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Augmentation in the Treatment of Major Depressive Disorder: The Role of Atypical Antipsychotics

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Educational Objectives:

Upon completion of this activity, the learner will be able to:

- Assess the goals of therapy and the current rates of remission and recovery with standard therapies in the treatment of major depressive disorder.
- Describe the mechanism of action of agents used as augmentation strategies in the treatment of MDD and their relationship to the neurobiology of depression.
- Evaluate the role of atypical antipsychotics, including their efficacy, safety and tolerability, as augmentation strategies in the management of MDD.

Who Will Benefit:

This activity was designed to meet the continuing education needs of psychiatrists and other physicians, physician assistants, registered nurses, and advanced practice psychiatric nurses. Other mental health professionals may find this activity informative and should check with their state licensing and certification boards to determine if it meets their continuing education requirements.

Disclosure

Dr. Thase is an advisor/consultant for AstraZeneca, Bristol-Myers Squibb Company, Cephalon, Inc., Cyberonics, Inc., Eli Lilly and Company, GlaxoSmithKline, Janssen, L.P., MedAvante, Inc., Neuronetics, Inc., Novartis Pharmaceuticals Corporation, Organon Pharmaceuticals USA Inc., Sepracor, Inc., Shire Pharmaceuticals, Inc., Supernus Pharmaceuticals, Inc., and Wyeth Pharmaceuticals. He is on the Speakers Bureau for AstraZeneca, Bristol-Myers Squibb Company, Cyberonics, Inc., Eli Lilly and Company, GlaxoSmithKline, Organon Pharmaceuticals USA Inc., sanofi-aventis U.S. Inc., and Wyeth Pharmaceuticals. He has equity holdings in MedAvante, Inc. Dr. Thase has provided expert testimony for Jones Day (Wyeth Pharmaceuticals litigation) and Phillips Lytle (GlaxoSmithKline litigation), and he receives royalty, patent and other income from American Psychiatric Publishing, Inc., Guilford Publications, and Herald House. Dr. Thase's wife is a Senior Medical Director at Advogent (formerly Cardinal Health).

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Introduction

by Michael E. Thase, MD

Major depressive disorder (MDD) is one of the world's greatest public health problems. Early recognition and prompt treatment to full remission represent the best method to reduce the suffering, morbidity and disability associated with this common illness.¹ Unfortunately, although a large number of proven treatments for MDD are available, no particular therapy is effective for more than one-half of patients with depression receiving outpatient care and about 20% will remain depressed despite three or four courses of treatment.² The process of finding the right treatment is complicated by the lack of reliable means for matching patients to specific interventions. For some, there is no alternative to an iterative, "trial and error" approach in which choices follow an algorithmic process typically moving from the newer first- and second-line medications to older antidepressants to various combinations of antidepressants and augmentation strategies.³

Results of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study generally supported the utility of this type of approach. For patients who did not respond to an initial course of citalopram (Celexa) therapy, STAR*D included a comparison of switching antidepressants (the SSRI sertraline [Zoloft] versus the serotonin norepinephrine reuptake inhibitor [SNRI] extended-release venlafaxine [Effexor XR] versus sustained-release bupropion [Wellbutrin SR]) and a comparison of two augmentation strategies (adding either bupropion SR or buspirone [BuSpar] to ongoing citalopram therapy). There were no significant differences among these therapies on the primary outcome measures.^{4,5} Patients who received bupropion or buspirone in combination with citalopram tended to have the best outcomes,^{4,5} although the novel approach to treatment assignment chosen by the investigators precluded direct comparisons with the switch strategies. In later phases of the STAR*D algorithm, other augmentation strategies (lithium [Eskalith, Lithobid] and thyroid hormone) and the combination of venlafaxine and mirtazapine (Remeron) were evaluated; again no significant differences were found.^{6,7}

Although switching medications is certainly the most

parsimonious approach to management of antidepressant response, clinicians often opt for augmentation strategies because of ease of implementation: no wash-out is required. Other "add-ons" used in contemporary practice include psychostimulants and atypical antipsychotics. Use of the former strategy is curbed by the fact that psychostimulants are controlled substances; concerns about cost, the potential for metabolic complications and uncertainty about longer-term risks of tardive dyskinesia necessarily limit use of the latter strategy. Nevertheless, there is evidence that adding an atypical antipsychotic can rapidly help a significant number of antidepressant non-responders,^{8,9} and this strategy is increasingly used. With these issues in mind, a brief review of recent controlled studies of augmentation therapy of atypical antipsychotics has been undertaken.

References

1. Kessler RC, Merikangas KR, Wang PS. Prevalence, comorbidity, and service utilization for mood disorders in the United States at the beginning of the twenty-first century. *Annu Rev Clin Psychol*. 2007;3:137-158.
2. Rush AJ, Trivedi MH, Wisniewski SR et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. 2006;163(11):1905-1917.
3. Thase ME. Therapeutic alternatives for difficult-to-treat depression: a narrative review of the state of the evidence. *CNS Spectr*. 2004;9(11):808-816, 818-821.
4. Rush AJ, Trivedi MH, Wisniewski SR et al.; STAR*D Study Team. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. *N Engl J Med*. 2006;354(12):1231-1242 [see comments].
5. Trivedi MH, Fava M, Wisniewski SR et al.; STAR*D Study Team. Medication augmentation after the failure of SSRIs for depression. *N Engl J Med*. 2006;354(12):1243-1252 [see comments].
6. McGrath PJ, Stewart JW, Fava M et al. Tranylcypromine versus venlafaxine plus mirtazapine following three failed antidepressant medication trials for depression: a STAR*D report. *Am J Psychiatry*. 2006;163(9):1531-1541 [see comments].
7. Nierenberg AA, Fava M, Trivedi MH et al. A comparison of lithium and T(3) augmentation following two failed medication treatments for depression: a STAR*D report. *Am J Psychiatry*. 2006;163(9):1519-1530 [see comment].
8. Thase ME, Corya SA, Osuntokun O et al. A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, and fluoxetine in treatment-resistant major depressive disorder. *J Clin Psychiatry*. 2007;68(2):224-236.
9. Shelton RC, Tollefson GD, Tohen M et al. A novel augmentation strategy for treating resistant major depression. *Am J Psychiatry*. 2001;158(1):131-134 [see comment]. ■

The Goals of Therapy in the Treatment of Major Depressive Disorder: Current Remission Rates

ABSTRACT

Remission of depression, rather than improvement in symptom severity, is increasingly emphasized as the principal goal of antidepressant therapy. Some experts also advocate complete recovery, with full restoration of psychosocial function, as the ultimate goal of therapy.

Clinical trials of antidepressant medications have traditionally focused on improvement in the severity of depressive symptoms as evidence of treatment effectiveness. These studies have often defined a clinically significant response to therapy as a reduction of at least 50% from pretreatment on a standardized depression rating scale, such as the Hamilton Rating Scale for Depression (HAM-D) or the Montgomery-Asberg Depression Rating Scale (MADRS).¹ However, many participants classified as responders using these criteria have residual depressive symptoms, which predict a greater likelihood of several undesirable outcomes, including depression recurrence, suicide and complications associated with other medical conditions. Clinical trials of major depressive disorder (MDD) thus should target remission, a more exacting therapeutic outcome (i.e., a final score of ≤ 7 on the 17-item HAM-D, a score < 10 on the 21-item HAM-D or a score of 1 on the Clinical Global Impression [CGI]¹ scale).^{1,2}

Residual Depressive Symptoms and the Goals of Therapy

The persistence of residual symptoms due to partial or incomplete remission following antidepressant therapy is associated with significant morbidity and mortality, including persistent impairment of normal psychosocial functioning.^{1,3} For example, Papakostas and colleagues⁴ examined the impact of residual depressive symptoms on psychosocial function in 222 patients with MDD who were treated with the selective serotonin reuptake inhibitor fluoxetine (Prozac). Compared with responders showing residual symptoms, patients who were in remission following fluoxetine treatment had signifi-

cantly better scores on a rating scale of psychosocial functioning (Social Adjustment Scale-Self-Report [SAS-SR]), including patient self-reported ability to work outside the home, interactions with family members and economic functioning. Miller et al.⁵ likewise found the same pattern of results in a study of chronic depression, with the remitting group achieving SAS-SR scores comparable to community norms and the nonremitting responders scoring closer to the nonresponders than “normal.”

Incomplete remission also heralds a stormier longitudinal course. Prospective studies of depression recurrence among patients who were treated to euthymia following an index depressive episode have found that the presence of residual symptoms after treatment is a significant predictor of depression recurrence.^{6,7} In a study by Judd and colleagues,⁸ the negative prognostic value of residual symptoms held true across 10 years of follow-up. Persistent residual symptoms after pharmacotherapy for MDD have also been associated with a number of other adverse outcomes, including increased suicide risk and higher rates of complications caused by comorbid medical conditions.⁹ Treatment to full remission, rather than symptomatic improvement, thus may represent the best strategy to improve patient functioning and reduce the risk of depression recurrence.^{1,2,10}

Some experts have further advocated that remission is only a short-term goal and that complete and sustained recovery from depression is the ultimate goal of therapy for patients with MDD.³ Recovery differs from remission in terms of the duration of symptomatic improvement, long-term normalization of psychosocial function and restoration of the patient's sense of well-being.³ Given the likelihood of full and partial symptomatic relapse, not all patients who remit go on to fully recover.

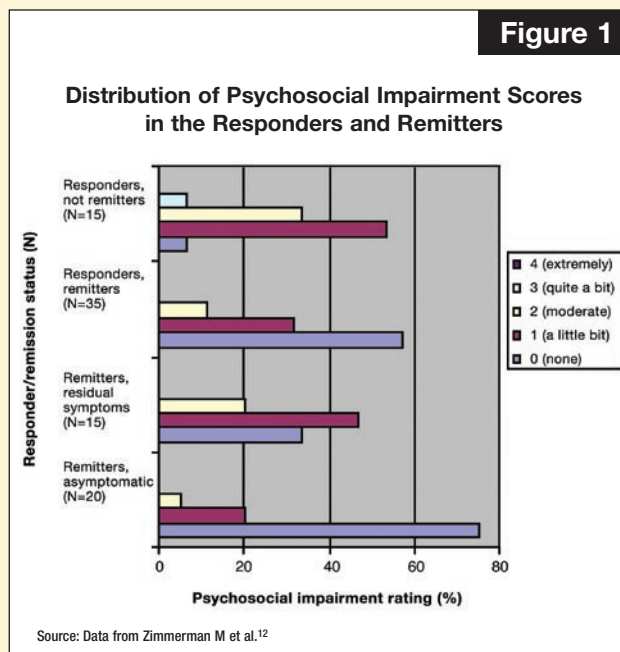
As the concept of remission has gained increasing acceptance, greater attention is being paid to its definition. One relevant observation has been that many patients who meet current definitions of remission continue to exhibit low, albeit persistent residual depressive symptoms, especially anxiety and somatic complaints.¹¹ The results of a recent prospective study suggest that these persistent depressive symptoms contribute to continuing impairment of normal functioning even for patients who meet the conventional criteria for remis-

sion.¹² These investigators found that among a group of 303 patients who achieved remission following antidepressant therapy (defined as a reduction in HAM-D score ≤ 7), psychosocial disability was lower for patients with extremely low residual symptoms (defined as HAM-D scores = 0-2) than for remitted patients who had a higher level of residual symptoms (defined as HAM-D scores > 2-7). Patients were asked to rate the extent to which their depressive symptoms interfered with their normal activities during the preceding week on a scale from 0 (no disability) to 4 (extreme disability). As shown in **Figure 1**, patients who attained remission reported less disability than patients who responded to treatment without attaining remission, but disability was lowest for patients who remitted and who had few or no residual depressive symptoms (HAM-D score < 2 after treatment).

Another critical objective of depression therapy is the long-term prophylaxis against recurrent depressive episodes. Whereas a six- to nine-month course of continuation phase therapy is now considered to be the standard of care to protect against depressive relapse, an indefinite course of maintenance phase therapy is recommended for patients who are at high risk of recurrence.¹³ In practice, maintenance therapy is routinely recommended for patients who have suffered ≥ 3 lifetime episodes as well as some patients who have experienced two episodes within a short time period (i.e., within five years).

Remission Rates With Current Therapies

Given the importance of remission for both shorter- and longer-term outcomes, one current unmet need in therapeutics is driven home by the low rates of remission documented in contemporary studies of antidepressant therapy; only about 20% to 40% of patients with MDD achieve complete symptom remission with current first-line treatments.¹⁴ Somewhat higher remission rates have been reported in some studies of newer antidepressant medications, including 46% with bupropion extended-release (Wellbutrin XL),¹⁵ 40% to 44% with duloxetine (Cymbalta),^{16,17} 47% with escitalopram (Lexapro),¹⁸ and up to 49% with venlafaxine extended-release (Effexor XR).^{15,18,19} Caution is needed in interpreting these results because the absolute numbers are heavily depen-



dent on the remission rate on placebo, which in turn depends on the specific patient population studied and the duration and intensity of treatment. For example, a 57% remission rate for a novel medication in a study with a 45% remission rate for placebo is about the same as a 35% remission rate in a study with a 25% remission rate for placebo. Meta-analyses that have synthesized the results from individual studies have reported conflicting results, ranging from comparable remission rates across classes of antidepressants to a modest advantage for antidepressants that work through dual (i.e., enhancement of both noradrenergic and serotonergic) mechanisms.^{20,21} For example, one recent meta-analysis of large and comprehensive (including both published and unpublished) clinical trials that compared the efficacy of two or more active treatments after six weeks or longer found the highest remission rate with serotonin norepinephrine reuptake inhibitors (SNRIs) (49%), followed by tricyclic antidepressants (44%) and SSRIs (38%).²²

Several studies have demonstrated higher remission rates

Figure 2

Treatment Strategies/Substrategies and Options		
Level 2		
Treatment Options	SER BUP VEN CT	CIT + BUP CIT + BUS CIT + CT
Treatment Strategy	Switch	Augment
Level 2A		
Treatment Options	BUP VEN	
Treatment Strategy	Switch	
Level 3		
Treatment Options	MRT NTP	SER + Li or THY BUP + Li or THY VEN + Li or THY CIT + Li or THY
Treatment Strategy	Switch	Augment
Level 4		
Treatment Options	TCP VEN + MRT	
Treatment Strategy	Switch	

Source: Rush AJ, Fava M, Wisniewski SR et al.; STAR*D Investigators Group. Sequenced treatment alternatives to relieve depression (STAR*D): rationale and design. *Control Clin Trials*. 2004;25(1):119-142. Reprinted with permission.

when patients who achieve only partial remission of symptoms receive additional, adjunctive pharmacologic or non-pharmacologic therapies. One recent study reported a remission rate of 49% for patients treated with antidepressant medication and interpersonal psychotherapy, versus 34% with pharmacotherapy alone.²³ Another recent study achieved a 50% remission rate using a four-step treatment algorithm that included lithium (Eskalith, Lithobid) augmentation, monoamine oxidase inhibitors and electroconvulsive therapy.²⁴

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial has examined remission of MDD using a strategy in which patients with inadequate response to first-line therapy progress through a series of up to four increasingly intensive treatments.²⁵ In general, inadequate response was defined as the failure to attain remission at each treatment step. More than 4,000 patients with nonpsy-

chotic depression were enrolled and treated using the treatment strategy shown in **Figure 2**.²⁶ Patients with inadequate response to citalopram (Celexa) were randomized to Level 2 treatments, which include four options to switch therapy (sertraline [Zoloft], bupropion, venlafaxine or cognitive therapy) or three augmentation treatments (bupropion, buspirone [BuSpar] or cognitive therapy). Patients who received cognitive therapy at Level 2 and who required additional therapy were eligible for Level 2A options of venlafaxine or bupropion. Level 3 options included either a switch to mirtazapine (Remeron) or nortriptyline (Aventyl, Pamelor), or augmentation with lithium or thyroid hormone. Finally, patients who were still unable to attain remission were randomized to Level 4 options of tranylcypromine (Parnate) or the combination of venlafaxine plus mirtazapine.

In general, random assignment to therapy was used at each step, although patients also had the option to decline specific treatments. The trial was therefore intended to resemble the typical clinical practice setting more closely than a conventional randomized, controlled clinical trial. Overall, it was estimated that 67% of patients were able to achieve remission using this multistep approach.²⁵ For patients with the most treatment-resistant depression, who were unable to attain remission with at least three prior treatment strategies, the remission rate even with Level 4 therapies was relatively low (approximately 10%).²⁷ For these treatment-resistant patients, the remission rate tended to be greater for those who received the combination of venlafaxine and mirtazapine (13.7%) than with the MAOI tranylcypromine (6.9%), but the difference between the two groups was not statistically significant. Moreover, only a minority of the tranylcypromine-treated patients received truly adequate trials of the MAOI (i.e., at least six weeks at 60 mg/day), which indicates that better results might be obtained by specialists who were more comfortable prescribing MAOIs. Although this study demonstrates higher rates of remission than has been reported with single-agent therapy, it should be noted that approximately one-third of the patients enrolled in the STAR*D trial did not attain remission of their symptoms even with intensive regimens that included lithium augmentation, thyroid hormone and combinations of several antidepressant medications.

CONCLUSION

Complete remission of depressive symptoms is associated with better functional recovery and a decreased risk of depression recurrence. Despite the importance of remission, most patients fail to obtain complete remission of depression with current antidepressant medications and psychotherapies. Intensive combination therapy strategies, including augmentation with lithium, thyroid hormone, or cognitive or interpersonal therapies, improve remission rates. Even with these approaches, however, new therapy options and creative applications of existing strategies are needed for the patients who do not attain remission.

References

1. Bakish D. New standard of depression treatment: remission and full recovery. *J Clin Psychiatry*. 2001;62(suppl 26):5-9.
2. Thase ME. Achieving remission and managing relapse in depression. *J Clin Psychiatry*. 2003;64(suppl 18):3-7.
3. Fava GA, Ruini C, Belaise C. The concept of recovery in major depression. *Psychol Med*. 2007;37(3):307-317.
4. Papakostas GI, Petersen T, Denninger JW et al. Psychosocial functioning during the treatment of major depressive disorder with fluoxetine. *J Clin Psychopharmacol*. 2004;24(5):507-511.
5. Miller IW, Keitner GI, Schatzberg AF et al. The treatment of chronic depression, part 3: psychosocial functioning before and after treatment with sertraline or imipramine. *J Clin Psychiatry*. 1998;59(11):608-619.
6. Bockting CL, Spinhoven P, Koeter MW et al. Prediction of recurrence in recurrent depression and the influence of consecutive episodes on vulnerability for depression: a 2-year prospective study. *J Clin Psychiatry*. 2006;67(5):747-755.
7. Kanai T, Takeuchi H, Furukawa TA et al. Time to recurrence after recovery from major depressive episodes and its predictors. *Psychol Med*. 2003;33(5):839-845 [see comments].
8. Judd LL, Akiskal HS, Maser JD et al. A prospective 12-year study of sub-syndromal and syndromal depressive symptoms in unipolar major depressive disorders. *Arch Gen Psychiatry*. 1998;55(8):694-700.
9. Kennedy N, Foy K. The impact of residual symptoms on outcome of major depression. *Curr Psychiatry Rep*. 2005;7(6):441-446.
10. Rush AJ, Kraemer HC, Sackeim HA et al. Report by the ACNP Task Force on response and remission in major depressive disorder. *Neuropsychopharmacology*. 2006;31(9):1841-1853.
11. Vieta E, Sanchez-Moreno J, Lahuerta J, Zaragoza S; For the EDHIPO Group (Hypomania Detection Study Group). Subsyndromal depressive symptoms in patients with bipolar and unipolar disorder during clinical remission. *J Affect Disord*. 2007; [Epub ahead of print].
12. Zimmerman M, Posternak MA, Chelminski I. Heterogeneity among depressed outpatients considered to be in remission. *Compr Psychiatry*. 2007;48(2):113-117.
13. Nierenberg AA, Petersen TJ, Alpert JE. Prevention of relapse and recurrence in depression: the role of long-term pharmacotherapy and psychotherapy. *J Clin Psychiatry*. 2003;64(suppl 15):13-17.
14. Ng F, Dodd S, Berk M. Combination pharmacotherapy in unipolar depression. *Expert Rev Neurother*. 2006;6(7):1049-1060.
15. Thase ME, Clayton AH, Haight BR et al. A double-blind comparison between bupropion XL and venlafaxine XR: sexual functioning, antidepressant efficacy, and tolerability. *J Clin Psychopharmacol*. 2006;26(5):482-488.
16. Nierenberg AA, Greist JH, Mallinckrodt CH et al. Duloxetine versus escitalopram and placebo in the treatment of patients with major depressive disorder: onset of antidepressant action, a non-inferiority study. *Curr Med Res Opin*. 2007;23(2):401-416.
17. Nemeroff CB, Schatzberg AF, Goldstein DJ et al. Duloxetine for the treatment of major depressive disorder. *Psychopharmacol Bull*. 2002;36(4):106-132.
18. Montgomery SA, Andersen HF. Escitalopram versus venlafaxine XR in the treatment of depression. *Int Clin Psychopharmacol*. 2006;21(5):297-309.
19. Shelton RC, Haman KL, Rapaport MH et al. A randomized, double-blind, active-control study of sertraline versus venlafaxine XR in major depressive disorder. *J Clin Psychiatry*. 2006;67(11):1674-1681.
20. Thase ME, Entsuah AR, Rudolph RL. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *Br J Psychiatry*. 2001;178:234-241 [see comments].
21. Nemeroff CB, Entsuah R, Benattia I et al. Comprehensive analysis of remission (COMPARE) with venlafaxine vs SSRIs. *Biol Psychiatry*. In press.
22. Machado M, Iskedjian M, Ruiz I, Einarson TR. Remission, dropouts, and adverse drug reaction rates in major depressive disorder: a meta-analysis of head-to-head trials. *Curr Med Res Opin*. 2006;22(9):1825-1837.
23. Schramm E, van Calker D, Dykierk P et al. An intensive treatment program of interpersonal psychotherapy plus pharmacotherapy for depressed inpatients: acute and long-term results. *Am J Psychiatry*. 2007;164(5):768-777.
24. Birkenhager TK, van den Broek WW, Moleman P, Bruijn JA. Outcome of a 4-step treatment algorithm for depressed inpatients. *J Clin Psychiatry*. 2006;67(8):1266-1271.
25. Rush AJ, Trivedi MH, Wisniewski SR et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. 2006;163(11):1905-1917.
26. Rush AJ, Fava M, Wisniewski SR et al.; STAR*D Investigators Group. Sequenced treatment alternatives to relieve depression (STAR*D): rationale and design. *Control Clin Trials*. 2004;25(1):119-142.
27. McGrath PJ, Stewart JW, Fava M et al. Tranylcypromine versus venlafaxine plus mirtazapine following three failed antidepressant medication trials for depression: a STAR*D report. *Am J Psychiatry*. 2006;163(9):1531-1541 [see comments]. ■

The Relationship Between the Mechanism of Action of Augmenting Agents and the Neurobiology of Depression

ABSTRACT

Traditional models of the pathophysiology of MDD and the effects of antidepressants have emphasized the importance of neural circuits that are modulated by the neurotransmitters serotonin, norepinephrine and dopamine. More recently, investigators have examined the ways in which abnormal functioning of nerve growth factors may cause atrophy of specific brain regions and contribute to the symptoms of depression. These findings may have important implications for understanding the mechanisms by which various medications improve depressive symptoms when used to augment SSRIs or other antidepressant medications.

Serotonergic circuits of the central nervous system participate in the regulation of many physiological processes, including appetite, sexual behavior, mood, pain and responding to stressful stimuli.^{1,2} Studies of individuals with MDD and related disorders have demonstrated a number of abnormalities of serotonergic neurotransmission, including decreased levels of serotonin metabolites in cerebrospinal fluid (CSF) and decreased serotonin receptor binding in cortical regions that are densely innervated by serotonergic neurons.^{3,4} Genetic polymorphisms of the serotonin transporter have been linked to depressive symptoms and to structural brain alterations in patients with depression.⁵ Selective serotonin reuptake inhibitors block the function of the serotonin transporter, increase serotonergic activity and improve the symptoms of depression.⁶ Similarly, studies of CSF metabolites and brain imaging studies have demonstrated alterations of central dopaminergic and noradrenergic function among individuals with depressive disorders.⁷

Neuronal Growth Factors and Depression

Brain imaging studies using high-resolution magnetic resonance imaging have identified structural alterations that are associated with MDD and with responses to antidepressant therapy. It has been hypothesized that depressive symptoms

may be specifically related to atrophy of portions of the hippocampus, perhaps as a result of diminished expression of nerve growth factors, and that the alleviation of hippocampal atrophy may be one mechanism by which some antidepressant medications work.^{8,9} In one of the first studies to examine hippocampal atrophy in patients with MDD, high-resolution MRI analysis of hippocampal volume was performed in medically healthy patients with a history of MDD who were currently in remission. Compared with matched control participants, patients with a history of depression exhibited a mean reduction of 15% in left hippocampal volume ($P=0.003$) and a mean reduction of 11% in right hippocampal volume ($P=0.02$).¹⁰ Subsequent research demonstrated that hippocampal atrophy is generally greater for patients who have had MDD for longer periods of time,¹¹ and is significantly correlated with the lifetime number of untreated days of depression.¹²

Hippocampal atrophy among individuals with depression has been linked to disturbances of neurotrophic factors, especially to brain-derived neurotrophic factor (BDNF). Brain-derived neurotrophic factor is a neuronal growth factor that is widely distributed throughout the CNS, and that is thought to participate in the regulation of neuronal survival, migration, axon and dendrite development, synaptic plasticity, memory, and cognitive function.⁹ Brain-derived neurotrophic factor concentrations in serum or plasma are significantly associated with depressive symptoms and with response to antidepressant therapy. A recent study of serum BDNF concentrations in 111 patients with depression and 107 matched control participants found that patients with depression had lower mean BDNF concentrations than the control participants.¹³ This effect was observed for women but not men, although only 20 of the 111 patients with depression enrolled in the study were men. Over a four-week follow-up period, patients who received antidepressant medications exhibited significantly greater mean BDNF concentrations than untreated patients. This effect was observed only among patients who responded to therapy; patients who did not improve with antidepressant therapy exhibited no increase in BDNF concentration from baseline.

A prospective clinical study examined the effects of paroxetine (Paxil) and the SNRI milnacipran on BDNF concentrations in patients with depression.¹⁴ As shown in the **Figure**, higher pretreatment HAM-D scores were significantly associated with lower baseline serum BDNF concentrations.

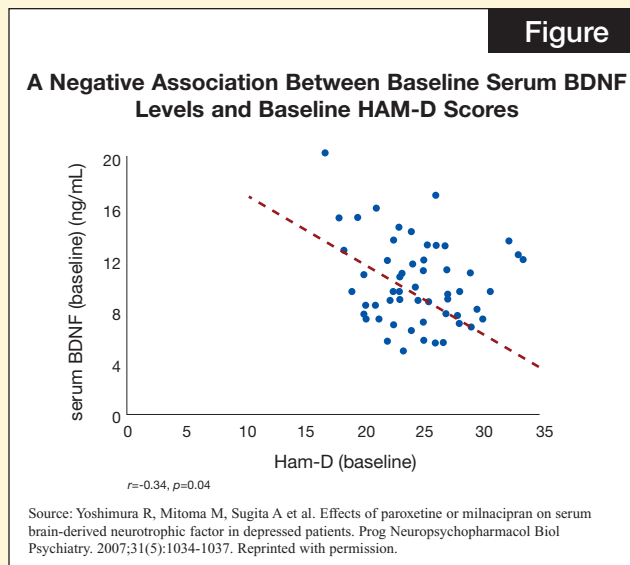
Among treatment responders, serum BDNF increased 2.6-fold and 1.8-fold from baseline with paroxetine and milnacipran, respectively. Brain-derived neurotrophic factor values increased only slightly from baseline in patients who did not respond to antidepressant therapy. For both paroxetine-treated and milnacipran-treated patients, responders had significantly higher BDNF values than nonresponders after eight weeks of treatment (Table). These findings suggest that increased expression of BDNF may be an important mechanism by which antidepressants produce their effects.⁹

Biological Mechanisms

Medications that are used to augment antidepressant therapy include lithium (Eskalith, Lithobid), thyroid hormone and atypical antipsychotics.¹⁵ Recent studies have begun to identify possible mechanisms by which these agents improve depressive symptoms when combined with conventional antidepressants. These agents may act at physiological targets that are distinct from the targets of conventional antidepressant drugs, possibly creating the opportunity for additive or synergistic effects when they are used for antidepressant augmentation.

Crossley and Bauer¹⁶ recently performed two meta-analyses of the efficacy of lithium for the augmentation of antidepressant therapy. One analysis demonstrated that patients who had not responded adequately to a variety of antidepressants were much more likely to respond to lithium treatment than to placebo (odds ratio, 3.11; $P < 0.0001$). The other analysis revealed that augmentation with lithium also decreased the time required for a response to antidepressant treatment, although this effect was not as robust. It is of course true that the therapeutic benefit of lithium may be derived from two different clinical pathways, one by enhancing the neurochemical effects of the antidepressant, the other by a primary antidepressant effect. In the latter case, better responses might be expected in studies that include a larger number of patients with depressions that fall within the bipolar spectrum (e.g., Thase et al.¹⁷).

The beneficial effects of lithium augmentation have been attributed by some experts to activity at central serotonergic receptors, possibly creating a synergistic interaction between antidepressants and lithium on serotonergic function. Lithium administration has been shown to increase prolactin release in response to the serotonin precursor L-tryptophan; increase plasma cortisol concentration when administered with the



serotonin agonist fenfluramine; and increase the plasma concentration of serotonin metabolites when combined with antidepressant therapy.¹⁸ Animal studies have also demonstrated heightened serotonergic activity in animals that received lithium in combination with TCAs, MAOIs or SSRIs.¹⁹

It is possible that lithium may also affect serotonergic function by means of a neurotrophic effect, perhaps by increasing the expression of BDNF. In animal models, lithium has been shown to induce the expression of BDNF and to activate receptors for BDNF in cortical neurons.²⁰ The importance of these neuroprotective or neurotrophic effects in patients with depression has not yet been clearly established.

Atypical antipsychotics improve psychotic symptoms in patients with schizophrenia and related disorders, with a generally lower risk of extrapyramidal motor effects than the conventional antipsychotics (e.g., haloperidol [Haldol]). The lower incidence of motor adverse effects with these agents has been attributed to reduced chronic blockade of central dopamine D₂ receptors.²¹ As described in more detail in the next discussion, “The Efficacy and Safety of Atypical Antipsychotics as Augmentation Strategies in the Treatment of Major Depressive Disorder,” controlled clinical trials have demonstrated that atypical antipsychotics significantly improve the response to antidepressant therapy for patients who do not initially respond.

Table

Serum BDNF Levels Before and 8 Weeks After Treatment

	0 week (ng/mL)	4 week (ng/mL)	8 week (ng/mL)
Paroxetine (responder)	9.1±7.7	11.6±8.3	22.0±8.5*
Paroxetine (nonresponder)	9.6±8.0	9.9±8.4	13.8±6.7
Milnacipran (responder)	9.9±9.0	10.9±7.9	18.2±9.1*
Milnacipran (nonresponder)	9.6±6.4	9.6±7.2	13.4±7.1
Control	23.4±10.1	None	None

Source: Yoshimura R, Mitoma M, Sugita A et al. Effects of paroxetine or milnacipran on serum brain-derived neurotrophic factor in depressed patients. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007;31(5):1034-1037. Reprinted with permission.

The precise mechanism by which these agents improve depressive symptoms is not known, but several possibilities have been suggested.

The atypical antipsychotics generally act as potent antagonists of 5-HT₂ receptors, and of the 5-HT_{2A} subtype in particular.²¹ The combination of serotonergic antidepressants and atypical antipsychotics may improve depression, at least in part, by stimulating central noradrenergic activity. Inhibitory 5-HT_{2A} receptors of the locus ceruleus normally suppress noradrenergic outflow throughout the brain, and blocking these receptors may therefore release this inhibition.⁶ This hypothesis implies that other antidepressant medications that block 5-HT_{2A} receptors would also improve depressive symptoms when used to augment SSRIs for treatment-resistant patients. Placebo-controlled clinical trials have demonstrated significant beneficial effects of antidepressant augmentation with both mirtazapine (Remeron) and nefazodone.^{22,23}

Individual atypical antipsychotics also modulate the effects of several different neurotransmitter systems, including other 5-HT receptor subtypes.²¹ Ziprasidone (Geodon) has high affinity for several 5-HT receptor subtypes, including 5-HT_{1A} and 5-HT_{2A} receptors, and acts as serotonin/norepinephrine reuptake blocker.^{24,25} Aripiprazole (Abilify) is a 5-HT_{1A} partial agonist.²⁶ Quetiapine (Seroquel) acts at 5-HT_{1A} receptors and also increases noradrenergic activity.²⁷ Activation of dopamine receptors in prefrontal cortical regions has also been proposed as a possible mechanism for both the improve-

ment in negative symptoms of schizophrenia and depressive symptoms with these agents.²⁸ In contrast with other atypical antipsychotics, aripiprazole acts as partial D₂ receptor agonist, perhaps contributing to its antidepressant effects.²⁹

Atypical antipsychotics may also produce other effects that contribute to their antidepressant efficacy. For example, some atypical antipsychotics, including ziprasidone, clozapine (Clozaril), olanzapine (Zyprexa) and quetiapine, have been shown to reduce serum cortisol in healthy participants, suggesting decreased activation of the hypothalamic-pituitary axis (HPA).^{25,30,31} The conventional antipsychotic haloperidol did not decrease cortisol secretion.³¹ Research from animal models suggests that the atypical antipsychotics also stimulate the expression of neurotrophic factors, including BDNF. Several studies have used an experimental model in which stress associated with chronic restraint decreases BDNF expression and promotes hippocampal atrophy in rats. These studies have found that atypical antipsychotics prevent the stress-induced decrease in BDNF expression and hippocampal atrophy.^{32,33} In contrast, animal model studies have suggested that conventional antipsychotics such as haloperidol may actually decrease brain BDNF activity.³⁴ These animal studies suggest that alterations in growth factor expression or activity may contribute to the effects of the atypical antipsychotics in depression and other psychiatric conditions, although no studies have specifically examined these issues in patients with

CONCLUSION

It is generally accepted that depressive symptoms reflect abnormal functioning of CNS pathways that are modulated by serotonin, norepinephrine and—to a lesser extent—dopamine. Depressive symptoms may also be related to diminished expression of nerve growth factors, especially BDNF, resulting in hippocampal atrophy. Low levels of BDNF predict more severe depressive symptoms, and increasing BDNF concentrations with antidepressant therapy parallel clinical responding. Atypical antipsychotics affect a broad range of serotonin receptors, and may also indirectly modulate other neurotransmitter systems.

depression.

References

- Gorman JM, Kent JM. SSRIs and SNRIs: broad spectrum of efficacy beyond major depression. *J Clin Psychiatry*. 1999;60(suppl 4):33-38.
- Firk C, Markus CR. Serotonin by stress interaction: a susceptibility factor for the development of depression? *J Psychopharmacol*. 2007;21(5):538-544.
- Owens MJ, Nemeroff CB. Role of serotonin in the pathophysiology of depression: focus on the serotonin transporter. *Clin Chem*. 1994;40(2):288-295.
- Fujita M, Charney DS, Innis RB. Imaging serotonergic neurotransmission in depression: hippocampal pathophysiology may mirror global brain alterations. *Biol Psychiatry*. 2000;48(8):801-812.
- Frodl T, Schule C, Schmitt G et al. Association of the brain-derived neurotrophic factor Val66Met polymorphism with reduced hippocampal volumes in major depression. *Arch Gen Psychiatry*. 2007;64(4):410-416.
- Blier P, Szabo ST. Potential mechanisms of action of atypical antipsychotic medications in treatment-resistant depression and anxiety. *J Clin Psychiatry*. 2005;66(suppl 8):30-40.
- Nutt DJ. The role of dopamine and norepinephrine in depression and antidepressant treatment. *J Clin Psychiatry*. 2006;67(suppl 6):3-8.
- Schmidt HD, Duman RS. The role of neurotrophic factors in adult hippocampal neurogenesis, antidepressant treatments and animal models of depressive-like behavior. *Behav Pharmacol*. 2007;18(5-6):391-418.
- Martinowich K, Lu B. Interaction between BDNF and serotonin: role in mood disorders. *Neuropsychopharmacology*. 2007;[Epub ahead of print].
- Sheline YI, Wang PW, Gado MH et al. Hippocampal atrophy in recurrent major depression. *Proc Natl Acad Sci U S A*. 1996;93(9):3908-3913.
- Sheline YI, Sanghavi M, Mintun MA, Gado MH. Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. *J Neurosci*. 1999;19(12):5034-5043.
- Sheline YI, Gado MH, Kraemer HC. Untreated depression and hippocampal volume loss. *Am J Psychiatry*. 2003;160(8):1516-1518 [see comment].
- Huang TL, Lee CT, Liu YL. Serum brain-derived neurotrophic factor levels in patients with major depression: effects of antidepressants. *J Psychiatr Res*. 2007;[Epub ahead of print].
- Yoshimura R, Mitoma M, Sugita A et al. Effects of paroxetine or milnacipran on serum brain-derived neurotrophic factor in depressed patients. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007;31(5):1034-1037.
- DeBattista C. Augmentation and combination strategies for depression. *J Psychopharmacol*. 2006;20(3 suppl):11-18.
- Crossley NA, Bauer M. Acceleration and augmentation of antidepressants with lithium for depressive disorders: two meta-analyses of randomized, placebo-controlled trials. *J Clin Psychiatry*. 2007;68(6):935-940.
- Thase ME, Kupfer DJ, Frank E, Jarrett DB. Treatment of imipramine-resistant recurrent depression: II. An open clinical trial of lithium augmentation. *J Clin Psychiatry*. 1989;50(11):413-417.
- Birkenhager TK, van den Broek WW, Fekkes D et al. Lithium addition in antidepressant-resistant depression: effects on platelet 5-HT, plasma 5-HT and plasma 5-HIAA concentration. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007;31(5):1084-1088.
- Haddjeri N, Szabo ST, de Montigny C, Blier P. Increased tonic activation of rat forebrain 5-HT(1A) receptors by lithium addition to antidepressant treatments. *Neuropsychopharmacology*. 2000;22(4):346-356.
- Hashimoto R, Takei N, Shimazu K et al. Lithium induces brain-derived neurotrophic factor and activates TrkB in rodent cortical neurons: an essential step for neuroprotection against glutamate excitotoxicity. *Neuropharmacology*. 2002;43(7):1173-1179.
- Wood MD, Scott C, Clarke K et al. Pharmacological profile of antipsychotics at monoamine receptors: atypicality beyond 5-HT2A receptor blockade. *CNS Neurol Disord Drug Targets*. 2006;5(4):445-452.
- Carpenter LL, Yasmin S, Price LH. A double-blind, placebo-controlled study of antidepressant augmentation with mirtazapine. *Biol Psychiatry*. 2002;51(2):183-188.
- Taylor FB, Prather MR. The efficacy of nefazodone augmentation for treatment-resistant depression with anxiety symptoms or anxiety disorder. *Depress Anxiety*. 2003;18(2):83-88.
- Patel NC, Keck PE Jr. Ziprasidone: efficacy and safety in patients with bipolar disorder. *Expert Rev Neurother*. 2006;6(8):1129-1138.
- Meier A, Neumann AC, Jordan W et al. Ziprasidone decreases cortisol excretion in healthy subjects. *Br J Clin Pharmacol*. 2005;60(3):330-336.
- Stark AD, Jordan S, Allers KA et al. Interaction of the novel antipsychotic aripiprazole with 5-HT1A and 5-HT 2A receptors: functional receptor-binding and in vivo electrophysiological studies. *Psychopharmacology (Berl)*. 2007;190(3):373-382.
- McIntyre RS, Soczynska JK, Woldeyohannes HO et al. A preclinical and clinical rationale for quetiapine in mood syndromes. *Expert Opin Pharmacother*. 2007;8(9):1211-1219.
- Quintin P, Thomas P. [Efficacy of atypical antipsychotics in depressive syndromes.] *Encephale*. 2004;30(6):583-589.
- Garcia-Amador M, Pacchiarotti I, Valenti M et al. Role of aripiprazole in treating mood disorders. *Expert Rev Neurother*. 2006;6(12):1777-1783.
- Cohrs S, Pohlmann K, Guan Z et al. Quetiapine reduces nocturnal urinary cortisol excretion in healthy subjects. *Psychopharmacology (Berl)*. 2004;174(3):414-420.
- Cohrs S, Roher C, Jordan W et al. The atypical antipsychotics olanzapine and quetiapine, but not haloperidol, reduce ACTH and cortisol secretion in healthy subjects. *Psychopharmacology (Berl)*. 2006;185(1):11-18.
- Xu H, Chen Z, He J et al. Synergistic effects of quetiapine and venlafaxine in preventing the chronic restraint stress-induced decrease in cell proliferation and BDNF expression in rat hippocampus. *Hippocampus*. 2006;16(6):551-559.
- Luo C, Xu H, Li XM. Quetiapine reverses the suppression of hippocampal neurogenesis caused by repeated restraint stress. *Brain Res*. 2005;1063(1):32-39.
- Parikh V, Khan MM, Mahadik SP. Olanzapine counteracts reduction of brain-derived neurotrophic factor and TrkB receptors in rat hippocampus produced by haloperidol. *Neurosci Lett*. 2004;356(2):135-139. ■

The Efficacy and Safety of Atypical Antipsychotics as Augmentation Strategies in the Treatment of Major Depressive Disorder

ABSTRACT

Evidence supporting the use of atypical antipsychotics for augmentation of antidepressant therapy has grown substantially in the last few years. A recent meta-analysis of randomized, controlled clinical trials demonstrated substantially higher rates of response and remission for treatment-resistant patients who received augmentation with olanzapine (Zyprexa), quetiapine (Seroquel) or risperidone (Risperdal). Recent clinical trials of aripiprazole (Abilify), quetiapine and risperidone have provided more evidence for the efficacy and safety of these agents for antidepressant augmentation.

Atypical antipsychotics have long been used to augment antidepressant medications for treatment-resistant patients, but controlled clinical trials demonstrating the efficacy of this strategy have appeared only during the last few years.¹ A recent meta-analysis examined the effectiveness of augmentation with the atypical antipsychotics olanzapine, risperidone and quetiapine using data from 1,500 patients with treatment-resistant MDD who were enrolled in 10 randomized, double-blind clinical trials. The response and remission rates for patients who were randomized to augmentation with an atypical antipsychotic were approximately double those of placebo-treated patients (**Figure**). No randomized, controlled clinical trials of aripiprazole or ziprasidone (Geodon) had been reported when this meta-analysis was conducted. More recent studies have demonstrated the efficacy of aripiprazole augmentation in treatment-resistant patients, and they have also added to the information available about augmentation with other atypical antipsychotics.

Efficacy of Atypical Antipsychotic Augmentation in Recent Clinical Trials

In the first of two posters reprinted here, which was presented at the 2007 Annual Meeting of the American Psychiatric Association in San Diego, Berman and colleagues examined the efficacy and safety of the atypical antipsychotic aripiprazole, in comparison with placebo, as adjunctive therapy

for patients who failed to respond adequately to antidepressant therapy and who had a previous history of treatment failure to at least one other antidepressant regimen. A total of 362 patients were randomized to treatment with placebo or aripiprazole at doses of 2 mg/day to 20 mg/day for six weeks. Aripiprazole treatment was associated with improvement on several clinical outcomes, including the rate of remission. As shown in **Poster Figures 4a** and **4b**, significant response to treatment was noted as early as the first week of therapy, compared with placebo, whereas a significant increase in the proportion of patients who attained remission was noted after three weeks. Aripiprazole treatment was also associated with significantly greater improvement from baseline than placebo for the MADRS mean score and for scores on the CGI-Severity (CGI-S) depression rating scales.

A separate analysis of data from this study, also presented at the 2007 Annual Meeting of the APA, described the effects of aripiprazole augmentation on patient functional abilities, which were assessed using the Sheehan Disability Scale (SDS).² The SDS is a three-item patient rating scale that assesses ability to function at work or school, in social interactions, and with family. It is scored on a scale of 0 (no disability) to 10 (extreme disability). When the data were analyzed using a last-observation-carried-forward (LOCF) approach, in which missing values for patients who discontinued the study prematurely were carried forward from their last observation, improvement from baseline for patient scores on the SDS tended to be greater with aripiprazole (mean improvement, 1.11 points) than with placebo (0.65 points), although this difference was not quite statistically significant ($P=0.055$). When the data were analyzed using only observed cases (OC) at each follow-up evaluation, improvement in SDS from baseline was significantly greater with aripiprazole (mean improvement, 1.17 points) than with placebo (0.64 points; $P=0.037$). These results suggest that augmentation with an atypical antipsychotic may improve patient functioning as well as scores on depression rating scales.

In the second poster shown here, which was presented at the 2006 Annual Meeting of the APA, Mattingly and colleagues examined augmentation with quetiapine for patients with persistent depressive symptoms (HAM-D score ≥ 20) after six weeks of antidepressant therapy. A total of 40 patients were randomized to eight weeks of double-blind placebo or quetiapine at doses of 200 mg/day to 400 mg/day, in combination with

ongoing therapy with either an SSRI or SNRI. As shown in **Poster Figure 4**, the proportion of patients who attained remission after eight weeks was significantly greater for patients who received quetiapine than placebo ($P<0.05$). Treatment response was also noted for more patients with quetiapine.

As shown in **Poster Figures 2 and 3**, quetiapine was also associated with significantly greater improvement than placebo on other measures of depressive symptom severity, including mean MADRS score and CGI ratings of severity and improvement. Quetiapine was recently approved by the FDA for use as monotherapy for patients with bipolar depression.

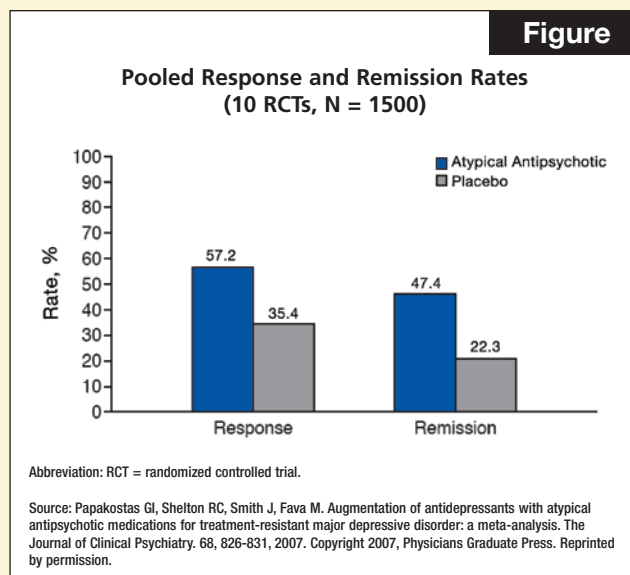
Other recent studies have also examined augmentation with atypical antipsychotic agents for patients with depressive disorders. An open-label study examined the efficacy of aripiprazole for eight weeks in 15 patients with no response or a partial response to antidepressant therapy after at least eight weeks of treatment.³ Six of the 15 patients achieved remission of depression (HAM-D score ≤ 7) after one week of treatment, and nine of the 15 patients achieved remission after two weeks. The study was completed by eight patients, all of whom exhibited remission of their depression by the end of the study.

A second open-label study examined the effects of aripiprazole on residual anxiety symptoms in patients who were taking SSRIs for depression or anxiety disorders.⁴ A total of 10 patients with persistent anxiety after at least six weeks of SSRI treatment were treated with open-label aripiprazole. After two weeks of treatment, eight of the 10 patients exhibited an improvement in anxiety of at least 50% on the Hamilton Rating Scale for Anxiety (HAM-A).

McIntyre and colleagues⁵ performed a double-blind, placebo-controlled clinical trial of quetiapine augmentation in 58 patients with MDD and comorbid anxiety disorders who had persistent symptoms following treatment with SSRIs or venlafaxine (Effexor) for at least six weeks. Mean scores on the HAM-D improved from baseline by an average of 11.2 points with quetiapine versus 5.5 points with placebo ($P=0.008$). Anxiety symptoms, which were measured using the HAM-A, also improved significantly more with quetiapine than with placebo (mean improvement of 12.5 versus 5.9 points for the quetiapine and placebo groups, respectively; $P=0.002$). The incidence of remission of depressive symptoms tended to be higher with quetiapine than with placebo (31% versus 17% after eight weeks), although this difference was not statistically

significant.

The efficacy of risperidone for antidepressant augmentation was examined in a three-part clinical trial of patients with MDD who had failed to respond previously to one to three different antidepressant medications.⁶ The patients were initially treated with citalopram (Celexa) for four to six weeks. Patients who did not improve by at least 50% on the HAM-D from baseline received open-label augmentation with risperidone for four to six weeks. Patients who attained remission during the open-label portion of the study entered a double-blind, randomized, discontinuation phase in which they received risperidone or placebo for 24 weeks. A total of 489 patients began the trial; 434 patients exhibited an inadequate response to citalopram treatment and entered the open-label risperidone phase. Of these, 241 patients remitted and entered the double-blind phase, during which patients received either placebo or risperidone. The study primary end point—the time to relapse in the 24-week, double-blind discontinuation phase—did not differ between the risperidone and placebo groups. The median time to relapse was 102 days for patients who received risperidone and 85 days with placebo (not statistically significant). The authors did note a significantly longer time to relapse in patients who were fully nonresponsive to citalopram mono-



therapy, which was defined as an improvement of less than 25% on the HAM-D during the initial citalopram monotherapy phase of the study. In this subgroup of patients, risperidone was associated with a lower overall relapse rate (64.1% versus 56.1%; $P \leq 0.05$) and longer median time to relapse (97 days versus 56 days; $P = 0.05$).

Antidepressant augmentation with ziprasidone was examined in a single-group, open-label study of 20 patients with SSRI-resistant MDD.⁷ Clinical response was defined as a reduction in HAM-D score of at least 50% from baseline. When analyzed on an intent-to-treat basis, 10 of the patients (50%) responded to augmentation with ziprasidone. The trial was completed by 13 patients. An analysis of only the completers found that eight patients (61.5%) met criteria for treatment response. The proportion of patients who achieved remission was five of 20 patients for the intent-to-treat analysis (25.0%), and five of 13 patients using the completer analysis (38.5%).

Few data are available to suggest which subgroups of patients might be most likely to benefit from augmentation with atypical antipsychotics. In the large clinical trial of risperidone described previously, long-term risperidone therapy was more effective than placebo at preventing depression relapse in patients who had the poorest initial response to antidepressant therapy.⁶ It is possible that other patient factors may predict an increased likelihood of responding to augmentation with an atypical antipsychotic agent, such as the presence of psychotic features, a family history of schizophrenia or even biochemical measures. At present, potential predictive factors are not well defined.

Safety and Tolerability of Augmentation

Atypical antipsychotics have the potential to produce a number of adverse effects, including extrapyramidal motor symptoms, sedation, tardive dyskinesia, weight gain and metabolic syndrome.¹ In the 10-trial meta-analysis, the rate of discontinuations due to adverse events was greater with atypical antipsychotic augmentation than with placebo, by approximately a factor of three. It should be noted that none of the studies in this meta-analysis extended beyond 12 weeks, and most were only four to eight weeks in duration. Therefore, it is important to note that conclusions regarding the long-term risk of weight

gain and/or metabolic syndrome with combination therapy cannot be drawn from this meta-analysis. In addition, weight gain or changes in glycemic control were not specifically assessed in this meta-analysis. Recent recommendations from the American Diabetes Association and other groups now urge psychiatrists to monitor these metabolic effects carefully in patients taking atypical antipsychotics.⁸

In the Posters presented here, atypical antipsychotics were generally well-tolerated by patients when used in combination with antidepressants, although adverse effects that are characteristic of the atypical antipsychotics were noted more often for patients who received augmentation. In the Poster by Berman and colleagues, aripiprazole was well-tolerated by the patients, with a low rate of discontinuations due to adverse effects. Adverse events that were related to extrapyramidal motor symptoms (mostly akathisia) were reported by 9.7% of patients who received placebo and 27.5% of patients who received aripiprazole augmentation. Although the incidence of akathisia was significantly higher with aripiprazole than with placebo, only one patient discontinued the study for this reason. Aripiprazole was also associated with more weight gain than placebo.

In the Poster by Mattingly and colleagues, the incidence of extrapyramidal symptoms and akathisia were not reported. Patient scores on rating scales of abnormal motor events were similar for the two groups, although the number of patients enrolled was relatively small. Weight gain was noted with quetiapine (mean increase, approximately 3 kg) but not for the placebo group.

Although none of the atypical antipsychotics is currently FDA-approved for augmentation of antidepressant therapy in patients with MDD, the manufacturers of both the olanzapine-fluoxetine combination (Symbyax) and aripiprazole have applied to the FDA for this indication. Pending the FDA's formal review, the studies reviewed here do suggest that these agents have therapeutic potential for at least a subset of patients with difficult-to-treat depression and are generally well-tolerated in this setting. It is not yet certain if augmentation effects are true across the class or, rather, if some agents are more effective than others when combined with antidepressants. Whether or not formal approval is forthcoming, physicians prescribing atypical antipsychotic agents for antidepressant augmentation should carefully monitor their patients for adverse events, par-

ticularly weight gain and the other risk factors of the metabolic syndrome. The detailed prescribing information provided by the manufacturers should be carefully reviewed before using an atypical antipsychotic for patients with treatment-resistant depression.

(On Nov. 20, 2007, the FDA approved aripiprazole as the first adjunctive treatment to antidepressant therapy in adults with MDD—Ed.)

CONCLUSION

The evidence supporting the use of atypical antipsychotics for the augmentation of treatment-resistant MDD has increased substantially in a relatively short period of time. The results of a large meta-analysis of risperidone, olanzapine and quetiapine demonstrated markedly greater proportions of patients who attained remission or treatment response with augmentation. These findings were supported by more recent studies of aripiprazole, quetiapine, risperidone and ziprasidone. Although these agents have generally been well-tolerated when used in this setting, long-term studies (>12 weeks) are lacking, and patients should be monitored carefully for extrapyramidal symptoms, akathisia, weight gain and other adverse events. It is also not clear at present whether augmentation with atypical antipsychotics is more or less effective than other effective augmentation strategies, such as the use of lithium (Eskalith, Lithobid) or thyroid hormone. Additional randomized, placebo-controlled clinical trials that directly compare the different augmentation strategies are needed to clarify this issue.

References

1. Papakostas GI, Shelton RC, Smith J, Fava M. Augmentation of antidepressants with atypical antipsychotic medications for treatment-resistant major depressive disorder: a meta-analysis. *J Clin Psychiatry*. 2007;68(6):826-831.
2. Corey-Lisle PK, Berman R, Swanink R et al. Aripiprazole as an adjunctive therapy in patients with major depressive disorders: impact on patient-reported functional disability. NR501. Poster presented at: 160th Annual Meeting of the American Psychiatric Association; Oct. 22, 2007; San Diego.
3. Simon JS, Nemeroff CB. Aripiprazole augmentation of antidepressants for the treatment of partially responding and nonresponding patients with major depressive disorder. *J Clin Psychiatry*. 2005;66(10):1216-1220.
4. Adson DE, Kushner MG, Fahnhorst TA. Treatment of residual anxiety symptoms with adjunctive aripiprazole in depressed patients taking selective serotonin reuptake inhibitors. *J Affect Disord*. 2005;86(1):99-104.
5. McIntyre A, Gendron A, McIntyre A. Quetiapine adjunct to selective serotonin reuptake inhibitors or venlafaxine in patients with major depression, comorbid anxiety, and residual depressive symptoms: a randomized, placebo-controlled pilot study. *Depress Anxiety*. 2006;24(7):487-494.
6. Rapaport MH, Gharabawi GM, Canuso CM et al. Effects of risperidone augmentation in patients with treatment-resistant depression: results of open-label treatment followed by double-blind continuation. [Published errata in *Neuropsychopharmacology*. 2006;31(11):2514. 2007;32(5):1208.] *Neuropsychopharmacology*. 2006;31(11):2505-2513.
7. Papakostas GI, Petersen TJ, Nierenberg AA et al. Ziprasidone augmentation of selective serotonin reuptake inhibitors (SSRIs) for SSRI-resistant major depressive disorder. *J Clin Psychiatry*. 2004;65(2):217-221.
8. American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care*. 2004;27(2):596-601 [see comments]. ■

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Efficacy and Safety of Aripiprazole as Adjunctive Therapy in Major Depressive Disorder: A Multicenter, Randomized, Double-blind, Placebo-controlled Study (Study CN138-139)

ABSTRACT

Objective: Evaluate the efficacy and safety of adjunctive aripiprazole vs. placebo to standard antidepressant therapy (ADT) in patients with major depressive disorder who showed an incomplete response to ≥ 1 historical ADT and one prospective ADT.

Methods: The study comprised a 7- to 28-day screening phase; an 8-week, prospective treatment phase; and a 6-week randomization phase. During prospective treatment, patients experiencing a major depressive episode (HAM-D17 Total score ≥ 18) received ADT dosed per label guidelines: escitalopram, fluoxetine, paroxetine CR, sertraline or venlafaxine XR, each with single-blind, adjunctive placebo. Patients with an incomplete response were then randomized to either continued adjunctive placebo or adjunctive aripiprazole (2-20 mg/day). Primary efficacy end point was the mean change in MADRS Total score from end of prospective treatment to end of randomized treatment (Week 14, Last Observation Carried Forward [LOCF]), assessed by ANCOVA, with the end of prospective treatment phase score as a covariate and treatment and study center as main effects.

Results: 178 patients were randomized to adjunctive placebo and 184 to adjunctive aripiprazole. Baseline demographics were similar between groups (mean MADRS Total score=26.0). Mean MADRS change was significantly greater with adjunctive aripiprazole vs. adjunctive placebo (-8.8 vs. -5.8; $P < 0.001$). Adverse events occurring in $\geq 10\%$ of patients with either adjunctive placebo or adjunctive aripiprazole groups were: akathisia (4.5 vs. 23.1%), headache (10.8 vs. 6.0%) and restlessness (3.4 vs. 14.3%). Incidence rates of adverse events leading to discontinuation were low in patients treated with adjunctive placebo (1.7%) and with adjunctive aripiprazole (2.2%); only one adjunctive aripiprazole-treated patient discontinued due to akathisia. Weight gain $\geq 7\%$ was seen in 1.2% and 7.1% of adjunctive placebo- and adjunctive aripiprazole-treated patients, respectively.

Conclusions: In patients with major depressive disorder who showed an incomplete response to standard antidepressant therapy, adjunctive aripiprazole is efficacious and well tolerated.

INTRODUCTION

- Achieving symptom response or remission is difficult in patients with major depressive disorder who have shown inadequate response to ≥ 1 prior antidepressant trial
- Many patients only achieve partial response or continue to experience residual symptoms. Such patients are likely to show reduced functioning and a poorer prognosis¹
- One approach to improving treatment is augmentation pharmacotherapy with an atypical antipsychotic plus an antidepressant
- Pharmacologically, aripiprazole has potential for use as adjunctive therapy in major depressive disorder, as it is a partial agonist at D_2/D_3 and serotonin_{1A} (5-HT_{1A}) receptors, and an antagonist at 5-HT_{2A} receptors^{2,3}
- Open-label studies have reported the efficacy of adjunctive aripiprazole in treatment-resistant depression⁴⁻⁶ and partial responders to antidepressant treatment⁷⁻⁹
- Two randomized, double-blind, placebo-controlled studies of identical design were undertaken to evaluate the efficacy and safety of adjunctive aripiprazole in major depressive disorder (CN138-163 and CN138-139). This poster reports on the results of the CN138-139 study

OBJECTIVE

- To evaluate the efficacy and safety of adjunctive aripiprazole (2-20 mg/day) vs. placebo to standard antidepressant therapy (ADT) in patients with major depressive disorder who have shown an incomplete response to ≥ 1 historical ADT and one prospective, 8-week ADT trial.

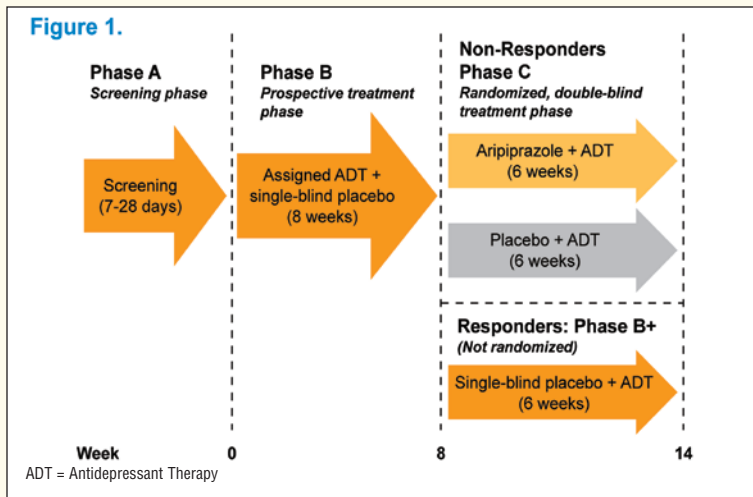
METHODS

- The study comprised a 7-28 day screening phase, an 8-week, prospective treatment phase and a 6-week randomized, double-blind phase (Figure 1)
- Eligible patients were aged 18-65 years and had a major depressive episode (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [DSM-IV-TR] criteria) lasting ≥ 8 weeks
- Patients also had to report an inadequate response to ≥ 1 and ≤ 3 adequate antidepressant (ADT) trials of >6 weeks duration (>3 weeks for combination treatments) at the minimum dose specified in the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (ATRQ)
- An 8-week prospective treatment (Phase B) with ADT further established inadequate response prior to randomization to double-blind treatment with aripiprazole or placebo
- During prospective treatment, patients experiencing major depression (17-item Hamilton Rating Scale for Depression [HAM-D17] Total score ≥ 18) received single-blind adjunctive placebo plus ADT, targeting the following doses by the end of the third week:
 - Escitalopram 10 or 20 mg/day
 - Fluoxetine 20 or 40 mg/day
 - Paroxetine controlled-release (CR) 37.5 or 50 mg/day
 - Sertraline 100 or 150 mg/day
 - Venlafaxine extended-release (XR) 150 or 225 mg/day
- Incomplete responders ($<50\%$ reduction in the HAM-D17 Total score from baseline to the end of the prospective treatment phase, a HAM-D17 Total score ≥ 14 or a Clinical Global Impression-Improvement [CGI-I] score ≥ 3) were randomized in the double-blind treatment phase
- In the 6-week, randomized, double-blind treatment phase, patients were assigned to adjunctive placebo or adjunctive aripiprazole (2-20 mg/day) plus continued ADT
 - Adjunctive aripiprazole started at 5 mg/day
 - Dose changes of 5 mg/day each week were allowed based on tolerability/efficacy
 - Patients with tolerability issues on 5 mg/day could have doses lowered to 2 mg/day
 - Target adjunctive aripiprazole dose was 10 mg/day if “well tolerated”
 - The maximum dose of adjunctive aripiprazole was 15 mg/day with fluoxetine and paroxetine CR

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STUDY DESIGN



STUDY END POINTS

- Efficacy evaluations were performed weekly
- Primary end point:
 - Mean change in Montgomery-Asberg Depression Rating Scale (MADRS) Total score from end of prospective treatment phase to end of randomized treatment phase (last observation carried forward [Week 14, LOCF])
- Secondary efficacy measures:
 - Mean change in Sheehan Disability Scale (SDS) mean score as well as family, social and work/school items
 - Remission: MADRS Total score of ≤ 10 and $\geq 50\%$ reduction in MADRS Total score from end of prospective treatment phase
 - Response: $\geq 50\%$ decrease from end of prospective treatment phase in MADRS Total score
 - CGI-I score and change from baseline in Clinical Global Impression-Severity of Illness (CGI-S) score
- Safety assessments included:
 - Adverse event (AE) reporting
 - Extrapyramidal symptoms (EPS) using Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (Barnes) and Abnormal Involuntary Movement Scale (AIMS)
 - Body weight

STATISTICAL ANALYSES

- Data from efficacy and safety ratings were evaluated using analysis of covariance (ANCOVA) with the end of prospective treatment phase score as the covariate and controlling for study center
- Body weight was evaluated with ANCOVA, including the weight at the end of prospective treatment phase as covariate
- Categorical data (response, remission rates) were evaluated using Cochran-Mantel-Haenszel procedure controlling for study center
- Primary analyses were LOCF, with observed cases (OC) analyses performed for confirmation

RESULTS

Table 1. Baseline Demographics of Randomized Patients

	Placebo (n=178)	Aripiprazole (n=184)
Age, years: mean (SD)	44.1 (10.9)	46.5 (10.6)
Gender, % male	36.0	38.0
Weight*, kg: mean (SD)	86.4 (20.8)	84.5 (19.5)
Duration of current episode, months: mean (SD)	43.6 (53.5)	38.4 (58.7)
Depressive episodes		
Mean number (SD)	3.6 (4.0)	4.2 (4.5)
Single (%)	30.9	22.3
Recurrent (%)	69.1	77.7
MADRS Total score*: mean (SD)	26.0 (6.5)	26.0 (6.0)

*Assessed at end of prospective treatment phase.
SD = Standard Deviation; MADRS = Montgomery-Asberg Depression Rating Scale.

Table 2. ADT Assignment

- Distribution of each ADT during double-blind treatment is shown in Table 2. The mean adjunctive aripiprazole dose across all ADTs during the last week of treatment was 11.8 (2-20) mg/day, and was similar between ADT treatment groups

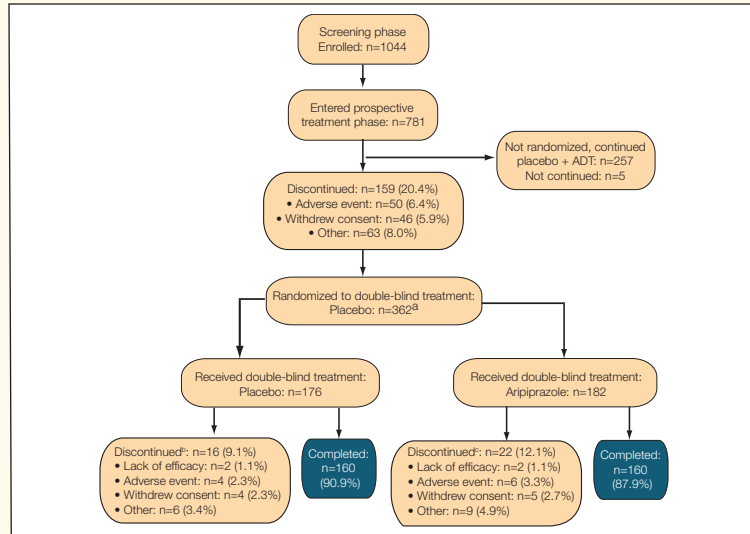
	Placebo (n=178)	Aripiprazole (n=184)
Escitalopram (%)	29.2	29.9
Fluoxetine (%)	14.0	14.1
Paroxetine CR (%)	7.9	10.3
Sertraline (%)	19.7	20.1
Venlafaxine XR (%)	29.2	25.5

ADT = Antidepressant Therapy; CR = Controlled Release; XR = Extended Release.

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Figure 2. Patient Disposition



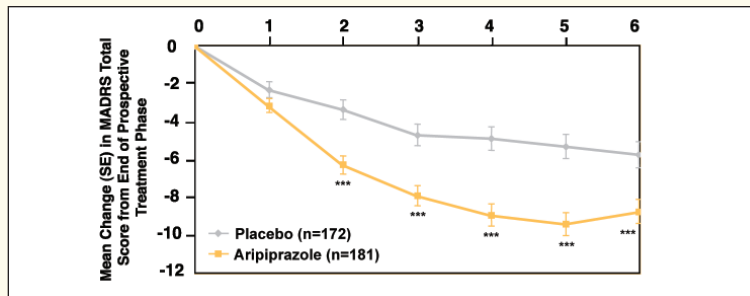
^a Four randomized patients were never treated with double-blind study medication (two of whom were randomized in error).

^b In the placebo group four patients discontinued prior to undergoing any efficacy assessment.

^c In the aripiprazole group one patient discontinued prior to undergoing any efficacy assessment.

Figure 3. MADRS Total Score (LOCF)

- Mean reduction in MADRS Total score was statistically significantly greater in patients receiving adjunctive aripiprazole vs. placebo from Week 2 through to end point (-8.8 vs. -5.8; $P < 0.001$; Figure 3)



*** $P \leq 0.001$ vs. placebo; MADRS Total score is rated from 0-60, where a negative change indicates improvement. MADRS Total scores at end of prospective treatment phase: placebo 25.7; aripiprazole 25.9. MADRS = Montgomery-Asberg Depression Rating Scale; LOCF = Last Observation Carried Forward; SE = Standard Error.

Change in MADRS Total Score by Gender

- The treatment-by-gender interaction at end point was statistically significant ($P=0.002$). The treatment difference was -5.0 in females (in favor of aripiprazole), and +0.5 in males. This interaction was not replicated in another identical study (Study CN138-163)

Table 3. Change in MADRS Total Score by ADT at Week 6 (LOCF)

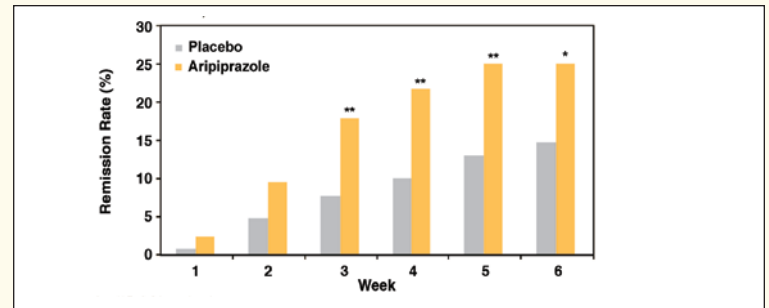
No significant treatment-by-ADT interaction ($P=0.472$) was observed (Table 3)

ADT	Placebo		Aripiprazole	
	n	Mean Change	n	Mean Change
Escitalopram	50	-4.3	54	-9.2
Fluoxetine	23	-8.1	26	-10.8
Paroxetine CR	13	-5.6	18	-8.3
Sertraline	35	-5.2	36	-9.3
Venlafaxine XR	51	-6.7	47	-7.5

MADRS Total score is rated from 0-60, where a negative change indicates improvement. MADRS = Montgomery-Asberg Depression Rating Scale; LOCF = Last Observation Carried Forward; ADT = Antidepressant Therapy; CR = Controlled Release; XR = Extended Release.

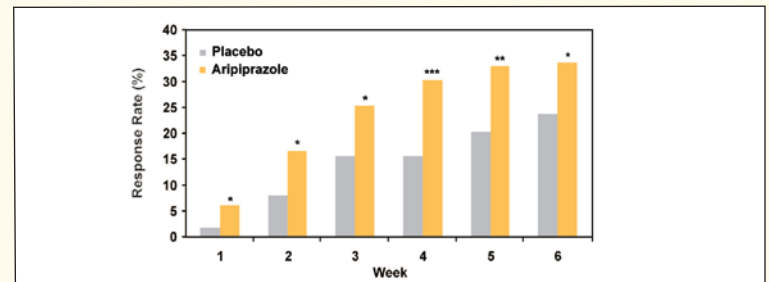
Figure 4a. MADRS Remission Rates (LOCF)

- Adjunctive aripiprazole produced statistically significantly greater remission (26.0 vs. 15.7% at end point, $P < 0.05$) and response rates (33.7% vs. 23.8% at end point, $P < 0.05$) than adjunctive placebo (Figures 4a and 4b)



* $P \leq 0.05$ vs. placebo; ** $P \leq 0.01$ vs. placebo. Remission = MADRS Total score ≤ 10 and $\geq 50\%$ reduction in MADRS Total score from end of prospective treatment. MADRS = Montgomery-Asberg Depression Rating Scale; LOCF = Last Observation Carried Forward.

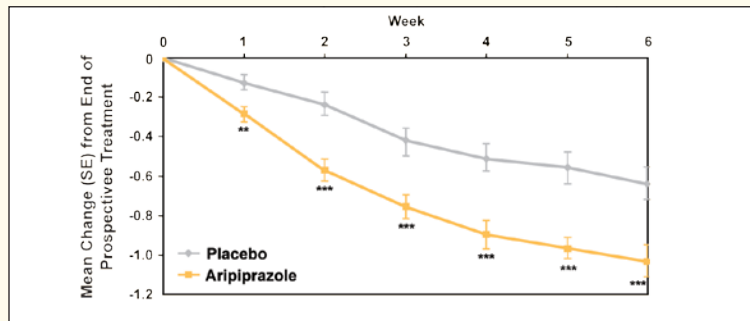
Figure 4b. MADRS Response Rates (LOCF)



* $P \leq 0.05$ vs. placebo; ** $P \leq 0.01$ vs. placebo; *** $P \leq 0.001$ vs. placebo. Response = $\geq 50\%$ decrease from end of prospective treatment phase in MADRS Total score. MADRS = Montgomery-Asberg Depression Rating Scale; LOCF = Last Observation Carried Forward.

Figure 5. CGI-Severity Scores (LOCF)

- Mean Clinical Global Impression-Severity of Illness (CGI-S) scores (Figure 5) and CGI-I scores both showed significant improvements with adjunctive aripiprazole vs. adjunctive placebo at all time points.



** $P \leq 0.01$ vs. placebo; *** $P \leq 0.001$ vs. placebo.

CGI-S scores at end of prospective treatment phase: placebo 4.1; aripiprazole 4.1.

LOCF = Last Observation Carried Forward; CGI-S = Clinical Global Impressions – Severity of Illness.

- SDS scores showed that patients who received adjunctive aripiprazole had statistically significantly greater improvements on their family and social activities than those who received adjunctive placebo

Table 4. Adverse Events ($\geq 5\%$ in either treatment group)

- Adjunctive aripiprazole was well tolerated (Table 4)

Adverse event	Incidence (%)	
	Placebo (n=176)	Aripiprazole (n=182)
Akathisia	4.5	23.1
Insomnia	2.3	7.7
Restlessness	3.4	14.3
Fatigue	3.4	6.0
URIs	4.0	8.2
Nausea	5.1	2.7
Headache	10.8	6.0
Diarrhea	5.7	3.3
Dry mouth	6.3	3.3
Blurred vision	1.7	6.6

URIs = Upper Respiratory Tract Infections.

Tolerability

- Overall EPS-related AEs were reported by 9.7% of adjunctive placebo-treated patients and 27.5% of adjunctive aripiprazole-treated patients
- Akathisia was reported by 4.5% of adjunctive placebo-treated and 23.1% of adjunctive aripiprazole-treated patients
- Discontinuations due to akathisia occurred in only one adjunctive aripiprazole-treated patient

(0.5%) and no patients discontinued due to restlessness

- Minimal changes (LOCF) were seen at end point on the SAS (placebo 0.08; aripiprazole 0.28, $P=0.137$), AIMS (placebo 0.01; aripiprazole 0.04, $P=0.560$) and Barnes (placebo 0.02; aripiprazole 0.24, $P<0.001$) scales
- Adjunctive aripiprazole was associated with a statistically significantly greater mean weight change than adjunctive placebo (LOCF) (+2.01 kg vs. +0.34 kg, $P<0.001$). Significantly more patients showed $\geq 7\%$ weight gain with adjunctive aripiprazole than with adjunctive placebo (7.1% vs. 1.2%, $P<0.01$)

CONCLUSIONS

- In patients with major depressive disorder who showed an incomplete response to standard antidepressant therapy, adjunctive aripiprazole augmented the efficacy of the antidepressant treatment
- Adjunctive aripiprazole is well tolerated; few patients discontinued treatment due to side effects
- This is one of two randomized, double-blind, placebo-controlled studies completed to date that both demonstrate the efficacy of adjunctive aripiprazole in major depressive disorder
- An ongoing study will evaluate the longer-term safety of adjunctive aripiprazole in this difficult-to-treat population

REFERENCES

1. Fava M et al. *J Psychopharmacol.* 2006;20(3 suppl):29-34.
2. Slattery DA et al. *Fundam Clin Pharmacol.* 2004;18(1):1-21.
3. Jordan S et al. *Eur J Pharmacol.* 2002;441(3):137-140.
4. Patkar AA et al. *Prim Care Companion J Clin Psychiatry.* 2006;8(2):82-87.
5. Papakostas GI et al. *J Clin Psychiatry.* 2005;66(10):1326-1330.
6. Barbee JG et al. *Ann Clin Psychiatry.* 2004;16(4):189-194.
7. Pae CU et al. *Depress Anxiety.* 2006;24(7):522-526.
8. Simon JS, Nemeroff CB. *J Clin Psychiatry.* 2005;66(10):1216-1220.
9. Worthington JJ 3rd et al. *Int Clin Psychopharmacol.* 2005;20(1):9-11.

Quetiapine Combination for Treatment-Resistant Depression

ABSTRACT

Objective: Growing evidence supports augmentation of antidepressant therapy with atypical antipsychotics in treatment-resistant depression.^{1,2} This study investigated augmenting concurrent treatment with quetiapine in depressed patients partially responsive to SSRI/SNRI treatment.

Methods: In this 8-week, double-blind, placebo-controlled trial, patients (18-65 years) with baseline HAM-D17 scores ≥ 20 following 6 weeks SSRI/SNRI treatment were randomized to receive quetiapine (200-400 mg) or placebo as augmentation to SSRI/SNRI treatment. Efficacy measures included HAM-D17, MADRS, CGI-S, and CGI-I at study end.

Results: Baseline HAM-D17 scores were 25.0 and 24.5, and baseline MADRS scores were 32.5 and 33.5, for quetiapine (mean dose 268 mg/day, n=21) and placebo (n=11), respectively. Following treatment, patients receiving quetiapine had significantly lower HAM-D17 scores versus placebo (8.3 versus 14.7, respectively, $p < 0.01$). More patients receiving quetiapine responded to treatment ($\geq 50\%$ reduction in HAM-D17 score) (67% versus 27%, $p = 0.015$), and achieved remission (HAM-D17 score < 7) (43% versus 15%, $p < 0.05$), versus placebo. Patients receiving quetiapine had significantly lower MADRS (15.4 versus 24.8, $p < 0.02$), CGI-S (2.8 versus 3.8, $p < 0.03$), and CGI-I (2.5 versus 3.5, $p < 0.04$) scores versus placebo. Quetiapine treatment was generally well tolerated.

Conclusion: Quetiapine augmentation of SSRI/SNRI treatment may benefit patients with treatment-resistant depression and warrants further investigation.

INTRODUCTION

- Major depressive disorder (MDD) remains a very common and under-treated condition, resulting in a high degree of disability.³
- Despite the proliferation of antidepressants, high rates of treatment resistance among patients with MDD remain a key challenge for clinicians.⁴
- Options for patients who do not respond to treatment with selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) include switching to another antidepressant or combining therapy with a different class of treatment.^{4,5}
- Growing evidence supports the combination of antidepressant therapy with atypical antipsychotics in treatment-resistant depression.^{1,2}
- We report the efficacy and tolerability of quetiapine in combination with existing antidepressant therapy in depressed patients partially responsive to SSRI/SNRI treatment.

METHODS

Study Design and Selection Criteria

- 8-week, double-blind, randomized, placebo-controlled study performed in the USA.
- This study included outpatients aged 18-65 years with a primary diagnosis of major depression who were not psychotic and had a baseline Hamilton Depression (HAM-D)-17 rating of ≥ 20 following a minimum of 6 weeks of ongoing treatment with an SSRI or SNRI. All patients met the DSM-IV criteria for recurrent major depression, had a HAM-D item 1 (depressed mood) score of ≥ 2 at baseline, and had failed ≥ 1 4-week trial of a clinically appropriate dose of another antidepressant.
- Patients were excluded from the study if they met DSM-IV criteria for substance abuse or dependence within 3 months, tested positive for illicit substances of abuse by urine toxicology, were judged a serious suicidal or homicidal risk or had made a suicide attempt within the past 3 months, had a history of clinically significant disease that would affect or be affected by trial

medication, had clinically significant abnormalities on ECG, were pregnant, lactating or planning to become pregnant, had participated in a clinical research study in the last 90 days, were judged at risk of non-compliance with the visit schedule or study procedures, had a known intolerance or lack of response to quetiapine, or had received treatment with mood stabilizers, other antipsychotics or antidepressants other than SSRIs/SNRIs for a minimum of 2 weeks prior to enrollment.

Study Treatments

- Patients were randomized (2:1 ratio) to receive quetiapine (200-400 mg/d) or placebo in combination with ongoing SSRI/SNRI treatment.
- Quetiapine was administered at an initial dose of 50 mg once daily at bedtime. The dosage was increased by 50 mg every 3 days to a minimum target level of 200 mg/d, up to a total maximum dose of 600 mg/d.

Efficacy Evaluations

- Primary efficacy endpoint was HAM-D17 score at Week 8.
- Secondary endpoints included
 - response to treatment ($\geq 50\%$ reduction in HAM-D17 score)
 - remission rates (HAM-D17 score < 7)
 - final Montgomery-Asberg Depression Rating Scale (MADRS)
 - Clinical Global Impressions - Severity of illness (CGI-S) and Global Improvement (CGI-I) scores at study end.
- Efficacy was assessed weekly during Weeks 1-4 and then at Weeks 6 and 8.

Safety Evaluations

- Adverse events (elicited from patients by questions), vital signs and body weight were recorded at each clinic visit; an ECG and laboratory tests (electrolytes, liver enzymes and prolactin levels) were conducted at baseline and Week 8.
- Extrapyramidal symptoms (EPS) were assessed using the Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Scale (BAS) and the Simpson-Angus Scale (SAS).

Statistical Analysis

- All patients who completed the study were included in the data analysis. All patients who received at least one dose of study medication were included in the safety analyses.
- Data were analyzed using the paired t-test with $p < 0.05$ considered an indication of statistical significance. p-values were not adjusted for multiple comparisons. HAM-D17, MADRS, CGI-S and CGI-I scores at study end and final study dose were compared between patients randomized to quetiapine and those receiving placebo. HAM-D17 scores were also compared between the two treatment groups at Weeks 1, 2, 3, 4 and 6.

RESULTS

Patients

- Forty patients were randomized to quetiapine (n=26) or placebo (n=14), three patients withdrew prior to taking study medication (quetiapine n=2, placebo n=1), five patients withdrew prior to study completion (quetiapine n=3, placebo n=2) and 32 patients completed the study (quetiapine n=21, placebo n=11).

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- Baseline patient and disease characteristics are summarized in **Table 1**.

Table 1. Patient and Disease Characteristics at Baseline (n=32)

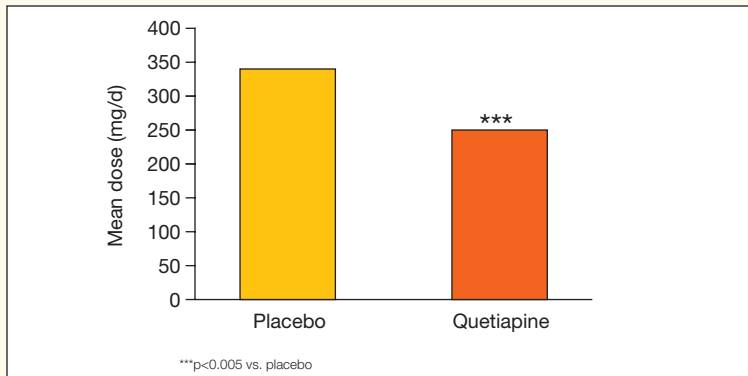
	Quetiapine (n=21)	Placebo (n=11)
Gender, n (%)		
Male	7 (33.3)	1 (9.1)
Female	14 (66.7)	10 (90.9)
Race, n (%)		
White	21 (100)	11 (100)
Median age, years (range)	53 (21-66)	49 (21-69)
Mean weight, kg	94	98
Mean HAM-D17 score (SD)	25.0 (4.6)	24.5 (3.8)
Mean MADRS score (SD)	32.4 (3.5)	33.5 (4.8)
Previous treatment, n (%)		
SSRI	14	7
SNRI	6	3
SSRI + SNRI	1	1

Treatment

- In this flexible-dose study, the mean final dose was significantly lower in the quetiapine treatment arm (268 mg/d, standard deviation [SD] 71.1 mg/d) compared to the placebo arm (341 mg/d, SD 53.9 mg/d; $p < 0.005$; **Figure 1**).

Figure 1. Final Mean Study Dose (mg/d) of Placebo and Quetiapine (in Combination with SSRI/SNRI)

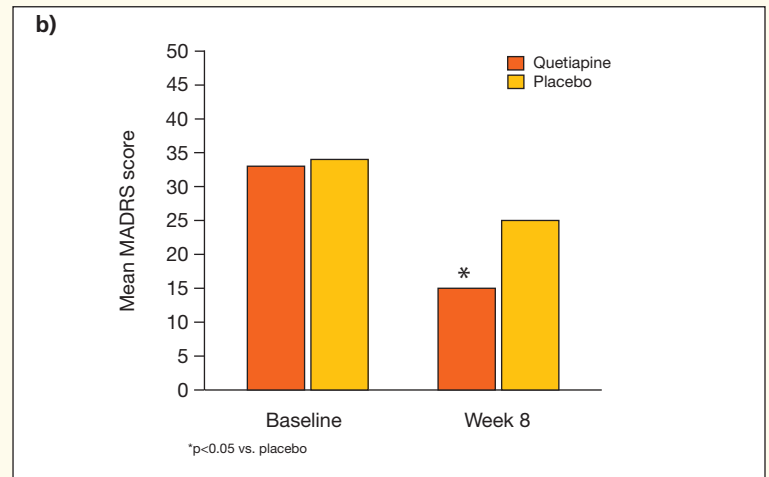
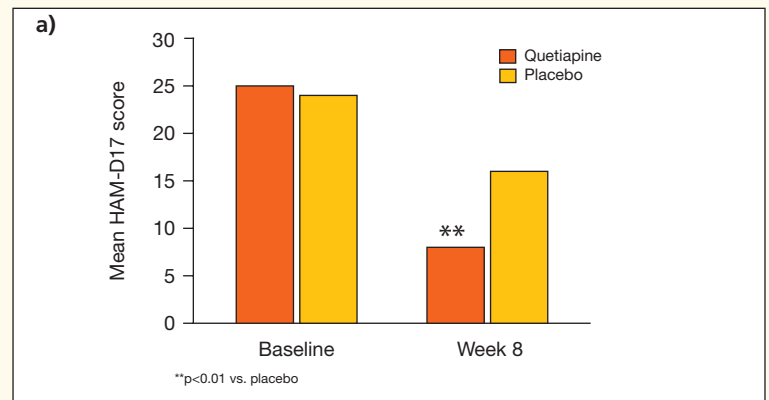
- The median (range) final dose was 300 mg/d (100-350 mg/d) in the quetiapine group, compared with 350 mg/d (250-400 mg/d) in the placebo group.



Efficacy

- Combination antidepressant-quetiapine treatment resulted in significantly lower mean HAM-D17 scores compared to placebo at study end (8.3 in the quetiapine group, 14.7 in the placebo group, $p < 0.01$; **Figure 2a**).
- Quetiapine treatment also resulted in a significantly lower mean MADRS score at study end compared to placebo ($p < 0.05$; **Figure 2b**).

Figure 2. Effect of 8 Weeks' Quetiapine or Placebo (in Combination with SSRI/SNRI) Treatment on (a) Mean HAM-D17 Score (b) Mean MADRS Score

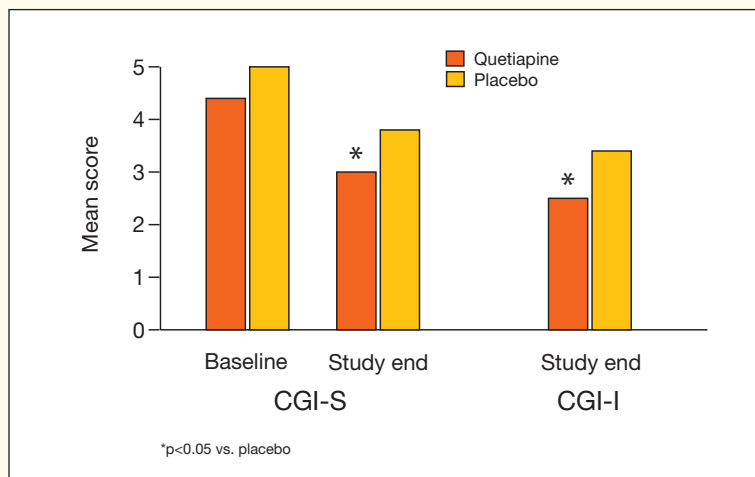


- Final mean CGI-S and CGI-I scores were also significantly lower at the end of the study in the quetiapine treatment arm than in the placebo arm (CGI-S: 2.8 in the quetiapine group, 3.8 in the placebo group, $p < 0.05$; CGI-I: 2.5 in the quetiapine group, 3.5 in the placebo group, $p < 0.05$; **Figure 3**).

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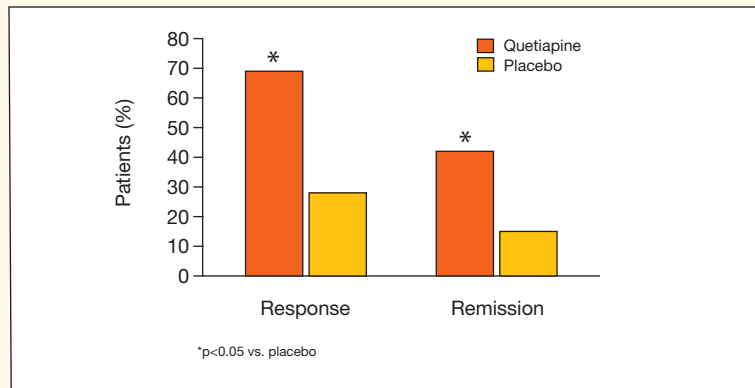
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Figure 3. Effect of 8 Weeks' Quetiapine or Placebo (in Combination with SSRI/SNRI) Treatment on Mean CGI-S and CGI-I Scores



- Significantly more patients receiving quetiapine responded (67% receiving quetiapine, 27% receiving placebo, $p<0.05$) to treatment and achieved remission (43% of patients receiving quetiapine, 15% of patients receiving placebo, $p<0.05$; **Figure 4**), compared to those receiving placebo.

Figure 4. Percentage of Patients Responding to Treatment ($\geq 50\%$ Reduction in HAM-D17 Score) or Achieving Remission (HAM-D17 Score <7) After 8 Weeks' Quetiapine or Placebo (in Combination with SSRI/SNRI) Treatment



Safety and Tolerability

- Quetiapine treatment was generally well tolerated.
- The most commonly observed adverse events with a higher incidence in the quetiapine group than in the placebo group were fatigue, dry mouth and sedation/somnolence. Headache was the most common adverse event in both treatment groups (**Table 2**).

Table 2. Adverse Events Occurring in $\geq 5\%$ of Patients Receiving Quetiapine

Adverse event	Quetiapine, n (%)	Placebo, n (%)
Headache	7 (29.2)	5 (45.4)
Fatigue	7 (29.2)	2 (18.2)
Dry mouth	3 (12.5)	0 (0.0)
Sedation/somnolence	2 (8.3)	1 (9.1)

- Two (15.4%) patients in the placebo group withdrew from the study due to a serious adverse event (panic attacks and sedation). Three (12.5%) patients in the quetiapine group withdrew from the study, for reasons that were not considered by the investigator to be related to treatment.
- No patients in either treatment group had a non-zero score on the AIMS scale. The mean BAS scores were similar between the quetiapine and placebo groups at baseline (0.48 and 0.64, respectively) and at study end (0.43 and 0.55, respectively), as were the mean SAS scores (0.00 quetiapine, 0.18 placebo at baseline, 0.33 quetiapine, 0.09 placebo at study end).
- A trend towards decreased serum prolactin levels was observed in the quetiapine group (-0.8 ng/mL baseline to study end) compared to placebo ($+0.1$ ng/mL baseline to study end).
- The mean weight at study end was 212 lbs (96 kg) in the quetiapine group ($n=21$), 215 lbs (98 kg) in the placebo group ($n=12$). However, the mean baseline weight was also lower in the quetiapine group (206 lbs, 94 kg) than in the placebo group (215 lbs, 98 kg).
- The mean weight gain was 6 lbs (3 kg) in the quetiapine group, while there was no mean weight change in the placebo group.

CONCLUSIONS

- In this study, quetiapine in combination with SSRI/SNRI was effective and generally well tolerated in patients with treatment-resistant depression.
- At study end, both mean HAM-D17 and mean MADRS scores were significantly lower in patients who had received quetiapine than those who had received placebo.
- This concordance between results derived from the HAM-D17 and MADRS scales suggests that quetiapine led to a genuine symptom improvement, and that the improvement in HAM-D17 scores (which are more sensitive to sedation) was not solely due to the sedative effect of quetiapine.
- These data are in line with those that have been previously reported on the use of quetiapine in patients with treatment-resistant depression.⁶
- Combination treatment of quetiapine and SSRI/SNRI may be of benefit to such patients and further investigation in this setting is warranted.

REFERENCES

1. Kennedy SH, Lam RW. *Bipolar Disord* 2003;5 Suppl 2:36-47.
2. Barbee JG et al. *J Clin Psychiatry* 2004;65:975-981.
3. Ebmeier KP et al. *Lancet* 2006;367:153-167.
4. Klein N et al. *CNS Spectr* 2004;9:823-832.
5. American Psychiatric Association. *Am J Psychiatry* 2000;157:1-45.
6. Vavrusova L. *Int J Neuropsychopharmacol* 2002;5(Suppl 1):S104.

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Posttest

1. Approximately _____ of patients with MDD achieve remission of depression with current first-line therapies.
 - a. 10% to 15%
 - b. 20% to 40%
 - c. 50% to 70%
 - d. 90% or more
2. In the STAR*D study, an intensive treatment regimen that included combination therapy with several antidepressant medications, psychotherapy, and augmentation with lithium or thyroid hormone produced a remission rate of approximately:
 - a. 25%
 - b. 50%
 - c. 67%
 - d. 95%
3. Depressive symptoms have been linked to specific of regions of atrophy within the:
 - a. Hippocampus
 - b. Hypothalamus
 - c. Pons
 - d. All of the above
4. _____ acts as a partial D₂ receptor agonist.
 - a. Aripiprazole
 - b. Olanzapine
 - c. Risperidone
 - d. None of the above
5. A recent randomized, double-blind clinical trial of aripiprazole demonstrated that, in comparison with placebo, aripiprazole:
 - a. Was associated with an increased rate of treatment response, but not remission
 - b. Improved scores on depression rating scales, but did not improve psychosocial functioning
 - c. Was discontinued by many patients due to akathisia
 - d. None of the above
6. A clinical trial of risperidone augmentation in which patients received risperidone or placebo during a 24-week discontinuation study found that risperidone significantly increased the time until relapse for:
 - a. Women but not men
 - b. Patients with mild symptoms at baseline
 - c. Patients who were fully nonresponsive to initial treatment with citalopram
 - d. None of the above

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