

Effects of quetiapine on sleep

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Abstract

Objectives: To determine effects of quetiapine on polysomnographic recorded sleep architecture and parameters.

Introduction and Hypothesis: Quetiapine receptor profile suggests that sleep-inducing and sleep-modifying properties may be causing changes in sleep architecture and parameter, which may have therapeutic value.

Methods: A cross-sectional retrospective study conducted at the sleep center. Polysomnographic sleep records were selected and reviewed from among patients who presented over 24-months for evaluation. Twenty-one patients were selected and matched based on age, sex, body-mass index (BMI), and the presence/absence of obstructive sleep apnea (OSA) to control subjects without quetiapine. Correlation analysis was performed to assess the association of quetiapine with sleep architecture and parameters.

Results: Quetiapine was not significantly associated with altered sleep efficiency, sleep latency, wake time after sleep onset, or the relative percentage of sleep stages. A notable but not significant ($p = 0.08$), increase in the rapid eye movement latency was observed.

Conclusions: Among the study population quetiapine was not found associated with changes in sleep architecture and parameters.

Keywords: quetiapine, polysomnography, sleep architecture and parameters.

Hypothesis : Use of quetiapine will be associated with shortened sleep latency (SL), increased total sleep time (TST), and increased non-rapid eye movement (NREM) stage III (most restorative sleep).

Introduction

Quetiapine is (dibenzothiazepine derivative) an atypical antipsychotic agent (serotonin-dopamine antagonist, also called second generation antipsychotic, and approved by the US FDA to treat schizophrenia (acute and maintenance), major depressive disorder (MDD), and both manic and depressive episodes associated with bipolar disorder. It is rapidly absorbed after oral administration, predominantly metabolized by

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cytochrome P450 3A4¹, with half-life of 6 to 7 h. It acts as an antagonist at serotonin (5-HT 1A and 5-HT 2), dopamine (D-1 and D-2), histamine (H-1) and adrenergic alpha-1 and alpha-2 receptors; there is virtually no action on cholinergic, muscarinic, and benzodiazepine receptors. This special receptor profile suggests a favorable effect on sleep, especially because of the combination of a 5 HT-2 receptor and an H-1 receptor blockade, which is similar to those of medications used as sedative includes anti-depressants such as mirtazapine and trazodone. In short quetiapine's sleep-inducing and sleep-modifying abilities are possibly linked to its receptor-binding profile, inclusive of its anti-histaminergic, anti-dopaminergic, and anti-adrenergic properties.

Literature Review

Several studies have been done owing to its sedating properties to determine its use for management of poor sleep, but current data are not conclusive.

Quetiapine in lower doses can modify the sleep architecture of healthy individuals^{2,3}. Quetiapine therapy in individuals who are not depressed has shown improvements in sleep continuity^{2,3}. On the first night of treatment, quetiapine (25 and 100 mg) significantly improved sleep induction and continuity and, increased in total sleep time (TST), sleep efficiency (SE), percentage of sleep stage II, and sleep quality in healthy individuals². Increases in TST, SE, percentage of sleep stage II, and subjective sleep quality were seen. Periodic leg movements during sleep (PLMS) increased significantly with 100 mg quetiapine treatment².

Acute quetiapine adjunctive therapy alters sleep architecture in depressed patients, after which these changes taper off toward baseline levels and are not significantly present after long-term treatment⁴. Sleep architecture in patients with major depressive disorder or bipolar disorder has been altered by adjunctive quetiapine treatment. Alterations in sleep architecture are more strong and noteworthy within 2 to 4 days of treatment initiation⁴.

Treatment with quetiapine (300 or 600 mg/day) provided broad-based improvements in quality of life, quality of sleep and disability compared with placebo⁵.

Treatment with quetiapine at 25 mg at night daily for 2 weeks showed a trend for enhancement of TST

and lowered SL, increased sleep satisfaction and improved daytime functioning compared with placebo in primary insomnia with few side effects but not attaining statistical significance. SL was reduced more than four times compared with placebo and nearly reached statistical significance. A study with a larger sample size is required to validate its effectiveness⁶.

Somnolence is a side-effect of quetiapine treatment, leading to prescription in an off-label fashion when this effect is desired⁷.

Quetiapine's favorable effect on sleep in healthy probands and in depressed patients has been demonstrated by an increasing number of studies^{2,8,13}.

Clozapine has consistently been reported to improve sleep continuity and increase sleep stage-II in particular¹⁴, while olanzapine also improves sleep continuity but appears to increase slow-wave sleep specifically¹⁵⁻¹⁶. In post-traumatic stress disorder (PTSD) the administration of 100 mg quetiapine was associated with a marked improvement in subjective sleep time¹⁷.

Data Collection

All sleep studies were reviewed at Mayo Clinic Health System, Regional Sleep Disorders Center, Mankato, MN, USA, starting January 1, 2010, to July 31, 2013. Only subjects on quetiapine were included.

Sample inclusion and exclusion criteria

All subjects in this study were on quetiapine therapy for various reasons. Sleep study was performed to evaluate and diagnose different sleep disorders.

Methods

A cross-sectional retrospective study of a convenience sample ($n = 42$) conducted at the regional sleep disorders center in a community-based, tertiary care hospital. Medical and polysomnographic records were selected and reviewed. Out of 32 subjects, 21 were selected (other 11 subjects received diagnosis of moderate to severe obstructive sleep apnea (OSA) and met protocol for split night study, they were excluded from study owing to split of sleep architecture and parameters with use of positive pressure therapy) and matched based on age, sex, body-mass index (BMI), and the presence/absence of OSA to control without quetiapine (to make control

and subject group statistically similar). Correlation analysis was performed to assess the association of quetiapine with SE, sleep and REM latency, wake time after sleep onset (WASO), and relative percentage of N-I, N-II, N-III and REM.

Results

The study population was 57% female subjects with a mean age of 44.8 years and mean BMI of 37.5 kg/m² (Table 1). A higher proportion of patients with OSA were in the group without use of quetiapine (81%, $n = 17$). Use of quetiapine was not significantly associated with altered SE, SL, WASO, or the relative percentage of sleep stages (N-I, N-II, N-III and REM). A notable, but not significant ($p = 0.08$), increase in the REM latency was observed (Table 2).

Observations on Mean Data Comparison With Use of Quetiapine:

1. Minimally reduced SE, with increase of SL and REM latency and increase of WASO noted.
2. Minimal increase of N-I, N-II and N-III noted.
3. Minimal reduced total REM sleep noted.

Table 1: Participant characteristics

Characteristics	Subject on quetiapine (N=21)	Control subjects not on quetiapine (N=21)	Total (N=42)	<i>p</i>
	Mean ±SD (range) or N (%)			
Age (years)	44.3±14.1 (16-73)	45.2 ± 14.4 (21-77)	44.8 ± 14.1 (16-77)	0.84
Sex				
Male	9 (43)	9 (43)	18 (43)	1.00
Female	12 (57)	12 (57)	24 (57)	1.00
Body mass index (BMI)	37.7±9.1 (24.2-52.6)	37.2±11.5 (23.4-61.1)	37.5±10.3 (23.4-61.1)	0.89
Obstructive sleep apnea (positive indication)	13 (62)	17 (81)	30 (71)	0.17
Fibromyalgia (positive indication)	7 (33)	3 (14)	10 (24)	0.14

Table 2: Objective sleep quality (polysomnography) results

Characteristics	Subjects on quetiapine (N=21)	Control subjects not on quetiapine (N=21)	P
	Mean ± SD (range)		
Sleep efficiency (%)	76.1±14.9 (48-100)	77.5±17.3 (23-96)	0.78
Sleep latency (min)	32.3±27.4 (0-106)	30.1±48.9 (2-227)	0.86
REM latency (min)	27.5±139.2 (0-491)	203.9±104.6 (68-417)	0.08
WASO (min)	85.0±54.9 (2-194)	77.3±57.1 (4-194)	0.66
N-I (%)	21.0±11.3 (4-52)	19.2±13.7 (7-60)	0.65
N-II (%)	53.3±13.3 (31-74)	55.0±13.5 (32-84)	0.93
N-III (%)	16.4±13.7 (0-58)	15.7±11.9 (0-39)	0.86
REM (%)	9.4±7.5 (0-26)	12.3±7.7 (0-25)	0.23

Strengths

1. Both groups were not statistically different in terms of age, sex, BMI, diagnosis of OSA and fibromyalgia.

Limitations

1. Subgroup analysis for each sleep parameter was not performed owing to small number.
2. Subjects and controls were from one sleep center.
3. It was convenience sample study and, may not have same statistical power as randomized-control study.
4. Author did not collect demographic information of subjects and control and, therefore, cannot speak about generalizability.
5. Overall sample size of study was small that could have lower statistical power.
6. Subjects were on different doses of quetiapine; therefore, effect of different doses of quetiapine cannot be commented.
7. First night effect cannot be ruled out; (adaptation to

the sleep laboratory is known as first night effect, which can affect sleep architecture and parameters).

8. Many subjects and controls subjects were on different medications such as selective serotonin reuptake inhibitor, serotonin-norepinephrine reuptake inhibitor, benzodiazepines and other medications, with known effect on sleep architecture and parameters.
9. Several subjects and control subjects showed diagnosis of various severity of OSA that could have affected sleep architecture and parameters.
10. Polysomnography data acquired during this study was at distinct time points, which may not be representative of the entire week; this study should be repeated as a randomized, placebo-controlled, double-blind assessment study with a large sample size.

Conclusions

Among the study population use of quetiapine was not associated with a change in SE, sleep and REM latency, WASO, or percentage of N-I, N-II, N-III and REM. Therefore author concludes that no statistical evidence from this study that supports quetiapine showed effect on sleep architecture and parameters.

Increased REM latency and reduced REM may be because of REM suppressant effect such as other medications affecting serotonergic receptors. Sedating effect of quetiapine may be subjective feeling.

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