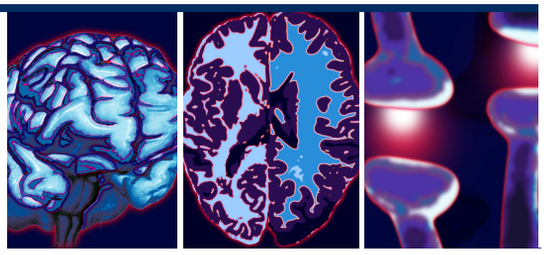
SHORT COMMUNICATION



Effect of extended-release quetiapine fumarate on quality of life and sleep in elderly patients with generalized anxiety disorder

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Practice points

- Generalized anxiety disorder (GAD) is the most commonly reported chronic anxiety disorder in the elderly, but is largely underinvestigated and undertreated in this patient population. In elderly patients, GAD significantly compromises quality of life (QoL) by causing limitations in daily activities, and can lead to depression if left untreated. In a recent study, a greater percentage of elderly patients with GAD reported moderate-to-severe problems with difficulty falling asleep, staying asleep and a tendency to wake up too early. The majority of patients with GAD also experienced moderate-to-severe insomnia.
- Once-daily extended-release quetiapine fumarate (quetiapine XR) has demonstrated efficacy as an acute and maintenance monotherapy for GAD in adults and as an acute monotherapy in elderly patients. This was a prospectively planned analysis of data from a previously reported study in elderly patients with GAD.
- In this analysis, the effects of quetiapine XR monotherapy versus placebo on QoL and sleep quality were assessed using the following patient-reported outcome measures: the Quality of Life, Enjoyment and Satisfaction Questionnaire (Q-LES-Q)-Short Form percentage maximum total score; Q-LES-Q item 15 ('satisfaction with medication') score; Q-LES-Q item 16 ('overall life satisfaction') score; and the Pittsburgh Sleep Quality Index.
- The analysis showed that improvements in Q-LES-Q-Short Form percentage maximum total score were significantly greater with quetiapine XR versus placebo, with improvements also seen with quetiapine XR versus placebo in Q-LES-Q item 15 and 16 scores. Quetiapine XR also improved the Pittsburgh Sleep Quality Index global score versus placebo.
- The study indicated that, compared with placebo, quetiapine XR significantly improved QoL, enjoyment and satisfaction in elderly patients with GAD. Quetiapine XR also improved sleep parameters in these patients.
- Patient-reported outcome measures represent important components of the clinical profile of new drug treatments for neuropsychiatric diseases.

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SUMMARY **Aims:** This prospectively planned analysis evaluates the effects of extended-release quetiapine fumarate (quetiapine XR) on quality of life and sleep quality in elderly patients (aged ≥66 years) with generalized anxiety disorder. **Methods:** Patients were randomized to quetiapine XR (flexible dosing 50–300 mg/day; n = 223) or placebo (n = 227). The primary end point was least squares mean change from baseline to week 9 in Hamilton Rating Scale for Anxiety total score. Secondary end points were patient-reported outcomes Quality of Life, Enjoyment and Satisfaction Questionnaire (Q-LES-Q)-Short Form percentage maximum total, Q-LES-Q item 15 ('satisfaction with medication'), Q-LES-Q item 16 ('overall life satisfaction') and Pittsburgh Sleep Quality Index global scores. **Results:** At week 9, quetiapine XR significantly improved the Hamilton Rating Scale for Anxiety total score versus placebo (least squares mean change: -14.97 vs -7.21; $p < 0.001$). Improvement was also observed in Q-LES-Q-Short Form percentage maximum total score, Q-LES-Q item 15 and 16 scores and Pittsburgh Sleep Quality Index global score for quetiapine versus placebo. **Conclusion:** In elderly patients with generalized anxiety disorder, quetiapine XR monotherapy (50–300 mg/day flexibly dosed) improved patients' quality of life, enjoyment, satisfaction and sleep quality.

Generalized anxiety disorder (GAD) is a highly prevalent and disabling disorder in the general population; patients with GAD report significant functional impairment and are highly likely to seek professional help [1,2]. GAD is the most commonly reported chronic anxiety disorder in the elderly, with a lifetime prevalence rate of 6% [3]. However, GAD is largely underinvestigated and undertreated in this patient population [4], with some data suggesting that patients with anxiety disorders may wait 3–8 years before receiving a first adequate pharmacological treatment [5].

In elderly patients, GAD significantly compromises quality of life (QoL) by causing limitations in daily activities and can lead to depression if left untreated [6]. In a recent study, a greater proportion of elderly patients with GAD (aged 60–94 years; n = 31) experienced a range of sleep disturbances in comparison with age-matched counterparts with no diagnosis of GAD (n = 21) [7]. A greater percentage of elderly patients with GAD reported moderate-to-severe problems with difficulty falling asleep (58.6 vs 21.1%, respectively), difficulty staying asleep (83.3 vs 21.1%, respectively) and a tendency to wake up too early (73.3 vs 36.8%, respectively). The majority of patients with GAD also experienced moderate-to-severe insomnia [7].

Once-daily extended-release quetiapine fumarate (quetiapine XR) has demonstrated efficacy as acute and maintenance monotherapy for GAD in adults [8–10] and as acute monotherapy in elderly patients [11]. Data from the study in elderly patients demonstrated that quetiapine XR (50–300 mg/day flexible dosing) had a tolerability profile consistent with the known profile of quetiapine [11]. Quetiapine XR is currently approved for GAD in Australia, Hong Kong, Kazakhstan, Latvia, Mexico, The Philippines, Venezuela and Vietnam.

Patient-reported outcomes, such as QoL and sleep quality, represent important components of the clinical profile of new drug treatments for neuropsychiatric diseases, and the efficacy of quetiapine in improving such outcomes has been investigated in other treatment settings, including bipolar disorder and major depressive disorder [12–15]. Here, we report the effects of quetiapine XR monotherapy versus placebo on QoL and sleep quality using patient-reported outcome measures in the previously published paper in elderly patients with GAD [11].

Methods

Study design

This was a prospectively planned analysis of data from a previously reported multicenter, randomized, double-blind, placebo-controlled study (D1448C00015; Chromium) [11]. This 11-week study consisted of a 9-week active, randomized treatment period, followed by a 2-week post-treatment follow-up period. All patients provided written informed consent before any study procedure, and the study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization/Good Clinical Practice guidelines [101].

Patients

Male or female outpatients aged ≥66 years with a DSM-IV [16] diagnosis of GAD, assessed by the Mini-International Neuropsychiatric Interview, were eligible for inclusion in this study. Inclusion and exclusion criteria are described in full in a previously published paper [11].

■ Study treatments

Eligible patients were randomized to treatment with quetiapine XR or placebo. After written informed consent had been obtained, patients were randomized 1:1 using a computer-based system. Study treatments and permitted and prohibited medications are described in a previously published paper [11].

■ Efficacy evaluations

The primary efficacy variable was least squares mean (LSM) change in the Hamilton Anxiety Rating Scale (HAM-A) total score from randomization to week 9 and is described in detail in the previously published paper [11]. Secondary efficacy end points included change in Montgomery Åsberg Depression Rating Scale (MADRS) item 4 ('reduced sleep').

■ Assessment of patient-reported outcomes

Patient-reported outcomes (LSM change from randomization to week 9) included the Quality of Life, Enjoyment and Satisfaction Questionnaire (Q-LES-Q) Short Form (Q-LES-Q-SF) [17] percentage maximum total score (calculated as a percentage of the maximum possible score for items 1–14 with a higher score indicating better QoL, enjoyment and satisfaction), Q-LES-Q item 15 ('satisfaction with medication') score (score range 1–5) and Q-LES-Q item 16 ('overall life satisfaction') score (score range 1–5). Each item of the Q-LES-Q-SF is rated on a five-point Likert scale ranging from 1 ('very poor') to 5 ('very good'); higher values indicate a higher perceived QoL and satisfaction. The Q-LES-Q-SF percentage maximum total score ranges from 0 to 100.

Sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI) [18]. Each domain of the PSQI derived from individual item scores ('sleep quality', 'sleep latency', 'sleep duration', 'habitual sleep efficiency', 'sleep disturbance', 'use of sleep medication' and 'daytime dysfunction') is scored from 0 ('no difficulty') to 3 ('severe difficulty'). The PSQI global score (range: 0–21) is derived from the sum of the seven domain scores; a global score ≤5 indicates good sleep quality.

■ Safety & tolerability

Safety and tolerability assessments are described in the previously published paper [11], and are, therefore, not discussed further here.

■ Statistical analyses

Efficacy analyses were based on the modified intent-to-treat population (defined as all randomized patients who received at least one dose of study medication and had both a randomization and at least one postrandomization HAM-A total score recorded).

For the primary analysis of change from randomization to week 9 in HAM-A total score, an analysis of covariance model (including baseline HAM-A total score as a covariate, treatment as a fixed effect and center as a random effect) was used. For change in Q-LES-Q-SF percentage maximum total score and PSQI change from randomization to week 9, the same analysis of covariance model as for the primary efficacy variable was used, with score at randomization as a covariate, treatment as a fixed effect and center as a random effect. A multiple testing procedure was applied to the primary end point and the change in the Q-LES-Q-SF percentage maximum total score at week 9. A stepwise, sequential testing procedure was used for handling multiple comparisons, such that the overall significance level of 0.05 was preserved.

A last observation carried forward approach was used for imputation of missing data, and results are presented as LSM change from randomization. All statistical comparisons were based on a two-sided test, with a significance level of 5%, unless otherwise specified. Where appropriate, point estimates and p-values are reported.

A comparison of changes in the PSQI domain scores for quetiapine XR versus placebo was performed as a *post hoc* analysis. For these data, $p < 0.05$ was used as evidence of a statistical difference; given the *post hoc* nature of the analysis, these data should be interpreted with caution.

Results

Here, we report QoL and sleep quality results from the previously published paper in elderly patients with GAD [11].

■ Patient population

In total, 450 patients were randomized to treatment. The modified intent-to-treat population comprised 448 patients (222 received quetiapine XR; 226 received placebo). The mean age of patients was 70.3 years in the quetiapine XR group and 70.6 years in the placebo group; 11.7 and 14.2% of patients were >75 years of age, respectively. Treatment groups were also similar

with respect to HAM-A total, MADRS total, Q-LES-Q-SF percentage maximum total and PSQI global scores at randomization (Table 1). The mean (standard deviation [SD]) daily dose was 167.6 (62.7) and 202.6 mg (54.4) in the quetiapine XR and placebo groups, respectively. In the quetiapine XR group, 17.0% of patients received a mean daily dose <100 mg, 50.2% of patients received a mean daily dose between 100 and 200 mg, and 32.7% of patients received a mean daily dose >200 mg.

Efficacy

Quetiapine XR significantly reduced HAM-A total score from randomization to week 9 compared with placebo (LSM change -14.97 vs -7.21; $p < 0.001$).

Quetiapine XR significantly improved the MADRS item 4 ('reduced sleep') score from randomization to week 9 (LSM change: -2.14; $p < 0.001$) versus placebo (-0.58).

Patient-reported outcomes

A significant improvement in Q-LES-Q-SF percentage maximum total score from randomization was seen with quetiapine XR (mean [SD] scores at randomization: 50.2 [13.4]; week 9: 65.3 [11.9]) compared with placebo (mean [SD] scores at randomization: 50.0 [12.0]; week 9: 55.3 [14.2]) at week 9 (LSM change: 14.82 vs 4.94; $p < 0.001$) (Figure 1A). LSM changes in Q-LES-Q-SF item 15 ('satisfaction with medication') and item 16 ('overall life satisfaction') scores were also both significantly improved

Table 1. Demographics and scores at randomization on Hamilton Rating Scale for Anxiety, Montgomery Åsberg Depression Rating Scale total score and patient-reported outcome measures (modified intent-to-treat population).

Characteristic	Placebo (n = 226)	Quetiapine XR 50–300 mg/day (n = 222)
Gender; n (%)		
Male	70 (31.0)	62 (27.9)
Female	156 (69.0)	160 (72.1)
Age (years)		
Mean (SD)	70.6 (4.4)	70.3 (4.3)
Time since onset of anxiety symptoms (h)		
Mean (SD)	9.1 (11.0)	9.2 (11.5)
Rating scale scores; mean (SD)		
HAM-A total score	25.1 (3.5)	25.2 (3.5)
MADRS total†	12.3 (2.3)	12.4 (2.6)
Q-LES-Q-SF; mean (SD)		
Q-LES-Q-SF percentage maximum total	50.0 (12.0)	50.2 (13.4)
Q-LES-Q-SF percentage item 15 (satisfaction with medication)	3.3 (0.8)	3.2 (0.8)
Q-LES-Q-SF percentage item 16 (overall life satisfaction)	2.7 (0.7)	2.7 (0.7)
PSQI; mean (SD)		
Global	12.1 (3.3)	12.1 (3.4)
Sleep quality	2.1 (0.6)	2.0 (0.6)
Sleep latency	2.5 (0.7)	2.5 (0.7)
Sleep duration	1.5 (0.9)	1.6 (0.9)
Habitual sleep efficiency	1.4 (1.2)	1.5 (1.2)
Sleep disturbances	1.9 (0.6)	2.0 (0.6)
Use of sleep medication	0.8 (1.1)	0.7 (1.1)
Daytime dysfunction	1.7 (0.7)	1.7 (0.7)

†Based on safety population.
HAM-A: Hamilton Rating Scale for Anxiety; MADRS: Montgomery Åsberg Depression Rating Scale; PSQI: Pittsburgh Sleep Quality Index; Q-LES-Q-SF: Quality of Life, Enjoyment and Satisfaction Questionnaire-Short Form; Quetiapine XR: Extended-release quetiapine fumarate; SD: Standard deviation.
Reproduced with permission from [11].

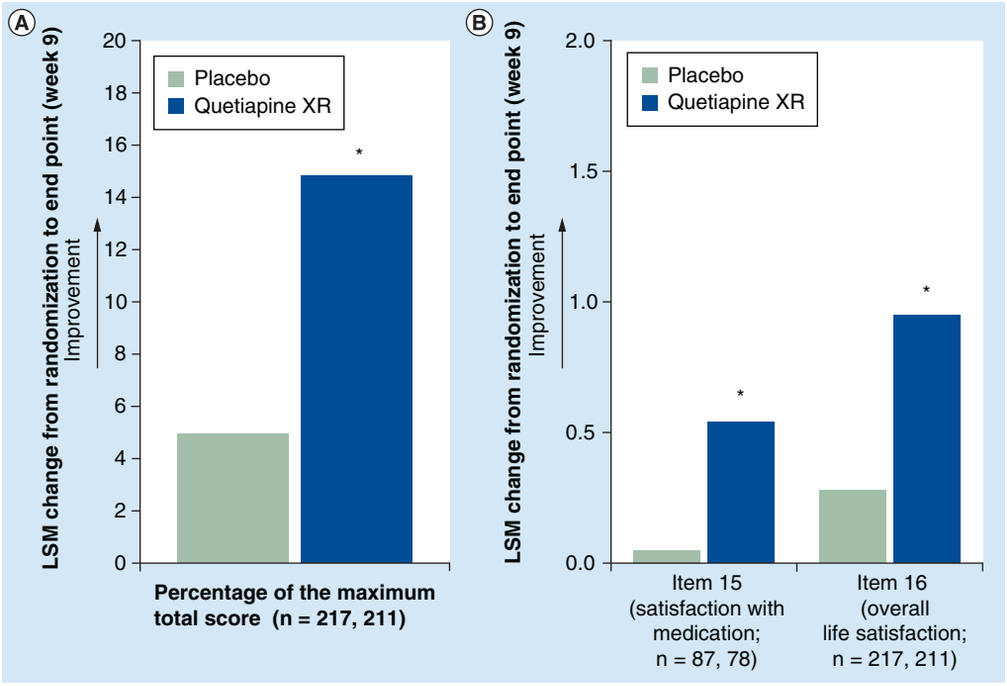

Figure 1. Least squares mean change from randomization to week 9 in Quality of Life, Enjoyment and Satisfaction Questionnaire-Short Form percentage maximum total score, item 15 and 16 scores (last observation carried forward, modified intent-to-treat population). (A) Percentage maximum total score, **(B)** item 15 and 16 scores. n = placebo, quetiapine XR, respectively.
*p < 0.001 versus placebo.
LSM: Least squares mean; Quetiapine XR: Extended-release quetiapine fumarate.

(p < 0.001) with quetiapine XR (LSM change: 0.54 and 0.95, respectively) compared with placebo (LSM change: 0.05 and 0.28, respectively) at week 9 **(Figure 1B)**.

At week 9, quetiapine XR improved PSQI global score compared with placebo (LSM change: -6.25 vs -2.09; p < 0.001) **(Figure 2)**. In addition, quetiapine XR treatment was associated with an improvement (p < 0.001) in six out of seven of the PSQI domain scores from randomization compared with placebo at week 9 **(Figure 2)**. LSM change from baseline to week 9 in the domain 'use of sleep medication' was -0.34 with quetiapine XR versus -0.26 with placebo (p = 0.34).

Discussion

The previously reported findings of this multicenter, randomized, double-blind, placebo-controlled study demonstrated that once-daily quetiapine XR monotherapy (50–300 mg/day flexibly dosed) was effective in reducing anxiety symptoms in elderly patients with GAD [11]. However, the current analysis showed that quetiapine XR monotherapy improved QoL, enjoyment, satisfaction and sleep quality in these patients.

In addition to improvements in anxiety symptoms, quetiapine XR significantly improved QoL, enjoyment and satisfaction compared with placebo, as measured by the Q-LES-Q-SF percentage maximum total score and offered improvements in terms of 'satisfaction with medication' (item 15) and 'overall life satisfaction' (item 16). Recent data suggest that in adult patients with GAD, the minimum clinically important score change in the Q-LES-Q-SF percentage maximum total score is 6.80 points [19]. As there is no established guideline for interpretation of Q-LES-Q scores, this value could be used as a guide for interpretation of changes and, as such, indicates that quetiapine XR resulted in clinically meaningful changes in elderly patients with GAD in the present study. These data are of particular relevance in light of the results of a recent cross-sectional study in a large cohort of older patients (n = 164), which showed that even after correcting for medical burden and comorbid depressive symptoms, older patients with GAD experienced greater disability and poorer QoL compared with healthy matched controls [6].

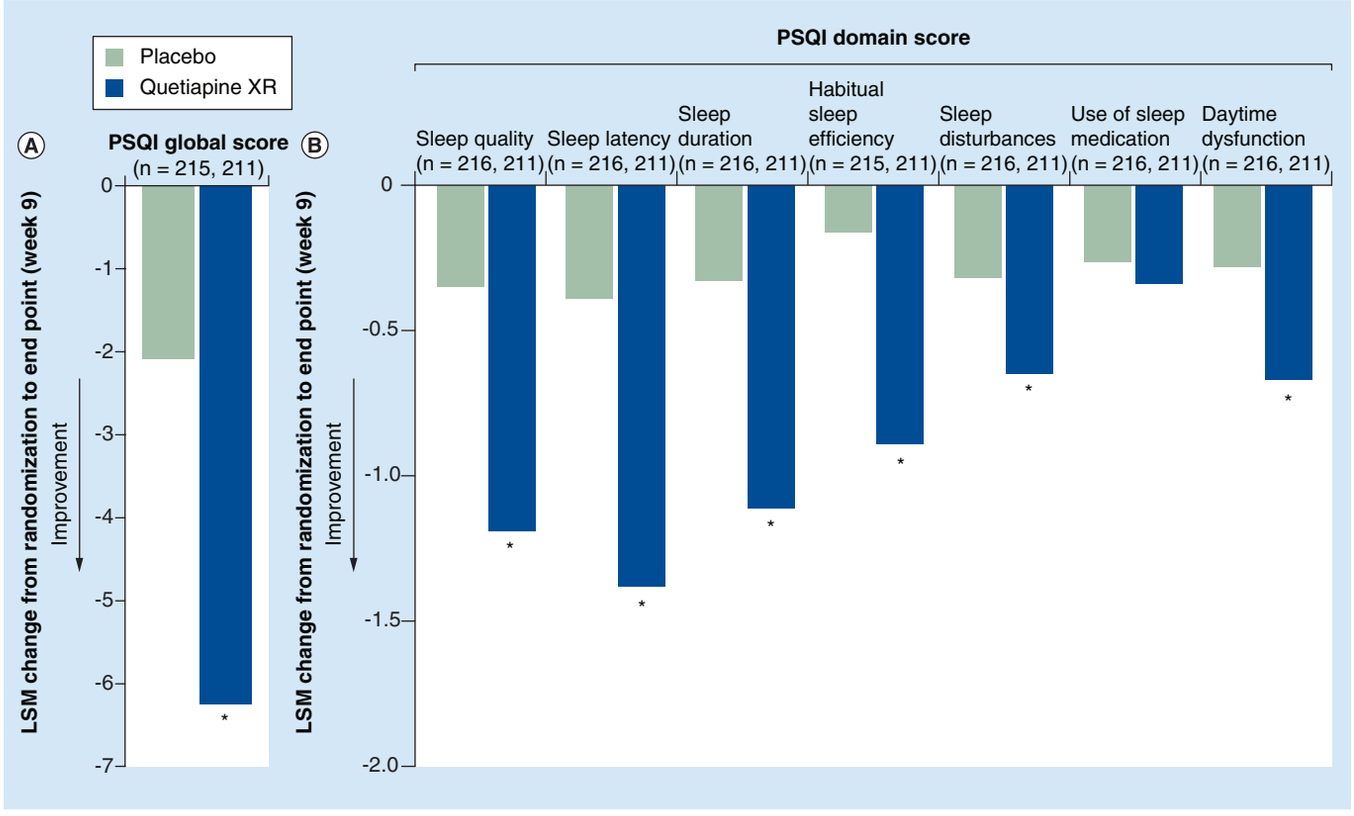

Figure 2. Least squares mean change from randomization to week 9 in Pittsburgh Sleep Quality Index global and domain scores (last observation carried forward, modified intent-to-treat population). (A) PSQI global and **(B)** domain scores. n = placebo, quetiapine XR, respectively.

*p < 0.001 versus placebo.

LSM: Least squares mean; PSQI: Pittsburgh Sleep Quality Index; Quetiapine XR: Extended-release quetiapine fumarate.

Quetiapine XR also improved the quality of sleep in this cohort of elderly patients with GAD compared with placebo, with a threefold greater numerical improvement in global PSQI score and improvements in six of the seven individual domains that comprise the PSQI. The lack of improvement in the domain 'use of sleep medication' may be related to the low numbers of patients receiving concomitant sleep medication during the study; a maximum of three patients in the placebo group and no patients in the quetiapine XR group received sleep medication at any time following randomization, with no patient in either group receiving sleep medication by study end. Support of the improvement in sleep quality with quetiapine XR, which is indicated by the PSQI scores, is provided by the improvement in MADRS item 4 ('reduced sleep') score, which suggests decreased sleep disturbance versus placebo.

Sleep disturbance is a key feature of GAD in later life [20] and appears to exacerbate many of the sleep disturbances commonly reported by elderly patients, including early awakening, difficulty falling asleep, nocturnal awakening and daytime napping [21]. Brenes *et al.* recently reported the results of a cross-sectional study among elderly patients (aged 60–94 years), and highlighted the range and prevalence of sleep disturbances reported by those diagnosed with GAD (n = 31) compared with age-matched counterparts without GAD (n = 21) [7]. Elderly patients with GAD were markedly more likely to complain of moderate-to-severe problems with difficulty falling asleep (58.6% among participants with GAD vs 21.1% among those without, respectively), difficulty staying asleep (83.3 vs 21.1%, respectively), difficulty waking up too early (73.3 vs 36.8%, respectively) and insomnia (51.6 vs 4.8%, respectively).

Current treatment guidelines recommend the use of a selective serotonin reuptake inhibitor (SSRI) or a serotonin norepinephrine reuptake inhibitor (SNRI) as first-line treatments for

GAD [22–24]. Evidence from clinical studies has demonstrated that treatment with escitalopram and duloxetine results in a significant improvement in the QoL of patients with GAD [25–27]. However, around 50% of patients with GAD do not respond to first-line treatment with SSRI/SNRI [28]. Furthermore, treatment with SSRIs and SNRIs has been associated with a reduction in sleep quality suggested by a greater likelihood of sleep disturbances, including poorer sleep efficiency, longer sleep latency and sleep fragmentation [29]. Thus, for some patients, the potential benefits of these treatments may be counteracted by the negative impact on sleep.

The lack of an active comparator arm, flexible-dose design (which precludes investigation of dose-related outcomes) and acute treatment period (lack of long-term data) represent limitations of the current analysis.

Conclusion

Quetiapine XR (50–300 mg/day) is effective in reducing the symptoms of anxiety in elderly patients with GAD. Quetiapine XR also offers benefits in terms of addressing key patient-reported outcomes, including QoL and sleep quality, which contribute to the burden of this prevalent and disabling disorder.

Future perspective

GAD is the most commonly reported chronic anxiety disorder in the elderly; however, it is largely underinvestigated and undertreated in this patient population. In elderly patients, GAD significantly compromises QoL by causing limitations in daily activities and can lead to depression if left untreated.

Current treatment guidelines recommend the use of an SSRI or an SNRI as first-line treatments for GAD, and evidence from clinical studies has demonstrated that treatment with escitalopram and duloxetine results in a significant improvement in QoL in patients with GAD. However, approximately 50% of patients with GAD do not respond to first-line treatment with SSRI/SNRI. Furthermore, treatment with SSRIs and SNRIs has been associated with a reduction in sleep quality suggested by a greater likelihood of sleep disturbances, including poorer sleep efficiency, longer sleep latency and sleep fragmentation, thus, for some patients, the potential benefits of these treatments may be counteracted by the negative impact on sleep.

Once-daily quetiapine XR has demonstrated efficacy as an acute and maintenance monotherapy for GAD in adults and as an acute monotherapy in elderly patients. Indeed as reported previously, quetiapine XR in this cohort of elderly patients with GAD had a tolerability profile consistent with the known tolerability profile of quetiapine. This paper showed that quetiapine XR monotherapy (50–300 mg/day flexibly dosed) improved QoL, enjoyment, satisfaction and sleep quality in elderly patients with GAD. As treatment for GAD may be long term, further investigations of the tolerability of antipsychotics in elderly patients are required in the future in order to more fully understand the safety profile.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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