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Low doses of mirtazapine or quetiapine for transient insomnia: A randomised, double-blind, cross-over, placebo-controlled trial

Julie Karsten¹, Loes A Hagenauw¹, Jeanine Kamphuis¹ and Marike Lancel^{1,2,3}

Abstract

Low doses of the antidepressant mirtazapine or the neuroleptic quetiapine are often prescribed off-label for insomnia. However, studies on the effects on sleep and hangover effects the following day are scarce. In this randomised, double-blind, cross-over, placebo-controlled trial, the influence of 7.5 mg mirtazapine and 50 mg quetiapine on both normal sleep and sleep disturbed by acoustic stress (traffic noise) as a model for transient insomnia was assessed. Additionally, hangover effects on next-day alertness and cognitive functioning were examined. A total of 19 healthy men without sleep complaints completed three treatment sessions, each session consisting of three consecutive nights in one of the mirtazapine, quetiapine or placebo conditions. Sleep was assessed using polysomnography and the Leeds Sleep Evaluation Questionnaire. Daytime sleepiness and cognitive functioning were assessed using the Leeds Sleep Evaluation Questionnaire, Karolinska Sleepiness Scale, Digit Symbol Substitution Task, Psychomotor Vigilance Task and an addition task. Under acoustic stress, both mirtazapine and quetiapine increased total sleep time by half an hour and reduced the number of awakenings by 35–40% compared to placebo. While quetiapine specifically increased the duration of non-rapid eye movement sleep, stage N2, mirtazapine mainly increased deep sleep stage N3. Subjects reported that both mirtazapine and quetiapine eased getting to sleep and improved sleep quality. Both drugs caused daytime sleepiness and lessened sustained attention. These findings support the use of low doses of mirtazapine and quetiapine for the treatment of insomnia. Further prospective studies on the long-term effects regarding effectiveness and adverse effects are needed.

Keywords

Mirtazapine, quetiapine, insomnia, sleep, daytime functioning, traffic noise

Introduction

Insomnia, defined as a persistent difficulty with sleep initiation, duration, consolidation and/or quality that occurs despite adequate opportunity and circumstances for sleep (American Academy of Sleep Medicine, 2014), is a highly prevalent condition in the general population. General population estimates range from 7% to well over 30%, depending on the employed definition and instruments (Ohayon and Reynolds, 2009; Roth et al., 2011). Estimates are even higher for psychiatric populations. For example, up to 80% of patients diagnosed with schizophrenia and 40–90% of patients with major depressive disorder suffer from insomnia (Cohrs, 2008; Thase, 2006). Subjectively reported sleep complaints in mentally disordered people are largely supported by aberrants in polysomnographic analyses (Argyropoulos and Wilson, 2005; Cohrs, 2008; Monti and Monti, 2004; Thase, 2006).

Insomnia is associated with the development of diverse medical health issues, such as heart diseases (Laugsand et al., 2014). Insomniacs use more medications and have increased health-care utilization compared to healthy individuals (Daley et al., 2009). Furthermore, daytime functioning and quality of life are strongly affected (Hofstetter et al., 2005; Katz and McHorney, 2002; McCall et al., 2000). Regarding mental health, disturbed sleep is a considerable risk factor for new-onset and relapse of various

psychiatric disorders, such as major depressive disorder (Gehrmann et al., 2010). Furthermore, it is a prodromal sign of psychotic episodes in patients with schizophrenia (Benson, 2015). Treating comorbid insomnia may not only ameliorate insomnia, but also improve treatment response of psychiatric symptoms (McCall et al., 2010; Manber et al., 2008; Myers et al., 2011).

Ideally, treatment for insomnia would normalise sleep quantity and sleep quality, thereby improving daytime functioning, i.e. greater alertness and concentration, without adverse effects. The first treatment option consists of nonpharmacological therapy, e.g. addressing sleep hygiene behaviour or cognitive

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behavioural therapy for insomnia (Riemann and Perlis, 2009). Recent meta-analyses showed that the latter is an efficacious therapy for insomnia, including insomnia comorbid with mental disorders and, to a smaller extent, medical diseases (Wu et al., 2015). However, in clinical practice hypnotics, such as benzodiazepines and the 'Z'-drugs, like zopiclone and zolpidem, are often used. Hypnotics, particularly the benzodiazepines, can have serious disadvantages, such as sleepiness and reduced cognitive performance during the next day, so-called 'hangover effects', rapid development of tolerance, rebound insomnia upon drug discontinuation, and a serious risk of misuse and abuse. Benzodiazepines should therefore be used for short periods of time or intermittently (Soldatos et al., 1999). However, there are cases when longer term use is justifiable and ultimately the assessment of the benefits and risks of benzodiazepines is a matter of clinical judgement (Baldwin et al., 2013). The continued use despite of the drawbacks (Lader, 2011) highlights the need for alternatives in the treatment of insomnia.

Epidemiologic studies show a steady rise in off-label prescriptions for low doses of sedative antidepressants and antipsychotics in the treatment of insomnia (Kamphuis et al., 2015; Lai et al., 2011). Off-label prescription is the practice of prescribing medication for purposes different from those approved by regulatory agencies. It enables the exploration of new indications for existing drugs, but scientific evidence on the efficacy is necessary to support the practice-based development.

In clinical practice, the antidepressant mirtazapine and the atypical antipsychotic quetiapine are often prescribed off-label for insomnia, either on its own, or as an add-on to, for instance, counteract the sleep disturbing effects of antidepressants, such as Selective Serotonin Reuptake Inhibitors or Selective Serotonin and Noradrenalin Reuptake Inhibitors (Kamphuis et al., 2015; Lai et al., 2011). When used in approved doses, i.e. 15–45 mg mirtazapine and 300–800 mg quetiapine, both drugs have been shown to improve sleep efficiency and increase total sleep time in healthy individuals as well as in people with mental disorders (Anderson and Vande Griend, 2014; Aslan et al., 2002; Schittecatte et al., 2002; Winokur et al., 2000). However, at these doses, hangover effects, such as daytime sleepiness, have been observed (Alberti et al., 2015; Anderson and Vande Griend, 2014). To treat insomnia, lower doses of both drugs are generally employed. Evidence for the efficacy of low doses of mirtazapine for insomnia is very limited (Savarese et al., 2015). Iwamoto and colleagues (2013) found that both 7.5 mg and 15 mg mirtazapine taken for eight consecutive days temporarily caused daytime sleepiness, but that 7.5 mg did not have a negative effect on driving performance tasks. Only a few studies have investigated the effect of low-dose quetiapine on sleep (Cohrs et al., 2004; Wiegand et al., 2008).

In order to further validate the use of low doses of mirtazapine and quetiapine for insomnia, the effects on objective and subjective sleep measures need to be assessed. This study was conducted to investigate the influence of 7.5 mg mirtazapine and 50 mg quetiapine – which are low doses compared to doses approved for the treatment of mental disorders – on the night-time sleep of 19 healthy male subjects. The effect of mirtazapine and quetiapine was compared to placebo, during normal sleep and on sleep disturbed by acoustic stress as a model for transient insomnia. Sleep was assessed using both polysomnography (PSG) and subjective sleep measures. Given the limited number of studies on

low doses of mirtazapine and quetiapine on sleep, and the multitude of ways in which they could influence sleep, multiple sleep variables were studied without a primary hypothesis. Additionally, possible hangover effects that may hamper daytime functioning, i.e. daytime sleepiness and cognitive functioning, were examined. For these purposes, the effect of mirtazapine and quetiapine were compared to placebo, both during undisturbed sleep and sleep under acoustic stress as a model for insomnia.

Methods

Subjects

Twenty-eight potential subjects were recruited between September 2014–May 2015. After screening their clinical history and a physical examination, nine individuals were ineligible or declined participation (Figure 1), resulting in a sample of 19 healthy, non-smoking male subjects (age 24.4 ± 4.3 years, range 18–33 years). Sample size was based on comparable studies on the influence of medication on sleep (Cluydts et al., 1995; Cohrs et al., 2004). Inclusion criteria were an age between 18–35 years and body mass index (BMI) between 18.0–30.0 kg/m². Subjects were excluded if they had a personal or family history of a sleep disorder or mental disease, alcohol or drug dependency, a clinically relevant medical disease, use of a (psychotropic) medication, or have a known intolerance for either mirtazapine or quetiapine. Subjects were also required to have a history of going to bed between 22:00–00:00 on at least 5–7 nights per week, with a reported sleep duration of 6.5–8.5 h over the previous three months before the start of the study, and to maintain regular bedtimes and to abstain from alcohol and drugs prior to and during the experiment. All subjects provided written informed consent and received a honorarium for participating.

Study design

This randomised, double-blind, cross-over, placebo-controlled, single-centre study consisted of three treatment sessions, each session consisting of three consecutive nights, with at least a four-day wash-out period between the sessions. The application of mirtazapine, quetiapine, and placebo was randomised per subject over the three treatment sessions using a random number generator by a researcher not involved in the present study, concealing treatment condition from subjects and assessors until the end of the trials. The first night (night 1) was an adaptation night, followed by the second night (night 2) with medication and the third night (night 3) with medication and all-night acoustic stress to model transient insomnia. Night 2 was used to evaluate the effects of medication on sleep and daytime functioning, without the disruptive effects of acoustic stimulation. Night 3 was used to evaluate the effects of medication on subjective and objective sleep measures during acoustic stress. On testing days, subjects arrived at the research centre at 18:00, where they remained in the centre's common room until 23:00. From 23:00 to lights out at 00:00, subjects stayed in their individual bedrooms, without the use of television, computer and cellphone. Subjects were allowed to read books or magazines, or to do puzzles. Medication was taken orally 30 min before lights out on night 2 and night 3, consisting of either 7.5 mg mirtazapine, 50 mg quetiapine or

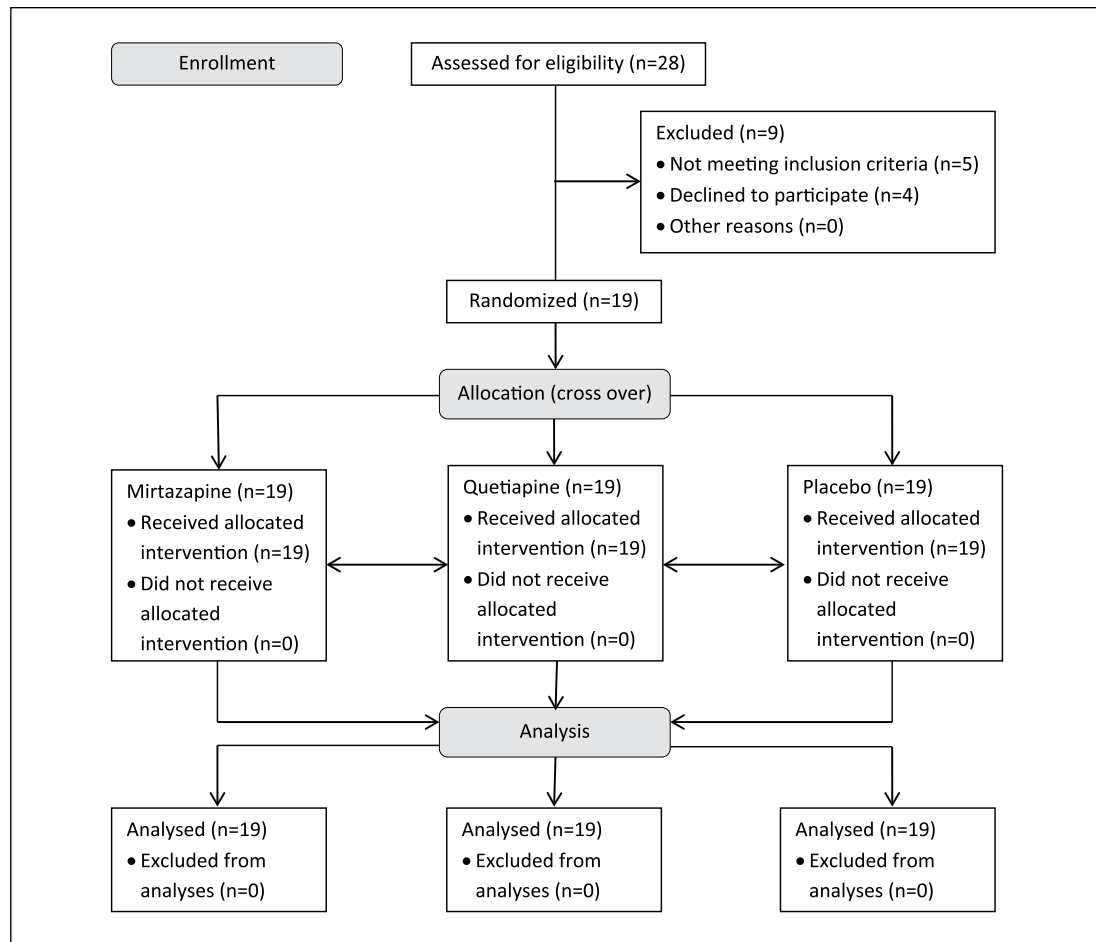


Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram.

placebo (lactose) in identical gelatin capsules. Subjects were instructed to remain in their beds from 00:00 to lights-on at 08:00, with the exception of restroom visits. PSG recordings were made each night, subjective sleep quality was assessed each morning within 15 min after rising. Hangover effects were assessed the morning following night 2 at 10:00, two hours after lights-on. The study followed the Declaration of Helsinki and was approved by the Isala Clinics Ethics Committee (approval number 13.11138; International Committee of Medical Journal Editors trial registry name: The effect of low doses of mirtazapine and quetiapine on sleep and daytime functioning; <http://www.isrctn.com/ISRCTN20011041>; study ID ISRCTN20011041).

Application of acoustic stress

To induce transient insomnia, sleep was disrupted on night 3 using continuous, prerecorded road traffic noise, mean level 52 dB, range 32–77 dB. The recording was played through identically placed speakers above the subjects' beds from lights-off to lights-on. Subjects were instructed not to sleep with their heads beneath their pillows and this was checked by continuous infrared camera recordings. Acoustic stress evoked by traffic noise is a validated model of transient insomnia and has been used to

evaluate the efficacy of hypnotics (Cluydts et al., 1995; Cohrs et al., 2004; Dijk et al., 2012).

Sleep measures

PSG recordings. Electrodes were applied between 18:00–20:00h on each testing day. Six electroencephalogram (EEG) channels (F3-A2, F4-A1, C3-A2, C4-A1, O1-A2 and O2-A1), the bilateral electrooculogram (EOG) and submental electromyogram (EMG) were recorded, with gold electrodes, on a Somnoscreen machine (Somnomedics). Signals were digitised at 256 Hz (EEG, EOG and EMG). Low- and high-frequency filter settings were 0.2 and 35 Hz for EEG, 0.2 and 10 Hz for EOG and for EMG the low-frequency filter was set at 10 Hz and a notch filter was used. PSGs of nights 2 and 3 were visually scored per 30 s epoch according to established criteria (Berry et al., 2014) by two experienced raters without prior knowledge of the subjects and conditions. For the analysis of the influence of acoustic stress and medication on sleep initiation, maintenance and duration the following measures were quantified: latency to rapid eye movement (REM) sleep and non-REM sleep (N2), total sleep time and time spent in each sleep stage, wakefulness after sleep onset and the number of awakenings.

Subjective sleep questionnaire. Subjective sleep quality was evaluated each morning within 15 min after lights-on using the Leeds Sleep Evaluation Questionnaire (LSEQ; Hindmarch, 1975), a standardised self-reporting instrument comprising 10 visual analogue scales (100 mm) that pertain to the ease of getting to sleep (GTS), quality of sleep (QOS), ease of awakening from sleep (AFS) and alertness and behaviour following wakefulness (BFW), the last item referring to balance and co-ordination. Sum scores were used for each of these scales, with higher scores indicating a more positive outcome. The LSEQ has been found to be a robust and reliable instrument for evaluating subjective sleep experience in pharmacological studies (Zisapel and Laudon, 2003).

Daytime functioning

Karolinska Sleepiness Scale (KSS). The KSS (Åkerstedt and Gillberg, 1990) was used to assess daytime sleepiness. It is a nine-point self-report scale measuring the subjective level of sleepiness, ranging from 1: 'very alert' to 9: 'very sleepy, fighting sleep, an effort to keep awake'. The KSS is useful in assessing the changes in response to environmental factors, circadian rhythm, and effects of drugs (Shahid et al., 2010). In this study, subjects rated their level of sleepiness at 10:00, two hours after lights-on, 10.5 h after drug intake.

Psychomotor Vigilance Task (PVT). The PVT (Basner and Dinges, 2011) is a commonly used 10-minute sustained-attention, reaction-time task that measures the speed with which subjects respond to a visual stimulus. Stimulus intervals range from 2–10 s. In this study, the task was executed on a tablet device and performance indices delivered by a standard application (extended PVT, version 2.4, Joggle Research, USA). Performance indices used consisted of reaction times (RTs), number of lapses (i.e. $RT > 500$ ms), mean lapse time, and number of false starts (i.e. $RT < 100$ ms).

Digit Symbol Substitution Test (DSST). The Wechsler DSST is a test of psychomotor performance (Lezak et al., 2004). It consists of a key in which nine symbols are paired with nine digits, above which random symbols, without their paired digits, are presented. Subjects are asked to select the appropriate digit as fast and accurately as possible. In this study, the task was executed on a tablet device and the number of correct responses was delivered by a standard application (DSST, version 2.4, Joggle Research, USA).

Addition task. A custom made pen and paper addition task was used as a measure of sustained attention. Subjects completed as many correct additions of two random two-digit numbers as possible within a five-minute interval (as designed by Van de Werken et al., 2013). The number of responses and errors were included as performance indices.

Statistical analyses

Data was analysed per protocol, all data of participants enrolled in the study was included in the analyses. First, repeated measures multivariate analyses of variance (RM-MANOVAs) were used to analyse the main and interaction effects of treatment

(mirtazapine, quetiapine, placebo) and acoustic stress (yes, no) on objective and subjective sleep indices. In the case of significant findings, post-hoc contrasts were used to compare mirtazapine and quetiapine to placebo. Second, RM-MANOVA were used to analyse the effects of treatment on next day performance. In the case of significant findings, post-hoc tests were conducted with two-sided, paired *t*-tests comparing mirtazapine and quetiapine to placebo.

Results

Sample characteristics

Nineteen healthy men were recruited, with a mean age of 24.4 ± 4.3 years. Mean height was 183 ± 0.5 cm, mean body weight was 76.1 ± 7.6 kg, resulting in a mean BMI of 22.6 ± 2.4 kg/m². All subjects completed the study.

Effects of the acoustic stress model in the placebo condition

Under placebo treatment the acoustic stress model had significant effects on many objective sleep parameters (Table 1). Compared to undisturbed sleep during night 2, acoustic stress in night 3 significantly reduced total sleep time ($F(1,16)=6.92$, $p=0.02$, $\eta=0.30$), time spent in N3 ($F(1,16)=10.35$, $p=0.005$, $\eta=0.39$), and REM sleep ($F(1,16)=56.15$, $p<0.001$, $\eta=0.78$) and increased the amount of N1 ($F(1,16)=8.82$, $p=0.009$, $\eta=0.36$) and N2 ($F(1,16)=7.33$, $p=0.02$, $\eta=0.31$). While the latency to non-REM sleep was only marginally lengthened ($F(1,16)=3.09$, $p=0.1$, $\eta=0.16$), acoustic stress significantly increased total duration of wakefulness after sleep onset ($F(1,16)=5.93$, $p=0.03$, $\eta=0.27$) as well as the number of awakenings ($F(1,16)=6.84$, $p=0.02$, $\eta=0.30$). For none of the PSG measures was a significant interaction found with placement of the placebo session, i.e. in week 1, 2, or 3, thereby indicating the absence of habituation to acoustic stress in the present experiment.

The acoustic stress model also exerted significant effects on various subjective sleep measures (Table 2). Compared to undisturbed sleep, acoustic stress was associated with significantly more trouble getting to sleep ($F(1,16)=15.95$, $p=0.001$, $\eta=0.50$) and a worse sleep quality ($F(1,16)=42.04$, $p<0.001$, $\eta=0.72$). It neither affected difficulty awakening nor alertness and behaviour following awakening. No significant interaction effects between placement of the placebo session and any of the sleep measures were found.

Effects of mirtazapine and quetiapine on objective sleep measures

Both mirtazapine and quetiapine exerted significant effects on sleep duration and sleep structure (Table 1). Compared to placebo, mirtazapine and quetiapine increased total sleep time, most prominently during the acoustic stress condition (Figure 2). Total sleep time did not differ between the mirtazapine and quetiapine treatment in either the undisturbed ($F(1,18)=0.93$, $p=0.35$, $\eta=0.05$) or the acoustic stress condition ($F(1,18)=2.93$, $p=0.10$, $\eta=0.14$). While acoustic stress was associated with a minor prolongation of sleep onset during all treatments, mirtazapine and

Table 1. Multivariate analysis of variance (MANOVA) of polysomnographic sleep parameters in minutes ($n=19$).

	No acoustic stress			Acoustic stress			Treatment		Acoustic stress		Treatment × acoustic stress	
	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	MANOVA	MANOVA	MANOVA	MANOVA	MANOVA	
	Placebo	Mirtazapine	Quetiapine	Placebo	Mirtazapine	Quetiapine	$F(2,36)$	η	$F(1,18)$	η	$F(2,36)$	η
TST	452.3 (19.1)	460.9 (25.3)	466.1 (5.5) ^b	427.8 (38.2)	459.8 (13.4) ^c	455.5 (19.4) ^b	16.56***	0.48	14.34**	0.44	3.52	0.16
N2 lat	11.7 (7.3)	9.4 (5.7)	9.2 (5.2)	15.7 (8.4)	11.3 (6.0) ^a	14.2 (9.1)	5.42**	0.23	11.15**	0.38	0.72	0.04
WASO	19.4 (17.2)	7.1 (3.3) ^b	7.3 (3.8) ^b	38.2 (29.4)	12.6 (10.3) ^c	14.6 (17.0) ^b	24.01***	0.57	8.07*	0.31	3.15	0.15
N Wake	16.5 (5.9)	9.7 (4.0) ^c	10.2 (4.2) ^c	21.8 (9.4)	14.2 (6.1) ^b	13.1 (6.4) ^c	21.21***	0.54	10.47**	0.37	1.22	0.06
N1	25.3 (8.3)	18.7 (7.1) ^b	17.8 (6.1) ^c	33.9 (13.1)	25.8 (10.5) ^b	22.3 (9.1) ^c	20.56***	0.53	14.15**	0.44	0.86	0.05
N2	199.8 (29.0)	213.7 (39.5)	225.3 (37.1) ^b	221.5 (27.3)	230.8 (41.5)	256.7 (33.1) ^c	16.26***	0.48	39.20***	0.69	0.60	0.03
N3	124.2 (31.4)	148.4 (34.6) ^b	132.1 (34.4)	101.4 (37.0)	122.1 (40.6) ^b	106.0 (37.9)	13.11***	0.42	31.01***	0.63	0.10	0.01
REM	103.7 (23.2)	80.8 (18.9) ^b	91.7 (22.7)	72.2 (19.0)	81.5 (21.0)	71.2 (20.3)	1.89	0.10	74.21***	0.81	12.05***	0.40
REM lat	85.5 (25.7)	149.2 (56.6) ^c	94.6 (41.8)	128.9 (41.7)	132.7 (50.7)	126.2 (56.6)	7.73**	0.30	11.23**	0.38	4.70*	0.21

M: Mean; SD: Standard Deviation; TST: Total Sleep Time; N2 lat: N2 latency; WASO: Wakefulness after sleep onset; N Wake: Number of awakenings; N1: Non-REM sleep stage one; N2: Non-REM sleep stage two; N3: Non-REM sleep stage three; REM: Rapid Eye Movement sleep; REM lat: REM sleep latency. Significance level of differences between mirtazapine/quetiapine and placebo, ^a $p<0.05$, ^b $p<0.01$, ^c $p<0.001$. * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

Table 2. Multivariate analysis of variance (MANOVA) Leeds Sleep Evaluation Questionnaire scales ($n=19$).

	No acoustic stress			Acoustic stress			Treatment		Acoustic stress		Treatment × acoustic stress	
	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	MANOVA	MANOVA	MANOVA	MANOVA	MANOVA	
	Placebo	Mirtazapine	Quetiapine	Placebo	Mirtazapine	Quetiapine	$F(2,36)$	η	$F(1,18)$	η	$F(2,36)$	η
GTS	14.1 (3.3)	16.5 (2.5) ^a	16.2 (2.7) ^b	9.8 (2.9)	12.8 (2.8) ^b	13.7 (3.2) ^b	15.48***	0.46	43.95***	0.71	3.19	0.02
QOS	9.2 (2.0)	10.8 (2.3) ^a	11.5 (2.0) ^b	4.9 (2.6)	7.4 (2.4) ^b	8.5 (3.3) ^b	12.55***	0.41	49.24***	0.73	0.62	0.03
AFS	10.8 (2.0)	9.5 (2.3)	8.6 (3.2) ^a	10.7 (3.3)	9.3 (2.5)	8.7 (3.3)	7.03**	0.28	0.01	0.00	0.03	0.00
BFW	15.2 (3.9)	11.0 (3.1) ^b	10.6 (3.8) ^c	13.4 (4.5)	12.5 (3.4)	11.4 (3.4)	11.09***	0.38	0.03	0.00	3.05	0.15

M: Mean; SD: Standard Deviation; GTS: Getting To Sleep; QOS: Quality Of Sleep; AFS: Awakening From Sleep; BFW: Behaviour Following Wakefulness. ** $p<0.01$, *** $p<0.001$. Significance level of differences between mirtazapine/quetiapine and placebo, ^a $p<0.05$, ^b $p<0.01$, ^c $p<0.001$.

quetiapine slightly shortened sleep latency, reaching the level of statistical significance only for mirtazapine during acoustic stress. Compared to placebo, mirtazapine and quetiapine significantly reduced wakefulness after sleep onset as well as the number of awakenings, both in the undisturbed and acoustic stress condition. There were no significant differences between mirtazapine and quetiapine sessions with respect to these two sleep measures: wakefulness after sleep onset during undisturbed sleep ($F(1,18)=0.04$, $p=0.84$, $\eta=0.002$) and acoustic stress ($F(1,18)=0.77$, $p=0.39$, $\eta=0.04$), and number of awakenings ($F(1,18)=0.23$, $p=0.63$, $\eta=0.01$) and ($F(1,18)=0.36$, $p=0.56$, $\eta=0.02$), respectively. Compared to placebo, both drugs diminished total amount of sleep stage N1, regardless of acoustic stress (Figure 2). Quetiapine selectively and markedly increased N2 during both the undisturbed and disturbed condition. In contrast, mirtazapine significantly enhanced N3 during both undisturbed sleep and acoustic stress, especially during the first half of the night (data not shown). As shown in Table 1, the amount of REM sleep in the quetiapine condition did not differ significantly from placebo when sleep was undisturbed ($F(1,18)=3.70$, $p=0.07$,

$\eta=0.17$) nor when sleep was disturbed by acoustic stress ($F(1,18)=0.07$, $p=0.79$, $\eta=0.004$). Mirtazapine resulted in a stable amount of REM sleep over the two nights ($F(1,18)=0.3$, $p=0.86$, $\eta=0.002$). While significantly lower than REM sleep duration in the undisturbed quetiapine and placebo condition, no differences were found between the treatments under acoustic stress. During the undisturbed condition, mirtazapine significantly delayed the latency to REM sleep. Under acoustic stress, REM sleep latencies were generally long and did not differ between the treatments.

Effects of mirtazapine and quetiapine on subjective sleep measures

Treatment effects were found on all LSEQ scales (Table 2), independent of acoustic stress. Compared to placebo, both drugs eased falling asleep and improved sleep quality, in both the undisturbed and the acoustic stress condition. Mirtazapine and quetiapine did not differ in their effects on falling asleep in silence ($t(18)=0.44$,

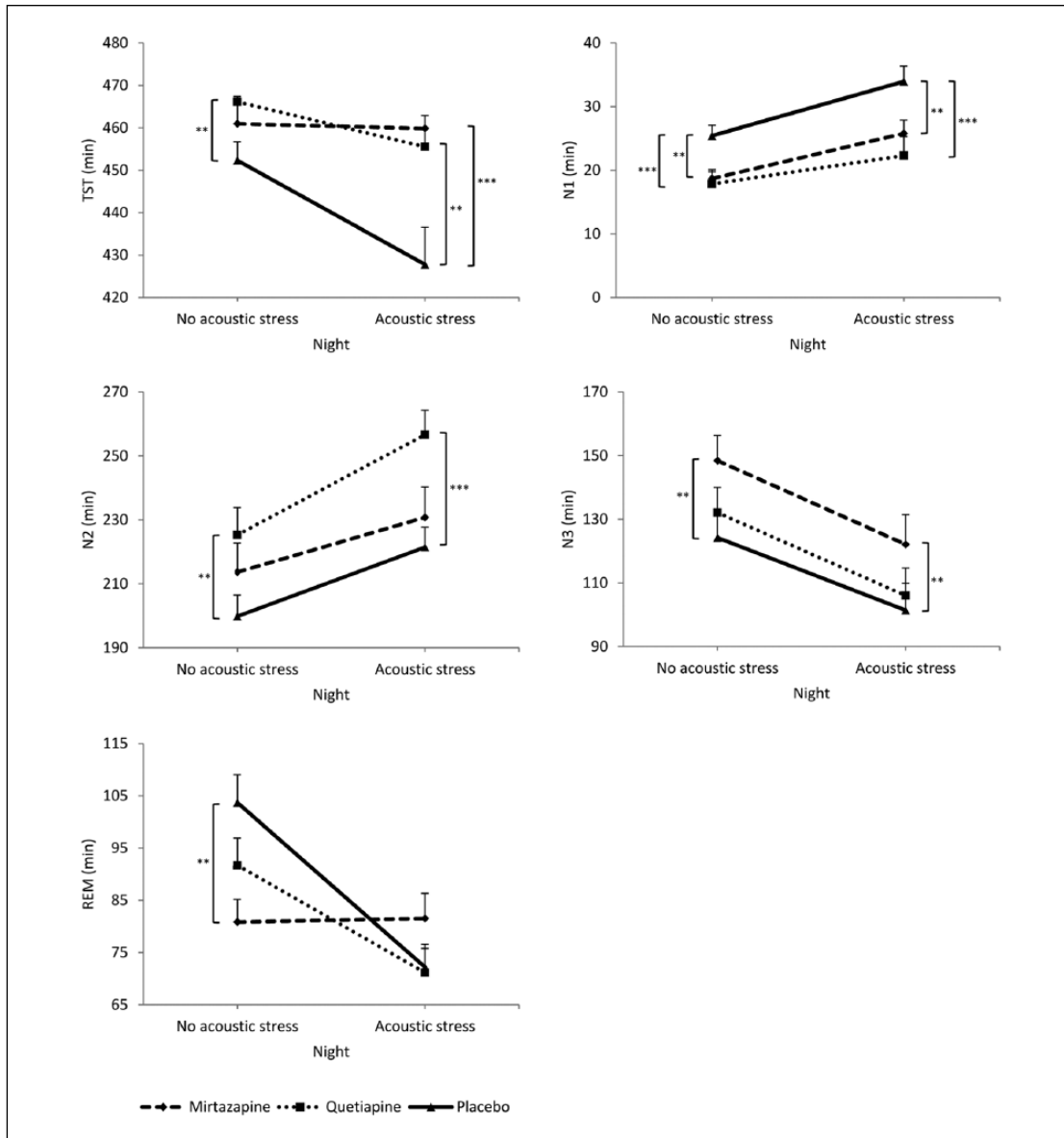


Figure 2. Effect of mirtazapine and quetiapine on total sleep time (TST) and sleep stages (N1, N2, N3, and REM) in minutes, compared to placebo. TST: Total Sleep Time; N1: Non-REM sleep stage one; N2: Non-REM sleep stage two; N3: Non-REM sleep stage three; REM: Rapid Eye Movement sleep. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

$p = 0.66$, $\eta = 0.01$) and under acoustic stress ($t(18) = -0.32$, $p = 0.75$, $\eta = 0.01$), or their effects on sleep quality in silence ($t(18) = -1.01$, $p = 0.33$, $\eta = 0.05$) and under acoustic stress ($t(18) = -0.79$, $p = 0.44$, $\eta = 0.03$). Subjects did find it more difficult to wake up in the morning when using quetiapine, but not mirtazapine, in the undisturbed condition and were less alert following awakening using either drug in the undisturbed condition. There was no difference between mirtazapine and quetiapine regarding alertness following awakening in silence ($t(18) = 0.39$, $p = 0.71$, $\eta = 0.01$) or under acoustic stress ($t(18) = 1.44$, $p = 0.17$, $\eta = 0.10$).

Effects on daytime functioning

As shown by KSS, compared to placebo, both mirtazapine and quetiapine were associated with significantly greater fatigue two

hours after lights-on (Table 3). Neither drug significantly affected performance on the DSST or the addition task. The mean number of responses and percentage of errors were comparable in all treatments, indicating no residual effects of mirtazapine and quetiapine on these performance measures. However, there was a significant effect of treatment on RT in the PVT task. Post-hoc comparisons showed that, compared with placebo, mirtazapine increased mean RT by 12.4% and doubled the mean number of lapses as well as mean lapse time. Similar, though insignificant, effects were found for quetiapine.

Discussion

In this study, we investigated the influence of low doses of mirtazapine and quetiapine, 7.5 mg and 50 mg respectively, on sleep

Table 3. Multivariate analysis of variance (MANOVA) hangover effects: Karolinska Sleepiness Scale (KSS), Psychomotor Vigilance Task (PVT), Digit Symbol Substitution Test (DSST) and addition task ($n=19$).

	<i>M</i> (SD)	<i>M</i> (SD)	<i>M</i> (SD)	Treatment	η
	Placebo	Mirtazapine	Quetiapine	MANOVA <i>F</i> (2,36)	
KSS	3.7 (1.4)	6.1 (2.1) ^c	6.0 (1.6) ^c	13.15 ^{***}	0.42
PVT					
Reaction time (ms)	301.6 (46.9)	338.9 (58.4) ^b	335.0 (64.2)	4.56 [*]	0.20
Number of lapses (>500 ms)	3.2 (3.8)	6.7 (5.5) ^b	6.1 (6.8)	2.93	0.14
Total lapse time (ms)	2347.8 (2749.1)	5264.6 (4397.8) ^b	4482.1 (5318.8)	3.19	0.15
DSST					
Number of responses	86.8 (8.9)	83.8 (9.2)	83.8 (8.0)	2.25	0.11
Errors (%)	0.9 (1.1)	1.2 (1.3)	1.2 (1.7)	0.38	0.02
Addition task					
Number of responses	68.9 (22.6)	69.0 (27.7)	67.6 (23.4)	0.14	0.01
Errors (%)	7.7 (7.3)	8.4 (7.2)	9.7 (11.8)	0.73	0.04

M: Mean; *SD*: Standard Deviation; KSS: Karolinska Sleepiness Scale; PVT: Psychomotor Vigilance Task; DSST: Digit Symbol Substitution Test.

^{*} $p<0.05$, ^{***} $p<0.001$.

Significance level of differences between mirtazapine/quetiapine and placebo, ^a $p<0.05$, ^b $p<0.01$, ^c $p<0.001$.

of 19 healthy males, whose sleep was disturbed by acoustic stress as a model for transient insomnia. Sleep was assessed using both PSG and subjective sleep measures. Additionally, we examined hangover effects that may hamper daytime functioning, i.e. daytime sleepiness and reduced cognitive functioning.

As expected from young, healthy individuals, the subjects slept very well during the undisturbed placebo condition: they fell asleep rapidly, had a high sleep efficiency (94.2±4.0%), a high amount of N3 (27.3±6.5% of total sleep time) and did not wake up very often. In line with previous studies, acoustic stress – as evoked by traffic noise – significantly impaired sleep (Cluydts et al., 1995; Cohrs et al., 2004; Dijk et al., 2012). It reduced total sleep time, at the expense of the deep sleep stage N3 and REM sleep. Furthermore, acoustic stress increased the time spent in the shallow sleep stages N1 and N2, and increased the number of awakenings and time spent awake after sleep onset. In the literature, acoustic stress generally results in marked increases in sleep onset latency. Since the same prerecorded road traffic noise was used and played at the same sound level as in an earlier study (Dijk et al., 2012), it is unclear why traffic noise evoked relatively minor increases in sleep latency in the present study. Acoustic stress also had a negative influence on several subjective sleep measures: it led to more trouble falling asleep and a dramatic drop in sleep quality. These findings indicate that acoustic stress disturbed sleep initiation and, to a larger extent, sleep maintenance and decreased sleep intensity and sleep quality, thereby confirming acoustic stress as an effective model for insomnia. Moreover, no habituation was found over the three treatment sessions, which is essential for effect studies spanning multiple nights.

Both mirtazapine and quetiapine increased total sleep time and to such an extent that they completely counteracted the negative effect of acoustic stress on total sleep duration. To illustrate: when taking either mirtazapine or quetiapine, total sleep time under acoustic stress did not differ from total sleep time ($F(1,18)=1.13$, $p=0.31$, $\eta=0.06$) when taking placebo and

sleeping undisturbed. These hypnotic actions were not associated with marked changes in sleep initiation. This is probably due to the fact that acoustic stress did not produce large increases in sleep onset latency in this study. As shown by consistent reductions in the number of awakenings and in wakefulness after sleep onset compared to placebo, the hypnotic effects of both drugs were particularly related to improved sleep maintenance. Thus, mirtazapine and quetiapine similarly and completely reversed the disrupting influence of acoustic stress on sleep continuity. This finding is in line with Cohrs et al. (2004), who reported improved sleep continuity in a similar study using 25 mg and 100 mg of quetiapine. Interestingly, we found that quetiapine specifically enhanced non-REM sleep stage N2, thereby exacerbating the increase in N2 caused by acoustic stress. In contrast, mirtazapine mainly increased time spent in N3, thereby counteracting the negative effect of acoustic stress on deep sleep. EEG slow waves, which mainly occur during N3, are generally thought to be of major importance for recovery from preceding wakefulness, for instance in the synaptic homeostasis hypothesis (Tononi and Cirelli, 2014). Due to its property to enhance N3, mirtazapine may produce sleep with a high restorative value. It would therefore be worthwhile to investigate alertness and daytime functioning during sub-chronic or long-term use of low, bedtime dosages of mirtazapine. Also with respect to REM sleep, the drugs exerted differential effects. While REM sleep duration and latency during the quetiapine treatment were similar to placebo, mirtazapine significantly decreased the amount of REM sleep and prolonged REM sleep latency during the undisturbed condition. Neither mirtazapine nor quetiapine counteract the negative influence of acoustic stress on the total duration of REM sleep. Possibly of higher importance to insomniac people, the subjects also reported that they fell asleep much easier and experienced a higher sleep quality under both mirtazapine and quetiapine treatment.

The sleep effects of 7.5 mg mirtazapine are in correspondence with earlier studies employing higher doses: in healthy volunteers a dose of 30 mg mirtazapine was found to promote sleep, to

increase sleep maintenance, and, as shown by a decrease of N1 and an increase of N3, to deepen non-REM sleep, and tended to increase the latency to REM sleep and reduce the total amount of REM sleep (Aslan et al., 2002; Ruigt et al., 1990). Studies in patients with a major depressive disorder revealed that most of the effects of 15–45 mg mirtazapine on sleep were sustained after several weeks (Schittecatte et al., 2002; Schmid et al., 2006; Shen et al., 2006). Regarding quetiapine, higher, clinical doses can have a disruptive effect on sleep, increasing sleep latency and wake time after sleep onset, and reducing slow wave sleep in healthy subjects and patients with schizophrenia (Keshavan et al., 2007; Monti et al., 2016). However, the positive effects of 50 mg quetiapine are in line with the literature on low doses of quetiapine: in healthy, young subjects and patients with primary insomnia quetiapine doses between 25–100 mg have been observed to increase total sleep time, particularly N2, and to improve sleep efficiency and subjective sleep quality (Cohrs et al., 2004; Wiegand et al., 2008). The present findings show and further substantiate the evidence that for the treatment of insomnia much lower doses of mirtazapine and quetiapine are generally required than the recommended dosages for approved indications.

Mirtazapine and quetiapine each have complex receptor-binding properties. Yet, for both drugs their potent blocking of central histamine H_1 as well as serotonin ($5-HT_2$) receptors is generally held responsible for most of their sleep effects (e.g. Coe and Hong, 2012; Radhakishun et al., 2000; Wiegand et al., 2008). Therapeutic doses of lipophilic histamine H_1 receptor antagonists, like diphenhydramine, acutely produce objective and subjective sleepiness and performance deficits (Richardson et al., 2002; Schweitzer et al., 1994). Depending on doses and dosing regimen, tolerance to the sedating effects of such antihistamines may develop fairly rapidly (e.g. Richardson et al., 2002; Schweitzer et al., 1994). Non-selective $5-HT_2$ receptor antagonists, such as ritanserin, lack a pronounced hypnogenic action, but may produce persistent, marked and dose-related increases in N3 and consequently reduce the time spent in N2 and lengthen the latency to REM sleep (Adam and Oswald, 1989; Idzikowski, et al., 1991). These sleep effects are probably largely mediated through $5-HT_{2A}$ receptors (Monti, 2011). For instance, in healthy subjects the selective $5-HT_{2A}$ antagonist eplivanserin has been shown to enhance N3 and decrease the percentage of REM sleep (Landolt et al., 1999) and the $5-HT_{2A}$ inverse agonist nelotanserin was found to enhance N3 and prolong the latency to REM sleep in a post-nap model of insomnia (Al-Shamma et al., 2010). This may explain the results of mirtazapine. As quetiapine also antagonises $5-HT_{2A}$ receptors, the biological mechanisms underlying its enhancement of a sleep stage with the EEG-characteristics of N2 is unclear. As benzodiazepines elicit comparable changes in the sleep EEG (Lancel, 1999), an indirect agonistic modulatory action at $GABA_A$ receptors has previously been hypothesized (Cohrs et al., 2004). The observation that quetiapine, in contrast to several other antipsychotics, for instance olanzapine, does not promote N3 has previously been related to its relatively weak $5-HT_2$ receptor antagonism (Krystal et al., 2008). In addition to $H1$ and $5-HT_{2A}$ receptors, quetiapine has high affinity for α_1 adrenergic receptors. As α_1 agonists stimulate wakefulness, while the α_1 receptor antagonist prazosin increases total sleep time and REM sleep and reduces the number of nightmares and distress awakenings in patients with PTSD (Green, 2014), the

anti-adrenergic activity of quetiapine may also contribute to its influence on sleep and wakefulness.

Although 7.5 mg mirtazapine and 50 mg quetiapine both benefited measures of sleep objectively and subjectively, they had some drawbacks as well. After undisturbed sleep, subjects reported more difficulty waking up after taking quetiapine and were more fatigued when taking either drug. Two hours after rising, both drugs were associated with increased subjective sleepiness. Despite the subjective somnolence, no decrements were found in two of three cognitive performance tasks. Mirtazapine, with quetiapine not far behind, did increase RT and the number of lapses on the 10-minute PVT, indicating a negative effect on sustained vigilance. These hangover effects are important when considering early morning activities in daily life, such as driving to work. There is some evidence that the initial decrease in daytime alertness may dissipate with continued use. Iwamoto and colleagues (2013) observed in their study that after eight days of continuous nocturnal administration of 7.5 mg mirtazapine, the initial daytime somnolence had decreased to non-clinically relevant levels. Radhakishun and colleagues (2000) found that when 15–30 mg mirtazapine was taken at bedtime for two weeks at a stretch by depressed patients, after an initial dip alertness progressively increased above baseline levels and subjective sleep duration improved. The authors argue that the increase in alertness induced by mirtazapine is at least partially attributable to improved sleep. Furthermore, the persistence of mirtazapine's sleep-enhancing effect suggests mediation by $5-HT_{2A/C}$ blockade.

Based on the findings of this study, both drugs could be useful for the treatment of insomnia. Given the specific promotion of deep sleep, mirtazapine may seem preferable over quetiapine. Yet, this does not mean that mirtazapine should necessarily be considered first. In the case of insomnia co-morbid to a psychiatric disorder, mirtazapine may be the more established choice where for instance depression or anxiety disorders are present. Insomnia co-morbid to schizophrenia or bipolar disorder may point to quetiapine. However, it should be noted that doses prescribed for insomnia are much lower than those indicated for a psychiatric disorder, making a direct effect on the psychiatric disorder unlikely.

Both drugs are associated with weight gain at standard doses (Hutton et al., 2015; Watanabe et al., 2010), for quetiapine there is also evidence at lower doses up to 100–200 mg (Cates et al., 2009; Coe and Hong, 2012). This problem may well apply also to 7.5 mg mirtazapine, although formal evidence is lacking. Other metabolic changes reported for standard doses of quetiapine and, to a lesser extent, mirtazapine should also be considered when selecting a suitable treatment. Quetiapine has been found to increase total cholesterol, low-density lipoprotein-cholesterol, and triglyceride levels and leptin and prolactin levels (Pérez-Iglesias et al., 2014), but not consistently (Bushe et al., 2010; Zhang and Lan, 2014). Glycaemic parameters seem to be less affected (Chen et al., 2011; Kelly et al., 2003; Pérez-Iglesias et al., 2014; Zhang and Lan, 2014), although insulin resistance and insulin secretion have been found to be increased (Chen et al., 2011). Fewer studies have been conducted on the effects of mirtazapine on metabolic syndrome variables, though 30 mg has been reported to increase total cholesterol and temporarily increase triglycerides, but not to affect LDL-cholesterol or HDL-cholesterol (Nicholas et al., 2003).

Furthermore, there are sleep related side effects that may determine preference. Low, nocturnal doses of quetiapine have been

shown to elicit and exacerbate periodic leg movements (Cohrs et al., 2004). Regarding mirtazapine, some case studies report an increase in nightmares, which may be especially important when treating insomnia related to posttraumatic stress disorder (Dang et al., 2009; Mathews et al., 2006). Given the inconclusiveness on the long-term effects of either mirtazapine or quetiapine in low doses, caution with respect to their use in the treatment of insomnia as a substitute for more traditional hypnotics is warranted. Side effects need to be closely monitored by the treating clinician.

Strengths and weaknesses

This is the first study including two drugs often prescribed off-label for insomnia, mirtazapine and quetiapine. Both drugs were tested on the same subjects, randomised and with appropriate wash-out periods in between, allowing a balanced comparison of the drugs to placebo. Both objective and subjective measures of sleep and measurements on daytime performance were included. One drawback is that drug effects were only studied for a limited number of days. Furthermore, while the effects of the order in which the drugs were tested were controlled for by randomisation, the night with acoustic stress always followed the night without acoustic stress. Comparison to placebo eliminated the effect of adaptation to sleeping in a laboratory setting, but it is possible that drug effects observed during the third night express a combination of sleep-enhancing effects from the third night and residual effects from the second night. Also, this study focused on two alternatives for medication traditionally used for insomnia. A study directly comparing the effects of low doses of quetiapine or mirtazapine with those of standard hypnotics, such as zolpidem or zopiclone, would allow for a better evaluation of their effects and uses in clinical practice. Last, in the present study we included only healthy subjects. As drug effects may differ between young, healthy subjects and for instance insomnia patients, elderly persons or patients with mental disorder, additional studies carried out in different patient samples are required.

Conclusion

In conclusion, both 7.5 mg mirtazapine and 50 mg quetiapine increased sleep considerably compared to placebo, by improving sleep continuity and total sleep time in a model of transient insomnia, with some hangover effects in the morning. These findings support their off-label use for insomnia in clinical practice, but given the inconclusiveness on the long-term effectiveness and adverse effects, further prospective studies are needed.

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