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The potential role of atypical antipsychotics in the treatment of panic disorder

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(Running head: Atypical antipsychotics in panic disorder**)**

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Abstract

Objective: Many studies have investigated the efficacy and tolerability of alternative pharmacotherapy for panic disorder. This study aims to provide a comprehensive review of the existing literature regarding the efficacy **and tolerability** of atypical antipsychotics **for** panic disorder.

Methods: We searched for relevant published articles using **Medline**, the Cochrane database, and EMBASE on June 19, 2013. Prospective studies that examined the efficacy **and tolerability** of atypical antipsychotics in the treatment of primary panic disorder or comorbid panic disorder (or symptoms) in other psychiatric disorders were included in this review.

Results: Seven prospective studies were included in this review. **Among these, four were open-label studies for refractory panic disorder. Two of the seven included studies were randomized controlled trials among patients with panic symptoms comorbid with bipolar disorder. The remaining study was a randomized controlled trial for panic disorder or panic attack comorbid with major depression.** Except one negative risperidone study, the reviewed studies showed the favorable efficacy results of atypical antipsychotics.

Conclusions: Although the majority of the evidence regarding the efficacy of atypical antipsychotics in the treatment of panic disorder comes from small, open-label studies, this review suggests the potential role of atypical antipsychotics in treating panic disorder.

INTRODUCTION

Panic disorder is a common anxiety disorder, occurring in 0.4-4.2% of the population as the community prevalence (Dick *et al*., 1994; Eaton *et al*., 1994; Hollifield *et al*., 2005). Accumulated research data on the neurobiology of panic disorder have revealed that noradrenergic and serotonergic systems play important roles in the pathophysiology of panic disorder (Coplan *et al*., 1997; Maron and Shlik, 2006; Prosser *et al*., 2009). At present, antidepressants such as selective serotonin reuptake inhibitors (SSRI) are the standard therapy in the treatment of panic disorder because of their efficacy and favorable side effect profiles (**Baldwin *et al*., 2005; Bandelow *et al*., 2008;** Sepede *et al*., 2006; Sheehan, 2002). **The mechanism of action of SSRIs for panic disorder is still under debate (Goddard and Charney, 1998). Based on previous findings, SSRIs are thought to exert their anti-panic action through serotonin/norepinephrine and serotonin/cholecystokinin interactions (Goddard *et al*., 1993; van Megen *et al*., 1994). Long-term administration of SSRIs is thought to cause increased serotonin neurotransmission through desensitization of autoreceptors (de Montigny *et al*., 1990), and this increased serotonin neurotransmission may regulate the dysfunctional cholecystokinin and noradrenergic system in panic disorder (Goddard and Charney, 1998).**

However, in spite of this first-line pharmacotherapy, many patients with panic disorder remain symptomatic (Hoge *et al*., 2008). In some studies, about 30% of patients with panic disorder did not respond adequately to pharmacotherapy (Liebowitz, 1997; Sepede *et al*., 2006; Zamorski and Albucher, 2002). In other studies, 50-80% of panic disorder patients receiving standard pharmacotherapy continued to have panic-related symptoms (Bandelow and Ruther, 2004; Prosser *et al*., 2009; Sepede *et al*., 2006). Considering the poor treatment response of panic disorder to standard pharmacotherapy, it is necessary to investigate the

efficacy of additional pharmacotherapeutic strategies for the treatment of panic disorder (Prosser *et al*., 2009).

As evidence grows for the efficacy of atypical antipsychotics in the treatment of other anxiety disorders, such as obsessive compulsive disorder and posttraumatic stress disorder (Bartzokis *et al*., 2005; Krashin and Oates, 1999; McDougle *et al*., 2000; Saxena *et al*., 1996), clinical trials to investigate the efficacy of these agents in panic disorder are increasing (Simon *et al*., 2006). However, there remains a relative paucity of relevant data for panic disorder (Hoge *et al*., 2008).

Thus, our aim is to review the extant published articles evaluating the efficacy and tolerability of atypical antipsychotics in the treatment of panic disorder or panic symptoms comorbid with other psychiatric disorders.

METHODS

Search Methods and Selection Criteria

To examine the efficacy and tolerability of atypical antipsychotics in the treatment of panic disorder, we performed a literature search using **Medline**, the Cochrane database, and EMBASE on June 19, 2013.The search terms were: “panic disorder”, “panic attack”, “panic symptom”, “neuroleptic agent”, “antipsychotic agent”, “atypical antipsychotics”, “atypical antipsychotic agent”, “olanzapine”, “risperidone”, “aripiprazole”, “quetiapine”, “ziprasidone”, “zotepine”, “blonanserin”, “amisulpride”, “paliperidone”, “lurasidone”, and “asenapine”.

All identified prospective studies that investigated the effects of atypical antipsychotics in the treatment of panic disorder or panic disorder (or symptoms) comorbid with other psychiatric disorders were included in our review. Among the articles regarding the efficacy of atypical antipsychotics in anxiety disorder**s** encompassing panic disorder, the

articles in which the sample size of panic disorder exceeded five patients were included. Only articles written in English were included. Case reports, case series, and studies with retrospective designs were excluded.

RESULTS

Search Results

Initially, we found 134 articles from **Medline**, 12 from the Cochrane database, and 698 from EMBASE. Of the 844 articles, 73 overlapped. Through reviewing the remaining 771 articles, we found 7 articles to meet the selection criteria for this review. The literature review was accomplished by two authors (WMB and HRW). Table 1 lists the characteristics of the seven articles selected.

Two of the reviewed studies investigated the efficacy of risperidone and quetiapine extended release (XR) for comorbid panic disorder or panic symptoms in patients with a primary diagnosis of bipolar disorder (Sheehan *et al*., 2009, 2013). **Another study examined the efficacy of low-dose risperidone in treating panic attacks among patients with panic disorder or major depressive disorder (MDD) (Prosser *et al.*, 2009). The remaining four studies examined the clinical efficacy of atypical antipsychotics for panic disorder (Hoge *et al*., 2008; Hollifield *et al*., 2005; Sepede *et al*., 2006; Simon *et al*., 2006).**

Atypical Antipsychotics for Panic Disorder

Hoge et al. (2008) investigated the effect of aripiprazole as an augmenting agent for the treatment of refractory panic disorder **or generalized anxiety disorder (GAD)** in an 8-week, flexible-dose, open-label trial. Aripiprazole initially was started at 2.5 mg/day and flexibly titrated to 30 mg/day based on efficacy and tolerability. The mean dose of

aripiprazole at the endpoint of the study was 10.5±4.95 mg/day. A total of 23 patients entered the study, and among them, 10 (43%) patients had panic disorder, and the other 13 (57%) had GAD. Five patients had both panic disorder and GAD. Prior to study entry, all subjects presented with significant anxiety symptoms, mean score of 4.8±0.7 on the Clinical Global Impression-Severity (CGI-S) score (Guy, 1976). **The mean total number of failed medication trials prior to study entry among patients was 3.4, and this reflected the degree of treatment refractoriness of the study population in this trial.** Remission was defined as a CGI-S score of 1 or 2. Thirty percent of the patients with panic disorder and 23% of GAD patients prematurely discontinued the trial. Among the 23 patients, aripiprazole augmentation resulted in a significant reduction in anxiety and depression symptoms assessed by CGI-S, Hamilton Anxiety Scale (HAM-A)(Hamilton, 1959), and the 17-item Hamilton Depression Rating Scale (HAM-D-17)(Hamilton, 1960). Twenty-three percent (n=3) of GAD patients and 10% (n=1) of panic disorder patients achieved remission. Among the panic disorder subgroup, a significant symptoms improvement was found in CGI-S scores from baseline to the endpoint of the study (4.8±0.9 to 4.0±1.1, $P<0.05$). The Panic Disorder Severity Scale (PDSS)(Shear *et al*., 2001) scores also decreased at endpoint; however, the changes did not reach statistical significance (15.2±4.8 to 13.0±5.0, $P=0.13$). Aripiprazole augmentation was relatively well tolerated among this sample, as reflected by a relatively low drop-out rate due to side effects (13%). The common side effects were sedation or fatigue, insomnia, jitteriness, dyspepsia, and nausea. **In this study, aripiprazole augmentation resulted in significant global symptom improvement, as measured by CGI-S, among the panic disorder subgroup. Even though improvement of panic-specific symptoms measured by PDSS didn't reach statistical significance, considering the degree of treatment refractoriness of the subjects and the small sample size, these favorable**

efficacy results suggest the potential of aripiprazole augmentation as an alternative option for treating refractory panic disorder. However, to confirm this, future well-designed, large-scale studies are warranted (Hoge *et al*., 2008).

Simon et al. (2006) investigated the efficacy of risperidone augmentation among refractory anxiety disorders including panic disorder, GAD, and social anxiety disorder (SAD) in an 8-week, flexible-dose, open-label study. A total of 30 patients with a primary diagnosis of panic disorder (n=7), GAD (n=16), or SAD (n=7) who showed refractoriness to initial pharmacotherapy were recruited. Patients with panic disorder were included if they scored 4 or more ("moderate") on the Massachusetts General Hospital Anchored Panic CGI Severity Rating (Panic CGI-S) (Pollack *et al*., 2003) and on the CGI-S. The starting dose of risperidone was 0.25 mg/ day, and risperidone was maintained in a flexible dose up to 3 mg/day according to efficacy and tolerability. The mean dose of risperidone at the endpoint was 1.12±0.68 mg/day. At baseline, 30 participants showed high levels of anxiety, scoring a mean of 5.0±0.9 on the CGI-S and 23.0±5.4 on the HAM-A scale. **In addition, the mean duration of previous pharmacotherapy was approximately 150 weeks and 16.7% of the subjects had comorbid MDD or dysthymia. Taken together, this suggests that patients with relatively chronic refractory anxiety disorders (including panic disorder) were included in this study.** Across the three anxiety disorders, there were significant improvements on the CGI-S ($t=5.14$, $p<0.001$) and HAM-A scores ($t=3.94$, $p=0.0005$) at the endpoint of the study. In the panic disorder subgroup (n=7), there was a significant improvement in the PDSS score ($t=2.50$, $p<0.046$) at the endpoint of the study. Risperidone was well tolerated. The common side effects included sedation/fatigue (n=14), appetite increase and weight gain (n=11), and dizziness (n=8). The side effects reported within each subgroup were not specified. **This study has several methodological limitations including**

an open-label design without a control group and small sample size. However, considering that chronically severe and refractory patients were included in this study, these favorable efficacy results still provide meaningful information regarding the role of low-dose risperidone augmentation in treating refractory panic disorder (Simon *et al*., 2006).

Sepede et al. (2006) investigated the efficacy of olanzapine augmentation among patients with treatment-resistant panic disorder with and without agoraphobia in a 12-week, open-label, fixed-dose (5mg/day) trial. A total of 31 patients were enrolled, and among them, 15 were without agoraphobia. Five patients prematurely discontinued the trial because of adverse effects, and the remaining 26 patients were included for the analysis. At the endpoint of the study, both groups (with and without agoraphobia) showed improvements on all the efficacy measurements including the Panic Attack and Anticipatory Anxiety Scale (Sheehan, 1983), HAM-A, and HAM-D**-17**. The response rate, defined by reduction of 50% or more in the number of panic attacks and scoring of 1 or 2 on the CGI-I scale, was high (81.8%). The remission rate, defined by no panic attacks and scoring 7 or less on the HAM-A, was also high (57.7%). Furthermore, the significant symptom improvement was seen as early as at the second week of treatment, suggesting the rapid anxiolytic effect of olanzapine. Olanzapine was well tolerated. The common adverse events included weight gain, drowsiness and dry mouth (Sepede *et al*., 2006).

Hollifield et al. (2005) investigated the efficacy of olanzapine among refractory panic disorder patients in an 8-week, flexible-dose, open-label trial. **Patients who failed to respond adequately to two previous treatment trials, including cognitive behavioral therapy or medication trials, were included.** The medication that participants had taken before the study was tapered off before study entry. Olanzapine initially was started at 2.5

mg/day. The maximum dose was 20 mg/day, and the dose could be changed based on efficacy and tolerability. A total of 15 patients were enrolled, and 10 of them completed the trial. The mean dose of olanzapine at the endpoint of the study was 12.3 mg/day. The number of panic attacks recorded on daily panic logs by the patients was reduced from 6.1 attacks per week at baseline to 1.1 at the endpoint of the study ($P<0.01$). The intensity of panic attacks, rated from 0 to 10, was also reduced from 4.6 to 0.8. The duration spent with anticipatory anxiety was reduced from 32% to 8% of each day ($P=0.011$). Clinician-Rated Physicians Panic and Phobic Disorders Scale scores also showed significant improvements in anticipatory anxiety, phobic avoidance, and impairment from baseline to the endpoint of the study. At the endpoint of the study, 50% of the completers had become panic free. The mean change in weight among the 10 completers was 0.18±4.4 kg, which was not significant ($P=0.85$). **Considering the treatment refractoriness and relatively long duration of panic disorder (mean duration, 10.5 years) among subjects, symptom improvements with olanzapine monotherapy in this study appear to be robust. However, with regard to its several limitations, such as open-label design and small sample size, the efficacy of olanzapine for refractory panic disorder needs to be confirmed in large-scale, well-designed studies in the future** (Hollifield *et al*., 2005).

Atypical Antipsychotics for Panic Attacks in Panic Disorder or MDD

Prosser et al. (2009) conducted an 8-week, randomized, single-blind (rater-blind) comparison study of low-dose risperidone with paroxetine monotherapy for the treatment of panic attacks among patients with primary panic disorder or MDD. To be included, the subjects had to meet the diagnosis of panic disorder, with or without agoraphobia, or MDD with panic attacks based on the DSM-IV criteria. Patients whose anxiety symptoms scored at

least 17 on the HAM-A scale could be enrolled. A total of 56 subjects were randomized to either risperidone monotherapy or paroxetine monotherapy. Among them, 43 subjects were diagnosed with primary panic disorder, and the remaining 13 were diagnosed with MDD with panic attacks. The mean dose of risperidone was 0.53 mg/day, and no subjects required treatment with a higher dose than 1.0 mg/day. 60.6% of the subjects in the risperidone group completed the study, and 39.1% of the subjects in the paroxetine group did. Regardless of treatment, all subjects showed an improvement in CGI scores during the study. There were no differences in changes in any efficacy measures, including scores on the CGI, PDSS, HAM-A, and HAM-D-17 between the risperidone and paroxetine groups. This study showed that risperidone and paroxetine were similarly efficacious in improving panic symptoms. **However, we should be cautious in interpreting the results. In this study, 23% of the subjects were MDD patients, and this could act as a confounding factor affecting the results of this study. In post hoc analysis, a correlation was found between HAM-D-17 and HAM-A scores among subjects. Thus, it is difficult to differentiate whether the observed improvement in panic symptoms associated with risperidone is due to improvement of depression symptoms. Meanwhile, numerically, the retention rate in the risperidone group seemed to be higher than that in the paroxetine group; however, this did not reach statistical significance. Considering this comparable retention rate, low-dose risperidone monotherapy seemed to be similarly tolerated compared with paroxetine** (Prosser *et al*., 2009).

Atypical Antipsychotics for Comorbid Panic Symptoms in Bipolar Disorder

We found two articles investigating the efficacy of atypical antipsychotics in the treatment of comorbid panic symptoms or panic disorder among patients with a primary

diagnosis of bipolar disorder (Sheehan *et al*., 2009, 2013).

Sheehan et al. (2013) compared the anxiolytic effects of quetiapine XR and divalproex extended release (ER) among bipolar disorder patients who had comorbid panic disorder or GAD of at least moderate severity in a randomized, placebo-controlled study. All the subjects discontinued their previously used psychotropic medication 7 days before baseline. Then, the subjects were randomly assigned to quetiapine XR monotherapy, divalproex ER monotherapy, or placebo with a flexible dose for 8 weeks. The primary outcome measure was the Clinical Global Improvement Scale for Anxiety (CGI-21 Anxiety) (Sheehan *et al*., 1993). A total of 149 patients were randomized. Of these, 113 subjects had current panic disorder. A total of 108 subjects completed the trial of 8 weeks. The mean HAM-A scores at baseline were similar among the three treatment groups. The mean daily dose of quetiapine XR was 11.5±39.9 mg/day at week 2, 184.1±97.2 mg/day at week 5, and 186.4±100.3 mg/day at the time of termination or week 8. The mean daily dose of divalproex ER was 1236±394 mg/day at week 2, 1992±824 mg/day at week 5, and 1991±866 mg/day at the time of termination or week 8. The repeated measures analyses of variance (ANOVA) of the CGI-21 Anxiety, the HAM-A, and the Sheehan Panic Disorder Scale (SPS) (Leon *et al*., 1997) showed there to be significant **differences in changes over time between groups.** Quetiapine XR showed a greater mean improvement on the scores of the CGI-21 Anxiety than divalproex ER and placebo ($p<0.07$). The improvement of the HAM-A and SPS scores were significantly greater for quetiapine XR than divalproex ER and placebo, suggesting superiority of quetiapine XR over placebo and divalproex ER in relieving anxiety symptoms. The repeated measures ANOVA **of Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) showed that there was a significant difference in changes over time between groups.** However, the analysis **of the Young**

Mania Rating Scale (YMRS) (Young *et al*., 1978) did not show a significant difference between groups. The subgroup analysis of 113 subjects with current panic disorder showed that the mean reduction on the scores of the SPS and HAM-A was significantly greater in the quetiapine XR group compared to the divalproex ER or placebo groups. The common adverse events reported in the quetiapine XR group were drowsiness, dry mouth, nausea or vomiting, tingling sensation, and increased appetite. Most adverse events were mild to moderate in severity. This study **provided preliminary favorable efficacy results of** quetiapine XR monotherapy in treating anxiety symptoms among bipolar patients. **However, we have to be cautious in interpreting the results of anxiety outcomes, because it is possible that improvement of depression symptoms may have resulted in the observed symptom improvement of comorbid panic disorder. Thus, future studies are needed investigating whether the anti-panic effect exerted by quetiapine XR in bipolar patients with comorbid panic disorder is mediated by, or is secondary to, its antidepressant effect** (Sheehan *et al*., 2013).

Sheehan et al. (2009) investigated the efficacy of risperidone monotherapy (0.5-4.0mg/day) in treating anxiety symptoms among 111 patients with a primary diagnosis of bipolar disorder and comorbid GAD or panic disorder of at least moderate severity in an 8 week, randomized, placebo-controlled, double-blind trial. To be included, bipolar symptoms had to be no more than moderate in severity (defined by a score of 4 or less on the Clinical Global Impression Scale for Bipolar Disorder (CGI-BP)) (Spearing *et al*., 1997). Among the 111 patients randomized, 80 patients had a prior history of panic disorder. The percentage of co-occurring panic disorder was higher in the risperidone group (83.3%) than in the placebo group (61.4%). The mean risperidone dose was 2.5 mg/day at the endpoint of the study. **Fifty percent (n=27) of the risperidone group and 63% (n=36) of the placebo group**

completed the study. Common reasons for premature discontinuation included 'lack of efficacy' and 'failed to return'. The primary efficacy measure was the CGI-21 Anxiety scale. The analysis showed that risperidone monotherapy was not more efficacious than placebo according to the CGI-21 Anxiety score and other anxiety measures including the HAM-A. Risperidone was relatively well tolerated. The secondary analysis done for the panic disorder subgroup revealed that the patients in the placebo group showed a tendency of greater improvement on the CGI-21 Anxiety score than did those in the risperidone group ($p<0.07$). This study failed to show superior efficacy of risperidone over placebo in improving anxiety symptoms including panic symptoms at the dose rage of 0.5-4.0 mg. The authors suggested the possibility that more severely ill patients were randomized to the risperidone group to explain this result. The risperidone group had a higher proportion of patients with mixed symptoms at the study entry, and such individuals have been known to have poorer treatment outcome and prognosis (Gonzalez-Pinto *et al*., 2007), and thus, the higher rates of mixed symptoms in the risperidone group may have resulted in a relatively poor response in this group. There is also the possibility that risperidone in itself does not have an anxiolytic or anti-panic effect among bipolar patients with comorbid panic disorder or GAD. Thus, further studies are needed to determine the efficacy of risperidone among bipolar populations with comorbid panic disorder (Sheehan *et al*., 2009).

DISCUSSION

We reviewed the extant articles on the efficacy of atypical antipsychotics among patients with primary panic disorder or panic disorder comorbid with other psychiatric disorders. We included 7 articles in this review. Among them, 3 were randomized controlled trials of quetiapine XR or risperidone, and the remaining 4 were open-label studies of

aripiprazole, risperidone or olanzapine. Except for one negative study by Sheehan et al. (2009), the included studies showed favorable efficacy of atypical antipsychotics in the treatment of panic disorder or panic symptoms comorbid with **MDD or** bipolar disorder, as either a monotherapy agent or an augmenting agent. **However, these results require careful interpretation because the study populations of selected studies were heterogeneous in terms of the presence of comorbid psychiatric conditions, disease severity, duration of illness, concomitant medication, gender and age. These various disease-related or sociodemographic variables could act as confounders, and, thus, such heterogeneity in the study population could affect study results. In addition, patients with panic disorder comorbid to other psychiatric disorders may respond differently to atypical antipsychotics compared to those with panic disorder alone. Furthermore, treatment response to atypical antipsychotics among patients with panic disorder could vary according to their comorbid psychiatric disorders, and this might explain in part the different efficacy results of risperidone monotherapy shown in Sheehan et al.'s study (2009) on a bipolar population and Prosser et al.'s study (2009) on a MDD population. Taken together, the favorable efficacy results shown in this review are still preliminary, and the role of atypical antipsychotics in panic disorder should be confirmed in future large-scale, well-designed studies among homogeneous panic disorder populations.**

Nevertheless, the favorable efficacy of aripiprazole, risperidone, and olanzapine shown in 4 studies (Hoge *et al*., 2008; Hollifield *et al*., 2005; Sepede *et al*., 2006; Simon *et al*., 2006) accomplished among treatment-refractory panic disorder was in line with previous study findings that showed the anxiolytic effect of atypical antipsychotics for other anxiety disorders (Ak *et al*., 2011; **Katzman *et al*., 2011; Khan *et al*., 2011; Merideth *et al*., 2012;** Pivac *et al*., 2004; Stein *et al*., 2002). **Several randomized controlled trials have**

demonstrated the efficacy of quetiapine in the treatment of GAD (Katzman *et al*., 2011; Khan *et al*., 2011; Merideth *et al*., 2012). In addition, aripiprazole and risperidone augmentation have exhibited efficacy in the treatment of obsessive-compulsive disorder (OCD) (Erzegovesi *et al*., 2005; Sayyah *et al*., 2012). Even though atypical antipsychotics have not yet been licensed for anxiety disorders such as GAD or OCD in Europe or the United States, previous studies have suggested the potential role of atypical antipsychotics as an alternative treatment for anxiety disorders.

Despite growing interest in the efficacy of atypical antipsychotics for panic disorder, the underlying mechanism of anti-panic effects of atypical antipsychotics is unclear. Previous studies regarding the neurobiology of panic disorder showed that neurotransmitter systems, such as serotonergic and noradrenergic systems, play roles in panic disorder (Coplan *et al*., 1997; Maron and Shlik, 2006; Prosser *et al*., 2009). Atypical antipsychotics seem to exert an anti-panic effect through acting on various neurotransmitter systems, such as serotonin and dopamine, for example, by 5-HT_2 receptor antagonistic or 5-HT_{1A} agonistic properties (Coplan *et al*., 1997; Gorman *et al*., 2000; Maron and Shlik, 2006; Prosser *et al*., 2009).

As the use of atypical antipsychotics is increasing among anxiety disorders, including panic disorder, there are some concerns for their use. In the articles included for this review, atypical antipsychotics seemed to be well tolerated. However, the studies included in this review were mostly short-term studies, and thus could not address possible long-term side effects, such as metabolic side effects or tardive dyskinesia. **Additionally, the mean daily doses of atypical antipsychotics used in the articles reviewed were lower than those used for schizophrenia or other psychotic disorders; thus, these lower medication doses could have resulted in the good tolerability observed. Hence, to investigate the long-term tolerability of atypical antipsychotics among panic disorder**

populations, future studies are needed.

During a literature search, no relevant articles were found comparing the efficacy of atypical antipsychotics with that of psychotherapy in treating panic disorder. Previous studies showed that both pharmacotherapy and psychotherapy have similar efficacy for acute treatment of panic disorder (Baldwin *et al*., 2005). However, for relapse prevention, cognitive behavioral therapy seems to have superior efficacy compared to tricyclic antidepressants (van Balkom *et al*., 1997). To identify the short-term and long-term clinical benefits of atypical antipsychotics in the treatment of panic disorder, future studies that compare psychotherapy and atypical antipsychotics would be helpful.

We found several methodological limitations of the articles included in this review. First, more than half of the included studies had an open-label design without a control group. Thus, the efficacy of atypical antipsychotics in these trials could be overestimated. Second, most studies in this review had small sample sizes, ranging from 7 to 43, except for the two bipolar studies (Sheehan *et al*., 2009, 2013). Third, there was heterogeneity of the study population, varying from primary panic disorder to panic disorder comorbid with bipolar disorder **or MDD**. Fourth, most studies had relatively short study durations; thus, they could not provide any information about long-term efficacy and tolerability of atypical antipsychotics among panic disorder populations.

In conclusion, this review suggested that atypical antipsychotics could have a role as an effective alternative treatment option for panic disorder either as a monotherapy or as an augmenting agent; however, much of the evidence of this comes from small, open-label studies. To draw a definitive conclusion regarding the clinical **role** of atypical antipsychotics for panic disorder, future well-controlled, large-sized studies with

long-term study duration are needed.

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References

Ak M, Bulut SD, Bozkurt A, Ozsahin A. 2011. Aripiprazole augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder: A 10-week open-label study. *Advances in Therapy* **28:**341-348.

Baldwin DS, Anderson IM, Nutt DJ, *et al.* 2005. Evidence-based guidelines for the pharmacological treatment of anxiety disorders: recommendations from the British Association for Psychopharmacology. *J Psychopharmacol* 19:567-596.

Bandelow B, Ruther E. 2004. Treatment-resistant panic disorder. *CNS Spectr* **9**: 725-739.

Bandelow B, Zohar J, Hollander E, *et al.* 2008. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorder – first revision. *World J Biol Psychiatry* 9:248-312.

Bartzokis G, Lu PH, Turner J, Mintz J, Saunders CS. 2005. Adjunctive risperidone in the treatment of chronic combat-related posttraumatic stress disorder. *Biol Psychiatry* **57**: 474-479. doi: 10.1016/j.biopsych.2004.11.039

Coplan JD, Papp LA, Pine D, *et al*. 1997. Clinical improvement with fluoxetine therapy and noradrenergic function in patients with panic disorder. *Arch Gen Psychiatry* **54**: 643-648. doi:10.1001/archpsyc.1997.01830190069007

de Montigny C, Chaput Y, Blier P. 1990. Modification of serotonergic neuron properties by long-term treatment with serotonin reuptake blockers. *J Clin Psychiatry* 51:4-8.

Dick CL, Bland RC, Newman SC. 1994. Epidemiology of psychiatric disorders in Edmonton. Panic disorder. *Acta Psychiatr Scand Suppl* **376**: 45-53.

Eaton WW, Kessler RC, Wittchen HU, Magee WJ. 1994. Panic and panic disorder in the

United States. *Am J Psychiatry* **151**: 413-420.

Erzegovesi S, Guglielmo E, Siliprandi F, Bellodi L. 2005. Low-dose risperidone augmentation of fluvoxamine treatment in obsessive-compulsive disorder: a double-blind, placebo-controlled study. *Eur Neuropsychopharmacol* 15:69-74.

Goddard AW, Charney DS. 1998. SSRIs in the treatment of panic disorder. *Depress Anxiety* 8:114-120.

Goddard AW, Woods SW, Sholomskas DE, Goodman WK, Charney DS, Heninger GR. 1993. Effects of the serotonin reuptake inhibitor fluvoxamine on yohimbine-induced anxiety in panic disorder. *Psychaitry Res* 48;119-133.

Gonzalez-Pinto A, Aldama A, Mosquera F, Gonzalez Gomez C. 2007. Epidemiology, diagnosis and management of mixed mania. *CNS Drugs* **21**: 611-626.

Gorman JM, Kent JM, Sullivan GM, Coplan JD. 2000. Neuroanatomical hypothesis of panic disorder, revised. *Am J Psychiatry* **157**: 493-505.

Guy W. 1976. Clinicial Global Impressions. ECDEU Assessment Manual Psychopharmacology, revised National Institute of Mental Health, Rockville MD.

Haddad P. 2005. Weight change with atypical antipsychotics in the treatment of schizophrenia. *J Psychopharmacol* **19**: 16-27. doi: 10.1177/0269881105058378

Hamilton M. 1959. The assessment of anxiety states by rating. *Br J Med Psychol* **32**: 50-55.

Hamilton M. 1960. A rating scale for depression. *J Neurol Neurosurg Psychiatry* **23**: 56-62.

Hoge EA, Worthington JJ 3rd, Kaufman RE, Delong HR, Pollack MH, Simon NM. 2008. Aripiprazole as augmentation treatment of refractory generalized anxiety disorder and panic disorder. *CNS Spectr* **13:** 522-527.

Hollifield M, Thompson PM, Ruiz JE, Uhlenhuth EH. 2005. Potential effectiveness and safety of olanzapine in refractory panic disorder. *Depress Anxiety* **1**: 33-40.

doi:10.1002/da.20050

Katzman MA, Brawman-Mintzer O, Reyes EB, Olausson B, Liu S, Eriksson H. 2011. Extended release quetiapine fumarate (quetiapine XR) monotherapy as maintenance treatment for generalized anxiety disroder: a long-term, randomized, placebo-controlled trial. *Int Clin Psychopharmacol* 26:11-24.

Khan A, Joyce M, Atkinson S, Eggens I, Baldytcheva I, Eriksson H. 2011. A randomized, double-blind study of once-daily extended release quetiapine fumarate (quetiapine XR) monotherapy in patients with generalized anxiety disorder. *J Clin Psychopharmacol* 31:418-428.

Krashin D, Oates EW. 1999. Risperidone as an adjunct therapy for post-traumatic stress disorder. *Mi Med* **164**: 605-606.

Leon AC, Olfson M, Portera L, Farber L, Sheehan DV. 1997. Assessing psychiatric impairment in primary care with the Sheehan Disability Scale. *Int J Psychiatry Med* **27**: 93-105.

Liebowitz MR. 1997. Panic disorder as a chronic illness. *J Clin Psychiatry* **58**: 5-8.

Maron E, Shlik J. 2006. Serotonin function in panic disorder: important, but why? *Neuropsychopharmacology* **31**: 1-11. doi: 10.1038/sj.npp.1300880

McDougle CJ, Epperson CN, Pelton GH, Wasylink S, Price LH. 2000. A double-blind, placebo-controlled study of risperidone addition in serotonin reuptake inhibitor-refractory obsessive-compulsive disorder. *Arch Gen Psychiatry* **57**: 794-801.

Merideth C, Cutler AJ, She F, Eriksson H. 2012. Efficacy and tolerability of extended release quetiapine fumarate monotherapy in the acute treatment of generalized anxiety disorder: a randomized, placebo controlled and active-controlled study. *Int Clin Psychopharmacol* 27:40-54.

Montgomery SA, Asberg M. 1979. A new depression scale designed to be sensitive to change. *Br J Psychiatry* **134**: 382-389.

Pivac N, Kozaric-Kovacic D, Muck-Seler D. 2004. Olanzapine versus fluphenazine in an open trial in patients with psychotic combat-related post-traumatic stress disorder. *Psychopharmacology (Berl)* **175**: 451-456. doi: 10.1007/s00213-004-1849-z

Pollack MH, Simon NM, Worthington JJ, Doyle AL, Peters P, Toshkov F, Otto MW. 2003. Combined paroxetine and clonazepam treatment strategies compared to paroxetine monotherapy for panic disorder. *J Psychopharmacol* **17:** 276-282.

Prosser JM, Yard S, Steele A, Cohen LJ, Galynker II. 2009. A comparison of low-dose risperidone to paroxetine in the treatment of panic attacks: a randomized, single-blind study. *BMC psychiatry* **9**: 25.

Saxena S, Wang D, Bystritsky A, Baxter LR Jr. 1996. Risperidone augmentation of SRI treatment for refractory obsessive-compulsive disorder. *J Clin Psychiatry* **57**: 303-306.

Sayyah M, Boostani H, Ghaffari SM, Hoseini A. 2012. Effects of aripiprazole augmentation in treatment-resistant obsessive-compulsive disorder (a double blind clinical trial). *Depress Anxiety* 2012;29:850-854.

Sepede G, De Berardis D, Gambi F, *et al*. 2006. Olanzapine augmentation in treatment-resistant panic disorder: A 12-week, fixed-dose, open-label trial. *J Clin Psychopharmacol* **26:** 45-49.

Shear MK, Rucci P, Williams J, *et al*. 2001. Reliability and validity of the Panic Disorder Severity Scale: replication and extension. *J Psychiatr Res* **35**: 293-296.

Sheehan DV. 1983. Sheehan Anxiety and Panic Attack Scales. Kalamazoo, Mich: Uphohn.

Sheehan DV. 2002. The management of panic disorder. *J Clin Psychiatry* **63:** 17-21.

Sheehan DV, Harnett-Sheehan K, Hidalgo RB, Janavs J, McElroy SL, Amado D, Suppes T.

2013. Randomized, placebo-controlled trial of quetiapine XR and divalproex ER monotherapies in the treatment of the anxious bipolar patient. *J Affect Disord* **145**: 83-94.

Sheehan DV, McElroy SL, Harnett-Sheehan K, *et al*. 2009. Randomized, placebo-controlled trial of risperidone for acute treatment of bipolar anxiety. *J Affect Disord* **115:** 376-385. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/738/CN-00703738/frame.html doi:10.1016/j.jad.2008.10.005

Sheehan DV, Raj AB, Harnett-Sheehan K, Soto S, Knapp E. 1993. The relative efficacy of high-dose buspirone and alprazolam in the treatment of panic disorder: a double-blind placebo-controlled study. *Acta Psychiatr Scand* **88**: 1-11.

Simon NM, Hoge EA, Fischmann D, Worthington JJ, Christian KM, Kinrys G, Pollack MH. 2006. An open-label trial of risperidone augmentation for refractory anxiety disorders. *J Clin Psychiatry* **67**: 381-385.

Spearing MK, Post RM, Leverich GS, Brandt D, Nolen W. 1997. Modification of the Clinical Global Impressions (CGI) Scale for use in bipolar illness (BP): the CGI-BP. *Psychiatry Res* **73**: 159-171.

Stein Mb, Kline Na, Matloff Jl. 2002. Adjunctive olanzapine for SSRI-resistant combat-related PTSD: a double-blind, placebo-controlled study. *Am J Psychiatry* **159**: 1777-1779.

van Balkom AJ, Bakker A, Spinhoven P, Blaauw BM, Smeenk S, Ruesink B. 1997. A meta-analysis of the treatment of panic disorder with or without agoraphobia: a comparison of psychopharmacological, cognitive-behavioral, and combination treatments. *J Nerv Ment Dis* 185: 510-516.

van Megen H, Westenberg H, den Boer J. 1994. Effect of the selective serotonin

reuptake inhibitor fluvoxamine of CCK-4 induced panic attacks. ***Neuropsychopharmacology*** **10:12S.**

Young RC, Biggs JT, Ziegler VE, Meyer DA. 1978. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry* **133**: 429-435.

Zamorski MA, Albucher RC. 2002. What to do when SSRIs fail: eight strategies for optimizing treatment of panic disorder. *Am Fam Physician* **66**: 1477-1484.

Table 1. Atypical antipsychotics for panic disorder or symptoms

Study	Sample Size	Psychiatric Diagnosis of Study Population	AAP[a] **(mean daily dose)**	Study Design	Treatment Duration	**Outcome Measures**	**Study Results**
Sheehan, 2013	149 randomized **(49 for quetiapine XR, 49 for divalproex ER, 51 for placebo)**	Comorbid panic symptoms in bipolar disorder	Quetiapine XR **(186.4±100.3mg/day)**	RCT[b]	8 weeks	**CGI-21 Anxiety[c] HAM-A[d] SPS[e] MADRS[f] YMRS[g]**	**Qeutiapine XR resulted in greater improvement in CGI-21 Anxiety, HAM-A, and SPS scores than divalproex ER or placebo.**
Sheehan, 2009	111 randomized **(54 for risperidone, 57 for placebo)**	Comorbid panic symptoms in bipolar disorder	Risperidone **(2.5mg/day)**	RCT	8 weeks	**CGI-21 Anxiety HAM-A**	**Risperidone monotherapy failed to induce greater improvement in CGI-21 Anxiety and HAM-A scores than the placebo.**
Prosser, 2009	56 randomized **(33 for risperidone, 23 for paroxetine)**	Panic disorder + MDD[h] with panic attacks	Risperidone **(0.53mg/day)**	Randomized, single-blind trial	8 weeks	**HAM-A CGI[i] PDSS[j] HAM-D-17[k]**	**There were no differences in changes in any efficacy measures, including CGI, PDSS, HAM-A, or HAM-D-17 scores between the risperidone monotherapy and paroxetine monotherapy groups.**
Hoge, 2008	23 (total) 10 (panic disorder)	Panic disorder + GAD[l]	Aripiprazole **(10.5±4.95mg/day)**	Open-label	8 weeks	**HAM-D-17 HAM-A PDSS CGI**	**Among the panic disorder population, aripiprazole augmentation resulted in significant improvement in CGI-S scores. Aripiprazole also resulted in decreased PDSS scores; however, the changes did not reach statistical significance.**
Simon, 2006	30 (total) 7 (panic disorder)	Panic disorder + GAD + SAD[m]	Risperidone **(1.12±0.68mg/day)**	Open-label	8 weeks	**PDSS HAM-A CGI**	**In the panic disorder subgroup, there was significant improvement in PDSS score from baseline to the endpoint of the study.**
Sepede, 2006	31	Panic disorder	Olanzapine **(5mg/day)**	Open-label	12 weeks	**PAAAS[n] HAM-A HAM-D-17 CGI**	**Olanzapine augmentation resulted in improvement in all efficacy measures, including PAAAS, HAM-A, and HAM-D-17.**
Hollifield, 2005	15	Panic disorder	Olanzapine **(12.3mg/day)**	Open-label	8 weeks	**PPPD[o]**	**Both the intensity of panic attacks and the duration of anticipatory anxiety were reduced from baseline to the endpoint. PPPD scores indicated significant improvement in anticipatory anxiety, phobic avoidance, and impairment from baseline to the endpoint.**

AAP[a]: atypical antipsychotic agent; RCT[b]: randomized controlled trial; CGI-21 Anxiety[c]: the Clinical Global Improvement Scale for Anxiety; HAM-A[d]: the Hamilton Anxiety Scale; SPS[e]: the Sheehan Panic Disorder Scale; MADRS[f]: Montgomery Asberg Depression Rating Scale; YMRS[g]: the Young Mania Rating Scale; MDD[h]: major depressive disorder; CGI[i]: the Clinigal Global Impressions scale; PDSS[j]: Panic Disorder Severity Scale; HAM-D-17[k]: the 17-item Hamilton Depression Rating Scale; GAD[l]: generalized anxiety disorder; SAD[m]: social anxiety disorder; PAAAS[n]: the Panic Attack and Anticipatory Anxiety Scale; PPPD[o]: clinician-rated Physician Panic and Phobic Disorders Scale.

Figure 1. Study Flowchart