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The place of quetiapine extended release in the treatment of mental disorders

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Summary

This article presents a summary of available data on the use of quetiapine extended release (QUE-XR). QUE-XR is an example of an atypical antipsychotic drug that can be used in a single dose, thereby simplifying the treatment regimen. From the therapeutic standpoint, this issue is of paramount importance, since approximately 50% of patients have adherence issues. Therefore, availability of the drug which is comfortable in administration can significantly improve treatment outcomes. Due to its antipsychotic, antidepre- sive, mood stabilizing and anxiolytic efficacy, QUE-XR seems to be a promising drug with potentially broad spectrum of indications (in patients with schizophrenia, bipolar disorder, major depression and some anxiety disorders – both in the acute phase of treatment, and the maintenance treatment). Notably, QUE-XR seems to ameliorate sleep disturbances, and it may also improve patients' quality of life (as suggested by some studies). Due to the simple dosing regimen of QUE-XR, conducting therapy with this drug may contribute to the improvement of compliance. Yet, the primary clinical criterion for selection of the type of formulation of quetiapine should be the individual preferences of the patient, and the knowledge and experience of the treating physician.

Key words: quetiapine XR, schizophrenia, bipolar disorder

Introduction

Introduction on the market drugs in the form of extended release (XR) responds to the needs of patients, who often emphasize the nuisance of taking several doses of the drug per day [1]. Almost 50% of patients have adherence issues. This results in an increased risk of relapse, frequency of hospitalization and higher risk of suicide attempts [2]. The authors of a recently published systematic review found that simplified drug regimens can help to improve compliance, both in patients with psychiatric and medical disorders [3].

QUE-XR is an example of an atypical antipsychotic drug that may be used in a single dose, thereby simplifying the treatment regimen. Thus, applying drug that is comfortable in administration, resulting in relatively few adverse effects could significantly contribute to the improvement in compliance [2].

According to the European Medicines Agency [4], QUE-XR can be used in the course of the following mental disorders:

1. schizophrenia (both in the acute phase, and in the maintenance therapy);
2. bipolar disorder (BD) – in the acute phase (in patients with mania with moderate or considerable degree of severity, as well as in patients with severe bipolar depression), or as a part of maintenance therapy (in patients with a history of mania or depression, who showed a therapeutic response to quetiapine);
3. severe episodes of major depressive disorder (MDD) (as adjuvant therapy)

Corresponding indications of registration have been adopted in Poland [5].

The use of quetiapine XR in patients with specific mental disorders

Schizophrenia

The effectiveness of QUE-XR both in the acute phase, and in the maintenance treatment of adult patients with schizophrenia have been confirmed in a number of phase III clinical trials. Majority of the data derive from double-blind randomized controlled trials (RCTs) (see Table 1) [6–9].

Table 1. **Summary of the results of randomized controlled trials on the efficacy of quetiapine XR in patients with schizophrenia**

Kahn et al., 2007 [8]	
Population	N = 588
Intervention in the study group	QUE-XR at the dose of 400 mg/day, 600 mg/day or 800 mg/day
Intervention in the control group	QUE-IR at the dose of 400 mg/day (200 mg twice a day) or placebo.
Results	In the QUE-XR-group a significant improvement in PANSS score at week 6 compared to placebo (-18.8), in subgroups: -24.8 ($p = 0.03$), -30.9 ($p < 0.001$), and -31.3 ($p < 0.001$) for the QUE-XR at 400, 600 or 800 mg/day and -26.6 ($p = 0.004$) for QUE-IR was obtained. Side effects in groups of XR and IR: dizziness and drowsiness.
Peuskens et al., 2008 [6]	
Population	N = 197
Intervention in the study group	QUE-XR (300 mg on day 1, 600 mg on day 2, and then individually adjusted dose of 400-800 mg/day. After 16 weeks all the subjects from the study group were treated with QUE-XR at a dose of 400-800 mg/day.
Intervention in the control group	QUE-XR (300 mg on day 1, 600 mg on day 2, and then individually adjusted dose of 400-800 mg/day. After 16 weeks all the subjects from the control group were using placebo.

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Results*	QUE-XR compared to placebo effectively prevented the relapse (10.7% vs. 41.4%): HR = 0.16 (95% CI: 0.08–0.34); NNT = 3 (95% CI: 3–7). Tolerance of the drug was comparable in both groups (incidence of adverse events: 18% in the QUE-XR and 21% in the placebo group, p > 0.05).
Lindenmayer et al., 2008 [9]	
Population	N = 565
Intervention in the study group	QUE-XR at the dose of 300 mg/day, 600 mg/day or 800 mg/day.
Intervention in the control group	QUE-IR at the dose of 300 mg/day, or 600 mg/day, or placebo.
Results	The improvement on the PANSS: QUE-XR 300 mg/day -5.01, 600 mg/day -13.01 and 800 mg/day -11.17, QUE-IR 300 mg/day -9.42 and 600 mg/day -6.97, and -5.19 placebo. Statistically significant difference in favour of QUE-XR used at a dose of 600 mg/day (p = 0.033).
Peuskens et al., 2010 [10]	
Population	N = 197
Intervention in the study group	QUE-XR at the dose of 400, 600 or 800 mg/day.
Intervention in the control group	Placebo.
Results	The risk of relapse was higher in the placebo group than QUE-XR (HR = 0.39; 95% CI: 0.19–0.81, p = 0.009). After 6 months, the probability of remission was 76% in the QUE-XR group and 52% in the placebo group.
Loebel et al., 2013 [11]	
Population	N = 353
Intervention in the study group	Lurasidone at the dose of 40–160 mg/day.
Intervention in the control group	QUE-XR at the dose of 200–800 mg/day.
Results	After 12 months the risk of relapse was 33.6% for QUE-XR and 23.7% for lurasidone.
Naber et al., 2013 [12]	
Population	N = 798
Intervention in the study group	QUE-XR at the dose of 400-800 mg/day.
Intervention in the control group	Risperidone at the dose of 2–6 mg/day.
Results	After 12 months, no statistically significant differences on the SWN-K scores were detected. The QUE-XR group: change in score of 23.2 points; in the risperidone group: change in score of 21.1 points; difference = 2.1 (95% CI: – 0.8; 5.0). Note: a non-inferiority study.
Harvey et al., 2013 [13]	
Population	N = 267
Intervention in the study group	Lurasidone at the dose of 80 mg/day or 160 mg/day or QUE-XR dosed 200–800 mg/day.
Intervention in the control group	Placebo.

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Results	Statistically significant improvement in cognitive function between the groups receiving active treatment and placebo was observed at the 6th week of the study (UPSA-B).
Loebel et al., 2013 [14]	
Population	Patients with schizophrenia with symptoms of agitation (N = 486)
Intervention in the study group	Lurasidone at the dose of 80 mg/day or 160 mg/day or QUE-XR dosed 600 mg/day.
Intervention in the control group	Placebo
Results	In the QUE-XR group there was a significant improvement in the PANSS--EC scores (determining the level of agitation of patients). Hypersomnia during the day did not remit in the group receiving QUE-XR (EES scale, $p < 0.01$), as compared to the placebo and lurasidone groups.

* The NNT value (with the 95% CI) was calculated on the basis of the data presented in the original study. Abbreviations: CI – confidence interval; EES – Epworth Sleepiness Scale; HR – hazard ratio; NNT – number needed to treat; PANSS – Positive and Negative Syndrome Scale; PANSS-EC – Positive and Negative Syndrome Scale, Excited Component; QUE-IR – quetiapine immediate release; QUE-XR – quetiapine extended release; SWN-K – Subjective Well-Being under Neuroleptics Scale; UPSA-B – University of California San Diego Performance-based Skills Assessment Brief

Kahn et al. [8] compared the efficacy of QUE-XR used in one of three doses (400, 600 or 800 mg/day in the evening) with the effects of taking quetiapine immediate release (QUE-IR, administered in two doses of 200 mg) or placebo. The target doses of QUE-XR were reached very quickly (400 and 600 mg on the second day of treatment, and 800 mg on the third day of observation). 76% of patients (n = 446) completed the study. After 6 weeks, each of the given doses QUE-XR (as well as QUE-IR) showed advantage over placebo, both in terms of the reduction of the symptoms of schizophrenia (as measured by the Positive and Negative Syndrome Scale (PANSS) scores, and the criteria of therapeutic response (≥ 30% reduction of the PANSS score, as compared to baseline, or the proportion of patients who achieved ≤ 3 points on the Clinical Global Impression (CGI) scale at the end of the trial).

Another placebo-controlled RCT, in which 532 patients with symptoms of acute schizophrenia were receiving QUE-XR and QUE-IR for six weeks (at the doses of 300, 600 or 800 mg/day) or QUE-IR (at a target dose of 300 mg/day or 600 mg/day), has shown that only patients receiving QUE-XR at dose of 600 mg/day had obtained a statistically significant reduction of disease severity (as measured by the PANSS scores). The statistical significance in the case of improvement observed on the CGI scale was found for both the daily dose of 800 mg QUE-XR and 300 mg QUE-IR [9].

Ganesan et al. [15] in the 12-week, multicenter, open-label study investigated tolerability and efficacy of QUE-XR used in patients with schizophrenia who have previously used atypical antipsychotic drugs other than quetiapine, but did not obtain a significant improvement in clinical status. In 62.8% of the 292 patients who completed the study, the switch has brought benefits in terms of a statistically significant reduction of disease severity (as indicated by the PANSS and CGI scores), and decrease of the

severity of extrapyramidal symptoms assessed using the Simpson-Angus Scale – SAS, and the Barnes Akathisia Rating Scale – BARS.

Peuskens et al. [6] studied the long-term efficacy of QUE-XR used at the doses of 400 or 800 mg/day in patients with schizophrenia in a stable condition. The patients were randomly assigned to one of two groups: receiving QUE-XR or placebo. After 16 weeks of observation, it was found that QUE-XR significantly extended the average time to relapse of symptoms. In addition, compared with placebo, in patients treated with QUE-XR the rate of relapse was significantly lower. Similar conclusions can be drawn from the study by Loebel et al. [11], who found that the QUE-XR at the doses of 200–800 mg/day similarly effectively prevents relapse of schizophrenia, as lurasidone used at the doses of 40–160 mg/day.

Bipolar disorder

As in the case of many atypical antipsychotic drugs, quetiapine plays an important role in treatment of BD [16, 17]. Since this drug exerts antipsychotic, antidepressive and mood stabilizing effects [18], taking quetiapine may benefit both patients suffering from bipolar disorder exacerbation and patients requiring maintenance therapy. However, although there have been many studies on the QUE-IR in the treatment of patients with bipolar disorder [16], the evidence based on the clinical profile of QUE-XR is largely incomplete.

Most of the data on the efficacy and safety of using QUE-XR in this clinical population derive from the five RCTs. With an exception of the study by Riesenberg et al. [19], there have been no RCT on direct comparisons between QUE-IR and QUE-XR in the treatment of patients with BD (see Table 2) [19–26]. Therefore, most of the recommendations regarding the use of QUE-XR in patients with bipolar disorder is a compilation of conclusions from studies on QUE-IR, pharmacokinetic considerations, and data on patients' individual preferences [20–23].

Table 2. **Summary of the results of randomized controlled trials on the efficacy of quetiapine XR in patients with bipolar disorder**

Suppes et al., 2010 [25]	
Population	Patients with bipolar depression in the course of BD type I or II.
Intervention in the study group	QUE-XR 300 mg once a day (N = 133).
Intervention in the control group	Placebo (N = 137).
Results *	After 8 weeks of observation in QUE-XR group it was found as follows: – greater reduction in symptoms of depression (ES = 0.61); – higher probability of obtaining a therapeutic response (65.4% vs. 43.1%): RB = 1.52 (95% CI: 1.21–1.91); NNT = 5 (95% CI: 3–10); – higher probability of obtaining a remission (54.1% vs. 39.4%): RB = 1.41 (95% CI: 1.09–1.83); NNT = 7 (95% CI: 4–23). Note: Compared with the placebo, in the QUE-XR group there was a significant reduction in the severity of depressive symptoms after 7 days of treatment.

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Cutler et al., 2011 [24]	
Population	Patients with bipolar disorder type I, during an episode of mania.
Intervention in the study group	QUE-XR 400–800 mg once a day (N = 149).
Intervention in the control group	Placebo (N = 159).
Results *	After 3 weeks of observation in QUE-XR group it was found as follows: – greater reduction in symptoms of mania (an average of -14.34 points. vs. -10.52 points. in YMRS, $p < 0.001$); – higher probability of obtaining a therapeutic response (55% vs. 33.3%): RB = 1.65 (95% CI: 1.2–2.15); NNT = 5 (95% CI: 4−10); – higher probability of obtaining a remission (41.6% vs. 27.7%): RB = 1.5 (95% CI: 1.1–2.06); NNT = 8 (95% CI: 5−30).
Riesenberg et al., 2012 [19]	
Population	Patients with a diagnosis of bipolar disorder type I or II, whose last episode was depression.
Intervention in the study group	QUE-XR in titrated doses (target dose: 300 mg 1x daily).
Intervention in the control group	QUE-IR in titrated doses (target dose: 300 mg 1x day).
Results *	After 1 week of observation less severe sedation after 1, 2 or 3 hours post-dose ($p \leq 0.05$) was found in the QUE-XR group.
Sheehan et al., 2013 [26]	
Population	Patients with a diagnosis of bipolar disorder with comorbid PD or GAD.
Intervention in the study group	QUE-XR 50–300 mg 1x daily (N = 49).
Intervention in the control group	DVP-ER 500–3000 mg/day (N = 49) or placebo (N = 51).
Results *	After 8 weeks of observation QUE-XR group compared to the DVP-ER group presented: – higher probability of obtaining a therapeutic response in the symptoms of PD or GAD (62% vs. 35%): RB = 1.76 (95% CI: 1.13−2.75); NNT = 4 (95% CI: 3−14); – higher probability of obtaining PD or GAD remission (45% vs. 22%): RB = 2 (95% CI: 1.09−3.67); NNT = 5 (95% CI: 3−24); – higher probability of obtaining a therapeutic response in BD symptoms (40% vs. 17%): RB = 2.5 (95% CI: 1.22−5.13); NNT = 5 (95% CI: 3−14); – similar probability of obtaining remission of BD symptoms (19% vs. 11%): RB = 1.8 (95% CI: 0.65−4.99). – Compared with the placebo in QUE-XR group presented: – similar probability of obtaining a therapeutic response in the symptoms of PD or GAD (62% vs. 47%): RB = 1.3 (95% CI: 0.9−1.88); – higher probability of obtaining PD or GAD remission (45% vs. 22%): RB = 2.08 (95% CI: 1.13−3.82); NNT = 5 (95% CI: 3−19); – similar probability of obtaining a therapeutic response in BD symptoms (40% vs. 36%): RB = 1.16 (95% CI: 0.7−1.91); – similar probability of obtaining remission of symptoms of bipolar disorder (19% vs. 12%): RB = 1.56 (95% CI: 0.6−4.06).

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Kim et al., 2014 [22]	
Population	Patients with a diagnosis of a depressive episode in the course of BD type I or II.
Intervention in the study group	QUE-XR 300 mg 1x daily (N = 12).
Intervention in the control group	Lithium carbonate at a starting dose of 600 mg/day (which is modified to obtain a concentration of lithium in serum = 0.8−1.2 mmol/l) (N = 17).
Results*	After 8 weeks of observation in QUE-XR group it was found as follows: – similar probability of obtaining a therapeutic response in depressive symptoms (58% vs. 35%): RB = 1.65 (95% CI: 0.74−3.69); – marginally higher probability of remission (50% vs. 12%): RB = 4.25 (95% CI: 1.03−17.57); NNT = 3 (95% CI: 2−17); – a significant improvement in quality of sleep.

Measures of effect (RB and NNT) with 95% CI were calculated on the basis of the data presented in the original studies. [§] Double-blind RCT. [#] Open-label RCT. Abbreviations: CI − confidence interval; DVP-ER – divalproex extended release, ES – effect size; GAD – generalized anxiety disorder, NNT – number needed to treat; PD – panic disorder, RB – relative benefit, RCT – randomized controlled trial, QUE-IR – quetiapine immediate release; QUE-XR – quetiapine extanded release; YMRS – Young Mania Rating Scale

The results of the three RCT (placebo- [24, 25] or QUE-IR-controlled [19]), suggest that treatment with QUE-XR is associated with a higher likelihood of obtaining a therapeutic response or remission in patients with mania [24] or bipolar depression [19, 25]. In the study encompassing patients with bipolar disorder with comorbid generalized anxiety disorder (GAD) or panic disorder (PD), Sheehan et al. found that, although the data on the effectiveness of QUE-XR in the symptoms of bipolar disorders are ambiguous, subjects treated with the drug enjoyed higher chance of obtaining a therapeutic response or remission of anxiety disorders [26] (However, the results of the recently published study by Gao et al. suggest that QUE-XR may not differ from placebo in antidepressant efficacy in patients whose GAD occurs with bipolar disorder type I or II [27]). Kim et al. noted that QUE-XR has similar antidepressant efficacy as lithium carbonate, but is more effective in reducing the severity of sleep disorders [22]. Based on a literature review, Pompili et al. pointed out that the rapid onset of action QUE-XR and the beneficial effect of this drug on the quality of sleep may significantly contribute to reduce the risk of suicide in patients with depression in the course of bipolar disorder or MDD [28].

It seems that people taking QUE-XR are not at a great risk for serious side effects. Suppes et al. found that the use of QUE-XR is associated with a significantly higher risk of occurrence of dry mouth (37.2% vs. 7.1%, $p < 0.05$), daytime sleepiness (29.2% vs. 5.7%, $p < 0.05$), sedation (23.4% vs. 7.1%, $p < 0.05$) and clinically significant (i.e. about $\geq 7\%$) increase in body weight (8.2% vs. 0.8%, $p < 0.05$) [25].

Currently, joint statement of experts from working groups of the Canadian Networks for Mood and Anxiety Treatments (CANMAT) and the International Society for Bipolar Disorders (ISBD) is the only set of guidelines enlisting QUE-XR among the drugs recommended for subjects with BD [17]. These researchers concluded that the use

of QUE-XR monotherapy is one of the first choice treatment options in patients with a history of mania or bipolar depression (both in the course of bipolar type I and II).

Overall, currently there is little evidence base for the use of QUE-XR instead of QUE-IR in the treatment of BD. Individual preferences of the patient should be the main criterion for selection of the formulation of quetiapine [16].

Major depressive disorder (MDD)

Several RCTs with placebo control group were conducted on the effectiveness of QUE-XR (at the doses of 50, 150 or 300 mg/day) as monotherapy in patients with acute phase of MDD [29, 30]. The observation time was six to eight weeks. In two of the cited studies an active treatment was used in the control groups (either duloxetine or escitalopram). QUE-XR has proven to be effective in reducing symptoms of depression. Importantly, the improvement could be seen as early as on the fourth day of treatment. This rapid positive effect was associated primarily with improving sleep and reducing tension, while in the later period of treatment improvement in all symptoms of depression could be observed.

Sanford [31] has summarized the results of studies on the effectiveness of QUE-XR in the adjuvant treatment of patients with MDD who have not obtained satisfactory results of therapy with antidepressants. According to this author the available data suggest that the use of QUE-XR, both at a dose of 150 mg/day and 300 mg/day can effectively reduce the severity of depressive symptoms, and is associated with a greater chance of obtaining remission (compared to placebo). Quality of life of people taking QUE-XR does not seem to differ from the well-being of patients receiving placebo.

In the meta-analysis of three RCTs (involving 1497 patients with MDD) Maneeton et al. [32] found that receiving QUE-XR is associated with a significant decrease in symptoms of depression and anxiety, as well as contributing to improve the quality of sleep (in comparison to placebo). The risk of discontinuation of treatment was similar in both groups. However, the authors emphasized the most common cause of resigning from therapy with QUE-XR were the side effects.

Anxiety Disorders

Authors of the Canadian guidelines for the treatment of anxiety disorders (published in 2014) attributed the most important role to the selective serotonin reuptake inhibitors (SSRI) and serotonin and norepinephrine reuptake inhibitors (SNRI). However, both in some clinical studies of anxiety disorders, as well as the guidelines themselves, attention has been drawn to the role of the atypical antipsychotic drugs, including QUE-XR [33]. So far, relatively few studies on the effectiveness of QUE-XR in the treatment of anxiety disorders have been conducted (see Table 3). Most scientific data pertain to the effects QUE-XR on the mental status of subjects diagnosed with generalized anxiety disorder (GAD) [34].

In patients with GAD, Katzman et al. evaluated the long-term (>12 weeks) efficacy of the drug compared to placebo. Initially, all the patients were receiving QUE-XR

(until the stabilization of mental status), and then patients were randomly assigned to one of four groups: QUE-XR 50 mg/day, 150 mg/day or 300 mg/day or placebo. A significant reduction in the risk of relapse of anxiety symptoms, lower risk of treatment discontinuation, and improvement in the quality of life was observed in subjects continuing treatment with QUE-XR [35].

In another clinical trial (conducted by Khan et al. [36]) changes in the severity of anxiety symptoms in patients with GAD were analysed using either the two-drug regimen: SSRI/SNRI + QUE-XR or SSRI/SNRI + placebo. After eight weeks of treatment there was no statistically significant decrease in the symptoms of anxiety or statistically significant improvement of quality of life in patients receiving QUE-XR as adjuvant therapy.

Slightly different conclusions were drawn from the study conducted by Endicott et al., who analysed the results of three RCTs on the use of QUE-XR as monotherapy in adults with a diagnosis of GAD, and one RCT performed in the population of elderly patients. Participants in the study received QUE-XR at a dose of 50 mg/day, 150 mg/day or 300 mg/day. After 8 weeks of treatment significant improvement in quality of life was observed in patients receiving this drug at a dose of 150 mg/day. There was no such effect in patients taking QUE-XR in different doses. At the same time QUE-XR (regardless of a dose) showed a significant anxiolytic efficacy [37].

Authors of the Canadian clinical guidelines have indicated that the QUE-XR may be more effective in the treatment of GAD in comparison with escitalopram. Meta-analyses conducted by Depping et al. [38] and LaLonde and Van Lieshout [39] suggest that QUE-XR is significantly more effective than placebo, and at least as effective as antidepressants in the treatment of GAD. However, compared with the use of antidepressants or placebo, therapy with using QUE-XR carries an increased risk of side effects such as weight gain or sedation, and is also associated with a higher risk of treatment discontinuation. Therefore, the authors of these guidelines recommend the use of QUE-XR (alone or as part of adjuvant therapy) as a second choice treatment option. Therapy with QUE-XR can be particularly beneficial in patients in whom the use of antidepressants or benzodiazepines may be harmful.

Table 3. **Summary of results of randomized trials on the efficacy of quetiapine XR in patients with anxiety disorders**

Bandelow et al., 2010 [40]	
Population	873 subjects diagnosed with GAD (quetiapine XR 50 mg/day = 221, 150 mg/day = 218, paroxetine = 217, placebo 217)
Intervention in the study group	QUE-XR 50 mg/day or 150 mg/day or paroxetine 20 mg/day (for 8 weeks)
Intervention in the control group	Placebo
Results *	Lowering the level of anxiety in the HAM-A: LSM placebo (-12.3), QUE-XR 50 mg/day LSM (-13.95), $p < 0.05$, QUE-XR 150 mg/day LSM (-15.96), $p < 0.001$, paroxetine LSM (-14.45), $p < 0.01$. A larger rate of remission in patients treated with QUE-XR at a dose of 150mg/day (42.6%, $p < 0.01$) than in the groups receiving paroxetine (38.8%, $p < 0.05$) or placebo (27.2%).

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Katzman et al., 2011 [35]	
Population	432 patients with GAD (study group: 216, control group: 216)
Intervention in the study group	Patients received 3 doses of quetiapine XR 50 (26.4%), 150 (49.1%) and 300 mg/day (24.5%).
Intervention in the control group	Patients in the control group received only placebo.
Results *	QUE-XR significantly extended the time to recurrence of anxiety symptoms compared to placebo (HR = 0.19; 95% CI = 0.12−0.31, p < 0.001). QUE-XR significantly reduced the number of discontinuations of therapy: 119 (55.1% placebo) and 54 (25.0% QUE-XR). The percentage of reported side effects in the compared groups was similar: 51.9% (QUE-XR) and 51.4% (placebo).
Merideth et al., 2012 [34]	
Population	854 patients with GAD (placebo = 215, QUE-XR 150 mg/day = 219, 300mg/day = 207, escitalopram = 213)
Intervention in the study group	Patients received for a period of eight weeks, depending on randomization QUE-XR 150 mg/day 300 mg/day or escitalopram 10 mg/day.
Intervention in the control group	Placebo.
Results *	A significant reduction in the total score on the HAM-A in the groups receiving escitalopram (-12.3, p < 0.05), quetiapine XR 150 mg/day (-13.9, p < 0.001) and 300 mg/day (-12.3, p < 0.05) compared to the placebo group (-10.7).
Khan et al., 2013 [36]	
Population	409 patients with GAD (study group 209, placebo group 200)
Intervention in the study group	Patients received SSRI/SNRI + QUE-XR 150 mg/day or 300 mg/day for 8 weeks.
Intervention in the control group	Patients received SSRI/SNRI + placebo for 8 weeks.
Results *	There was no statistically significant reduction in the HAM-A score in the research group after 8 weeks of the study (-10.74, p = 0.079). The reduction in the HAM-A score in 1 (-6.43; p < 0.001) and 6 (-11.13; p < 0.05) weeks of treatment. After 8 weeks of treatment there was not a significant improvement in quality of life in the study group (compared to placebo).

Abbreviations: CI − confidence interval; GAD − generalized anxiety disorder; HAM-A − Hamilton Anxiety Rating Scale; HR − hazard ratio; LSM − least squares method; QUE-XR – quetiapine extanded release; SSRI – selective serotonin reuptake inhibitors, SNRI − serotonin and norepinephrine reuptake inhibitors

Recapitulation

In this article we have presented an outline of the current evidence base on the use of QUE-XR in patients with mental disorders. Despite the numerous advantages of

QUE-XR, the data presented are not sufficient to unambiguously determine whether it would be better to use QUE-XR instead of QUE-IR. There is a need for direct comparative studies of the drug formulations, encompassing larger groups of participants. Still, the primary clinical criterion for selection of the quetiapine formulation should be the individual preferences of the patient, and the knowledge and experience of the treating physician. Taking into account the fact that modern psychiatry does not only search for correction of the psychopathological symptoms, but it also sets a goal to improve the quality of life and functioning of the patients during the symptomatic remission [41, 42], the convenience of application and the confirmed effectiveness of QUE-XR can contribute to the further improvement of treatment compliance.

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