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Atypical antipsychotics in primary generalized anxiety disorder or comorbid with mood disorders

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Abstract

Generalized anxiety disorder (GAD) is a chronic, highly prevalent and debilitating disorder that commonly co-occurrs with mood disorders. Current available agents for GAD are limited either by their slow onsets of actions, unsatisfactory anxiolytic effects or potential for abuse/dependence. Atypical antipsychotics have been studied as alternatives. Olanzapine, risperidone and quetiapine immediate release have been explored in the treatment of refractory GAD and risperidone in bipolar anxiety with randomized, double-blind, placebo-controlled trials, but the results were not consistent. By contrast, quetiapine extended release (quetiapine-XR) 150 mg/day monotherapy yielded consistent anxiolytic effects across three studies that were superior to placebo and as effective as paroxetine 20 mg/day and escitalopram 10 mg/day but with an earlier onset of action. In a 52-week treatment of GAD, quetiapine-XR was superior to placebo in the prevention of anxiety relapses. Overall, atypical antipsychotics were relatively well tolerated, with common side effects of somnolence and sedation. However, in contrast to antidepressants and benzodiazepines, the long-term risk and benefit of atypical antipsychotics in the treatment of GAD is yet to be determined.

Keywords

atypical antipsychotics; diagnosis; efficacy; generalized anxiety disorder; impact; mood disorder; prevalence; safety

Generalized anxiety disorder (GAD) is a prevalent, chronic psychiatric disorder, that commonly co-occurrs with mood disorders and other psychiatric disorders [1–20]. As a sole disorder, its impact on the quality of life is as severe as major depressive disorder [21–25]. As a comorbid disorder, it not only increases the severiry of mood disorders, but also

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complicates the treatment, especially for bipolar disorder (BPD) [26–31]. Even with current available treatments, a considerable proportion of patients with primary GAD remains symptomatic [32–34]. There are no guidelines or consensus on how to treat comorbid GAD with mood disorders. Alternatives to traditional pharmacological agents, such as atypical antipsychotics, have been investigated [35–44], In this review, clinical trials of atypical antipsychotics in the treatment of GAD with randomized, placebo-controlled design are examined.

In clinical practice, different diagnostic criteria for GAD have been used in different countries, the Diagnostic and Statistical Manual of Mental Disorder – Fourth Edition (DSM-IV) versus the International Classification of Disease (ICD) version-10[45,46]. However, the Hamilton Anxiety Rating Scale (HAM-A) has been used in most clinical trials of GAD [47]. As a severity measure of anxiety symptoms prior to the development of DSM-IV, the HAM-A does not cover all DSM-IV diagnostic criteria for GAD. In order to help clinicians apply results from clinical trials into practice, the differences between diagnostic criteria for GAD and the HAM-A are discussed.

What is GAD

According to the DSM-IV Text Revision (DSM-IV-TR) [45], the criteria for diagnosis of GAD include A: excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (e.g., work or school performance); B: the person finds it is difficult to control the worry; C: the anxiety and worry are associated with at least three out ot seven Symptoms: restlessness, feeling keyed-up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, sleep disturbance; D: the focus of the anxiety and worry is not confined to features of another Axis I disorder; E: the anxiety, worry or physical symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning; F: the disturbance is not due to a direct physical effect of a substance or a general medical condition and does not occur exclusively during a mood disorder, a pychotic disorder or a pervasive developmental disorder.

However, according to the ICD-10 criteria, the essential feature of GAD is generalized and persistent anxiety, but not restricted to, or even strongly predominating in, any particular environmental circumstance (i.e., it is ‘free-floating’) [46]. The dominant symptoms are highly variable, but complaints of continuous feelings of nervousness, trembling, muscular tension, sweating, lightheadedness, palpitations, dizziness and epigastric discomfort are common. Its course is variable but tends to be fluctuating and chronic. Primary symptoms of anxiety are present most days for at least several weeks at a time, and usually for several months. These symptoms should usually involve elements of apprehension, motor tension and autonomic overactivity. The transient appearance (for a few days at a time) of other symptoms, particularly depression, does not rule out GAD as a main diagnosis, but the full criteria for depressive episode, phobic anxiety disorder, panic disorder or obsessive–compulsive disorder should not be met.

Although the ICD-10 criteria are largely consistent with the DSM-IV criteria, with a fair concordance ($\kappa = 0.39$), two sources of discrepancy between DSM-IV and ICD-10 GAD have been identified [48]. When DSM-IV was positive and ICD-10 was negative, the discrepancy resulted from the requirement in the ICD-10 that the respondent endorses symptoms of autonomic arousal (ICD-10 criterion B) and the requirement that ICD-10 GAD does not co-occur with panic/agoraphobia, social phobia or obsessive–compulsive disorder (ICD-10 criterion C). When ICD-10 was positive and DSM-IV was negative, the two major sources of discrepancy resulted from the requirement in DSM-IV that the worry be

excessive (DSM-IV criterion A) and that it cause clinically significant distress or impairment (DSM-IV criterion E). Moreover, DSM-IV-only GAD cases had significantly higher levels of disability than ICD-10-only GAD cases after controlling for demographic variables and the presence of comorbid psychiatric disorders. While the prevalence rates for DSM-IV and ICD-10 GAD are almost identical, these classification systems diagnose different groups of people.

In Europe, the ICD-10 is commonly used to diagnose GAD, but the ICD-10 GAD has not been validated in pivotal placebo-controlled efficacy studies. Therefore, the European College of Neuropsychopharmacology Consensus Meeting in 2000 recommended use of the DSM-IV diagnostic criteria for GAD to investigate the efficacy of pharmacological treatments [49]. Some early clinical trials and epidemiological studies used DSM-II, DSM-III or DSM-III-R criteria for GAD. The differences in the diagnostic criteria for GAD in these diagnostic systems have been reviewed elsewhere [50].

Prevalence of DSM-IV GAD

The prevalence of GAD has heen estimated in different countries with either DSM or ICD diagnostic criteria. In the general population, lifetime and 12-month prevalence of DSM-IV GAD were reported to range from 0.8% in Mainland China to 5.7% in the USA and from 1% in South Korea to 3.6% in Australia, respectively [1–5,51–54]. In primary-care settings, the prevalence of GAD is much higher, ranging from 2.8 to 10% [24,25,55,56]. Longitudinal studies have found that ‘pure’ GAD is infrequent. In an 8-year longitudinal study [6], among those with GAD at intake, 39% of participants also had a major depressive disorder (MDD) and 42% had panic disorder with agoraphobia [6,7]. Only 11% had pure GAD. Among the 20 participants with pure GAD at intake, all but one developed some comorbidities during the follow-up period.

In addition to MDD [1,2,4,6,13], BPD [14–19], other anxiety disorders [1] and substance use disorders [1,20] are also frequently comorbid with GAD. Comorbid GAD in mood disorders increases the risk for substance use disorders [15], which further complicates the treatment of GAD either alone or comorbid with other psychiatric disorders [57,58].

The sequential development of GAD with MDD or vice versa has heen demonstrated in a birth cohort of 1037 members from 1 April 1972 to 20 March 1973 in New Zealand’s South Island [7]. At the age of 32 years, 44% of the cohort experienced at least one episode of MDD as a juvenile and adult, and 29% experienced a juvenile anxiety disorder or adulr GAD. Anxiety began before or concurrently in 37% of depression cases, but depression began before or concurrently in 32% of anxiety cases. Cumulatively, 72% with lifetime anxiety had a history of depression and 48% with lifetime depression had anxiety. In a subset of members with adult GAD plus MDD comorbidity, juvenile anxiety or GAD was diagnosed first in 42%, but MDD was diagnosed first in 32%. The GAD and MDD began concurrently in the remaining 26%.

Impact of GAD

Pure GAD can cause impairment as severe as MDD [5,21–25]. In a reanalysis of two national surveys, Kessler and colleagues found that the role impairments (work and social role) in past month caused by pure GAD was comparable to that of MDD [21]. In the recent National Epidemiological Survey on Alcohol and Related Conditions, Grant and colleagues also found the disability and impairment caused by pure GAD was equivalent to pure mood disorders [22]. The high impairment of GAD has also been reported in studies from Europe [21,22], Australia [5] and Canada [25]. However, compared with those with MDD, patients with GAD were more likely to be unrecognized or undertreated [10,25,57–61].

An incremental increase in work and social life impairment in GAD and MDD compared with those with only GAD or MDD has heen reported [21,23,26–28]. In the elderly, comorbid GAD with MDD was associated with a greater decline in memory compared with those with MDD alone [26]. Pharmacological treatment of GAD was associated with a significantly lower risk of MDD [62], suggesting that effective treatment of GAD might reduce the risk for the development of MDD. Patients with BPD and GAD also had more severe symptoms than those with BPD alone [17,63]. In the Systematic Treatment Enhancement Program for BPD (STEP-BP) studies, percent days of anxiety in the past year or a history of GAD independently predicted a longer time to achieve remission and a higher risk of relapse after achieving remission [30,31].

How to measure the severity of GAD in clinical trials

In clinical practice, the DSM-IV or ICD-10 guides clinicians to diagnose GAD, but cannot help clinicians to measure the severity of GAD. There are self-reported or clinician-rated scales and questionnaires to measure the severity of anxiety symptoms, but the validity of these scales/questionnaires to measure the severity of DSM-IV GAD remains unclear. In most clinical trials of GAD, the change in the HAM-A total score from baseline to the end of study is used as a primary outcome measure [47]. The HAM-A is a clinician-rated scale, including psychic and somatic subscales. The HAM-A total score ranges from 0 to 56. Commonly, a total score of less than 17 is mild, 18–24 is mild to moderate and 25–30 or greater is moderate to severe.

In most GAD clinical trials, a total score of 18–20 or greater is required for eligibility. A 40–50% reduction in the HAM-A total score is a typical criterion for defining treatment response [64,65]. A total score of 8–10 or less is commonly used to define treatment remission.

The psychic subscale is useful in assessing the severity of GAD based on the DSM-IV criteria [45], but the somatic subscale is somewhat less typical for the DSM-IV GAD. However, the somatic subscale is more related to the ICD-10 CAD [46]. Somatic symptoms are also common in panic disorders [45]. Therefore, patients with GAD, panic disorder or both can have a high HAM-A total score [66]. Similarly, owing to symptom overlaps between GAD and a major depressive episode, patients with a major depressive episode, either of MDD or BPD, can also have a high HAM-A total score. For this reason, in most GAD studies, patients with a current major depressive episode are excluded. The IAM-A is also limited in not evaluating that worries are excessive or difficult to control worries, which are core symptoms of the DSM-IV GAD. This limitation has prompted researchers to develop new scales for the DSM-IV GAD. One example is the DSM-Based Generalized Anxiety Disorder Symptoms Severity Scale [67]; however, the psychometric data for such a measure have not yet been established.

Traditional pharmacotherapy for GAD

Newer antidepressants, including selective serotonin-reuptake inhibitors (SSRIs) and serotonin-norepinephrine-reuptake inhibitors (SNRIs), other antidepressants, including tricyclics, monoamine oxidase inhibitors, trazondone, nefazodone and mirtazapine, benzodiazepines, antipsychotics, anticonvulsants and β-blockers, have been recommended by the British Association for Psychopharmacology and other consensus panels for consideration for the treatment of anxiety disorders, including GAD [68–70]. Recently, the World Federation of Socienties of Biological Psychiatry guideline for the pharmacological treatment of anxiety disorders recommended SSRIs, SNRIs and pregabalin be considered as the first-line options [71]. In treatment-resistant cases, benzodiazepines may be used when the patient does not have a history of substance use disorders. However, in the USA, only

escitalopram, paroxetine, venlafaxine-extended release (XR), duloxetine, alprazolam, trifluoperazine and buspirone have been approved by the US FDA for the treatment of GAD [72,73]. Psychotherapies, especially cognitive–behavioral therapy, have also been recommended for the treatment of GAD [68–71].

Evidence of the benefit from current pharmacological agents for the treatment of GAD is undisputable and the benefits far outweigh the risk, although they have limitations [68–71]. SSRIs and SNRIs are limited by their slow onset of action and high rates of unwanted sexual dysfunction. Some of these current antidepressants either have 'activating' effects, including an increase in the occurrence of nervousness, insomnia, agitation and tremor [74], or withdrawal symptoms [75], which may exacerbate anxiety symptoms in patients with GAD. Benzodiazepines have a fast onset of action, but their abuse and dependence potential, especially in patients with co-occurring substance use disorders, have limited their use. Pregabalin has been approved by the EU for GAD, but has not been approved by the FDA for this indication.

In addition to potential unwanted side effects, a considerable proportion of patients remains symptomatic when they are treated with current pharmacological treatments [32–34,65]. So far, there are no guidelines or consensus on how to treat comorbid GAD with mood disorders. These limitations have lead to a search for alternative treatments for GAD. Although there is a long history of interest in antipsychotics in the treatment of anxiety disorders, the evidence on their use in the treatment of GAD was limited until recently [73].

Atypical antipsychotic adjunctive therapy in primary refractory GAD

Risperidone

In the first risperidone study, 40 patients with a DSM-IV primary diagnosis of GAD who were treated wiih anxiolytics, such as buspirone, antidepressants and/or benzodiazepines, for 4 weeks and continued to have a HAM-A total score of 18 or higher were randomly assigned to risperidone (0.5–1.5 mg/day) or placebo for 5 weeks [35]. In total, 15 out of 19 patients on risperidone and 16 out of 20 patients on placebo completed the study. In a last observation carried forward (LOCF) primary outcome analysis, adjunctive risperidone was significantly more effective than placebo in reducing the HAM-A total score (Table 1). Secondary outcome analyses showed that adjunctive risperidone was significantly more effective than placebo in reducing the HAM-A psychic suhscore (-6.3 ± 3.7 vs -3.8 ± 4.0; $p = 0.047$), but not in scores of the HAM-A somatic subscale, the Clinical Global Impression Severity of Illness (CGI-S), the Montgomery–Asberg Depression Rating Scale (MADRS), the Hospital Anxiety and Depression Scale – anxiety subscale, the Sheehan Disability Scale and the Quality of Life Enjoyment Satisfaction Questionnaire (Q-LES-Q). The significant differences between risperidone and placebo in psychic subscores and HAM-A total scores started at the end of week 1 and week 2, respectively, and persisted thereafter. A treatment response (rated with the CGI – Improvement scale of much or very much improved) was achieved by 58% of patients in the risperidone group and 35% in the placebo group ($p = 0.152$).

However, in a large study of patients with GAD ($n = 417$) who were treated with anxiolytics for 8 weeks or more and continued having CGI-S of 4 or more [36], both adjunctive risperidone and placebo were effective in reducing anxiety symptoms from baseline to the end of week 4 as measured by the Patient-Rated Troubling Symptoms for Anxiety (PaRTS-A). There was no significant difference between risperidone and placebo in the primary outcome analysis, the reduction of PaRTS-A total score ($-8{,}45 \pm 0.63$ vs -7.61 ± 0.64). In a *post-hoc* analysis of PaRTS-A, patients with symptom severity from moderate to severe at baseline had greater improvement with risperidone than with placebo ($p = 0.04$).

Olanzapine

The efficacy of olanzapine adjunctive therapy in the treatment of refractory GAD was explored in patients who were treated with fluoxetine 20 mg/day for 6 weeks and continued having CG1-S score of 4 and above and a less than 50% reduction in HAM-A total score [37]. After the fluoxetine 20 mg/day treatment, 24 out of 46 patients were randomized to olanzapine (8.7 ± 7.1 mg) or placebo for 6 weeks. Seven patients received olanzapine and ten received placebo completed the study. In a LOCF analysis, there were no significant differences between the two arms in the reduction of HAM-A total score (Table 1). However, the effect size of olanzapine in the reduction of HAM-A total score from the baseline to the end of study was moderate (effect size = 0.58). The responder rates (≥50% reduction in HAM-A total score or CGI-S≤3) were higher in the olanzapine group than the placebo group, but there was no significant difference between the two groups in the remission (HAM-A total score ≤7) rates, 44% for olanzapine and 8% for the placebo.

Quetiapine

Similar to olanzapine, the adjunctive therapy of quetiapineimmediate release (IR) to paroxetine-controlled release (CR) in the treatment refractory of GAD was not superior to placebo adjunctive to paroxetine-CR [38]. In this study, 50 patients with GAD were treated with a maximum of paroxetine-CR 62.5 mg/day for 10 weeks, who had HAM-A total score of 7 and above (n = 22), were randomly assigned (within two groups based on HAM-A total Score ≤ 16 or > 16) to receive addition of quetiapine 25–400 mg/day or placebo to paroxetine-CR treatment for 8-weeks. In total, six out of 11 patients in the quetiapine group and ten out of 11 in the placebo group completed the study. At the end of the study, there was no significant difference between quetiapine and placebo in the changes from the baseline in HAM-A total score (Table 1), the scores of the CGI-S, the MADRS and the Q-LFS-Q.

Atypical antipsychotic monotherapy in mood disorders with comorbid GAD

Only one study has investigated the efficacy of an atypical antipsychotic in the treatment of bipolar anxiety (BPD comorbid with GAD) [39]. In this study, 111 patients with DSM-IV BPD and comorbid GAD (88%) or panic disorder (59%) were randomly assigned to receive risperidone 0.5–4 mg/day or placebo monotherapy for 8 weeks. Out of 104 patients, 63 completed the study. No statistically significant differences or numeric differences between risperidone and placebo were found on the primary CGI Scale for Anxiety-21 [CGI-21]) or the secondary outcome measures (HAM-A, Sheehan Panic Disorder Scale, Inventory of Depression Symptoms, Young Mania Rating Scale, CG1-21, and Sheehan Disability Scale). Risperidone was less effective on the CG1-21 and the HAM-A scales in those with BPD comorbid wirh panic disorder than in those who had BPD without panic disorder.

Atypical antipsychotic monotherapy in primary GAD Quetiapine-extended release: acute treatment

In the first quetiapine monotherapy study, patients wiih GAD and HAM-A (total score ≥ 20) were randomized to quetiapine-IR 25–300 mg/day (n = 19) or placebo (n = 19) for 6 weeks. At the end of the study, patients treated with quetiapine-IR had a greater reduction in the HAM-A total score than those treated with placebo, but this difference was not statistically significant [40].

Subsequently, three large, randomized, double-blind, placebo-controlled studies of quetiapine extended release (quetiapine-XR) monotherapy in the acute treatment of GAD were completed. All three studies used the same inclusion and exclusion criteria and

analysis strategy (LOCF) in the intent-to-treat population [41–43]. These studies required eligible patients meet DSM-IV-TR GAD criteria and have a HAM-A total score of 20 or more, a HAM-A item 1 (anxious mood) and item 2 (tension) at least 2, a CGI-S score of at least 4, and a MADRS total score of no more than 16. The primary outcome measure for these three studies was the difference between active arms and placebo in the reduction of the HAM-A total score from the baseline to the end of study.

In the first study, 873 patients were randomly assigned to quetiapine-XR 50 mg/day (n = 219), quetiapine-XR 150 mg/day (n = 216), paroxetine 20 mg/day (n = 214) or placebo (n = 217) for 8 weeks, with an additional 2 weeks of discontinuation [41]. The changes from baseline to the end of week 8 in HAM-A total score were significantly greater in patients treated with quetiapine-XR 50 mg, quetiapine-XR 150 mg/day or paroxetine 20 mg/day compared with those treated with placebo (Table 1). Compared with placebo there was a statistically significant difference at day 4 in the HAM-A total score in patients treated with quetiapine- XR 50 mg/day and quetiapine-XR150 mg/day, but not those with paroxetine. The responder rates (≥50% reduction in HAM-A total score) of quetiapine-XR 50 mg/day, quetiapine-XR 150 mg/day and paroxetine 20 mg/day were significantly higher than those of placebo. In addition, the remission rates (HAM-A total score ≤7) of quetiapinc-XR 150 mg/day and paroxetine 20 mg/day, but not quetiapine-XR 50 mg/day, were significantly higher than that of placebo.

In the second study, 951 patients at 57 centers in the USA were randomly assigned to quetiapine-XR 50 mg/day (n = 234), quetiapine-XR 150 mg/day (n = 241), quetiapine-XR 300 mg/day (n = 241) or placebo (n = 235) [42]. Compared with placebo there was a statistically significant difference in the HAM-A total change score from baseline to the end of week 8 in patients treated with quetiapine-XR 50 mg/day and quenapine XR 150 mg/day groups, but not with quetiapine XR-300 mg/day (Table 1). However, at the end of week 1, all active arms were statistically superior to placebo in the reduction of anxiety symptoms. The responder rates were higher in the quetiapine-XR 50 mg/day and quetiapine-XR 150 mg/day, but not in quetiapine-XR 300 mg/day group compared with that in the placebo group. Only quetiapine 150 mg/day was superior to placebo in terms of remission rates. Both quetiapine-XR 50 mg/day and 150 mg/day were superior to placebo in the reduction of psychic and Somatic clusters, but not quetiapine-XR 300 mg/day.

In the third study, 828 patients were randomly assigned to quetiapine-XR 150 mg/day (n = 212), 300 mg/day (n = 201), escitalopram 10 mg/day (n = 203) and placebo (n = 212) [43]. At the end of week 8, quetiapine-XR 150 mg/day, quetiapine-XR 300 mg/day and escitalopram 10 mg/day were significantly superior to placebo in the reduction of HAM-A total score from the baseline (Table 1). At day 4, only quetiapine-XR 150 mg/day and quetiapine-XR 300 mg/day were statistically different from placebo in reducing the HAM-A total score and the psychic anxiety subscale of the HAM-A. However, only quetiapine-XR 150 mg/day was significantly superior to placebo in terms of responder and remitter rates and in the reduction of somatic subscore at the end of day 4 and week 8.

Quetiapine-XR: maintenance treatment

In a maintenance treatment study of quetiapine-XR in GAD, 762 patients wirh DSM-IV GAD, a HAM-A score of 20 or above and a CGI-S of 3 or above were treated open label with quetiapine-XR 50 mg/day, 150 mg/day, or 300 mg/day during a 4–8-week run-in period, followed by a 12–18 week stabilization phase [44]. Those patients who were stabilized for a minimum of 12 weeks (HAM-A ≤ 12, CGI-S ≤ 3 and MADRS ≤ 16) were randomly assigned to quetiapine-XR (n = 216) or placebo (n = 217) for up to 52 weeks. The primary outcome measure was the time of recurrence of anxiety symptoms (an anxiety

event), which was defined as: initiation of pharmacological treatment by the investigator or the patient to treat anxiety symptoms, hospitalization due to anxiety symptoms, a HAM-A total score of at least 15 at two consecutive assessments 1 week apart or at the final assessment, and CGI-S of at least 5, and a suicide attempt or discontinuation due to an imminent risk of suicide.

In a Cox proportional hazards analysis, the risk of a anxiety event was significantly reduced with quetiapine-XR compared with that of placebo, with a hazard ratio of 0.19 (95% CI: 0.120–31; $p<0.001$). In total, 10.2% of quetiapine-XR- and 38.9% of of placebo-treated patients had a recurrence of anxiety symptoms. Other secondary outcome measures, such as score changes in the HAM-A, HAM-A psychic subscale, HAM-A somatic subscale, CGI-S, MADRS and Q-LES-Q, also showed that quetiapine-XR was statistically superior to placebo.

The safety & tolerability of atypical antipsychotic in GAD

Overall, atypical antipsychotics were relatively well tolerated, with a severe adverse event rate for quetiapine-XR treatments of less than 2.5%. The discontinuation rate due to adverse events in the quetiapine-XR arms ranged from 11.8% (50 mg/day) to 25.2% (300 mg/day) relative to placebo (4.1–6.5%), escitalopram 10% and paroxetine 7.9% [41–43]. The most common side effects from quetiapine-XR were dry mouth, somnolence and sedation. The most common reasons for discontinuation were somnolence/sedation and farigue. The changes in fasting glucose, lipids and prolactin levels were relatively small on all treatments. The mean weight gain was 0.6 kg for quetiapine-XR 50 mg/day, 0.5–1.1 kg for quetiapine-XR 150 mg/day, approximately 1 kg for quetiapine-XR 300 mg/day, 0 kg for paroxetine, −0.1 kg for escitalopram, and 0.1–0.3 kg lor placebo. The proportion of patients who gained at least 7% of their weight during the study period was 1.8–4.6% for quetiapine XR 50 mg/day, 2.7–6.9% for quetiapine-XR 150 mg/day, approximately 4.0% for quetiapine-XR 300 mg/day, 4.7% for paroxetine, 0.5% for escitalopram and 0.9–2.3% for placebo.

As for quetiapine-XR, somnolence/sedation was also the most common side effect in olanzapine and risperidone studies [35,37], and the common reason for premature discontinuation [37], which is similar to that of quetiapine and olanzapine in the treatment of bipolar depression [76]. Weight gain and increased appetite were more common in the olanzapine-treated patients than placebo treated (11.0 ± 5.1 vs 0.7 ± 2.4 lb) [37]. Among patients with 7% or more weight gain, the rate was 22% on olanzapine and 0% on placebo.

In the long-term quetiapine-XR maintenance study, the most common side effects (≥10%) during the open-label phase were dry mouth, Somnolence, sedation, fatigue, dizziness and constipation. During the double-blind phase, only headache, nausea and insomnia occurred at a rare of 10% or above in the placebo group. No side effects occurred at a rate of 10% or above in the quetiapine-XR group. Patients in the quetiapine-XR group gained a mean weight of 1.5 kg, while patients in the placebo group had a mean weight change of 0.9 kg. The proportion of patients having a weight gain of 7% or more was 1.5% for both quetiapine-XR and placebo groups. The proportion of patients who had a clinically important shift in fasting glucose (≥126 mg/dl) at the end of treatment was 2.6% for the quetiapine-XR group and 0.7% for the placebo group. The levels of total cholesterol, low-density lipoprotein, high-density lipoprotein and triglycerides were all decreased in both groups.

Expert commentary

Generalized anxiety disorder is a chronic, highly prevalent and debilitating disorder, whether alone or co-occurring with mood disorders. To reduce the burden in patients with GAD,

early diagnosis and adequate treatment are essential. Owing to the differences in the diagnostic criteria between DSM-IV and ICD-10, using different diagnostic systems may yield a different group of patients with GAD and with different symptom clusters. A bigger challenge is how to apply the data from standardized clinical trials into routine clinical practice. In the majority of clinical trials in GAD, only patients with relatively pure GAD are allowed to enroll. Therefore, in clinical practice, a medication may not perform as well as expected from a clinical trial(s).

The current available first-line agents are limited by their slow onsets of action and by the proportion of patients remaining symptomatic on treatment. The treatment of comorbid GAD in mood disorders, especially in BPD, is an unmet need. The short-comings of currently available agents have led investigators to find alternatives. Among the potential candidate agents, atypical antipsychotics have been studied with randomized, double-blind, placebo-controlled trials. However, the data from all quetiapine-XR monotherapy studies in the treatment of primary GAD have not gone through a vigorous peer-review process. Clearly, there is a relative lack of overall risk–benefit evaluation of these medications as a class relative to other classes of treatments, such as SSRIs, SNRIs and benzodiazepines. The best available data from this class are with quetiapine-XR, which provides a fuller understanding of the risk and benefits of treatment than other atypical antipsychotics.

Adjunctive therapy to antidepressants

Risperidone and olanzapine adjunctive therapy to anxiolytics showed some efficacy in reducing anxiety symptoms in patients with refractory GAD with moderate severity of anxiety symptoms, but the results were inconsistent [35,37]. The small sample sizes of these two studies might account for the inconsistent results. The moderate effect size of olanzapine suggests that a large sample size study may produce more robust results. The flexible-dosing schedule used in these studies could also reduee the possibility of separating active arms from placebo. It is unclear whether using the PaRTS-A as a primary outcome measure was responsible for the negative results of the largesized sample study of risperidone [36]. Seemingly, one thing is clear: the severity of anxiety at randomization can affect the treatment of outcome [36,38], in other words the more severe the anxiety at baseline, the more likely active arms are to separate from placebo. Therefore, large studies with vigorous design consideration are needed before atypical antipsychotic adjunctive iherapy can be recommended in clinical practice for the treatment of refractory GAD.

Monotherapy

In terms of monotherapy, quetiapine-XR has been tested in the treatment of relatively pure primary GAD and risperidone has been studied in BPD with comorbid GAD. The negative results of the risperidone study suggest that further studies of atypical antipsychotics in the treatment of mood disorders with comorbid GAD are warranted. With regard to the treatment of primary GAD, quetiapine-XR 150 mg/day produced the most consistent results in the primary and secondary outcome measures in the three studies. Therefore, it is reasonable to target the dose of quetiapine-XR at 150 mg/day. Considering quetiapitie-XR 50 mg/day and 300 mg/day were also superior to placebo on some primary or secondary outcome measures, it is also reasonable to try a dose of lower than 150 mg/day for those who cannot tolerate 150 mg/day. The long-term efficacy, safety and tolerability in the maintenance study suggest that quetiapine-XR might be considered for maintenance treatment, but more studies are needed to further investigate these findings.

Role of atypical antipsychotics versus other drugs in GAD

Current safety and efficacy data suggest that atypical antipsychotics may play a role in the treatment of primary GAD or GAD comorbid with mood disorders: however, thus far, there

is no regulatory approval of any atypical antipsychotic for the treatment of GAD. Therefore, when selecting an atypical antipsychotic for the treatment of GAD, the risks and benefits should be carefully considered. From an efficacy point of view, overall, the magnitude of difference between the active treatment arms and placebo (Table 1) is quite similar to the findings of other drug monotherapy treatments for primary GAD [77,78]. The mean effect sizes from a recent meta-analysis were estimated as 0.5 for pregabalin, 0.45 for hydroxyzine, 0.42 for venlafaxine-XR, 0.38 for benzodiazepines, 0.36 for SSRIs and 0.17 for buspirone [78]. The effect sizes of quetiapine-XR studies were more likely to be from small to moderate (Table 1). The onset of action of quetiapine-XR was faster than that of escitalopram or paroxetine, but it is unclear whether this statistical significance is compelling enough for the justification of choosing quetiapine-XR over an antidepressant.

However, owing to their hypnotic effect, atypical antipsychotics either as monotherapy or adjunctive therapy may be particularly useful for patients wirh GAD and insomnia. A recent study of eszopiclone plus escitalopram versus placebo plus escitalopram in the acute treatment of GAD with insomnia showed that the combination of eszopiclone and escitalopram was significantly superior to escitalopram in the improvement of sleep and daytime functioning, the reduction of HAM-A total score from weeks 4 to 10, and rates of response and remission [79]. Atypical antipsychotics may also be useful for patients with anxiety and substance use disorders or patients wiih anxiety and BPD. However, large, randomized, placebo-controlled studies are needed to test these possibilities.

From a safety point of view, atypical antipsychotics pose different concerns compared with antidepressants and benzodiazepines [80,81]. Although these short-term studies of atypicals in the treatment of GAD showed the changes in metabolic panels were relatively benign, metabolic side effects from the atypicals cannot be ignored. Until additional long-term safety data are available, all patients with GAD treated with atypical antipsychotics should be monitored closely, as per the consensus set of guidelines of the American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, and North American Association for the Study of Obesity [82]. These guidelines recommend monitoring patients on atypical antipsychotics (second-generation antipsychotics), including personal/family history, weight (BMI), waist circumference, blood pressure, fasting plasma glucose and fasting lipid profile at baseline and then from every 4 weeks for weight gain to every 5 years for fasting lipid profile, according to any changes in those parameters. A recent report of the increased risk of sudden cardiac death from atypical antipsychotics poses further challenges for the justification of atypical antipsychotics in the treatment of GAD [83]. Clearly, a personalized treatment plan is essential for each individual patient. This plan should at least take previous treatment history, symptom presentation, medical history, and efficacy and safety data of each medication into account.

Class effect versus individual effect

In the treatment of bipolar depression, aripiprazole [84], quetiapine [85,86] and olanzapine [87] have shown different efficacies in reducing depressive symptoms. It is also possible that atypical antipsychotic have different anxiolytic efficacies in the treatment of primary or comorbid GAD, either as monotherapy or adjunctive to anxiolytics. Before more data are available, atypical antipsychotics for GAD should be considered as individual drug effects, not as a class effect.

Five-year view

The diagnosis of GAD will continue to be a controversial issue, especially with the DSM-IV criteria of excessive worry and duration of 6 months [3,88,89]. In the National Comorbidity

Survey-Replication (NCS-R) data, 'nonexcessive' worry cases suffered the substantial persistence and impairment associated with GAD, as well as significantly elevated comorbidity compared with those without GAD. Similarly, cases with episodes lasting 1–5 months did not differ greatly from those with episodes lasting 6 months or more in onset, persistence, impairment, comorbidity, parental GAD or sociodemographic correlates [3,88]. Removing excessive worry and reducing the duration from 6 months to 1 month doubled the prevalence of GAD [89]. Such a broadened definition may be debated for future versions of the DSM and ICD classification systems.

On the treatment front, studies of the atypical antipsychotics in the treatment of primary GAD or comorbid GAD with mood disorders will continue. Ongoing studies of atypical antipsychotics in the treatment of GAD are available at the clinical trials website [101]. Riluzole, a glutamate release inhibitor, has been studied in the acute treatment of GAD in an open-label design [90]. With the increased evidence of the role of glutamate system in anxiety disorders [91,92], agents targeting this system may be the next generation of anxiolytics.

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Key issues

- Generalized anxiety disorder (GAD) is a chronic, highly prevalent and debilitating disorder, which is commonly underdiagnosed and undertreated.
- Mood disorders comorbid with GAD are common. However, there are no guidelines or consensus on how to treat this comorbidity. There is a need to conduct clinical trials in this comorbid population.
- Owing to strict diagnostic, inclusion and exclusion criteria, and as standardized rating scales are used in clinical trials, a studied population (with relatively pure GAD) in a clinical trial may be quite different from that seen in clinical practice (mostly with comorbid GAD). Therefore, in clinical practice, a medication may not work as effectively as in clinical trials.
- Current first-line agents, antidepressants, are limited by a slow onset of action and sometimes incomplete response in patients with GAD. New therapeutic agents, such as atypical antipsychotics, merit investigation.
- Atypical antipsychotics, such as quetiapine-extended release monotherapy, have shown efficacy in patients with relatively pure GAD, but risperidone was not effective in the treatment of patients with bipolar disorder (BPD) and GAD.
- The adjunctive therapy of atypical antipsychotics in the treatment of refractory, primary GAD or GAD comorbid with mood disorders needs large-scale, randomized, placebo-controlled trials to confirm or refute the preliminary findings.
- Atypical antipsychotics were relatively well tolerated. Somnolence/sedation was the most common side effect and the main reason for premature discontinuation.
- As in the treatment of bipolar depression, anxiolytic efficacy of atypical antipsychotics in the treatment of GAD may be different. Therefore, until more data become available, selecting an antipsychotic for anxiety should be based on evidence instead of assumptions concerning the class.
- However, in view of the concerns of metabolic syndrome with all these agents, patients require careful monitoring. Only additional studies in larger samples of for more extended treatment periods will properly inform us of the risk-benefit trade-off with these atypical antipsychotics in GAD compared with the alternative treatment options, such as selective serotonin-reuptake inhibitors, serotonin–norepinephrsne reuptake inhibitors, benzodiazepines and anticonvulsants.

Table 1

Summary of randomized, double-blind, placebo-controlled clinical of atypical antipsychotics in the treatment of generalized anxiety disorder.

Drug	Index	Study design	Treatment arms	Duration (weeks)	Outcome			Ref.
					HAM-A toal score change from baseline	*Differnce in change of HAM-A (active treatmetn-PBO)*	*vs PBO* pvalue	
Risperidone	Refractory primary GAD Anxioulytic or antidepressant for ≥ 4 weeks HAM.A≥ 18, CGI-5≥4 CAS > RSDS HAM-A item 1,2≥2	Acute adjunctive therapy	Risperidone(0.5–1.5 mg/day);n = 19 PBO; n = 2	5	−9.8±5.5 −6.2±4.9	−3.6	0.034	[35]
Olanzapine	Refractory GAD Fluoxetine 10 mg/day for 1 week then 20 mg/day for 5 weeks CGI-S ≥ 4 Reduction in HAM-A <50%	Acute adjunctive therapy	Olanzapine(8.7 ± 7.1 mg/day); n = 9 PBO; n = 12	6	−7 −3.9	−3.1	0.4	[37]
QTP-IR	Refractory praimary GAD paraoxtine CR up to 62.5 mg/day for 10 weeks HAM.A≥7	Acute adjunctive therapy	QTP-IR(25–400 mg/day);n = 11 PBO; n = 11	8	−2.6 ± 5.8 −0.3 ±5.5	−2.3	NS	[38]
QTP-IR	primary GAD HAM-A ≥ 20.CGI-S ≤ 4 HAM-A item 1.2 ≥ 2	Acute monotherapy	QTP-IR(25–300 mg/day); n = 19 PBO; n = 19	6	−12.1 ± 6.1 −9.3 ± 8.5	−2.8	0.225	[40]
QTP-XR	primary GAD HAM-A ≥ 20.CGI-S ≥ 4 HAM-A item 1,2 ≥ 2 MADRAS ≥ 16	Acute monotherapy	QTP-XR(50 mg/day); n = 219 QTP-XR(150 mg/day); n = 216 Paroxetine (20 mg/day); n = 214 PBO: n = 217	8	−13.95 −15.96 −15.45 −12.30	−1.65 −3.66 −3.15	<0.05 <0.001 <0.01	[41]
QTP-XR	primary GAD HAM-A ≥ 20.CGI-S ≥ 4 HAM-Aitem 1.2 ≥ 2 MADRAS ≥ 16	Acute monotherapy	QTP-XR(50 mg/day); n = 219 QTP-XR(150 mg/day); n = 226 QTP-XR (300 mg/day); n = 224 PBO: n = 225	8	−13.31 −13.54 11.87 −11.10	−2.21 −2.44 −0.77	<0.001 <0.001 0.79	[42]
QTP-XR	primary GAD HAM-A ≥ 20.CGI-S ≥ 4 HAM-A item 1.2 ≥ 2 MADRAS ≤ 16	Acute monotherapy	QTP-XR(150 mg/day); n = 212 QTP-XR(300 mg/day); n = 201 Escitalopram (10 mg/day); n = 203 PBO: n = 212	8	−13.9 −12.3 12.3 −10.7	−3.2 −1.6 −1.6	<0.001 <0.05 <0.05	[43]

HAM-A item 1; anxious: HAM-A item 2; tension,

CAS: covi anxious scale: CGI-S: Clinical Global Impression-Severity Scale; GAD; Generalised anxiety; HAM-A; Hamilton Anxiety Rating Scale; MADRAS; Montgomery-Asberg Depression Rating Scale; NS; Not Signficant; PBO; Placebo; QTP-IR; Quetiapine immediate release; QTR-XR: Quetiapine extended release; RSDS: Raskin Severity of Depression Scale.