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Drug Development for Anxiety Disorders: New Roles for Atypical Antipsychotics

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ABSTRACT *~ Anxiety disorders are prevalent and frequently comorbid with depression. Rates of response and remission for anxiety disorders are low despite marked improvements in treatment in the past several decades. Antidepressants and anxiolytics remain the most frequently prescribed agents for anxiety disorders, but the numbers of prescriptions for novel forms of therapy, such as anticonvulsants and atypical antipsychotics are increasing. For the atypical antipsychotics, agonist activity at the 5-HT_{1A} receptor has been hypothesized to translate into anxiolytic effects. A small, but growing, literature suggests that atypical antipsychotics are useful as augmentation therapy for treatment of refractory anxiety disorders. The next generation antipsychotic, aripiprazole, has a unique mechanism of action (ie, combined D_2 and 5-HT_{1A} partial agonist and 5-HT_{2A} antagonist) and improves depressive and depressive/anxiety symptoms in patients with schizophrenia. Further studies examining the effect of aripiprazole and other atypical antipsychotic drugs on depressive and anxiety symptoms in patients with refractory anxiety disorders are warranted.* Psychopharmacology Bulletin. *2004;38(Suppl 1): 38–45.*

INTRODUCTION

Despite the remarkable advances in the treatment of anxiety disorders that have been achieved in the last 2 decades, important limitations remain. Anxiety disorders are chronic, recurrent illnesses. The findings of the Harvard/Brown Anxiety Research Program (HARP), which is a longitudinal, naturalistic study of 711 patients with anxiety disorders, demonstrate surprisingly low rates of recovery after 6 months for panic disorder (28%), social anxiety disorder (8%), and generalized anxiety disorder (GAD) (12%). Although long-term rates of recovery increase for panic disorder (60%), social anxiety disorder (27%), and GAD (37%), the majori-

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ty of patients remain ill. Relapse rates are high, particularly for panic disorder; 70% of patients with panic disorder relapse within 5 years.[1] A naturalistic study of 66 patients with obsessive compulsive disorder (OCD) revealed similar findings: only 12% of patients fully remitted after 2 years, and the probability of relapse in recovered patients was 48%.[2]

Response rates to treatment are not ideal. Although the SSRIs have emerged as first-line therapy for the anxiety disorders, response rates of 40% to 70% underscore the point that a marked proportion of patients remain ill even after adequate courses of treatment.[3]

Anxiety disorders also are frequently comorbid with depression. Indeed, comorbid depression is the rule rather than the exception in patients with an anxiety disorder. Epidemiologic and naturalistic studies have demonstrated high lifetime rates of comorbid depression in patients with PTSD (48%), GAD (62%), OCD (67%), panic disorder (56%), and social anxiety disorder (34% to 70%).[4-9]

ANXIOLYTIC PRESCRIBING PATTERNS

Data from a large, national prescription database illustrates which agents were prescribed for the treatment of anxiety disorders in 2002.[10] The number of prescriptions written for anxiety disorders, particularly PTSD, GAD, and OCD, increased in 2002, which is likely indicative of increased awareness of these disorders rather than increased incidence. Not surprisingly, antidepressants were the most commonly prescribed therapeutic class, followed by anxiolytics. Antipsychotics and anticonvulsants also were prescribed for treatment of anxiety disorders, and the number of new prescriptions of antipsychotics for treating PTSD, GAD, OCD, and panic disorder also increased in 2002. Taken together, data from the literature and new prescription databases shows that the antipsychotics, particularly the atypical antipsychotics, are being increasingly used in the treatment of anxiety disorders.

RECEPTOR PHARMACOLOGY

An understanding of the mechanisms underlying the increasing role of the atypical antipsychotics in the treatment of anxiety disorders is important. The anxiolytic effects of antipsychotics, particularly atypical agents, can be explained in part by consideration of receptor pharmacology. Activity as an agonist at the 5-HT_{1A} receptor has been hypothesized to translate into anxiolytic effects, especially for aripiprazole and ziprasidone.[11,12] Although they are grouped as a class, each atypical antipsychotic agent exhibits a unique receptor affinity profile. One generalization that can be made about this class of compounds is that older atypical antipsychotics—olanzapine, quetiapine, and risperidone—are characterized by relatively low affinity for dopamine D_2 and serotonin 5-HT_{1A}

receptors.[13,14] Of the older atypical antipsychotics, ziprasidone has the highest affinity for dopamine and serotonin receptors[12,15] and has the highest affinity for the monoamine transporters, particularly serotonergic and noradrenergic transporters. A next generation antipsychotic, aripiprazole, exhibits unique structural and pharmacological properties that are distinct from other antipsychotic agents. Aripiprazole is a partial agonist of dopamine D_2 and serotonin 5-HT_{1A} receptors and an antagonist of serotonin 5-HT_{2A} receptors.[16-18]

CLINICAL USE OF ATYPICAL ANTIPSYCHOTICS IN ANXIETY DISORDERS

The use of atypical antipsychotics in the treatment of schizophrenia is supported by a large body of evidence from randomized, controlled trials[19-21] and treatment guidelines.[22,23] Depression and anxiety represent an important, but often unrecognized, symptom cluster in schizophrenia. Findings from randomized, controlled trials demonstrate that baseline depression/anxiety symptom cluster scores in patients with schizophrenia improve significantly with risperidone and olanzapine treatment.[20,21] In a six-week, open-label study, ziprasidone also improved anxiety factor scores compared to baseline and patients with the most severe symptoms of anxiety achieved the greatest improvements.[24]

As the therapeutic profile of the atypical antipsychotics expands, an emerging body of clinical evidence supports their use as augmentation therapy for anxiety disorders. Currently, the literature on the use of atypicals as augmenting agents for anxiety disorders consists of small controlled trials, open-label studies, and case reports. Obsessive-compulsive disorder is the best studied anxiety disorder. A number of open-label studies[25-27] and case reports suggest efficacy of risperidone as augmentation therapy for SSRI-refractory OCD. One randomized, double-blind study of risperidone augmentation (mean dose: 2.2 mg/day) of SSRI treatment-refractory patients (baseline Y-BOCS score=27) demonstrated a 50% response rate to risperidone (mean endpoint Y-BOCS score=19) compared with a 0% response rate for placebo-treated patients (mean endpoint Y-BOCS score=25; $P<.001$).[31] A small, single-blind study of quetiapine[32] and several open-label trials of olanzapine[33-35] also suggest that the atypical antipsychotics have efficacy as augmentation therapy for refractory OCD. One interesting retrospective analysis of 18 patients with refractory OCD who responded to atypical antipsychotic augmentation revealed that 72% of patients relapsed within 2 months of discontinuing the antipsychotic,[36] which suggests that atypical antipsychotic augmentation must be continued over the long-term in order to sustain the initial clinical response.

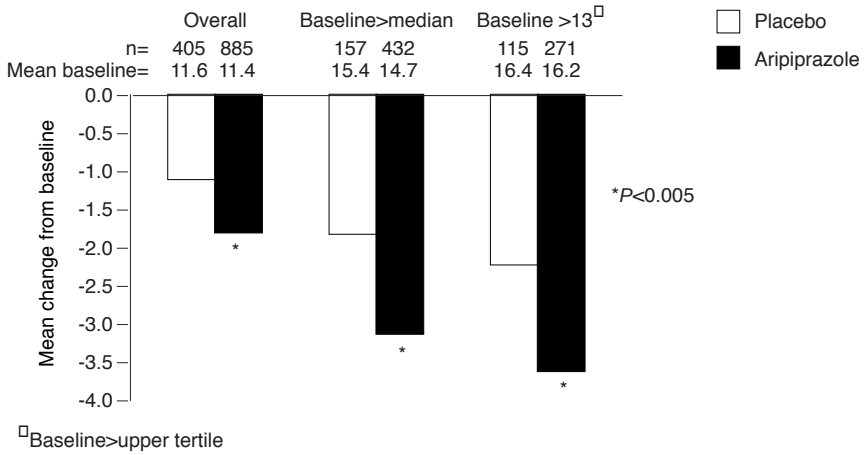
Other anxiety disorders are less well-studied. However, the findings of a randomized, double-blind, placebo-controlled study in refractory GAD suggest efficacy for olanzapine augmentation.[37] Small, double-blind, placebo-controlled studies suggest efficacy of olanzapine augmentation for SSRI partial responders with PTSD[38] and social anxiety disorder,[39] and case reports describe two patients with refractory panic disorder who responded to the addition of olanzapine.[40]

ARIPIPRAZOLE

Aripiprazole, which is a next generation dopamine system stabilizer and is the newest addition to the antipsychotic armamentarium, has been shown to be efficacious in treating the full spectrum of symptoms in schizophrenia,[41-42] including the anxiety/depressive components of schizophrenia.[43] Starting doses range from 10 mg to 30 mg per day, without the need for initial titration.[44] Data from five double-blind, placebo-controlled studies of aripiprazole treatment of patients with schizophrenia or schizoaffective disorder were assessed using analysis of covariance.[43] The studies were of identical design and assessed safety and efficacy for a treatment course of four to six weeks in 885 patients randomized to aripiprazole (dose range: 2 mg to 30 mg per day) and 405 patients randomized to placebo. Outcome measures were change from baseline in the mean PANSS depression/anxiety cluster and the PANSS depression item scores. Mean baseline scores for the depression/anxiety cluster were similar for the aripiprazole (11.4) and placebo (11.6) groups, but at study endpoint, the

FIGURE 1

MEAN CHANGE FROM BASELINE IN THE PANSS DEPRESSION/ANXIETY CLUSTER (LOCF)[43]



Carson WH, Kitagawa H, Nemeroff CB. *Psychopharmacology Bulletin.* Vol. 38. Suppl. 1. 2004.

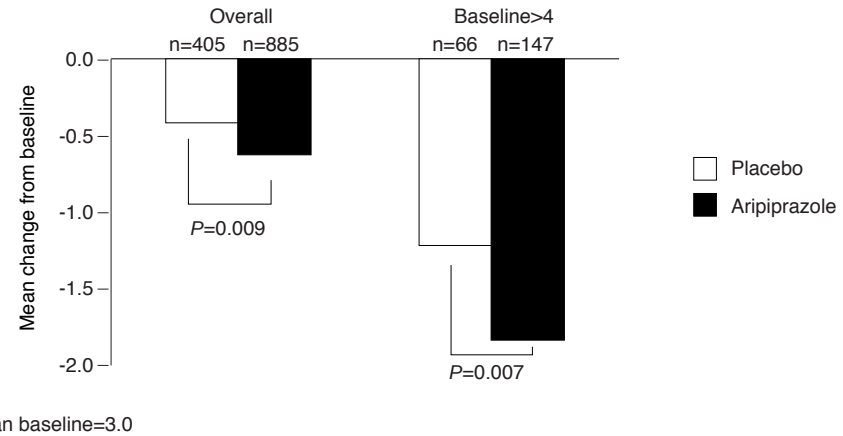
aripiprazole group achieved a significantly greater improvement in baseline scores compared with placebo-treated patients ($P<.005$) (Figure 1). Between-group differences at endpoint were even more pronounced in patients with more severe symptoms at baseline (Figure 1). Similarly, mean baseline scores were identical for both groups (3.0) on the depression item of the PANSS. At endpoint, patients in the aripiprazole group achieved significantly greater reductions in mean baseline depression scores ($P=.009$) compared with placebo, and patients with more severe depressive symptoms at baseline exhibited greater improvements at endpoint ($P=.007$ versus placebo) (Figure 2).

A separate analysis of pooled data from two fixed-dose, four-week, double-blind, placebo-controlled comparisons of aripiprazole and haloperidol treatment of patients with schizophrenia also was conducted.[43] The intent-to-treat patient population consisted of 304 patients in the aripiprazole group, 153 patients in the haloperidol group, and 160 patients randomized to placebo. At endpoint, aripiprazole resulted in significantly greater improvement in the depressive/anxiety symptom cluster score on the PANSS compared with placebo ($P<.05$). Haloperidol did not separate statistically from placebo at endpoint.

Of note, aripiprazole has a desirable safety profile, which is an important consideration in patients with anxiety disorders who often are highly intolerant of medication adverse events. Rates of adverse events for aripiprazole are comparable to placebo for sedation, weight gain, emergent anxiety, measures of serum lipids and glucose, extrapyramidal

FIGURE 2

MEAN CHANGE FROM BASELINE IN THE PANSS DEPRESSION ITEM (G6) (LOCF)[43]



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symptoms, hyperprolactinemia, and QT interval changes.[42,45] Adherence to short- and long-term therapy is a challenge for patients and is critical to successful outcomes in schizophrenia treatment.[46] Rates of premature treatment withdrawal due to adverse events in clinical studies of aripiprazole were not statistically different than placebo.[45]

CONCLUSIONS

Deficits in existing treatment strategies for anxiety disorders exist which have prompted the evaluation of augmentation therapies for treatment-resistant or partially responsive patients. Antipsychotic agents, particularly atypical antipsychotics, are increasingly being used to augment treatment of refractory anxiety disorders. Although OCD is the best studied anxiety disorder in this regard, an emerging literature also supports the further study of antipsychotic agents as augmentation therapy for refractory PTSD, GAD, and panic disorder. The next generation antipsychotic agent, aripiprazole, has been shown to be effective in improving depressive and depressive/anxiety symptom cluster scores on the PANSS in patients with schizophrenia. The unique mechanism of action of aripiprazole, with its combined D_2 and 5-HT_{1A} partial agonist and 5-HT_{2A} antagonist activity, may impart beneficial effects in the treatment of depressive and anxiety symptoms. Further studies examining the effect of aripiprazole on depressive and anxiety symptoms in patients with refractory anxiety disorders are warranted. ✤

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ery of lithium and methods to estimate serotonin and norepinephrine transporter occupancy after drug treatment using patient or animal serum.

DISCLOSURE OF UNLABELED OR UNAPPROVED USES OF DRUGS

The following drugs are discussed in this article for off-label use: risperidone, olanzapine, ziprasidone, and aripiprazole for anxiety, and aripiprazole for depression.

REFERENCES

1. Keller MB. Raising the expectations of long-term treatment strategies in anxiety disorders. *Psychopharmacol Bull*. 2002;36(Suppl 2):166-174.
2. Eisen JL, Goodman WK, Keller MB, et al. Patterns of remission and relapse in obsessive-compulsive disorder: a 2-year prospective study. *J Clin Psychiatry*. 1999;60:346-351.
3. Ballenger JC. Current treatment of the anxiety disorders in adults. *Biol Psychiatry*. 1999;46:1579-1594.
4. Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. *Arch Gen Psychiatry*. 1995;52:1048-1060.
5. Rasmussen SA, Eisen JL. Clinical and epidemiologic findings of significance to neuropharmacologic trials in OCD. *Psychopharmacol Bull*. 1988;24:466-470.
6. Roy-Byrne PP, Stang P, Wittchen HU, Ustun B, Walters EE, Kessler RC. Lifetime panic-depression comorbidity in the National Comorbidity Survey. *Br J Psychiatry*. 2000;176:229-235.
7. Stein MB, Kean YM. Disability and quality of life in social phobia: epidemiologic findings. *Am J Psychiatry*. 2000;157:1606-1613.
8. Van Ameringen M, Mancini C, Styan G, Donison D. Relationship of social phobia with other psychiatric illness. *J Affect Disord*. 1991;21:93-99.
9. Wittchen H-U, Zhao S, Kessler RC, Eaton WW. DSM-III-R generalized anxiety disorder in the National Comorbidity Survey. *Arch Gen Psychiatry*. 1994;51:355-364.
10. IMS Health, NDTI Quarterly data, 4th quarter 2002- 3rd quarter 2003, Sept 2003.
11. Olivier B, Pattij T, Wood SJ, Oosting R, Sarnyai Z, Toth M. The 5-HT(1A) receptor knockout mouse and anxiety. *Behav Pharmacol*. 2001;12:439-50.
12. Wilner KD, Anziano RJ, Johnson AC, Miceli JJ, Fricke JR, Titus CK. The anxiolytic effect of the novel antipsychotic ziprasidone compared with diazepam in subjects anxious before dental surgery. *J Clin Psychopharmacol*. 2002;22:206-10.
13. Arnt J, Skarsfeldt T. Do novel antipsychotics have similar pharmacological characteristics? A review of the evidence. *Neuropsychopharmacol*. 1998;18:63-101.
14. Bymaster FP, Hemrick-Luecke SK, Perry KW, Fuller RW. Neurochemical evidence for antagonism by olanzapine of dopamine, serotonin, alpha 1-adrenergic and muscarinic receptors in vivo in rats. *Psychopharmacol (Berl)*. 1996;124:87-94.
15. Schmidt AW, Lebel LA, Howard HR Jr, Zorn SH. Ziprasidone: a novel antipsychotic agent with a unique human receptor binding profile. *Eur J Pharmacol*. 2001 ;425:197-201.
16. Burris KD, Molski TF, Xu C, et al. Aripiprazole, a novel antipsychotic, is a high-affinity partial agonist at human dopamine D2 receptors. *J Pharmacol Exp Therap*. 2002;302:381-389.
17. Shapiro DA, Renock S, Arrington E, et al. Aripiprazole, a novel atypical antipsychotic drug with a unique and robust pharmacology. *Neuropsychopharmacol*. 2003;28:1400-1411.
18. Yokoi F, Grunder G, Biziere K, et al. Dopamine D2 and D3 receptor occupancy in normal humans treated with the antipsychotic drug aripiprazole (OPC 14597): a study using positron emission tomorgraphy and [11C]raclopride. *Neuropsychopharmacol*. 2002;27:248-259.
19. Daniel DG, Zimbroff DL, Potkin SG, Reeves KR, Harrigan EP, Lakshminarayanan M. Ziprasidone 80 mg/day and 160 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 6-week placebo-controlled trial. *Neuropsychopharmacol*. 1999;20:491-505.
20. Davis JM, Chen N. The effects of olanzapine on the 5 dimensions of schizophrenia derived by factor analysis: combined results of the North American and international trials. *J Clin Psychiatry*. 2001;62:757-771.
21. Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. *J Clin Psychiatry*. 1997;58:538-546.
22. Expert Consensus Guideline Series: Treatment of schizophrenia 1999. *J Clin Psychiatry*. 1999;60(Suppl 11):1-80.
23. Lehman AF, Steinwachs DM. Translating research into practice: the Schizophrenia Patient Outcomes Research Team (PORT) treatment recommendations. *Schizophr Bull*. 1998;24:1-10.

24. Schooler NR, Siu C. Ziprasidone's effect on anxiety in a group of outpatients with stable schizophrenia (poster #105). Presented at: 40th Annual Meeting of New Clinical Drug Evaluation Unit (NCDEU). Boca Raton, FL; May 30 – June 2, 2000.
25. Pfanner C, Marazziti D, Dell'Osso L, et al. Risperidone augmentation in refractory obsessive-compulsive disorder : an open-label study. *Int Clin Psychopharmacol*. 2000;15:297-301.
26. Ravizza L, Barzega G, Bellino S, Bogetto F, Maina G. Therapeutic effect and safety of adjunctive risperidone in refractory obsessive-compulsive disorder (OCD). *Psychopharmacol Bull*. 1996;32:677-682.
27. Saxena S, Wang D, Bystritsky A, Baxter LR Jr. Risperidone augmentation of SRI treatment for refractory obsessive-compulsive disorder. *J Clin Psychiatry*. 1996;57:303-306.
28. Agid O, Lerer B. Risperidone augmentation of paroxetine in a case of severe, treatment-refractory obsessive-compulsive disorder without comorbid psychopathology. *J Clin Psychiatry*. 1999.60:55-56.
29. Kawahara T, Ueda Y, Mitsuyama Y. A case report of refractory obsessive-compulsive disorder improved by risperidone augmentation of clomipramine treatment. *Psychiatry Clin Neurosci*. 2000;54:599-601.
30. Sun TF, Lin PY, Wu CK. Risperidone augmentation of specific serotonin reuptake inhibitors in the treatment of refractory obsessive-compulsive disorder: report of two cases. *Chang Gun Med J*. 2001;24:587-592.
31. McDougle CJ, Epperson CN, Pelton GH, Wasylink S, Price LH. A double-blind, placebo-controlled study of risperidone addition in serotonin reuptake inhibitor-refractory obsessive-compulsive disorder. *Arch Gen Psychiatry*. 2000;57:794-801.
32. Atmaca M, Kuloglu M, Tezcan E, Gecici O. Quetiapine augmentation in patients with treatment resistant obsessive-compulsive disorder: a single-blind, placebo-controlled study. *Int Clin Psychopharmacol*. 2002;17:115-119.
33. Bogetto F, Bellino S, Vaschetto P, Ziero S. Olanzapine augmentation of fluvoxamine-refractory obsessive-compulsive disorder (OCD): a 12-week open trial. *Psychiatry Res*. 2000;30:91-98.
34. Koran LM, Ringold AL, Elliott MA. Olanzapine augmentation for treatment-resistant obsessive-compulsive disorder. *J Clin Psychiatry*. 2000;61:514-517.
35. Weiss EL, Potenza MN, McDougle CJ, Epperson CN. Olanzapine addition in obsessive-compulsive disorder refractory to selective serotonin reuptake inhibitors: an open-label case series. *J Clin Psychiatry*. 1999;60:524-527.
36. Maina G, Albert U, Ziero S, Bogetto F. Antipsychotic augmentation for treatment resistant obsessive-compulsive disorder: what if antipsychotic is discontinued? *Int Clin Psychopharmacol*. 2003;18:23-28.
37. Kinrys et al. Poster presented at the 22nd Annual Conference of the Anxiety Disorders Association of America. Austin, TX; March 21-24, 2002.
38. Stein MB, Kline NA, Matloff JL. Adjunctive olanzapine for SSRI-resistant combat-related PTSD: a double-blind, placebo-controlled study. *Am J Psychiatry*. 2002;159:1777-1779.
39. Barnett SD, Kramer ML, Casat CD, Connor KM, Davidson JRT. Efficacy of olanzapine in social anxiety disorder: a pilot study. *J Psychopharmacol*. 2002;16:365-368.
40. Etxebeste M, Aragues E, Malo P, Pacheco L. Olanzapine and panic attacks. *Am J Psychiatry*. 2000;157:659-660.
41. Bandelow B, Meier A. Aripiprazole, a "dopamine-serotonin system stabilizer" in the treatment of psychosis. *German J Psychiatry*. 2003;6:9-16.
42. Potkin SG, Saha AR, Kujawa MJ, et al. Aripiprazole, an antipsychotic with a novel mechanism of action, and risperidone vs placebo in patients with schizophrenia and schizoaffective disorder. *Arch Gen Psychiatry*. 2003;60:681-690.
43. Otsuka Pharmaceutical. Data on file, 2003.
44. Bowles TM, Levin GM. Aripiprazole: a new atypical antipsychotic drug. *Ann Pharmacother*. 2003;37:687-694.
45. Marder SR, McQuade RD, Stock E, et al. Aripiprazole in the treatment of schizophrenia: safety and tolerability in short-term, placebo-controlled trials. *Schizophr Res*. 2003;61:123-126.
46. Pinikahana J, Happell B, Taylor M, Keks NA. Exploring the complexity of compliance in schizophrenia. *Issues Ment Health Nurs*. 2002;23:513-528.