88]. Riluzole, a treatment of amyotrophic lateral sclerosis, may also have antidepressant effects. It inhibits glutamate release by blocking presynaptic calcium and

sodium ion channels. In an open-label trial, Zarate and colleagues [Zarate CA Jr, et al. *Am J Psychiatry* 2004;161:171–174] found significant improvement as early as week 3 in 19 patients with treatment-resistant depression.

Other possible targets have little evidence of antidepressant efficacy in humans. However, several of these agents may be implicated in regional decreases in brain volume seen in both postmortem and in vivo examinations of depression people (see Figure). Manji and colleagues have hypothesized that, just as neurochemical dysfunction can be regulated with medications such as antidepressants and mood stabilizers, so too can impairments in cellular resilience and structural plasticity be alleviated via the possible neurotrophic effects of these agents [*Psychopharmacol Bull* 2001;35:5–49; *Biol Psychiatry* 2003;53:707–742]. ■

Drug Names: citalopram (Celexa), fluoxetine (Prozac and others), ketamine (Ketalar and others), lamotrigine (Lamictal), memantine (Namenda), mirtazapine (Remeron and others), olanzapine (Zyprexa), paroxetine (Paxil and others), riluzole (Rilutex and others), risperidone (Risperdal).