Efficacy of Typical and Atypical Antipsychotics for Primary and Comorbid Anxiety Symptoms or Disorders: A Review

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Objective: The efficacy of antipsychotics in the treatment of primary or comorbid anxiety disorders or anxiety symptoms in major depressive disorder or bipolar disorder was reviewed.

Data Sources: English-language literature cited in MEDLINE from January 1, 1968, to December 31, 2005, was searched with the keywords *anxiety disorder*, *anxiety symptoms*, *generalized anxiety disorder*, *panic disorder*, *obsessive-compulsive disorder*, *posttraumatic stress disorder*, *social phobia*, *bipolar disorder*, *major depressive disorder*, *Hamilton Rating Scale for Anxiety*, *antipsychotics*, *typical antipsychotics*, *atypical antipsychotics*, *fluphenazine*, *haloperidol*, *perphenazine*, *pimozide*, *thiothixene*, *trifluoperazine*, *loxapine*, *molindone*, *chlorpromazine*, *mesoridazine*, *thioridazine*, *fluspirilene*, *penfluridol*, *pipothiazine*, *flupenthixol*, *clozapine*, *olanzapine*, *risperidone*, *quetiapine*, *ziprasidone*, *aripiprazole*, *amisulpride*, and *clinical trial*. Randomized, double-blind, placebo-controlled trials and open-label studies with a minimum of 20 subjects with a DSM-III/IV or ICD-10 diagnosis of anxiety disorder and studies without a DSM-III/IV or ICD-10 diagnosis of anxiety disorder but with Hamilton Rating Scale for Anxiety (HAM-A) scores as an outcome were prioritized. Studies on bipolar disorder or major depressive disorder with the analysis of changes in anxiety symptoms were reviewed. Early studies on neurosis/anxiety or anxious depression without a HAM-A component were also reviewed.

Data Synthesis: Six trials in primary generalized anxiety disorder (GAD), 15 in refractory obsessive-compulsive disorder (OCD), 8 in posttraumatic stress disorder (PTSD), 6 in neurosis with the HAM-A, 1 in social phobia, and 2 in anxiety symptoms in bipolar depression were identified. Low doses of trifluoperazine were superior to placebo in the treatment of GAD. Most of the less well-designed studies showed that other typical antipsychotics might be superior to placebo or as effective as benzodiazepines in the treatment of GAD and other anxiety conditions. In most studies, risperidone, olanzapine, and quetiapine augmentation to antidepressants was superior to placebo in treating refractory OCD and PTSD. Both olanzapine and quetiapine significantly reduced anxiety compared to placebo in studies of bipolar depression.

Conclusion: Except for trifluoperazine, there is no large, well-designed study of antipsychotics in the treatment of primary or comorbid anxiety symptoms or disorders. The efficacy of these agents in various anxiety conditions needs to be further investigated with large, well-designed comparison studies.

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Anxiety disorder has the highest prevalence of any mental illness. It can manifest as a primary disorder or comorbid with other psychiatric disorders such as major depressive disorder (MDD), bipolar disorder, schizophrenia, or substance use disorders. Similar to anxiety disorders, subthreshold anxiety symptoms and disorders are also very common[1–4] and can be present alone or comorbid with other psychiatric disorders. These subthreshold comorbidities also have a negative impact on patients' quality of life and treatment response.[5–9] Comorbid anxiety disorders in patients with bipolar disorder are more prevalent than traditionally believed[9–13] and have negative impact on the treatment outcome and quality of life of these patients.[14–20] Currently, options for treating primary anxiety disorders include tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors, and other antidepressant agents. Benzodiazepines are commonly used for patients with generalized anxiety disorder (GAD) and panic disorder (PD) if substance use disorder is not a concern. Buspirone has been approved for treatment of GAD, but its efficacy in other anxiety conditions is limited. Although generally effective in the treatment of pri-

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mary anxiety disorders, current available anxiolytics are far from perfect. Refractory cases of patients with primary anxiety disorder(s) have been reported during treatment with current agents.[21–25]

Patients with MDD and comorbid anxiety can be treated with current available agents without much concern except for benzodiazepines in those patients with comorbid substance use disorder. The management of comorbid anxiety in patients with bipolar disorder is far more challenging than that in nonbipolar patients. Antidepressants, although still thought controversial,[26] may trigger mania or destabilize the course of the bipolar illness.[27,28] Benzodiazepines, the second-line agents for most patients, may be riskier to prescribe for patients with bipolar disorder and substance use disorder because (1) patients with severe mental illness and substance use disorder have an increased risk of abuse or dependence on prescribed benzodiazepines[29] and (2) co-occurrence of anxiety disorder and substance use disorder is common, especially in patients with bipolar disorder.[9,30–33] It is clear that the search for alternative treatments for those patients with bipolar disorder and anxiety disorder with or without a substance use disorder and those patients unresponsive to current available agents presents an unmet urgent need.

Typical antipsychotics, "the major tranquilizers," have been studied extensively, although with methodological problems, for the treatment of a variety of anxiety symptoms and disorders as monotherapy or combination therapy with tricyclic antidepressants,[34–54] but they have never been widely accepted, especially in the United States, because of the fear of the irreversible side effect, tardive dyskinesia. With the realization of the imperfect effect of SSRIs in the treatment of primary anxiety disorders, especially obsessive-compulsive disorder (OCD) and chronic posttraumatic stress disorder (PTSD), the interest in antipsychotics, especially the atypicals, in the treatment of anxiety disorders has reemerged.[55–78] However, there is no pharmacologic study designed for a cohort of patients with bipolar disorder and a specific comorbid anxiety disorder or a large study of atypical antipsychotics in patients with primary GAD. The purpose of this article is to review the efficacy of typical and atypical antipsychotics in the treatment of anxiety in patients with primary anxiety disorder, MDD, or bipolar disorder to provide a foundation for future studies and optimized clinical management.

DATA SOURCES

English-language literature cited in MEDLINE from January 1, 1968, to December 31, 2005, was searched with the terms *anxiety disorder*, *anxiety symptoms*, *generalized anxiety disorder*, *panic disorder*, *obsessive-compulsive disorder*, *posttraumatic stress disorder*, *social phobia*, *bipolar disorder*, *major depressive disorder*, *Hamilton Rating Scale for Anxiety*, *antipsychotics*, *typical antipsychotics*, *atypical antipsychotics*, *fluphenazine*, *haloperidol*, *perphenazine*, *pimozide*, *thiothixene*, *trifluoperazine*, *loxapine*, *molindone*, *chlorpromazine*, *mesoridazine*, *thioridazine*, *fluspirilene*, *penfluridol*, *pipothiazine*, *flupenthixol*, *clozapine*, *olanzapine*, *risperidone*, *quetiapine*, *ziprasidone*, *aripiprazole*, *amisulpride*, and *clinical trial*. Randomized, double-blind, placebo-controlled trials and open-label studies with a minimum of 20 subjects with a DSM-III/IV or ICD-10 diagnosis of anxiety disorder and studies without a DSM-III/IV or ICD-10 diagnosis of anxiety disorder but with the Hamilton Rating Scale for Anxiety (HAM-A) as an outcome measure were prioritized. Studies on bipolar disorder or MDD with the analysis of changes in anxiety symptoms were reviewed. Early studies on neurosis/anxiety or anxious depression without an HAM-A component were also discussed.

DATA SYNTHESIS

This search uncovered 6 clinical trials with DSM-III/IV or ICD-10 diagnoses of primary GAD,[50–55] 6 of neurosis with the HAM-A,[43–47] 15 of refractory OCD,[56–70] 8 of PTSD,[71–77] 1 of social phobia (SP),[78] and 2 of bipolar depression with secondary analysis of anxiety symptoms[79,80] (Tables 1–3).

Antipsychotics in the Treatment of Primary GAD

Although there is a long history of interest in antipsychotics in the treatment of anxiety disorders, the data in the treatment of GAD were limited to the typical agents until recently.[55] The dilemma between the efficacy of benzodiazepines in GAD and the potential of abuse/dependence propelled investigators to find alternatives. Prior to the early 1980s, researchers used different inclusion criteria for anxiety studies under the umbrella of neurosis or anxiety.[34–49] Most of these studies were head-to-head comparisons of an antipsychotic, a benzodiazepine, a tricyclic antidepressant, and/or placebo. Their outcome measures were also variable, from self-defined rating scales[34,35] and currently uncommonly used standardized scales[36–40] to the currently still widely used HAM-A.[41–46] The overall impression was that typical antipsychotics were as effective as benzodiazepines or tricyclic antidepressants but superior to placebo in the treatment of a variety of anxiety symptoms (Table 1).

After the publication of the official DSM-III in 1980, Mendels and colleagues[50] published the first large, randomized, double-blind, placebo-controlled trial of trifluoperazine in the short-term treatment of GAD according to DSM-III diagnosis in 1986. In this multicenter study, 415 patients with moderate to severe symptoms of GAD (HAM-A score ≥ 20) were randomly assigned to receive 2 to 6 mg/day of trifluoperazine (N = 207) or

placebo (N = 208) for 4 weeks. The efficacy was assessed with the HAM-A and other scales. The Hopkins Symptom Checklist was also used to provide a subjective measure of the emotional state for each patient. More than 85% of patients completed the study. Trifluoperazine showed superiority to placebo in all outcome measures including HAM-A total scores and subscores (Table 1). Although adverse experiences were more common in trifluoperazine treatment compared with placebo, 69% versus 46%, the discontinuation rate due to adverse effects was low: 5.7% for trifluoperazine-treated patients and 4.1% for placebo. Based on this landmark study, in 2001, trifluoperazine was approved by the U.S. Food and Drug Administration for the short-term treatment of nonpsychotic GAD.

Because of the skepticism regarding the effectiveness of benzodiazepines in primary GAD,[81] the efficacy of bromazepam was compared with placebo and chlorprothixene, a thioxanthene typical antipsychotic.[52] In this 3-arm randomized, double-blind trial, 245 patients with DSM-III GAD were treated for 2 weeks with 2 daily doses of bromazepam 3 mg, chlorprothixene 15 mg/day, or placebo. After 2 weeks of treatment, median reductions in HAM-A scores were 12 points for bromazepam, 10.3 for chlorprothixene, and 7.3 for placebo in the 239 patients eligible for analysis. The study revealed significant superiority of bromazepam over placebo but not over chlorprothixene (Table 1). Because the duration of this study was too short in comparison with most recent anxiety efficacy studies (8–24 weeks), the true differences between chlorprothixene and bromazepam might be obscured.

The dose-effect relationship between the magnitude of anxiolysis and an antipsychotic was explored with fluspirilene, a diphenylbutylpiperidine typical antipsychotic that is available in Europe and other countries.[51] In this randomized, double-blind, without placebo study, 106 patients with DSM-III GAD (67.9%), PD (22.6%), OCD (5.7%), and anxiety disorder unspecified (3.8%) randomly received 0.5 mg (N = 35), 1.0 mg (N = 35), or 1.5 mg (N = 35) of fluspirilene weekly for 6 weeks. At the end of the study, there was significant difference between all groups according to physician's judgment and HAM-A scores, with higher doses having more reductions in anxiety symptoms (Table 1).

More recently, the efficacy and safety of olanzapine in the treatment of GAD were explored in a study of 24 patients who failed 6 weeks of fluoxetine 20-mg/day treatment (Table 1).[55] These refractory cases were randomly assigned to receive either addition of olanzapine (mean ± SD dose of 8.7 ± 7.1 mg/day) or placebo to the ongoing fluoxetine treatment for 6 weeks. Among the 20 patients eligible for analysis, olanzapine resulted in a greater proportion of responders based on a Clinical Global Impressions (CGI)-Severity of Illness scale endpoint score of 1 or 2 ("Not ill at all" or "borderline ill") or a 50% reduction in HAM-A score ($p < .05$). There were no other significant differences between olanzapine and placebo augmentation in other efficacy measures.

Antipsychotics in the Treatment of Refractory OCD

Prior to the introduction of SSRIs, chlomipramine (chlorimipramine) was commonly used for the treatment of OCD, either alone or in combination with benzodiazepines or typical antipsychotics. In one of the early studies, Cassano et al.[49] reported that there were no differences among the 3 groups, chlorimipramine, chlorimipramine-haloperidol, and chlorimipramine-diazepam, in the treatment of phobic-obsessive psychoneurosis as measured with the Brief Psychiatric Rating Scale and Inpatient Multidimensional Psychiatric Scale. However, in the predifference and postdifference analysis, the chlorimipramine-haloperidol combination had the most remarkable effect on phobic symptoms, tension, anxiety, and excitement.

In 1994, McDougle and colleagues[56] explored the role of haloperidol in the treatment of DSM-III OCD refractory to fluvoxamine in a randomized, double-blind, placebo-controlled haloperidol augmentation study (Table 2). Sixty-two patients with a primary diagnosis of OCD with and without tics received placebo fluvoxamine for 1 week followed by 8 weeks of active fluvoxamine. Thirty-four patients who were refractory to fluvoxamine were randomly assigned to either haloperidol (N = 17) or placebo (N = 17) in addition to the ongoing treatment for 4 weeks. All 34 patients completed the study. Haloperidol addition was significantly better than placebo in reducing the Yale-Brown Obsessive Compulsive Scale (YBOCS) scores. Eleven of 17 patients responded (≥ 35% improvement) to haloperidol compared with none of the 17 patients given placebo.

With the introduction of atypical antipsychotics and the challenge of managing refractory OCD (ROCD), investigators quickly switched their focus on the augmentation of these agents to SSRI treatment of OCD. After a small open-label, positive study of risperidone augmentation to the treatment of ROCD,[57] the efficacy of risperidone in ROCD was further assessed with open-label and double-blind, placebo-controlled trials[58–62] (Table 2). In the first randomized, double-blind, placebo-controlled study,[58] 70 adult patients with a primary DSM-IV diagnosis of OCD received a 12-week SSRI treatment initially. Thirty-six patients who were refractory to the treatment were randomly assigned to receive a 6-week addition of risperidone (mean ± SD dose of 2.2 ± 0.7 mg/day, N = 20) or placebo (N = 16). Those patients treated with placebo subsequently received an identical open-label trial of risperidone addition. For study completers, 9 of 18 risperidone-treated patients were responders (≥ 35% improvement in the YBOCS) compared with 0 of 15 in the placebo group ($p < .005$). For those patients who initially received placebo, 7 of 14 responded during

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Table 1. Clinical Trials of Typical and Atypical Antipsychotics in the Treatment of Generalized Anxiety Disorder (GAD), Neurosis, and Anxiety Symptoms in Bipolar Depression

Trial	Index	Study Design	Treatment Arm	Duration, wk	Reduction of HAM-A Score[a]
Atypical antipsychotic agent					
Olanzapine[55]	Refractory GAD	RCT	Olanzapine mean ± SD dose of 8.7 ± 7.1 mg/d (N = 10) or placebo (N = 10) added to fluoxetine 20 mg/d (N = 20)	6	Olanzapine vs placebo 50% reduction in responders, $p < .05$
Olanzapine and OFC[79]	Bipolar I depression	RCT	Olanzapine 9.7 mg/d (N = 309), olanzapine 7.4 mg/d + fluoxetine 39.3 mg/d (N = 71), or placebo (N = 315)	8	Olanzapine vs placebo, $p = .002$ OFC vs placebo, $p < .001$ Olanzapine vs OFC, p = NS
Quetiapine[80]	Bipolar I and II depression	RCT	Quetiapine 600 mg/d (N = 180), quetiapine 300 mg/d (N = 181), or placebo (N = 181)	8	Quetiapine 600 mg vs placebo, $p < .05$ Quetiapine 300 mg vs placebo, $p < .05$
Typical antipsychotic agent					
Chlorprothixene[52]	GAD	RCT	Chlorprothixene 15 mg/d (N = 93), bromazepam 6 mg/d (N = 97), or placebo (N = 49)	2	Bromazepam vs placebo, $p < .05$ Bromazepam vs chlorprothixene, $p > .10$
Flupenthixol[53]	GAD	RCT	Flupenthixol 1 mg/d (N = 15) or placebo (N = 16)	4	Flupenthixol vs placebo, p = NS
Trifluoperazine[50]	GAD	RCT	Trifluoperazine 2–6 mg/d (N = 207) or placebo (N = 208)	4	Trifluoperazine vs placebo, $p < .001$
Haloperidol[44]	Neurotic anxiety	RCT	Haloperidol 1.02 mg/d (N = 19) or placebo (N = 20)	4	HAM-A-EC, haloperidol vs placebo, $p < .07$
Pimozide[43]	SPFD	RCT	Pimozide 2 mg/d (N = 24), diazepam 10 mg/d (N = 25), or placebo (N = 26)	4	HAM-A-P, pimozide vs placebo, $p = .006$ HAM-A-P, diazepam vs placebo, $p = .09$ HAM-A-S, pimozide vs placebo, $p = .046$ HAM-A-S, diazepam vs placebo, $p = .30$ Pimozide vs diazepam, p = NS
Melperone[46]	Anxious neurosis	RCT	Melperone 30 mg/d (N = 18), melperone 75 mg/d (N = 19), or placebo (N = 23)	2	Melperone 30 mg vs placebo, $p < .01$ Melperone 75 mg vs placebo, $p < .001$ Melperone 30 mg vs melperone 75 mg, p = NS
Fluspirilene[51]	GAD (67.9%) PD (22.6%) OCD (5.7%) NOS (3.8%)	Randomized, double-blind	Fluspirilene 0.5 mg/wk (N = 35), fluspirilene 1.0 mg/wk (N = 35), or fluspirilene 1.5 mg/wk (N = 36)	6	$p < .001$ for all groups $p < .01$ between groups
Fluspirilene vs bromazepam[47]	MMPI neurotic disorder	Randomized, double-blind	Fluspirilene 1.5 mg IM/wk + placebo/d (N = 22) or bromazepam 6 mg/d + placebo IM/wk (N = 23)	6	Fluspirilene vs bromazepam, p = NS HAM-A-P, fluspirilene vs bromazepam, $p < .05$
Loxapine vs chlordiazepoxide[45]	Neurotic anxiety	Randomized, double-blind	Loxapine maximal 20 mg/d (N = 24) or chlordiazepoxide maximal 100 mg/d (N = 28)	4	Loxapine vs chlordiazepoxide, p = NS
Fluspirilene[54]	GAD	Open-label	Fluspirilene 1.5 mg/wk (N = 205)	6	Early signs of side effects were predictors of poor response

[a]The outcome only listed the difference in the reduction of HAM-A scores and a few other outcome measures.

Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety; HAM-A-EC = Hamilton Rating Scale for Anxiety-emotional cluster; HAM-A-P = Hamilton Rating Scale for Anxiety-psychic anxiety subscale; HAM-A-S = Hamilton Rating Scale for Anxiety-somatic anxiety subscale; IM = intramuscular injection; MMPI = Minnesota Multiphasic Personality Inventory; NOS = anxiety disorder unspecified; NS = not significant; OCD = obsessive-compulsive disorder; OFC = olanzapine-fluoxetine combination; PD = panic disorder; RCT = randomized, double-blind, placebo-controlled trial; SPFD = stress-induced psychic and functional disorder.

Table 2. Clinical Trials of Antipsychotic Addition to the Treatment of Antidepressant-Refractory Obsessive-Compulsive Disorder (ROCD)

Trial	Index	Study Design	Treatment Arm[a]			Duration, wk	Outcome[b]
Atypical antipsychotic agent							
Amisulpiride[70]	ROCD to 12 wk antidepressant	OLP	Amisulpiride mean ± SD dose of 325 ± 106 mg/d (N = 20)	added to	Sertraline 100–200 mg/d (N = 7) Paroxetine 30–60 mg/d (N = 6) Fluoxetine 40–60 mg/d Venlafaxine 150–225 mg/d	12	Baseline vs endpoint YBOCS (p = .0001)
Olanzapine[69]	ROCD to 8 wk fluoxetine	RCT	Olanzapine 5–10 mg/d (N = 22) or placebo (N = 22)	added to	Fluoxetine 40 mg/d (N = 44)	6	Olanzapine vs placebo YBOCS (p = NS)
Olanzapine[68]	ROCD to 12 wk SSRI	RCT	Olanzapine mean ± SD dose of 11.2 ± 6.5 mg (N = 13) or placebo (N = 13)	added to	Fluoxetine 60 mg/d (N = 16) Paroxetine 80 mg/d (N = 7) Clomipramine 200–250 mg/d (N = 2)	6	Olanzapine vs placebo YBOCS (p = .04) HAM-A (p = NS)
Olanzapine[67]	ROCD to 12 wk paroxetine	OLP	Olanzapine 10 mg/d (N = 21)	added to	Paroxetine 60 mg/d (N = 21)	12	Baseline vs endpoint YBOCS (p < .001)
Olanzapine[66]	ROCD to 6 mo fluvoxamine	OLP	Olanzapine 5 mg/d (N = 23)	added to	Fluvoxamine 300 mg/d (N = 23)	12	Baseline vs endpoint YBOCS (p < .0005)
Quetiapine[64]	ROCD to 8 wk SSRI	RCT	Quetiapine 300 mg/day (N = 20) or placebo (N = 20)	added to	Paroxetine 20–60 mg/d (N = 14) Citalopram 20–60 mg/d (N = 11) Fluoxetine 20–60 mg/d Fluvoxamine 50–200 mg/d Venlafaxine 300 mg/d Clomipramine 75 mg/d	8	Quetiapine vs placebo YBOCS (p < .001) HAM-A (p = .019)
Quetiapine[63]	ROCD to 12 wk antidepressant	RCTS	Quetiapine 50–200 mg/d (N = 14) or placebo (N = 13)	added to	Clomipramine 300 mg/d Fluvoxamine 300 mg/d Fluoxetine 80 mg/d	8	Quetiapine vs placebo YBOCS (p < .05)
Quetiapine[65]	ROCD to ≥ 10 wk antidepressant	OLP	Quetiapine mean ± SD dose of 116 ± 72 to 169 ± 57 mg/d (N = 30)	added to	Fluvoxamine 100–400 mg/d (N = 12) Citalopram 40–120 mg/d (N = 7) Fluoxetine 20–60 mg/d (N = 5)	8	Baseline vs endpoint YBOCS (p < .01 at site 1 but not site 2)
Risperidone[58]	ROCD to 12 wk SSRI	RCT	Risperidone mean ± SD dose of 2.2 ± 0.7 mg/d (N = 20) or placebo (N = 16)	added to	Fluvoxamine 300 mg/d (N = 17) Fluoxetine 40–80 mg/d Paroxetine 40 mg/d Clomipramine 150–250 mg/d Sertraline 150–250 mg/d	6	Risperidone vs placebo YBOCS (p < .001) HAM-A (p = .003)
Risperidone[60]	ROCD to 12 wk antidepressant	RCT	Risperidone mean ± SD dose of 2.25 ± 0.86 mg/d (N = 10) or placebo (N = 6)	added to	Fluoxetine 60 mg/d Fluvoxamine 150 mg/d Citalopram 60 mg/d Sertraline 150 mg/d Venlafaxine 325 mg/d Clomipramine 200 mg/d	12	Risperidone vs placebo YBOCS (p = .115)
Risperidone[62]	ROCD to 12 wk fluvoxamine	RCT, R&N	Risperidone 0.5 mg/d (N = 20) or placebo (N = 19)	added to	Fluvoxamine 150–300 mg/d	6	Risperidone vs placebo YBOCS (p < .001 only in nonresponders)
Risperidone[61]	ROCD to 12 wk SSRI	RCTC	Risperidone 1 mg/d (N = 12), haloperidol 2 mg/d (N = 12), or placebo (N = 12)	added to	Paroxetine ≥ 40 mg/d Fluoxetine ≥ 40 mg/d Sertraline ≥ 100 mg/d Fluvoxamine ≥ 200 mg/d	9	Haloperidol vs placebo YBOCS (p = .006) Risperidone vs placebo YBOCS (p = .065)

continued

Table 2. Clinical Trials of Antipsychotic Addition to the Treatment of Antidepressant-Refractory Obsessive-Compulsive Disorder (ROCD) (cont.)

Trial	Index	Study Design	Treatment Arm[a]			Duration, wk	Outcome[b]
Risperidone[57]	ROCD to 12 wk antidepressant	OLP	Risperidone 2.75 mg/d (N = 21)	added to	Clomipramine Fluoxetine Fluvoxamine Paroxetine Sertraline	Variable	Substantial reduction in OCD symptoms
Risperidone[59]	ROCD to 6 mo antidepressant	OLP	Risperidone 3 mg/d (N = 20)	added to	Sertraline 100 mg/d (N = 7) Clomipramine 200–300 mg/d (N = 7) Fluoxetine 40–60 mg/d Fluvoxamine 250 mg/d	8	Baseline vs endpoint YBOCS ($p < .001$)
Typical antipsychotic agent							
Haloperidol[56]	ROCD to 8 wk fluvoxamine	RCT	Haloperidol mean ± SD dose of 6.2 ± 3.0 mg/d (N = 17) or placebo (N = 17)	added to	Fluvoxamine 282–300 mg/d (N = 34)	4	Haloperidol vs placebo YBOCS ($p < .005$)

[a]The listed number of patients highlights the antidepressants taken by patients in each individual study.
[b]The outcome only listed the difference in the reduction of YBOCS and HAM-A scores.
Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety; NS = not significant; OLP = open-label prospective study; R&N = responder and nonresponder; RCT = randomized, double-blind, placebo-controlled trial; RCTC = randomized, double-blind, placebo-controlled crossover trial; RCTS = randomized, single-blind, placebo-controlled trial; SSRI = selective serotonin reuptake inhibitor; YBOCS = Yale-Brown Obsessive Compulsive Scale.

the open-label risperidone addition. In contrast to a favorable response of patients with comorbid tic disorder to haloperidol treatment,[56] there was no difference between patients with and without a tic disorder in response to risperidone. Furthermore, an early open-label risperidone addition study showed that patients with tics had the lowest rate of response and highest rate of akathisia.[57]

More recently, the efficacy of risperidone and haloperidol augmentation to SSRI treatment of ROCD was compared in a randomized, double-blind, placebo-controlled crossover study (Table 2).[61] Sixteen patients with OCD refractory to a minimal 12-week SSRI treatment (YBOCS obsession scores ≥ 10 and total scores ≥ 16) were randomly assigned to receive 2 weeks of placebo, risperidone (1 mg/day), or haloperidol (2 mg/day) after a 1-week single-blind period. The patients received the 3 treatments in different sequences in a crossover fashion with a 1-week placebo washout period between each treatment. In the completer analysis (risperidone phase N = 12, haloperidol phase N = 7), both risperidone and haloperidol significantly reduced YBOCS obsession scores compared with placebo. Haloperidol decreased total YBOCS score significantly compared with placebo, but risperidone did not ($p = .065$). There was no difference between risperidone and haloperidol. However, haloperidol demonstrated a stronger and significant reduction in total YBOCS score relative to placebo. The overall treatment effect for compulsion was not significant. This study was confounded by a small sample size, crossover design, and a relatively low dose of risperidone.

Furthermore, differential responses of patients with or without ROCD to risperidone addition were also assessed in a double-blind, placebo-controlled fashion (Table 2).[62] Forty-five inpatients with at least a 1-year history of OCD, more than a 3-week drug-free period, and no previous adequate antiobsessional treatments were openly treated with 12 weeks of fluvoxamine; both responders (≥ 35% reduction in YBOCS scores and a CGI rating ≥ "much improved") and nonresponders were randomly assigned to receive risperidone 0.5 mg/day or placebo for 6 weeks. During the double-blind phase, of the 39 completers, the effect of risperidone add-on treatment was significant only in the fluvoxamine-resistant subgroup (N = 20) and not in the responders' group (N = 19). On the contrary, fluvoxamine responders taking risperidone showed a poorer outcome compared with those taking placebo. This study is innovative of randomized responders but confounded by a small sample size and different severity at randomization of nonresponders: 26.4 points on the YBOCS for placebo versus 30.9 points for risperidone.

The efficacy of quetiapine in the treatment of ROCD was also investigated (Table 2).[63–65] In a double-blind, randomized, placebo-controlled trial,[64] 40 patients with OCD refractory to at least 2 different SSRIs at a maximum tol-

erated dose for 8 weeks were randomly assigned to an 8-week addition of a fixed dose of quetiapine 300 mg/day on day 8 (N = 20) or placebo (N = 20). In an intent-to-treat last-observation-carried-forward (LOCF) analysis, quetiapine-treated patients had a significant decrease in YBOCS scores compared with those in the placebo group. Eight of 20 patients in the quetiapine group were responders (≥ 35% improvement in YBOCS scores and final CGI-Improvement scale ratings of 1 or 2) compared with 2 of 20 in the placebo group. These results are consistent with those of a single-blind (rater blind), placebo-controlled study [63] and an open-label study.[65]

Olanzapine in the treatment of ROCD produced inconsistent results (Table 2).[66–69] In 2004, Bystritsky and colleagues[68] published the first double-blind study of olanzapine augmentation to SSRI treatment of ROCD. Twenty-six patients who had not responded to a 12-week SSRI treatment were treated with a 6-week addition of either olanzapine (up to 20 mg/day, mean dose = 11.2 mg/day) or placebo. In an LOCF analysis, there was a mean decrease in YBOCS score of 4.2 points in the olanzapine group compared with a 0.54-point increase in the placebo group. Six of 13 patients were responders (≥ 25% improvement in YBOCS score) in the olanzapine group compared with none in the placebo group. This result was consistent with those of early open-label studies.[66,67]

However, Shapira et al.[69] reported that there was no additional advantage of adding olanzapine (5–10 mg/day) to fluoxetine (N = 22) over placebo addition (N = 22) in the treatment of ROCD to an initial 8-week fluoxetine treatment, with significant decrease from baseline in YBOCS scores in both treatment arms but no difference in changes in YBOCS scores between the 2 arms. They opined that an unsteady level of OCD severity at study entry might be responsible for the negative findings.

Antipsychotics in the Treatment of PTSD

With the official introduction of PTSD in the DSM-III and the awareness of this disorder in both medical and public sectors, more and more cases of PTSD have been diagnosed and treated. Currently, SSRIs are the first-line treatment of PTSD.[82] However, response rates rarely exceed 60%, and even fewer patients (20%–30%) experience improvement that could be characterized as remission. On the other hand, psychotic symptoms are also relatively common in this population[83] that is less responsive to conventional treatment. Early case reports suggested that thioridazine and clozapine might be effective in treating comorbid psychosis as well as core PTSD symptoms,[84,85] but no well-designed study of antipsychotics in PTSD existed until recently.

Similar to the OCD studies, the results of olanzapine in the treatment of PTSD were inconsistent (Table 3).[71–73] In the first 10-week, double-blind, placebo-controlled study,[71] 15 patients were randomly assigned 2:1 to either olanzapine (5–20 mg/day) or placebo. Patients in both groups showed improvement in PTSD symptoms with no between-group differences.

In the second double-blind, placebo-controlled study,[73] olanzapine was added for patients with combat-related PTSD (N = 19) who were minimally responsive to a 12-week SSRI treatment at maximal tolerated doses. After 8 weeks of augmentation, the olanzapine group was associated with significantly greater reduction in specific measures of posttraumatic, depressive, and sleep disorder symptoms than the placebo group. However, clinician-rated global response rates did not significantly differ between groups. These results are inconsistent with the results of a relatively larger open-label study (N = 48 enrolled in the study, N = 46 eligible for analysis).[72]

The first randomized, placebo-controlled study of risperidone adjunctive therapy was carried out in 40 combat veterans who had chronic PTSD with psychotic symptoms and received steady treatment of antidepressants and other psychotropics for at least 1 month prior to and during the study (Table 3).[74] Risperidone (maximum dose of 6 mg/day, N = 20 randomized, N = 19 eligible for analysis) or placebo (N = 20 randomized, N = 18 eligible for analysis) was added for 5 weeks. An intent-to-treat LOCF analysis (N = 37) showed that risperidone-treated patients had a moderate but significantly greater decrease from baseline in the scores of the Positive and Negative Syndrome Scale (PANSS total scores) than placebo-treated patients. Clinician-Administered PTSD Scale (CAPS) ratings declined significantly in both groups, but did not differ significantly between groups. However, CAPS re-experiencing subscale scores had significantly greater improvement in the risperidone-treated patients at week 5 in the completer analysis (risperidone N = 10, placebo N = 12).

The second randomized, placebo-controlled study of risperidone adjunctive therapy in the treatment of chronic combat-related PTSD produced more robust results (Table 3).[75] Sixty-five of 73 veterans with PTSD were randomly assigned to receive addition of risperidone (3 mg/day) or placebo to their ongoing treatments including antidepressants (N = 57), anxiolytics (N = 21), hypnotics (N = 18), and no medication (N = 5) for 16 weeks with an initial 5-week residential treatment. Of the 65 randomly assigned patients, 48 completed the entire 4-month period. In a mixed-model repeated-measure analysis, there were no differences between the 2 groups in the reduction in HAM-A, Hamilton Rating Scale for Depression, and PANSS-positive symptom subscale (PANSS-P) scores at week 4, with significant reductions in the scores of these scales from baseline within both groups. However, at the end of week 16, the risperidone group had significantly more reduction in total CAPS and CAPS hyperarousal subscale scores as well as HAM-A and PANSS-P scores than placebo. CAPS item analysis on sleep disturbance,

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Table 3. Clinical Trials of Antipsychotics in the Treatment of Posttraumatic Stress Disorder (PTSD) and Social Phobia

Trial	Index	Study Design	Treatment Arm			Duration, wk	Outcome
Olanzapine[71]	PTSD	RCT monotherapy	Olanzapine 14.1 mg/d (N = 10) or placebo (N = 5)			10	Olanzapine vs placebo SIP (p = NS) TOP-8 (p = NS) DTS (p = NS) SDS (p = NS)
Olanzapine[73]	PTSD resistant to 12 wk SSRI	RCT add-on	Olanzapine 15 mg/d (N = 10) or placebo (N = 9)	added to	Fluoxetine 40 mg/d (N = 5) Paroxetine 40 mg/d (N = 7) Sertraline 200 mg/d (N = 7)	8	Olanzapine vs placebo CAPS (p < .05) PSQI (p < .01)
Olanzapine[72]	PTSD	OLP monotherapy	Olanzapine 14 mg/d (N = 46)			8	Baseline vs endpoint CAPS (p < .001) HAM-A (p < .001) BPRS (p < .005)
Olanzapine[78]	Social phobia	RCT monotherapy	Olanzapine 5–20 mg/d (N = 7) or placebo (N = 5)			8	Olanzapine vs placebo BSPS (p = .02) SPIN (p = .01) LSAS (p = .12) SDS (p = .50) CGI-I (p = .17)
Quetiapine[77]	PTSD	OLP add-on	Quetiapine mean ± SD dose of 100 ± 70 mg/d (N = 20)	added to	SSRIs (N = 16) Trazodone (N = 6) Tricyclics (N = 3) Sedative/hypnotics (N = 7) Anticonvulsants (N = 4)	6	Baseline vs endpoint CAPS (p < .0005) PANSS (p < .007) PSQI (p < .0005)
Risperidone[74]	PTSD, psychotic symptoms, PANSS score > 60	RCT add-on, 1 mo open lead-in	Risperidone maximal 6 mg/d (N = 19) or placebo (N = 18)	added to	Fluoxetine 20–40 mg/d (N = 8) Paroxetine 20–60 mg/d (N = 8) Sertraline 50–200 mg/d (N = 5) Nefazodone 200–400 mg/d (N = 8) Bupropion 300 mg/d (N = 1)	5	Risperidone vs placebo PANSS (p < .05) CAPS (p = NS)
Risperidone[75]	PTSD, CAPS score ≥ 65	RCT add-on	Risperidone 3 mg/d (N = 33) or placebo (N = 32)	added to	Antidepressants (N = 57) Anxiolytics (N = 21) Hypnotics (N = 18) No medication (N = 5)	16	Risperidone vs placebo CAPS (p < .05) CAPS hyperarousal (p < .01) HAM-A (p < .001) PANSS-P (p < .01)
Risperidone[76]	PTSD, psychotic, resistant to antidepressants	OLP monotherapy	Risperidone 2–4 mg/d (N = 27)			6	Baseline vs end of wk 3 or 6 PANSS (p < .05) PTSD-I (p < .05) CGI-S (p < .05)

Abbreviations: BPRS = Brief Psychiatric Rating Scale; BSPS = Brief Social Phobia Scale; CAPS = Clinician-Administered PTSD Scale; CGI-I = Clinical Global Impressions-Improvement scale; CGI-S = Clinical Global Impressions-Severity of Illness scale; DTS = Davidson Self-Rating; HAM-A = Hamilton Rating Scale for Anxiety; LSAS = Liebowitz Social Anxiety Scale; NS = not significant; OLP = open-label prospective study; PANSS = Positive and Negative Syndrome Scale; PANSS-P = Positive and Negative Syndrome Scale-positive symptoms subscale; PSQI = Pittsburgh Sleep Quality Inventory; PTSD-I = PTSD Interview; RCT = randomized, double-blind, placebo-controlled trial; SDS = Sheehan Disability Scale; SIP = Structured Interview for PTSD; SPIN = Social Phobia Inventory; SSRI = selective serotonin reuptake inhibitor; TOP-8 = Treatment Outcome PTSD scale.

subjective disturbance, impairment in social functioning, and global severity of PTSD symptoms showed significantly greater improvement in patients treated with risperidone than in those treated with placebo, but no difference in the reexperiencing subscale.

Antipsychotics in the Treatment of SP

Like the treatment of other anxiety disorders, the current available agents for SP most often produce partial symptomatic improvement rather than high end-state functioning.[86] The possible role of antipsychotics in the treatment of SP was explored in 12 patients in an 8-week, double-blind, olanzapine monotherapy (mean dose of 9 mg/day, N = 7) versus placebo (N = 5) study (Table 3).[78]

Antipsychotics in the Treatment of Anxiety Symptoms and Disorders in Bipolar Disorder

There were 2 large randomized, double-blind, placebo-controlled trials of olanzapine and quetiapine in the acute treatment of bipolar depression.[79,80] Their efficacy in the treatment of bipolar depression was reviewed elsewhere.[87] In both studies, changes in HAM-A scores were used as secondary outcome measures. In the olanzapine (mean dose of 9.7 mg/day) and olanzapine-fluoxetine combination (OFC, mean dose of 7.4/39.3 mg/day) versus placebo 8-week study,[79] HAM-A scores of 695 patients (placebo N = 315, olanzapine N = 309, and OFC N = 71) were analyzed. Both olanzapine and OFC were significantly superior to placebo in reducing HAM-A total scores, but there was no difference between olanzapine monotherapy and OFC.

In the quetiapine study,[80] changes in HAM-A scores of 542 patients (360 bipolar I, 182 bipolar II) were analyzed in 3 treatment groups: quetiapine 600 mg/day (N = 180), quetiapine 300 mg/day (N = 181), and placebo (N = 181). Both doses of quetiapine significantly reduced HAM-A total scores compared with placebo. A post hoc analysis[88] showed that the significant reduction occurred as early as the end of week 1, and the items of anxious mood, depressed mood, insomnia, genitourinary symptoms, and tension separated quetiapine from placebo.

A preferential response of patients with OCD and bipolar disorder to a 6-week risperidone (3 mg/day) augmentation over those with OCD and MDD was shown in a subgroup analysis of an open-label study of patients with OCD (N = 20).[59] In addition to an overall significant reduction in the YBOCS total scores, patients with bipolar disorder (N = 8) had significantly greater reduction in YBOCS scores than those with MDD (N = 12) (33% versus 20%, $p < .001$). Because of other comorbidities, it is difficult to determine how much bipolar disorder or MDD had affected these differential decreases in YBOCS scores.

Antipsychotics in the Treatment of Anxiety Symptoms and Disorders in MDD

Comorbid anxiety, anxiety disorder, or subthreshold anxiety symptoms with depressive disorder is well known. Prior to the introduction of DSM-III diagnosis, the co-occurrence of anxiety and depression was commonly referred to as mixed anxiety/depressive states, illness, or conditions.[89–95] It is believed that anxious depression is only applied to MDD with subthreshold anxiety symptoms.[96] Randomized, double-blind studies of antipsychotics for this comorbidity are limited to typical antipsychotics. Overall, the combination of fluphenazine and nortriptyline did significantly better than an antidepressant or antipsychotic monotherapy in reducing depressive and anxiety symptoms. These studies were confounded by unstandardized methodologies.

DISCUSSION

To our knowledge, this article represents the first review of typical and atypical antipsychotics in the treatment of anxiety symptoms in patients with primary anxiety disorder, MDD, or bipolar disorder. The good quality data of typical antipsychotics in the short-term treatment of GAD are limited to trifluoperazine, which was well tolerated and superior to placebo in reducing anxiety symptoms. Data from most less well-designed studies suggest that low doses of typical antipsychotics are superior to placebo and appear to be as effective as benzodiazepines in the short-term treatment of GAD and neurotic anxiety, but well-designed, standardized, large sample size studies are needed to confirm these findings. Considering the methodological flaws of most of these studies and lack of long-term efficacy and safety data, typical antipsychotics should not be used as first-line agents for long-term treatment. The adjunctive use of the atypical antipsychotic agents appears useful in treatment-refractory OCD and chronic PTSD. Considering the nature of secondary analysis, the effect of quetiapine and olanzapine on anxiety during bipolar depression should be viewed with caution and as hypothetical.[79,80] The results of typical antipsychotics, either as monotherapy[89,90] or in combination with tricyclic antidepressants,[91–95] in the treatment of depression with anxiety symptoms and disorders should be interpreted cautiously because of methodological flaws. Since refractory cases occur across the whole spectrum of anxiety disorders and given the limitation of current anxiolytics to patients with bipolar disorder, short-term and long-term studies of the efficacy and safety of antipsychotics, especially the atypicals, in primary anxiety disorders, comorbid anxiety disorders, or subthreshold anxiety symptoms in MDD or bipolar disorder are worthy of systematic study. Before these data are available, the use of antipsychotics for anxiety symptoms and disorders should be cautiously justified.

Selective serotonin reuptake inhibitors, buspirone, benzodiazepines, tricyclic antidepressants, and other newer antidepressants are options for patients with GAD or MDD with anxiety. In those patients with comorbid substance use disorder, the use of benzodiazepines should be carefully documented and monitored in respect of its abuse/dependence potential. There was fair evidence that typical antipsychotics, especially trifluoperazine, were effective in the short-term treatment of GAD. Generally speaking, typical agents were well tolerated in patients with primary anxiety disorders for up to 6 weeks. One important factor was that the dose of antipsychotics was much lower than that recommended for schizophrenia. For example, maximal dose of trifluoperazine in the GAD study was 6 mg/day (2–6 mg/day),[50] but the recommended maximal dose for psychosis is 25 mg/day (effective dose 15–20 mg/day). This nonpsychotic effective dose for anxiety may also be applied to atypical antipsychotics. Taking the unknown long-term safety of antipsychotics in anxious patients and the chronicity of GAD into account, if it is indicated, an antipsychotic with minimal long-term side effects should be chosen regardless of the drug class. Although the anxiolytic effect of antipsychotics appeared to be positively correlated with the dosages,[51] an initial lower dose and slower titration can be key factors for success.

Besides the overall benefit of typical antipsychotics in patients with GAD, patients with some specific symptoms may benefit more from antipsychotics than from benzodiazepines or antidepressants. For instance, there was no difference in overall improvement of HAM-A scores between fluspirilene and bromazepam,[47] but fluspirilene was superior to bromazepam, especially in patients with more severe somatic anxiety. Fluspirilene also had a particularly favorable effect on deactivation, fatigue, depression, insecurity in social contact, and aggressiveness. Differential effects between pimozide and diazepam[43] and trifluoperazine and doxepin[48] were also reported. The symptom specificity of antipsychotics, antidepressants, and benzodiazepines on anxiety should be considered when monotherapy or combination therapy is indicated.

The efficacy of typical and atypical antipsychotics in the treatment of OCD most likely depends on the severity of the illness at the study entry. Patients without refractory OCD had limited or no benefit from antipsychotic augmentation to antidepressants over placebo,[49,69] and those with refractory OCD had significantly better response to antipsychotic augmentation than to placebo.[56–68,70] Seemingly, "refractory" status is a key factor for the benefit of antipsychotics in the treatment of OCD, but how to achieve refractory status and the criteria for refractory cases varied in different studies, which may account for the inconsistency of results among the studies. One criterion for refractory cases is the duration of SSRI treatment (≥ 12 weeks for most studies),[57–63,66–68,70] but duration is not a reliable indicator for the refractory determination. For example, in 1 study, patients who were defined as refractory after an 8-week SSRI treatment were true refractory cases as reflected by no significant improvement on placebo augmentation during the double-blind phase,[64] but in another study, patients continued showing significant improvement on placebo augmentation during the entire 6-week double-blind phase after an initial 8-week SSRI treatment.[69] The number of prior treatments is not necessary for refractory cases. In the risperidone augmentation to SSRI study,[58] 15 of 36 refractory patients had no previous SSRI trials but achieved a refractory state during a 12-week SSRI treatment. The involvement of the dopaminergic system in OCD has been reported and reviewed.[97,98] It is unclear whether antipsychotic monotherapy has any role in the treatment of OCD.

According to the American Psychiatric Association's *Practice Guideline for the Treatment of Patients With Acute Stress Disorder and Posttraumatic Stress Disorder* in 2004,[82] SSRIs were recommended as the first-line treatment based on 4 reasons: (1) they ameliorate all 3 PTSD symptom clusters (i.e., reexperiencing, avoidance/numbing, and hyperarousal), (2) they are effective treatments for psychiatric disorders that are frequently comorbid with PTSD (e.g., depression, PD, SP, and OCD), (3) they may reduce clinical symptoms (such as suicidal, impulsive, and aggressive behaviors) that often complicate management of PTSD, and (4) they have relatively few side effects. Atypical antipsychotics were carefully recommended for patients with psychotic features or when the first-line approaches were ineffective in controlling symptoms.

The preliminary data for atypical antipsychotics in the treatment of PTSD are promising, especially for psychotic symptoms, but generalizability may be limited because the majority of the study subjects were combat veterans. The benefit of patients with PTSD from atypical antipsychotics seemingly also depends on their disease severity. Patients in all 6 positive studies[72–77] had combat-related PTSD, and most of them had a chronic course or were refractory to treatment with SSRIs. In the negative study,[71] however, only 2 of 15 patients with PTSD were combat-related, and 14 of 15 were women. Most of the patients had rape-related PTSD. It is unclear whether the difference was due to the severity of illness, gender, or sample sizes. Another important factor is the treatment duration. In the study by Bartzokis et al.,[75] the conversion from no difference to significant difference from week 4 to week 16 between risperidone and placebo in the reduction of HAM-A and PANSS-P scores suggests that the benefit from antipsychotics may take a longer time.

Biological and familial research has shown that there are genetic connections between bipolar disorder and panic disorder.[99–101] Negative impacts of comorbid anxiety disorders on the outcome of patients with bipolar disorder

have been reported.[9–20] So far, however, there are still no data or consensus to guide clinicians to manage these comorbidities. With the controversy of antidepressant-induced manic switching in bipolar disorder,[26–28] and lack of evidence of the efficacy of antidepressants in anxious bipolar patients, a search for new agents for this population is urgently needed. Among the available pharmacologic agents, atypical antipsychotics can be viable alternatives because they have lower rates of extrapyramidal side effects and no or low risk of switching into mania. The preliminary data of olanzapine and quetiapine in reducing anxiety symptoms in bipolar depression and a greater response of patients with bipolar disorder and OCD to risperidone augmentation[59] suggest that atypical antipsychotics may be efficacious in the treatment of anxiety symptoms and disorders in patients with bipolar disorder. This hypothesis needs to be tested by well-designed, randomized, double-blind, placebo-controlled studies.

Similar to patients with bipolar disorder, patients with MDD also have a high prevalence of comorbid anxiety disorder or subthreshold anxiety symptoms. Data from the National Epidemiologic Survey on Alcoholism and Related Conditions have shown that more than a third of patients with current or lifetime MDD had comorbid anxiety disorders.[102] Among the patients with MDD in the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) trial, 46% were classified with anxious depression.[103] More importantly, subthreshold anxiety in MDD had an even worse impact on severity of MDD than an anxiety disorder in MDD as reflected by the fact that MDD patients with subthreshold anxiety had more frequent suicidal ideation, psychomotor retardation, sexual dysfunction, hypochondriacal ideation, weight loss, and diurnal variation of symptoms and less efficient response to antidepressants.[8] It is suggested that subthreshold anxiety should be treated as aggressively as anxiety disorders with current available agents. The role of antipsychotics in this population is unclear. A better efficacy of the combination of a typical antipsychotic with a tricyclic antidepressant than an antidepressant alone in anxious depressed patients suggests that an early addition of an antipsychotic may accelerate the recovery.

A detailed discussion on the theory and mechanism of anxiety is beyond the scope of this review. The neural basis for anxiety is complex and unclear, but it is believed that the amygdala plays a very important role in conditioned fear and anxiety in animals and anxiety disorder in humans.[104–106] Dysfunction of the mesolimbic dopaminergic system was observed in patients with OCD[97,98] or SP.[107,108] Preclinical studies have shown that anxiety-provoking environments increase dopamine release in the amygdala,[106] prefrontal cortex,[109,110] and other brain areas of mice or rats.[111] The increase in dopamine in the prefrontal cortex during stress or anxiogenic administration can be totally blocked by anxiolytics, such as diazepam,[112] or antidepressants.[113,114] It is well known that excessive release of dopamine caused by stimulants such as amphetamine or cocaine can produce anxiety symptoms or panic attacks in humans. The anxiogenic-like response induced by chronic amphetamine treatment in rats was totally blocked by haloperidol injection before an anxiety behavioral test (elevated plus-maze).[115] Other typical and atypical antipsychotics could also block the acquisition of conditioned fear behavior.[116–118] These data suggest that it is possible to reduce anxiety through direct modulation of the dopamine system instead of through action of benzodiazepines and SSRIs.

The treatment of anxiety disorder may be complicated by occurrence of akathisia, a common movement side effect of antipsychotics, and to a lesser extent of antidepressants. Patients with akathisia are unable to sit or keep still and complain of inner restlessness or anxiousness.[119] There is no valid methodology to differentiate akathisia from preexisting anxiety. Worsening and changing patterns of symptoms after antipsychotic initiation or dose increase may be an indication of akathisia.[119] Other acute movement side effects such as dystonia and parkinsonism occur not only with typical antipsychotics, but also with atypicals, especially risperidone.[120]

Anxious patients treated with antipsychotics may have similar risks for metabolic complications as those patients with schizophrenia or bipolar disorder. Metabolic abnormalities have been reported in patients treated with typical or atypical antipsychotics.[121–123] Patients treated with antipsychotics should be closely monitored as recommended by the Consensus of the Mount Sinai Conference[124] and the Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes[125] regardless of the drug classes. In contrast to the extrapyramidal side effects and metabolic complications of antipsychotics, the tolerance, withdrawal, and abuse/dependence from benzodiazepines are the main concerns if they are prescribed. To minimize the risk of abuse or withdrawal, long half-life benzodiazepines should be used.

Anxiety is a very complicated phenomenon. Comorbidity with other Axis I disorders makes treatment of anxiety more challenging. So far, no single agent can be applied to all patients effectively and safely. A systemic consideration of the risk and benefit from antidepressants, antipsychotics, benzodiazepines, and other agents should be carried out before the initiation of a treatment. Physicians should not hesitate to change treatments if a side effect becomes a concern of an anxious patient, because early signs of side effects were predictors of poor response to fluspirilene.[54]

LIMITATION

This review is limited by the following restrictions: computer search, English language only, minimum of

20 patients for open-label studies, and studies with DSM-III/IV or ICD-10 diagnosis of anxiety disorder(s) or a HAM-A rating scale component only. Other studies containing valuable information may have been excluded because of these restricted criteria.

CONCLUSION

Low doses of trifluoperazine were well tolerated and superior to placebo in the short-term treatment of GAD, but there has never been a study of atypical antipsychotics in primary GAD or GAD comorbid with bipolar disorder or MDD. Although other typical antipsychotics appeared to be superior to placebo or as effective as benzodiazepines in the short-term treatment of GAD and other anxiety conditions, the results should be interpreted with caution because of the methodological flaws. Well-designed, large-sample studies are needed to confirm these findings. Haloperidol, risperidone, olanzapine, and quetiapine may be useful as adjunctive agents to SSRI treatment of refractory OCD or chronic PTSD. There exists an urgent need to conduct large sample size, randomized, controlled trials of the various atypical antipsychotic agents in patients with bipolar disorder comorbid with specific anxiety disorders, especially those with substance use disorder, as well as those with refractory primary anxiety disorders. If an antipsychotic is prescribed, extrapyramidal side effects, prolactin elevation, metabolic complications, and other side effects should be closely monitored regardless of the drug classes.

Drug names: aripiprazole (Abilify), bupropion (Wellbutrin), buspirone (Buspar and others), chlordiazepoxide (Limbitrol and others), chlorpromazine (Thorazine, Sonazine, and others), citalopram (Celexa and others), clomipramine (Anafranil and others), clozapine (Clozaril, FazaClo), diazepam (Valium, Diastat), doxepin (Sinequan and others), fluoxetine (Prozac and others), fluphenazine (Prolixin), haloperidol (Haldol), loxapine (Loxitane and others), molindone (Moban), nortriptyline (Pamelor, Aventyl, and others), olanzapine (Zyprexa), olanzapine-fluoxetine combination (Symbyax), paroxetine (Paxil and others), pimozide (Orap), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft), thiothixene (Navane and others), trazodone (Desyrel), trifluoperazine (Stelazine), venlafaxine (Effexor), ziprasidone (Geodon).

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