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QUETIAPINE ADD-ON THERAPY MAY IMPROVE PERSISTENT SLEEP DISTURBANCES IN PATIENTS WITH PTSD ON STABILE COMBINED SSRI AND BENZODIAZEPINE COMBINATION: A ONE-GROUP PRETEST-POSTTEST STUDY

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SUMMARY

Background: *To assess potential benefits of quetiapine for persistent sleep disturbances in patients with posttraumatic stress disorder (PTSD) on stable combined SSRI and benzodiazepine therapy, who previously failed to respond to various benzodiazepine and non-benzodiazepine hypnotic adjuvant treatment as well as to first-generation antipsychotic add-on treatment.*

Subjects and methods: *Fifty-two male PTSD outpatients on stable combination treatment with SSRI and benzodiazepines, with persistent sleep disturbances not responding to prescription of zolpidem, flurazepam, nitrazepam, promazine, and levopromazine, were assessed for sleep disturbances improvements after prescription of quetiapine in the evening. Each patient met both ICD-10 and DSM-IV criteria for PTSD. Psychiatric comorbidity and premorbidity were excluded using the Mini-International Neuropsychiatric Interview (MINI). Improvement on the CAPS recurrent distressing dream item, reduction in the amount of time needed to fall asleep, prolongation of sleep duration, and reduction in average number of arousals per night in the last 7 days before the assessment period were used as efficacy measures.*

Results: *All sleep-related parameters improved significantly at the end of a five-week follow-up: sleep duration increased by one hour ($p<0.001$), sleep latency decreased by 52.5 minutes ($p<0.001$), median number of arousals per night decreased from two to one ($p<0.001$), CAPS recurrent distressing dream item median decreased from five to four ($p<0.001$), and the number of patients dissatisfied with their sleep quality and quantity decreased from 45 to two ($p<0.001$).*

Conclusion: *Quetiapine prescribed in the evening may be successful therapy for persistent sleep disturbances in patients with PTSD and generally good response to an SSRI and benzodiazepine combination, who previously failed to respond to some of the usual hypnotic medication or addition of first-generation antipsychotics: zolpidem, flurazepam, nitrazepam, promazine, and levopromazine.*

Key words: *posttraumatic stress disorder – insomnia – quetiapine – sleep - nightmares*

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INTRODUCTION

Posttraumatic stress disorder (PTSD) is an anxiety disorder (Babic 2012, Drožđek et al. 2020) frequently associated with sleep disturbances (Lewis et al. 2020), such as difficulty in falling or staying asleep, recurrent distressing dreams of the traumatic event, and chronicity of such sleep disturbances. Repetitive trauma-content nightmares occur in 19-71% of patients with PTSD, while 70-91% of them experience initial and/or middle insomnia (Maher et al. 2006, Rosen et al. 2013, van Liempt et al. 2007). Insomnia and nightmares are viewed as core symptoms of PTSD (Lancel et al. 2021). Sleep problems result in decreased daily alertness, significant functional impairments, as well as quality of life reduction and generally poor health. Various studies have suggested different approaches regarding sleep problems treatment in patients with PTSD. Based on currently available literature data, despite some behavioral (Margolies et al. 2013, Ulmer et al. 2011, Ehlers & Clark 2008, Benz et al. 2020, Maher et al. 2021) and various pharmacological interventions showing promise, there is still an insufficient number of controlled studies to formulate adequate evidence-based guidelines. Various psychotropic drugs have been found to improve sleep quality in patients with PTSD. In that context, selective serotonin reuptake inhibitors (SSRIs), commonly used in PTSD treatment, have a small but significant positive effect on sleep disruption (Colvonen et al. 2019). Nefazodone and trazodone, which are serotonin-potentiating non-SSRIs, also significantly reduce insomnia and nightmares in patients with PTSD (Aurora et al. 2010). Augmentation of SSRIs with olanzapine may be beneficial for patients with chronic insomnia and treatment-resistant nightmares, despite

adverse effects that may occur (Jakovljević et al. 2003). Some other medications, including zolpidem, mirtazapine, buspirone, and gabapentin, can also improve sleep in some patients with PTSD (Maher et al. 2006). Alpha-blockers, particularly prazosin, reduce nightmares in patients with both combat and noncombat-related trauma (Taylor et al. 2008, Salviati et al. 2013, Raskind et al. 2013, Zhang et al. 2020).

Atypical antipsychotic quetiapine showed various benefits in alleviating PTSD symptoms other than PTSD-related sleep disturbances and is sometimes prescribed "off label". In that context, some studies confirmed clinical improvements in treatment-resistant patients with psychotic PTSD (Kozaric-Kovacic & Pivac 2007), and some have suggested that quetiapine can be an effective therapeutic choice for refractory hyperarousal symptoms (Mihaljević-Peleš et al. 2008), while the other studies emphasized the improvement in autonomic stability and decrease in anxiety response that arose due to a specific trigger (Rowe 2007) in patients with PTSD after quetiapine prescription. A literature search found no systematic studies exploring potential benefits of low doses of quetiapine on PTSD-related persistent sleep disturbances/symptoms in patients with chronic PTSD and a generally good response to combined SSRI and benzodiazepine therapy, who previously failed to respond to various adjuvant treatment, including benzodiazepine and non-benzodiazepine hypnotic medication and addition of first-generation antipsychotics (FGA).

Quetiapine has a moderate affinity for 5-HT_{2A} serotoninergic, α_1-adrenergic, muscarinic and histaminergic receptors, minor affinity for D_2 and 5-HT_{1A} receptors, and low affinity for 5-HT_{2C}, α_2-adrenergic and D_1 receptors, and has been shown to be beneficial for a wide range of PTSD-related symptoms. Its efficacy regarding intrusive symptoms could be explained by its sedative and sleep-improving effects. It is hypothesized that somnolence is a result of 5-HT_{2A}, H_1, and α_1 blockade. Antiadrenergic and antihistaminic activity could be associated with diminished irritability. Quetiapine's activity through 5-HT_{1A} and 5-HT_{2C} receptors could explain reduction of anxiety and depression. D_2 receptor antagonism correlates with flashbacks, hypervigilance, and intrusive thoughts reduction.

Persistent trauma-related repetitive nightmares are an almost universal symptom of PTSD (Germain et al. 2008, Levin & Nielsen 2007, Lancel et al. 2021), while other sleep-related abnormalities, including shorter total sleep duration and increased sleep onset latency, are frequently present in some subgroups of PTSD patients (Krakov et al. 2018). It seems that PTSD trauma-related nightmares are primarily a rapid eye movement (REM) sleep phenomenon (Gieselmann et al. 2019), but they may also occur during non-REM (NREM) sleep in patients with PTSD (van der Kolk et al. 1984). Insomnia in patients with PTSD is believed to result primarily from NREM sleep disruption. α_1 adrenergic activity is associated with increased stage 1 and stage 2 and, as well as disrupted REM sleep, and thus a psychopharmaceutical with blocking central α_1 adrenergic activity (one of quetiapine's properties is α_1-receptor antagonism) may be beneficial for PTSD-related sleep difficulties. On the other hand, REM sleep (as the primary origin of PTSD-related nightmares) is inhibited by serotonergic neurotransmission (Gillin et al. 2001) – a function of both SSRIs and quetiapine. In that context, we assumed that patients on a stable SSRI and benzodiazepine combination who previously failed to respond to various add-on/adjuvant therapy for PTSD-related persistent sleep disorder would benefit from low dose adjuvant therapy with quetiapine.

Our 25 years of clinical experience with patients with war-related, chronic PTSD resulted in an observation on the potential benefits of quetiapine, prescribed before sleep, for persistent PTSD-related sleep problems in patients with good response to combined SSRI and benzodiazepine therapy, who previously failed to respond to various benzodiazepine and non-benzodiazepine hypnotic medication and addition of first-generation antipsychotics (FGA).

The aim of this study was to assess possible PTSD-related sleep disturbance improvements in patients with chronic, war-related PTSD on stable combined SSRI and benzodiazepine therapy, who previously failed to respond to each of the following adjuvant/add-on therapies: zolpidem, flurazepam, nitrazepam, promazine, and levopromazine.

SUBJECTS AND METHODS

Participants and procedure

Prior to beginning of the study, ethical approval was received from the Ethical Committee of the University Psychiatric Hospital Vrapče, Zagreb, Croatia, which conforms to the provisions of the Declaration of Helsinki in 1995 (as revised in Edinburg 2000 and with the last revision 2013) (World Medical Association Declaration of Helsinki 2013).

A prospective, open-label, five-week study was conducted in 52 patients with chronic, war-related PTSD. The participants were recruited as a consecutive sample from the pool of patients who received outpatient psychiatric treatment at the University Psychiatric Hospital Vrapče in Zagreb, Croatia. Informed consent was obtained prior to any study procedure, and patient anonymity will be preserved. Inclusion criteria were: a PTSD diagnosis according to ICD-10 (World Health Organisation 1992) and DSM-IV (American Psychiatric Association 2000) criteria, a stable treatment with one of the SSRIs (escitalopram, citalopram, paroxetine, fluvoxamine, or sertraline) in combination with one of the benzodiazepines (alprazolam, lorazepam, clonazepam or diazepam) for at least 25 weeks prior to study entry, defined by

CGI-improvement (Guy 1976) between 1-2 in comparison with the beginning of the treatment (SSRI therapy was taken continuously, while benzodiazepine was taken in repeated, continuous four-week periods, each period including three weeks of benzodiazepine followed by one week of pause); a previous non-response to add-on therapy prescribed before sleep, each drug prescribed for at least five weeks continuously: 5 mg of nitrazepam, 10 mg of zolpidem, 30 mg of flurazepam, 100 mg of promazine, and 100 mg of levopromazine; and chronic, severe war-related trauma-content nightmares, as defined by score of ≥5 (of a maximum of six) in the recurrent distressing dreams item of the Clinician Administered PTSD Scale (CAPS) in Croatian (Blake et al. 1996, Kulenovic et al. 2016) for at least 25 weeks. The average dose and dose ranges [median (min-max)] for each of the five SSRIs was as follows: escitalopram [10 (10-20) mg/day], citalopram [20 (20-20) mg/day], paroxetine [20 (20-20) mg/day], fluvoxamine [100 (100-100) mg/day], and sertraline [100 (50-100) mg/day].

The average dose and dose ranges [median (min-max)] for each of four benzodiazepines were as follows: alprazolam [1.5 (1.0-2.0) mg/day], lorazepam [4.0 (3.0-7.5) mg/day], clonazepam [1.5 (0.75-6.0) mg/day], and diazepam [15.0 (10.0-30.0) mg/day]. Exclusion criteria were psychiatric comorbidity and premorbidity found using the Croatian translation of the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al. 1998, Dzubur Kulenović et al. 2008) and a somatic premorbidity or comorbidity with possible influence on sleep patterns. Despite a stable combination of SSRI and benzodiazepine with each of the following adjuvant/add-on therapies: zolpidem, flurazepam, nitrazepam, promazin, and levopromazin, each prescribed for at least five weeks, a total of 190 screened patients had persistent nightmares, insomnia middle, and shortened sleep duration. Of the 190 screened patients, 25 patients refused to participate and 113 did not meet all the study criteria.

Before entering the study, the last add-on therapy for PTSD-related sleep disorder was discontinued and a dose of 100 mg of quetiapine was added to a previously stable SSRI and benzodiazepine drug regime, half an hour before going to sleep.

Measurements

The parameters of sleep improvements were evaluated at week 5. CAPS recurrent distressing dream item, duration of total sleep, the amount of time needed to fall asleep, and average number of arousals per night in the last 7 days before the assessment period were evaluated at baseline and after the five-week follow-up.

Each patient kept a sleep diary (including information from the bedpartner to get a more accurate report of nightly behaviors as well as sleep-wake behavior) and recorded the following: bedtime and waking time (from which total sleep time was calculated), sleep latency, number of awakenings after sleep onset, and number of unpleasant dreams about traumatic event and related distress. Data regarding the number of unpleasant dreams about the traumatic event and related distress collected from diaries were confirmed during clinical interview with the patient and were used for the assessment of CAPS recurrent distressing dream item.

Statistical analysis

Statistical analysis was performed using STATA/IC for Windows (StataCorp LP, USA) ver11.2. Differences between two time points were assessed using the Wilcoxon signed ranks test.

RESULTS

The socio-demographic characteristics of participants and severity of the disorder at baseline are shown in Table 1.

Three of five prescribed SSRIs (sertraline, escitalopram, and fluvoxamine) were prescribed more frequently than the other two (citalopram and paroxetine), while the alprazolam and diazepam were equally prescribed (each taken by 32.7% of patients) and more frequently taken than the other two benzodiazepines: lorazepam and clonazepam (Table 2).

Table 1. Baseline characteristics of 52 male patients with posttraumatic stress disorder (PTSD)

Socio-demographic characteristics	
Age (years), mean±SD	51.67±6.74
Educational level	n (%)
elementary school	15 (28.8%)
high school	32 (61.5%)
> high school	5 (9.6%)
Marital status	
married or stable relationship	42 (80.8%)
divorced	6 (11.5%)
single	4 (7.7%)
Employment status	
full-time	2 (3.8%)
unemployed but able to work	1 (1.9%)
on the sickleave and unemployed unable to work	8 (15.4%)
retired	41 (78.8%)
PTSD symptoms severity score	(min-max)
CAPS total, median	72 (55-79)
*PTSD-related CGI-S**	n (%)
moderately ill	9 (17.3%)
markedly ill	41 (78.8%)
severely ill	2 (3.8%)

CAPS - Clinician Administered PTSD Scale (Blake et al. 1996, Croatian translation: Kulenovic et al. 2016); higher score reflects higher PTSD severity; CGI-S - Clinical Global Impressions of Severity Scale (Guy 1976); higher score reflects higher PTSD severity

Table 2. SSRIs and benzodiazepines combined therapy

		Benzodiazepines - N (%)				Total
		Alprazolam	Lorazepam	Diazepam	Clonazepam	
SSRI N (%)	Fluvoxamine	3 (5.8)	2 (3.8)	5 (9.6)	2 (3.8)	12 (23.1)
	Sertraline	5 (9.6)	1 (1.9)	4 (7.7)	3 (5.8)	13 (25)
	Paroxetine	4 (7.7)	1 (1.9)	0 (0)	1 (1.9)	6 (11.5)
	Escitalopram	5 (9.6)	3 (5.8)	3 (5.8)	2 (3.8)	13 (25)
	Citalopram	0 (0)	3 (5.8)	5 (9.6)	0 (0)	8 (15.4)
Total		17 (32.7)	10 (19.2)	17 (32.7)	8 (15.4)	52 (100)

Table 3. PTSD-related sleep disturbances/parameters at baseline and the end point of study comparison

	Start-point (median, min-max)	End-point (median, min-max)	*p* value
Sleep duration (hours)	5 (4.25-5.75)	6 (4.5-7)	<0.001
Sleep latency (minutes)	80 (45-115)	27.5 (20-40)	<0.001
Arousals per night (number)	2 (1-3)	1 (0-2)	<0.001
CAPS recurrent distressing dream item score	5 (5-8)	4 (4-6)	<0.001
Number of satisfied/ number of dissatisfied patients	0/45	39/2	<0.001

Significant improvements regarding all four analysed sleep-related parameters were observed at the end of the follow-up period: CAPS recurrent distressing dream item median decreased from five to four (p<0.001), sleep was prolonged from five to six hours (p<0.001), sleep latency decreased from 80 to 27.5 minutes (p<0.001), and the number of arousals per night was reduced from two to one (p<0.001). Ten patients showed no change on the CAPS item, while seven of them had no changes in total sleep duration. All the other patients showed significant improvements in sleep prolongation. Sleep latency was shortened in all of the patients. Most of patients (84.6%) had fewer arousals per night (Table 3).

At the end of study, patients predominantly reported satisfaction with improvements in PTSD-related sleep disturbances (75.0% of patients), less than one quarter were neither satisfied nor unsatisfied (21.2%), while only two patients (3.8%) were unsatisfied, in contrast to the beginning of study when most of patients (86.5%) were unsatisfied and a small percentage (13.5%) was neither satisfied nor unsatisfied with their current adjuvant/add-on therapy for PTSD-related sleep disorder. After finishing study, 41 of the patients (78.85%) continued with quetiapine adjuvant/add-on therapy.

DISCUSSION

The key finding from this study is that quetiapine, prescribed in a low dose of 100 mg as an adjuvant/add-on therapy to a stable SSRI and benzodiazepine combination, may be successful for treating PTSD-related sleep problems in patients who previously failed to respond to add-on of zolpidem, flurazepam, nitrazepam, promazine, and levopromazine. A low dose of quetiapine was well-tolerated, and no significant side-effects were found, whereas significant clinical benefits regarding various aspects of persistent sleep problems in patients with PTSD already stabilized on combined SSRI and benzodiazepine therapy were achieved. Anticipating that the long-term use of benzodiazepines may be risky and may lead to addiction in patients with chronic PTSD, an addition of quetiapine to the antidepressant (with avoidance of benzodiazepines use) seems to be a preferable choice for long-term treatment.

Currently available data suggests various treatment strategies in patients with PTSD with consequently varying clinical efficacy in this population. This is due to the possibility that PTSD might include a wide spectrum of syndrome states (Jakovljevic 2012). SSRIs have been established as a treatment option for patients with both war-related or civilian PTSD for more than a decade. Everyday clinical practice (including our two decades of clinical work with patients suffering from war-related PTSD) (Vilibic et al. 2014) as well as currently available data (Rowe 2007, Asnis et al. 2004, Bajor et al. 2011, Kozaric-Kovacic 2008, Kim et al. 2008, Panahi et al. 2011, Middleton et al. 2011), suggest varying efficacy of SSRIs when prescribed to patients with PTSD. The percentage of non-responders to SSRIs in PTSD patients varies between 30% and 60% (Rowe 2007). Addition of various psychopharmaceuticals, including second generation antipsychotics (SGA), is suggested for patients who are partial responders to SSRIs. In that context, some previous studies suggested olanzapine might be an effective option for patients with persistent PTSD-related nightmares and insomnia when added to an already stable SSRI and benzodiazepine combination (Jakovljević et al. 2003), while others emphasized that quetiapine might be a beneficial adjunctive therapy for those patients with refractory

hyperarousal symptoms who are already on a stable SSRI and benzodiazepine combination (Mihaljević-Peleš et al. 2008). Some recent studies highlighted improvements in sleep quality after adjunctive risperidone therapy in patients with chronic military-related PTSD (Krystal et al. 2016).

In our opinion, targeting a specific and particularly troubling PTSD symptom cluster (nightmares/sleep disturbances) in a treatment-refractory clinical sample represents a significant clinical contribution. In our study, the targeted population included patients with war-related PTSD without co-occurring psychiatric disorders, although psychiatric comorbidity (particularly depression, addiction, and personality disorders) is highly prevalent within this population. By selecting such a diagnostically homogeneous population, we focused on sleep disturbances in PTSD, bearing in mind the reciprocal relations between sleep disturbances and PTSD with the consequent suggestion that disturbed sleep represents a causal factor in PTSD (Pace-Schott et al. 2015, Spoormaker & Montgomery 2008). Because of these characteristics of the sample, the generalization of the results to the whole PTSD population with sleep disturbances is not possible. Recent data predominantly suggest that sleep disturbances are essentially involved in the etiology of PTSD, rather than being secondary symptoms resulting from this anxiety disorder (Babson & Feldner 2010, Mellman 2008, Spoormaker & Montgomery 2008, Babson et al. 2012, Alvaro et al. 2013, Germain 2013). Persistent trauma-related repetitive nightmares are an almost universal symptom of PTSD (Germain et al. 2008, Levin & Nielsen 2007), while other sleep-related abnormalities, including shorter total sleep duration and increased sleep onset latency, are frequently found in some subgroups of patients with PTSD, such as in our patients. Additional sleep-related abnormalities have been frequently reported in some subgroups of patients with PTSD: increased stage 1 non-rapid eye movement (NREM) sleep, decreased slow wave sleep, increased average number of rapid eye movements per minute in REM sleep, reduced stage 2 NREM sleep, and increased rapid eye movement (REM) sleep as a percentage of total sleep time (Kobayashi et al. 2007, Endgdahl et al. 2000).

Our patients' PTSD-related sleep disorder failed to respond to previous add-ons of various hypnotics as well as first-generation antipsychotics with documented sedative and sleep-inducing properties, namely promazine and levopromazine. Promazine, via its potent sedative and anticholinergic properties, has been shown to be a beneficial agent in patients with PTSD-related sleep disorder. Levopromazine is characterized by strong 5-HT_{2A}, H_1 and α_1 blockade, a 5-HT_2:D_2 affinity ratio of 5:1, a medium anticholinergic effect, and low D_1, D_2 and D_4 blockade (Shiloh et al. 2000). On the one hand, psychopharmaceutical blocking of central α_1 adrenergic activity may be beneficial in the treatment of PTSD-related sleep difficulties. On the other hand, REM sleep is inhibited by both serotonergic (Gillin et al. 2001) and anticholinergic effects – both properties of levopromazine (Neylan et al. 1998). Despite their well-known sedative and hypnotic properties, promazine and levopromazine did not show beneficial effects for PTSD-related sleep disorder in our sample when added to stable SSRI and benzodiazepine.

Quetiapine is an atypical antipsychotic that is available in immediate and extended-release oral formulations. Its original immediate-release (IR) formulation has a short half-life (seven hours) and acts as an antagonist for serotonin (5-HT_{1A} and 5-HT_{2A}), dopamine (D_1 and D_2), histamine (H_1), and α_1- and α_2-adrenergic receptors (Nemeroff et al. 2002). It is hypothesized that somnolence is a result of 5-HT_{2A}, H_1, and α_1 blockade. This side effect of a low-dose quetiapine regime is widely used "off-label" as a treatment for insomnia. According to a recent review, there is limited evidence to support the use of quetiapine for insomnia in the absence of psychiatric comorbid disorders (Anderson & Vande Griend 2014). Guidelines for the treatment of insomnia have recommended quetiapine use only in patients with specific comorbid psychiatric conditions. Although we found significant improvements in all of the four analysed persistent PTSD sleep-related parameters after quetiapine augmentation, significant medium-term and long-term issues related to quetiapine such as weight gain, disturbances in glucose metabolism/glucose homeostasis, and/or hyperlipidemia (Allison et al. 1999) should be noted. Therefore, the introduction of quetiapine should be considered only after a detailed cost-benefit evaluation in each individual case of a patient with PTSD and a generally good response to prescribed selected SSRIs, when PTSD-related sleep problems persist.

Some reports revealed that quetiapine was the most frequently prescribed second-generation antipsychotic (SGA) among veterans with PTSD (Hermes et al. 2014) as well as for sleep/sedation (Hermes et al. 2013). Based on the prescription frequency of quetiapine in treatment combat-related PTSD with sleep disturbances, it seems it has a significant efficacy with tolerable neurological extrapyramidal adverse effects. But the main limitation is the lack of data for that specific indication and dosage. Previous studies showed that other SGAs, such as olanzapine (Jakovljević et al. 2003) and risperidone (Krystal et al. 2016), may be beneficial for insomnia and PTSD-related nightmares when added to an already stable SSRI and benzodiazepine combination, despite the adverse effects that may occur. Possible medium-term and long-term SGA-related challenges should always be taken into account prior to choosing SGA as adjuvant therapy to an already stable SSRI and benzodiazepine combination or (even more preferably) to SSRI monotherapy.

Our study did not include a randomized and blinded control group not treated with quetiapine but instead switched to some other adjuvant therapy for PTSD-related sleep disorder, nor did it include another control group that was not switched to any new drug. For this reason, we cannot not rule out the placebo effect of changing the drug and the first introduction of antipsychotic. The direction of this effect was against the null hypothesis, but we cannot speculate on its magnitude. Our results should thus be considered over-optimistic. The only solution to this limitation is conducting future randomized and blinded studies/experiments with control groups.

We used an instrument constructed for this study as the outcome measure. The instrument has not been previously validated on an independent sample from the same target population and its metric characteristics are unknown. We therefore cannot accurately assess whether any biases caused by potential weaknesses of the outcome measure were in favor of or against the null hypothesis, nor can we estimate their magnitude. The solution to the possible biases thus induced are future studies that would use validated instruments such as Pittsburgh Sleep Quality Index (PSQI) or PTSD-specific measures such as PSQI-A.

The third study limitation is related to the use of a consecutive sample. The consecutive sample that we used is not a probability-based sample and is vulnerable to seasonality and selection biases. Selecting a consecutive sample instead of a random one could have resulted in oversampling of patients who came to check-ups more regularly. Such patients may have better adherence, more severe subjective symptoms, stronger motivation, and better social support. What is important, and unclear, is whether these patients respond better to quetiapine therapy.

At the end of our 5-week follow up, patients predominantly reported satisfaction with add-on quetiapine therapy, particularly in relation to quality-of-life improvements and generally better functioning in everyday life activities. Sleep is essential in maintaining day-to-day emotional homeostasis as well as long-term well-being and mental health. Therefore, all available preventive interventions targeting potential development of sleep disturbances in high-risk individuals after a traumatic experience should be applied in each individual case. All the available therapeutic measures should be mobilized in patients with chronic PTSD and persistent sleep-related problems, including quetiapine add-on in selected patient subgroups, with the aim of reaching the highest possible level of emotional homeostasis in the patient. Significant improvements related to patient well-being, quality of life, and better functioning in everyday life activities should be achieved by reducing PTSD-related sleep disturbances to the lowest possible level.

CONCLUSIONS

The results of this study suggest that quetiapine, prescribed in a low dose of 100 mg as an adjunct/add-on to stable SSRI and benzodiazepine therapy, may be successful for treating PTSD-related sleep problems in patients who previously failed to respond to the following adjuvant psychopharmaceuticals: zolpidem, flurazepam, nitrazepam, promazine, and levopromazine. Further long-term studies on a much larger patient sample are needed to clarify the role of quetiapine as a potentially acceptable beneficial add-on therapy for patients with PTSD who generally responded well to combined SSRI and benzodiazepine therapy (with avoidance of chronic benzodiazepines use or, even better, without use of benzodiazepines at all) except for persistent PTSD-related sleep problems.

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Contribution of individual authors:

Maja Vilibić: study design, conception of the manuscript, data collection, literature search, statistical analysis, interpretation of the obtained results, drafting and revising the article critically.

Vjekoslav Peitl: data collection, literature search, statistical analysis, interpretation of the obtained results, drafting and revising the article critically.

Maja Živković: conception of the manuscript, data collection, literature search, interpretation of the obtained results, drafting and revising the article critically.

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