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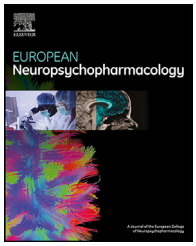

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Effects of quetiapine on sleep: A systematic review and meta-analysis of clinical trials

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Abstract
Quetiapine is a common off-label antipsychotic drug for treating insomnia. Its effects in different disease conditions and dosages remain unclear. We conducted a systematic review and meta-analysis in clinical trials examining the efficacy of low-dose quetiapine in sleep.
We obtained 21 clinical trials. Mean difference (MD), standard mean difference (SMD), and odds ratio (OR) were used to estimate the effect sizes using a random-effects model.
The pooled results showed that quetiapine improved sleep quality compared with placebo (SMD: -0.57 [95%CI: -0.75, -0.4]). The SMD of sleep quality was correlated with age (coefficient:

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-0.0174) and sex (coefficient: -0.012). The significant effects were observed in the general anxiety disorder (SMD: -0.59 [95%CI: -0.92, -0.27]), major depressive disorder (SMD: -0.47 [95%CI: -0.66, -0.28]), and healthy (SMD: -1.33, [95%CI [-2.12, -0.54]) subgroups, at the dosage of 50 mg (SMD: -0.36 [95%CI: -0.36, -0.11]), 150 mg (SMD: -0.4 [95%CI: -0.52, -0.29]), and 300 mg (SMD: -0.17 [95%CI: -0.31,-0.04]). Quetiapine increased total sleep time compared with placebo (MD: 47.91 [95%CI: 28.06, 67.76]) but not when compared with other psychiatric drugs (MD: -4.19 [95%CI: -19.43, 11.05]). Adverse events (AEs) and discontinuation due to AEs were common among the quetiapine users.

Quetiapine is effective as a sleep-helping drug. Precaution is suggested when interpreting the results on the elderly due to the high heterogeneity caused by incorporating patients over 66 years in the meta-analyses. We recommend an initial dosage of 50-150 mg/day with priority consideration for the elderly with GAD or MDD while monitoring its potential AEs.

1. Introduction

Insomnia is a common health problem with a prevalence of about 30% in the general population (Roth, 2007) and as high as 67.4% and 43.0% in hospitalized and non-hospitalized psychiatric patients (Talih et al., 2018). Poor sleep can be a symptom, harbinger, or comorbid problem of psychiatric disorders, especially in depression, anxiety disorders, and substance disorders (Khurshid, 2018), and has a reciprocal influence on the disorders. The Food and Drug Administration (FDA) has approved therapeutics with different mechanisms, including benzodiazepine receptor agonists, tricyclic antidepressants, orexin receptor antagonists, melatonin receptor agonists, and histamine receptor antagonists as hypnotics. Despite the official acceptance, serious side effects such as somnolence in the daytime, rapid tolerance, rebound insomnia after abrupt discontinuation, and cognition affecting were noted in the hypnotic users, especially benzodiazepines (Lie et al., 2015). In addition, the risk of misuse and abuse is high among these sleep-helping drugs (Votaw et al., 2019). Considering the disadvantage of hypnotics and sometimes concurrent use for multiple conditions such as anxiety and behavioral disturbance in the elderly, off-label use of sedating atypical antipsychotics for insomnia has become a common practice, among which quetiapine is the most popular choice, and there was a noticeable trend of increasing use in the last two decades (Kelly et al., 2018).

Quetiapine is an FDA-approved atypical antipsychotic drug for schizophrenia, acute manic episodes, and adjunctive treatment for major depressive disorder with two therapeutic dose ranges - 400–800 mg/day and 150-300 mg/day (Maan et al., 2022). The different treatment indications of quetiapine may be attributable to the different pharmacologic properties observed at different dose ranges. At a lower dose, quetiapine occupies the H1 and 5-HT2C receptors extensively and induces sedative effects, thus an effective agent for insomnia treatment. On the other hand, except for histamine-1 and 5HT2A receptors, quetiapine occupancy at the D2 receptors, norepinephrine transporters, and 5HT2C receptors is more significant at a higher dose and thus contributes to mainly antipsychotic effect (Stahl, 2021). Generally speaking, the prescription of quetiapine seldom exceeds 300 mg unless the patients meet the indication of schizophrenia or acute manic episodes (Riedel et al., 2007; Zhornitsky et al., 2011); because of its sedating properties, quetiapine is the most used off-label drug for insomnia treatment (Anna, 2014; Maan et al., 2022). An earlier systematic review suggested that quetiapine might reduce the latency to sleep onset and improve total sleep time and sleep efficiency in non-psychiatric and psychiatric populations (Wine et al., 2009). With more trials published today, there is a need to synthesize the current evidence of the effects of quetiapine on insomnia. In this study, we conducted a systematic review and meta-analysis of clinical trials to examine the efficacy of low-dose quetiapine in sleep quality in psychiatric and non-psychiatric patients.

2. Materials and Methods

We conducted the analyses and reported the results according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Page et al., 2011).

2.1. Inclusion and Exclusion Criteria

2.1.1. Participants

The current study included randomized control trials (RCTs) and crossover trials evaluating sleep quality outcomes after quetiapine treatment in psychiatric or non-psychiatric diseases. The participants of the included trials were male and female adults (≥18 years old) with generally good health or diseases. Also, we excluded trials that did not describe the inclusion and exclusion criteria of the participants.

2.1.2. Interventions

The interventions considered in the current study were quetiapine treatment using immediate-release formulation (quetiapine IR) or extended-release formulation (quetiapine XR). We excluded trials using quetiapine dose >300 mg to prevent potential influences exceeding a hypnotic effect on the target outcomes. Also, we excluded trials with obscure interventions.

2.1.3. Comparators

The comparators were placebo or other drugs.

2.1.4. Outcomes

The primary outcome of our study was sleep quality. The secondary outcomes were total sleep time, adverse effects (AEs), anxiety, and depression.

2.2. Search Strategy and Study Selection

We searched relevant publications from PubMed, EMBASE, Cochrane Library, International Clinical Trials Registry Platform, and Clinicaltrials.gov till September 2022. We used the following terms and text words to search the literature: (quetiapine) AND (insomnia or sleep*). The full search strategies for all databases are presented in Supplementary Materials 1. We used the "related articles" option in PubMed to the extent of the search scope and reviewed all retrieved abstracts, studies, and citations. Furthermore, we recognized additional trials from the references of relevant papers. We did not apply restrictions on language or region. PROSPERO, an online international prospective register of systematic reviews curated by the National Health Service, United Kingdom, has accepted our review protocol (file number: CRD42021291672).

2.3. Data Extraction and Methodological Quality Appraisal

The details of study designs, sample characteristics, inclusion and exclusion criteria, and outcome data of the included trials were extracted by two reviewers (Che-Yin Lin and Cheng-Hen Chiang). After that, the two reviewers evaluated the methodological quality of each crossover trial and each randomized controlled trial according to the revised Cochrane risk of bias tool - additional considerations for crossover trials (released on October 20, 2016) and the revised Cochrane risk of bias tool for randomized trials (Version 2.0, released on August 22, 2019), respectively. Five domains - randomization process, deviations from intended interventions, missing outcome data, measurement of outcome, and selection of the reported result - were assessed. The disagreement was discussed and consulted with the senior reviewer (El-Wui Loh) and resolved afterward.

2.4. Statistical Analyses

Data were imported and analyzed using the Review Manager, version 5.4 (The Cochrane Collaboration, Oxford, England). The effect size of dichotomous outcomes was analyzed using the odds ratio (OR) and that of continuous outcomes using the mean differences (MD). A standardized mean difference (SMD) was used if the continuous outcome was measured using different measurement tools or the included trials had different ranges of distribution. The precision of effect sizes was reported as a 95% CI. We pooled data using the random-effects model. For the continuous variable, we estimated the standard deviation from the CI limits for those trials that did not provide the information. To not overestimate the sample size, the participant number in crossover trials was divided by two if final endpoint results were used in our study. We multiplied -1 if the improved tendency of the tool is different compared to others. The Cochrane Q tests and I^2 statistics were used to evaluate the heterogeneity and inconsistency of treatment effects across trials, respectively. Statistical significance was set at $P < 0.10$ for Cochrane Q tests. Subgroups were analyzed by pooling available estimates to obtain similar subsets of participants according to different health conditions, quetiapine dosages, and quetiapine formulations across trials. For ease of reporting, we classified I^2 values of 25%-50%, 51%-75%, and 76%-100% as low, moderate, and high heterogeneity, respectively. We also conducted meta-regression analyses using Comprehensive Meta-Analysis V3 to examine the potential modifier effects from mean age, male proportion, and quetiapine dosage.

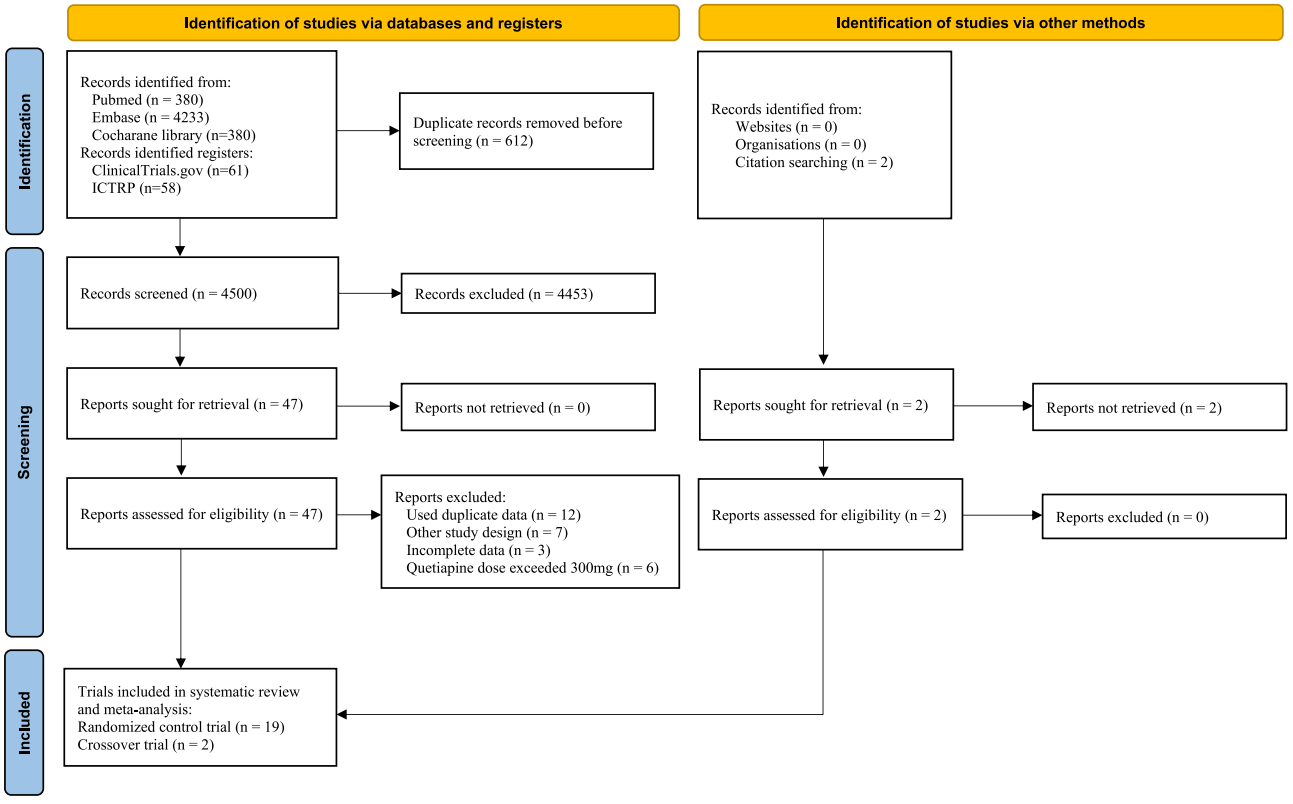

Fig. 1 Flowchart of trial selection.

3. Results

3.1. Study selection

Fig. 1 outlines the screening and selection process for trials to be analyzed. The initial search strategy yielded 5112 citations from PubMed, Embase, Cochrane Library, ClinicalTrials.gov, International Clinical Trials Registry Platform (ICTRP) and reference lists. After removing 612 duplicates, titles and abstracts of the remaining 4500 records were screened for potentially relevant citations. A total of 4453 irrelevant records were removed, and the full texts of the 47 remaining records were retrieved for further evaluation. We removed 12 articles using duplicate data, seven articles reporting trials using non-randomized or single-arm designs, and three articles reporting incomplete data. All potentially relevant studies that have been read in the full text but excluded from the current study are listed in Supplementary Materials 2. Finally, we obtained 21 trials, among which 19 were RCTs, and two were crossover trials.

3.2. Study characteristics

Table 1 shows the characteristics of the 21 included trials. They were published between 2004 and 2017, with sample sizes ranging from 16 to 894 subjects. Among these trials, three recruited healthy adults (Cohrs et al., 2004; Karsten et al., 2017; Rock et al., 2016) (Cohr et al. and Karsten et al. excluded subjects with insomnia, and Rock et al. excluded subjects with psychiatric disorders), five recruited general anxiety patients (Bandelow et al., 2010; Katzman et al., 2011; Khan et al., 2011; Merideth et al., 2012; Mezhebovsky et al., 2013), nine recruited primary depression patients (Bauer et al., 2009; Bortnick et al., 2011; Cutler et al., 2009; El-Khalili et al., 2010; Garakani et al., 2008; Katila et al., 2013; Liebowitz et al., 2010; Wang et al., 2014; Weisler et al., 2009), and five recruited patients with other diseases (Calandre et al., 2014; Maneeton et al., 2013; Potvin et al., 2012; Tassniyom et al., 2010). The mean age of the participants ranged from 24 to 71 years. Three trials recruited only males (Cohrs et al., 2004; Karsten et al., 2017; Potvin et al., 2012). Eight trials reported the baseline PSQI score (Bortnick et al., 2011; Calandre et al., 2014; Cutler et al., 2009; El-Khalili et al., 2010; Katila et al., 2013; Merideth et al., 2012; Potvin et al., 2012; Wang et al., 2014), and the range was 10.8 to 14.9. While most trials designed quetiapine as monotherapy, two trials used quetiapine as an adjuvant treatment for antidepressants (El-Khalili et al., 2010; Garakani et al., 2008). Extended-release quetiapine (XR) was used within the dose range of 50-300 mg in 16 trials (Bandelow et al., 2010; Bauer et al., 2009; Bortnick et al., 2011; Calandre et al., 2014; Cutler et al., 2009; El-Khalili et al., 2010; Katila et al., 2013; Katzman et al., 2011; Khan et al., 2011; Liebowitz et al., 2010; Merideth et al., 2012; Mezhebovsky et al., 2013; Potvin et al., 2012; Rock et al., 2016; Wang et al., 2014; Weisler et al., 2009), while the final mean dose in the flexible design trials was from 121 to 176 mg. Five trials used immediate-release quetiapine (IR) within 25-100 mg (Cohrs et al., 2004; Garakani et al., 2008; Karsten et al., 2017; Maneeton et al., 2013; Tassniyom et al., 2010); flexi-

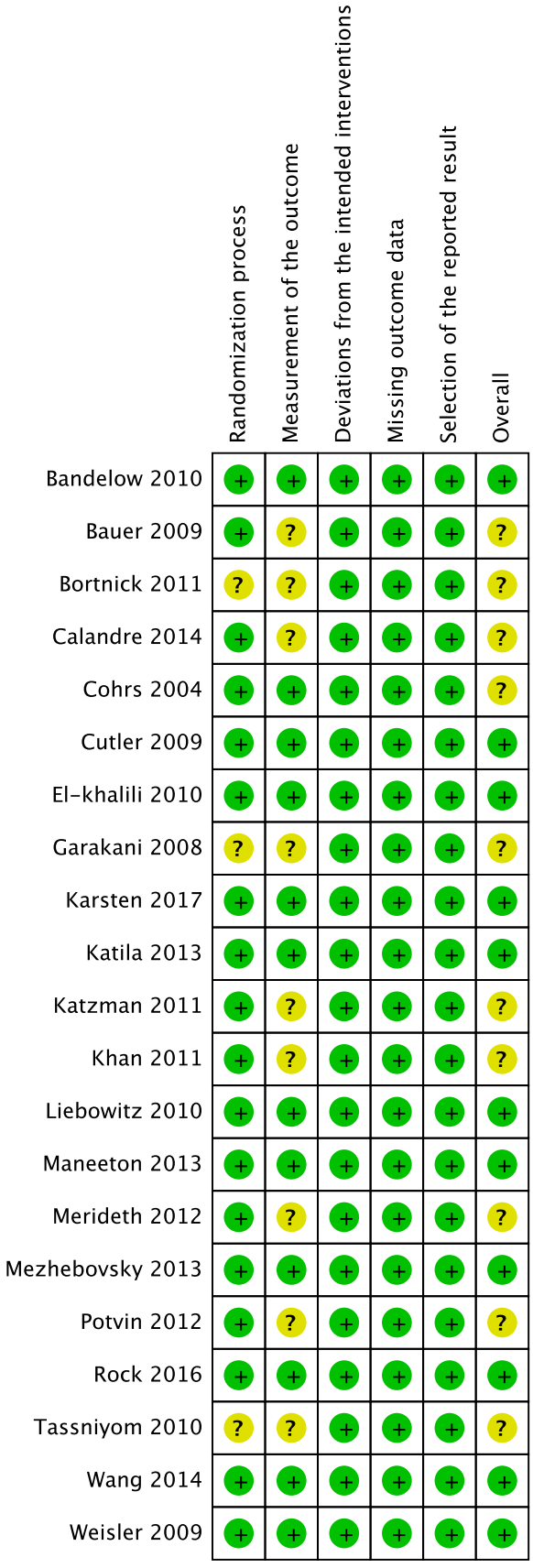

Fig. 2 Methodological quality assessment for randomized controlled trials and cross-over trials. Red: high risk of bias; yellow: some concerns: green: low risk of bias.

Table 1 Characteristics of included trials.

Trial	Inclusion criteria	Setting	No. patients (% male)	Age	PSQI baseline	Interventions	Outcomes measures
Randomized controlled trials							
Bandelow 2010	Age 18-65, GAD	Outpatients; multi-center	Q1: 219 (32) Q2: 216 (33) P: 217 (38) C: 214 (36)	Q1: 40.7±11.6 Q2: 42.3±12.4 P: 41.2±12.8 C: 41.6±11.8	NI	Q1: Quetiapine XR 50 mg x 8 w Q2: Quetiapine XR 150 mg x 8 w P: Placebo x 8 w C: Paroxetine 20 mg x 8	CGI-I, CGI-S, HAM-A*, MADRS, PSQI
Bauer 2009	Age 18-65, MDD with inadequate response to antidepressant	Outpatients; multi-center	Q1: 166 (31) Q2: 161 (32) P: 160 (35)	Q1: 46.0±10.1 Q2: 45.5±11.1 P: 44.8±10.4	NI	Q1: Quetiapine XR 150 mg x 6 w Q2: Quetiapine XR 300 mg x 6 w P: Placebo x 6 w	CGI-I, CGI-S, HAM-A, HAM-D, MADRS*, PSQI, Q-LES-Q
Bortnick 2011	Age 18-65, MDD	Outpatients; multi-center	Q: 147 (35) P: 152 (36)	Q: 43.3±10.5 P: 42.6±11.7	Q: 12.2±3.6 P: 11.6±3.7	Q: Quetiapine XR 150 mg x 8 w (if inadequate response at 2 w, then 300 mg x 6 w) P: Placebo x 8 w	CGI-I, CGI-S, HAM-A, HAM-D, MADRS*, PSQI, Q-LES-Q
Calandre 2014	Age 18-70, fibromyalgia; FIQ $\geq$ 40, BPI $\geq$ 4	Outpatients; single-center	Q:45 (0) C:45 (2)	Q:49.7 ± 7.9 C:50.6 ± 8.2	Q: 14.9±3.8 C: 14.9±3.9	Q: Quetiapine XR 50-300 mg x 16 w C: Amitriptyline 10-75 mg x 16 w	BDI, BPI, FIQ*, PGI, PSQI, SF-36, STAI
Cutler 2009	Age 18-65, MDD	Outpatients; multi-center	Q1: 147 (37) Q2: 147 (49) P: 152 (36) C: 141 (38)	Q1: 40.9±12.3 Q2: 41.6±12.0 P: 42.3±11.5 C: 40.2±12.5	Q1: 11.4±3.6 Q2: 11.3±3.5 P: 11.9±3.9 C: 12.1±4.0	Q1: Quetiapine XR 150 mg x 6 w Q2: Quetiapine XR 300 mg x 6 w P: Placebo x 6 w C: Duloxetine 60 mg x 6 w	CGI-I, CGI-S, HAM-A, HAM-D, MADRS*, PSQI
El-khalili 2010	Age 18-65, MDD with inadequate response to antidepressant	Outpatients; multi-center	Q1: 143 (24) Q2: 146 (27) P:143 (32)	Q1: 45.9±11 Q2: 44.3±11.3 P: 46.2±10.9	Q1: 11.4±3.8 Q2: 11.1±4.0 P: 11.4±3.8	Q1: Quetiapine XR 150 mg + antidepressant x 6 w Q2: Quetiapine XR 300 mg + antidepressant x 6 w P: Placebo + antidepressant x 6 w	CGI-I, CGI-S, HAM-A, HAM-D, MADRS*, PSQI, Q-LES-Q-SF
Garakani 2008	Age 18-65, MDD	Outpatients; three-site	Q: 57 P: 57	41.4±11.5	NI	Q: Quetiapine 25-100mg + Fluoxetine 20-40mg x 8 w P: Placebo + Fluoxetine 20-40 mg x 8 w	CGI-I, HAM-A, MADRS*

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Table 1 (*continued*)

Trial	Inclusion criteria	Setting	No. patients (% male)	Age	PSQI baseline	Interventions	Outcomes measures
Katila 2013	Age ≥ 66, MDD	Outpatients; multi-center	Q: 164 (30) P: 171(30)	Q: 71.3±4.6 P: 71.2±4.9	Q: 12.8±3.4 P: 12.9±3.5	Q: Quetiapine XR 50-300 mg x 9 w P: Placebo x 9 w	CGI-I, CGI-S, HAM-A, HAM-D, MADRS*, pain VAS, PSQI, Q-LES-Q-SF
Katzman 2011	Age 18-65, GAD; 16-26 w pretreatment with quetiapine XR 50-300mg; HAM-A≤12; CGI-S ≤ 3; MADRS ≤ 16	Outpatients; multi-center	Q: 216 (33) P: 216 (37)	Q: 44.8±11 P: 41.7±12.2	NI	Q: Quetiapine XR 50-300 mg x 52 w P: Placebo x 52 w	CGI-S, HAM-A, PSQI, Q-LES-Q, SDS, time from randomization to relapse*
Khan 2011	Age 18-65 y, GAD	Outpatients; multi-center	Q1: 219 (43) Q2: 226 (37) Q3: 224 (39) P: 225 (34)	Q1: 39±11.7 Q2: 40.7±11.7 Q3: 41±11.9 P: 39.2±11.6	NI	Q1: Quetiapine XR 50 mg x 8 w Q2: Quetiapine XR 150 mg x 8 w Q3: Quetiapine XR 300 mg x 8 w P: Placebo x 8 w	CGI-I, CGI-S, HAM-A*, MADRS, PSQI, Q-LES-Q
Liebowitz 2010	Age 18-65, MDD; 16-26 w pretreatment with quetiapine XR 50-300mg; MADRS ≤ 12; CGI-S ≤ 3	Outpatients; multi-center	Q: 387 (34) P: 384 (34)	Q: 45.4±11.2 P: 43.8±11.5	NI	Q: Quetiapine XR 50-300 mg x 52 w P: Placebo x 52 w	CGI-S, HAM-A, HAM-D, MADRS, PSQI, Q-LES-Q, SDS, time from randomization to relapse*
Maneeton 2013	Age 18-75, delirium; exclude substance-induced delirium	Inpatients; single-center	Q:24 (63) C:28 (71)	Q: 56.6±12.0 C: 57.0±11.9	NI	Q: Quetiapine 25-100 mg x 1 w C: Haloperidol 0.5-2.0 mg x 1 w	CGI-I, DRS-R-98*, TST
Merideth 2012	Age 18-65, GAD	Outpatients; multi-center	Q1: 212 (33) Q2: 201 (29) P: 212 (36) C: 203 (35)	Q1: 38.2±11.5 Q2: 39±12.6 P: 36.6±12.3 C: 40.4±11.6	Q1: 10.8±3.5 Q2: 11.2±3.5 P: 10.9±3.7 C: 11.0±3.4	Q1: Quetiapine XR 150 mg x 8 w Q2: Quetiapine XR 300 mg x 8 w P: Placebo x 8 w C: Escitalopram 10 mg x 8 w	CGI-I, CGI-S, HAM-A*, HAM-D, MADRS, PSQI, Q-LES-Q
Mezhebovsky 2013	Age ≥ 66, GAD	Outpatients; multi-center	Q: 222 (62) P: 226 (70)	Q: 70.3±4.3 P: 70.6±4.4	NI	Q: Quetiapine XR 50-300 mg x 9 w P: Placebo x 6 w	CGI-I, CGI-S, HAM-A*, MADRS, pain VAS, PSQI, Q-LES-Q-SF
Potvin 2012	Age ≥ 18, fibromyalgia; partial response with pain item of FIQ ≥ 4	Outpatients; single-center	Q: 25 (100) P: 25 (100)	50 ± 11.7	Q: 12.0±3.5 P: 12.8±4.3	Q: Quetiapine XR 50-300 mg x 12 w P: Placebo x 12 w	CGI-S, FIQ*, HAM-A, HAM-D, PSQI, tender point threshold

(*continued on next page*)

Table 1 (*continued*)

Trial	Inclusion criteria	Setting	No. patients (% male)	Age	PSQI baseline	Interventions	Outcomes measures
Rock 2016	Healthy adults	Volunteers; single-center	Q: 20 (55) P: 20 (45)	Q: 25.4±1.42 P: 23.6±0.71	NI	Q: Quetiapine XR 150 mg x 1 w P: Placebo x 1 w	BFS, emotional word categorization and memory, facial expression recognition, MEQ, PANAS, sleep parameters, STAI, vRTs
Tassniyom 2010	Age 16-65, primary insomnia	Outpatients; single-center	Q: 8 (10) P: 8 (10)	Q: 44.9 P: 47	NI	Q: Quetiapine 25 mg x 2 w P: Placebo x 2 w	TST, sleep latency, sleep satisfaction VAS
Wang 2014	Age 18-65, MDD	Outpatients; multi-center	Q: 154 (28) P: 153 (33) C: 152 (24)	Q: 40.1±11.6 P: 39.7±11.1 C: 40.3±12.5	Q: 12.5±4.0 P: 12.8±4.3 C: 12.3±3.9	Q: Quetiapine XR 150 mg x 8 w (if inadequate response at 2 w, then 300 mg x 6 w) P: Placebo x 8 w C: Escitalopram 10 mg x 8w (if inadequate response at 2 w, then 20 mg x 6 w)	CGI-I, CGI-S, HAM-A, HAM-D, MADRS*, PSQI, Q-LES-Q
Weisler 2009	Age 18-65, MDD	Outpatients; multi-center	Q1: 178 (47) Q2: 168 (38) Q3: 176 (42) P: 178 (37)	Q1: 40.6±11.1 Q2: 41.5±11.7 Q3: 40.7±12.2 P: 40.3±11.8	NI	Q1: Quetiapine XR 50 mg x 6 w Q2: Quetiapine XR 150 mg x 6 w Q3: Quetiapine XR 300 mg x 6 w P: Placebo x 6 w	CGI-I, CGI-S, HAM-A, HAM-D, MADRS*, PSQI, Q-LES-Q
Cross over trials							
Cohrs 2004	Age 18-65, healthy adults without insomnia	Volunteers; single-center	14 (100)	26.7±3.9	NI	3 sessions with randomized Quetiapine 25 mg, Quetiapine 100 mg or Placebo x 3 d, separated by 4 d washout	SF-A, sleep parameters, VIS-M
Karsten 2017	Age 18-35, healthy adults without insomnia	Volunteers; single-center	19 (100)	24.4±4.3	NI	3 sessions with randomized Quetiapine 50 mg, Mirtazapine 7.5 mg or Placebo x 3 d, separated by 4 d washout	DSST, KSS, PVT, sleep parameters, LSEQ

Age is presented in year.

BDI: Beck Depression Inventory, BFS: Befindlichkeitsskala, BPI: Brief Pain Inventory, C: control group, CGI-S: Clinical Global Impression- severity scale, CGI-I: Clinical Global Impression-Improvement scale, DRS-R-98: Delirium Rating Scale-revised-98, DSST: Digit Symbol Substitution Test, FIQ: Fibromyalgia Impact Questionnaire, GAD: general anxiety disorder, HAM-A: Hamilton Anxiety Rating Scale, HAM-D: Hamilton Depression Rating Scale, MADRS: Montgomery-Åsberg depression rating scale, KSS: Karolinska Sleepiness Scale, LSEQ: Leeds Sleep Evaluation Questionnaire, MDD: major depressive disorder, MEQ: Morningness-Eveningness Questionnaire, NI: no information, P: placebo group, PANAS: Positive and Negative Affect Schedule, PGI: Patient Global Improvement scale, PSQI: Pittsburgh Sleep Quality Index, PVT: Psychomotor Vigilance Task, Q: quetiapine group, Q-LES-Q: Quality of Life Enjoyment and Satisfaction Questionnaire, Q-LES-Q-SF: Quality of Life Enjoyment and Satisfaction Questionnaire -Short Form, SF-36: Short Form Health Survey, SF-A: Schlaffragebogen A, STAI: State and Trait Anxiety Inventory, TRD: treatment-resistant major depressive disorder, TST: total sleep time, VAS: Visual Analog Scale, VIS-M: Visuelle Analogskalen morgens, vRTs: Vigilance reaction times

ble designs were used in two with a final mean dose of 47mg and 67 mg, respectively. The treatment duration was 1 to 52 weeks in the RCTs and three days per treatment session in two crossover trials (Cohrs et al., 2004; Karsten et al., 2017). We only analyzed the intent-to-treat data.

3.3. Methodological quality

Fig. 2 summarizes the methodological quality of 21 trials. Among these trials, three had some concerns arising from the randomization process due to the lack of information on allocation concealment (Bortnick et al., 2011; Garakani et al., 2008; Tassniyom et al., 2010), and nine had some concerns in measurement of the outcome because they did not clearly explain the blinding approach of the interventions (Bauer et al., 2009; Bortnick et al., 2011; Calandre et al., 2014; Garakani et al., 2008; Katzman et al., 2011; Khan et al., 2011; Merideth et al., 2012; Potvin et al., 2012; Tassniyom et al., 2010). Other domains were of low risk. Ten trials had some concerns for overall risk of bias, and eleven had a low risk of bias.

3.4. Sleep quality

A total of 19 trials measured the sleep quality after quetiapine treatment. Among them, 15 trials used Pittsburgh Sleep Quality Index (PSQI) (Bandelow et al., 2010; Bauer et al., 2009; Bortnick et al., 2011; Calandre et al., 2014; Cutler et al., 2009; El-Khalili et al., 2010; Katila et al., 2013; Katzman et al., 2011; Khan et al., 2011; Liebowitz et al., 2010; Merideth et al., 2012; Mezhebovsky et al., 2013; Potvin et al., 2012; Wang et al., 2014; Weisler et al., 2009). The rest used the Leeds Sleep Evaluation Questionnaire (LSEQ) (Karsten et al., 2017), sleep satisfaction by visual analog scale (VAS) (Tassniyom et al., 2010), Schlaffragebogen A (SF-A), Visuelle Analogskalen morgens (VIS-M) (Cohrs et al., 2004), and the reduced sleep item of the MADRS (Montgomery-Åsberg Depression Rating Scale) (Garakani et al., 2008), respectively.

Twelve RCTs and two crossover trials reporting mean and standard deviation or in exchangeable formats were used in our meta-analysis (Bandelow et al., 2010; Bortnick et al., 2011; Cohrs et al., 2004; Garakani et al., 2008; Karsten et al., 2017; Katila et al., 2013; Katzman et al., 2011; Khan et al., 2011; Liebowitz et al., 2010; Merideth et al., 2012; Mezhebovsky et al., 2013; Potvin et al., 2012; Tassniyom et al., 2010; Wang et al., 2014). Eight of them published the change score of least square mean (LSM) of PSQI (Bandelow et al., 2010; Bortnick et al., 2011; Katzman et al., 2011; Khan et al., 2011; Liebowitz et al., 2010; Merideth et al., 2012; Mezhebovsky et al., 2013; Wang et al., 2014). We selected the 100 mg or 150 mg groups for analysis when multiple dose groups were examined since the mean doses on flexible design trials were mainly around 150 mg. In the two crossover trials investigating healthy subjects excluding insomnia (Cohrs et al., 2004; Karsten et al., 2017), sleep quality was evaluated with and without acoustic stress – an approach for inducing transient insomnia, and the endpoints were reported. To compare the effect of disrupted sleep with other diseases, we used the data in acoustic stress conditions. Thus, the endpoint and change score results of the abovementioned trials were pooled. In the trials conducted by Cohr et al. and Karsten et al., we selected the item of sleep quality from VIS-M and LSEQ for analysis. Fig. 3 shows the forest plot for the pooled effects of quetiapine versus placebo on sleep quality. Quetiapine demonstrated a significant effect in improving sleep quality (SMD: -0.57 [95% CI: -0.75, -0.4]) with a high statistical heterogeneity across trials ($I^2 = 83\%$, $P < 0.00001$).

3.4.1. Sleep quality – subgroup analysis according to health status

Fig. 4 summarizes the forest plot of subgroup analysis according to health status. A significant improvement in sleep quality was found in the quetiapine group compared with placebo in general anxiety disorder (GAD) (SMD: -0.59 [95% CI: -0.92, -0.27]), major depressive disorder (MDD) (SMD: -0.47 [95%CI: -0.66, -0.28]), and healthy (SMD: -1.33 [95%CI:-2.12, -0.54]) subgroups. High statistical heterogeneity was observed across trials ($I^2 = 92\%$, $P < 0.00001$) in the GAD subgroup. Further sensitivity analysis by removing Mezhebovsky et al. examining GAD patients over 66 years old (Mezhebovsky et al., 2013) resulted in no statistical het-

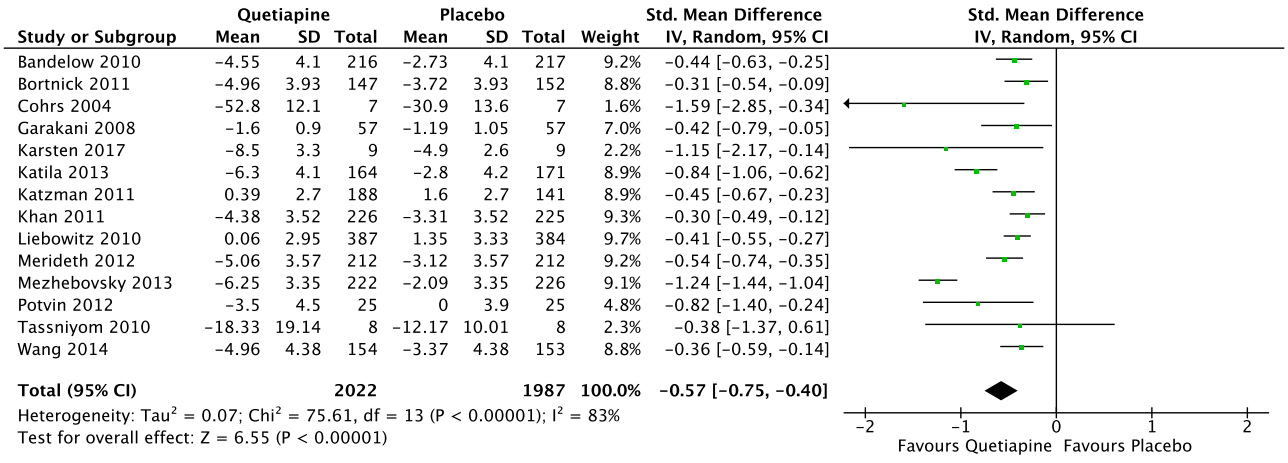

Fig. 3 Forest plot of the comparison between quetiapine and placebo groups in sleep quality.

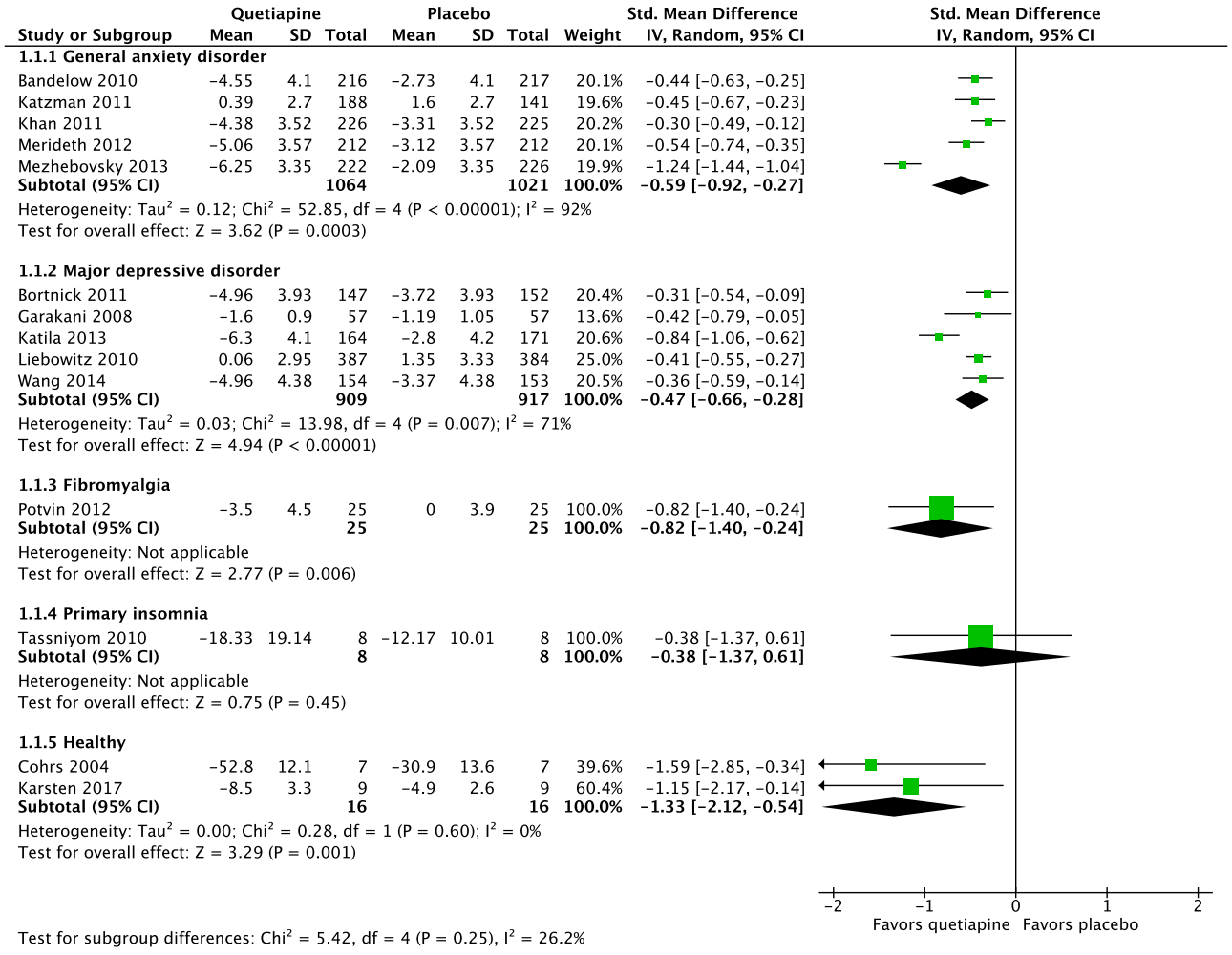

Fig. 4 Forest plot of the comparison between quetiapine and placebo groups in sleep quality in different health status subgroups.

erogeneity ($I^2 = 4\%$, $P = 0.37$). High statistical heterogeneity across trials was also observed in the MDD subgroup ($I^2 = 71\%$, $P < 0.007$). The exclusion of Katila et al. which examined MDD patients over 66 years old (Katila et al., 2013) resulted in no statistical heterogeneity ($I^2 = 0\%$, $P = 0.91$). The single trial that examined fibromyalgia patients demonstrated an improvement in sleep quality in the quetiapine group compared with placebo (SMD: -1.82 [95% CI: -1.4, -0.24]) but not in the single trial examining primary insomnia patients (SMD: -0.38 [95%CI: -1.37, 0.61]). Overall, quetiapine demonstrated a significant effect in improving sleep quality (SMD: -0.57 [95% CI: -0.75, -0.4]) with a high statistical heterogeneity across trials ($I^2 = 83\%$, $P < 0.00001$). Test for subgroup differences demonstrated no significant statistical evidence ($I^2 = 26.2\%$, $P = 0.25$).

3.4.2. Sleep quality – subgroup analysis according to quetiapine formulations

Fig. 5 summarizes the forest plot of subgroup analysis according to quetiapine formulations. In comparison with the placebo, both quetiapine XR (SMD: -0.56 [-0.75, -0.37]) and quetiapine IR (SMD: -0.7 [-1.2, -0.19]) showed significant improvement in sleep quality. A low statistical heterogeneity across trials was observed in the quetiapine IR subgroup ($I^2 = 35\%$, $P = 0.2$), and a high statistical heterogeneity was observed in the quetiapine XR subgroup ($I^2 = 87\%$, $P < 0.00001$). No subgroup difference was observed ($I2 = 0\%$, $P = 0.62$).

3.4.3. Sleep quality – subgroup analysis according to fixed quetiapine dosages

Fig. 6 summarizes the subgroup analyses according to different fixed quetiapine dosages. In comparison with placebo, quetiapine treatment showed significant improvement in sleep quality when the subjects were treated with 50 mg/day (SMD: -0.36 [95%CI: -0.60, -0.11]), 150 mg/day (SMD: -0.4 [95%CI: -0.52, -0.29]), and 300 mg/day (SMD: -0.17 [95%CI: -0.31,-0.04]), but not when treated with 25 mg/day (SMD: -0.38 [95%CI: -1.11,0.34]). No statistical heterogeneity across trials was observed in 25 mg/day, 100 mg/day, and 300 mg/day subgroups ($I^2 = 0\%$, $P = 0.99$; $I^2 = 22\%$, $P = 0.28$; $I^2 = 0\%$, $P = 0.85$) but a moderate heterogeneity was observed in the 50 mg/day subgroup ($I^2 = 57\%$, $P = 0.10$). A moderate subgroup difference was observed ($I^2 = 57\%$, $P = 0.07$).

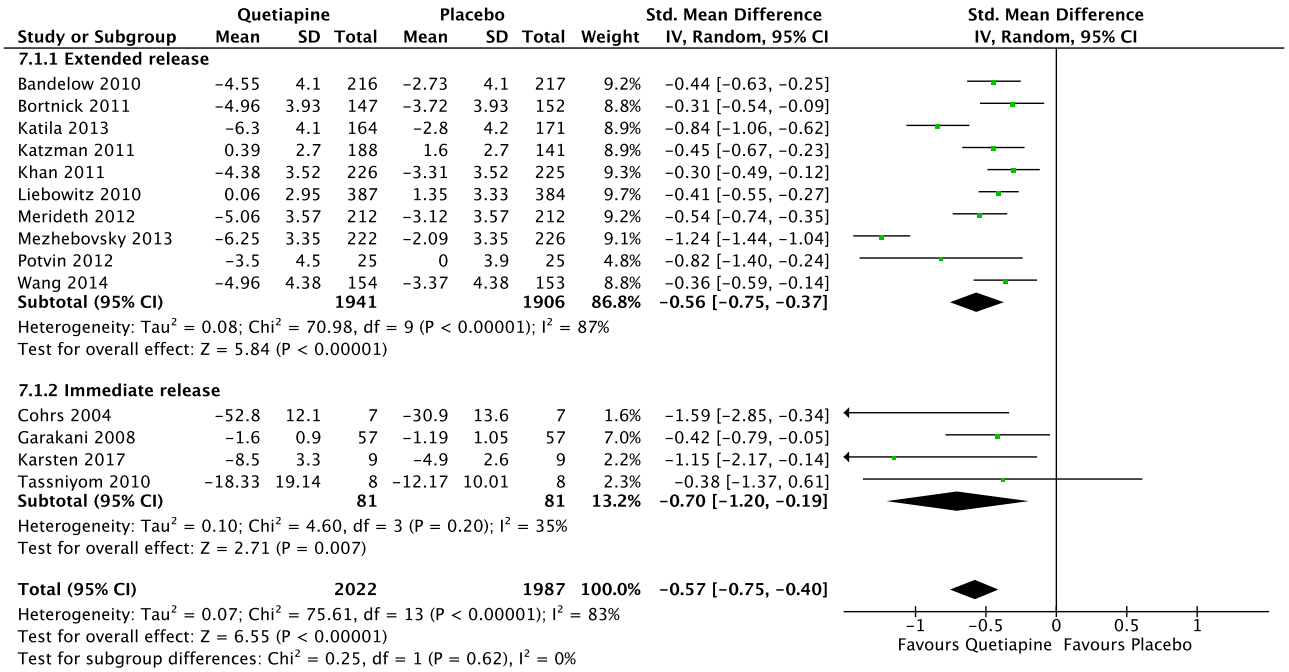

Fig. 5 Forest plot of the comparison between quetiapine and placebo groups in sleep quality in different quetiapine formulation subgroups.

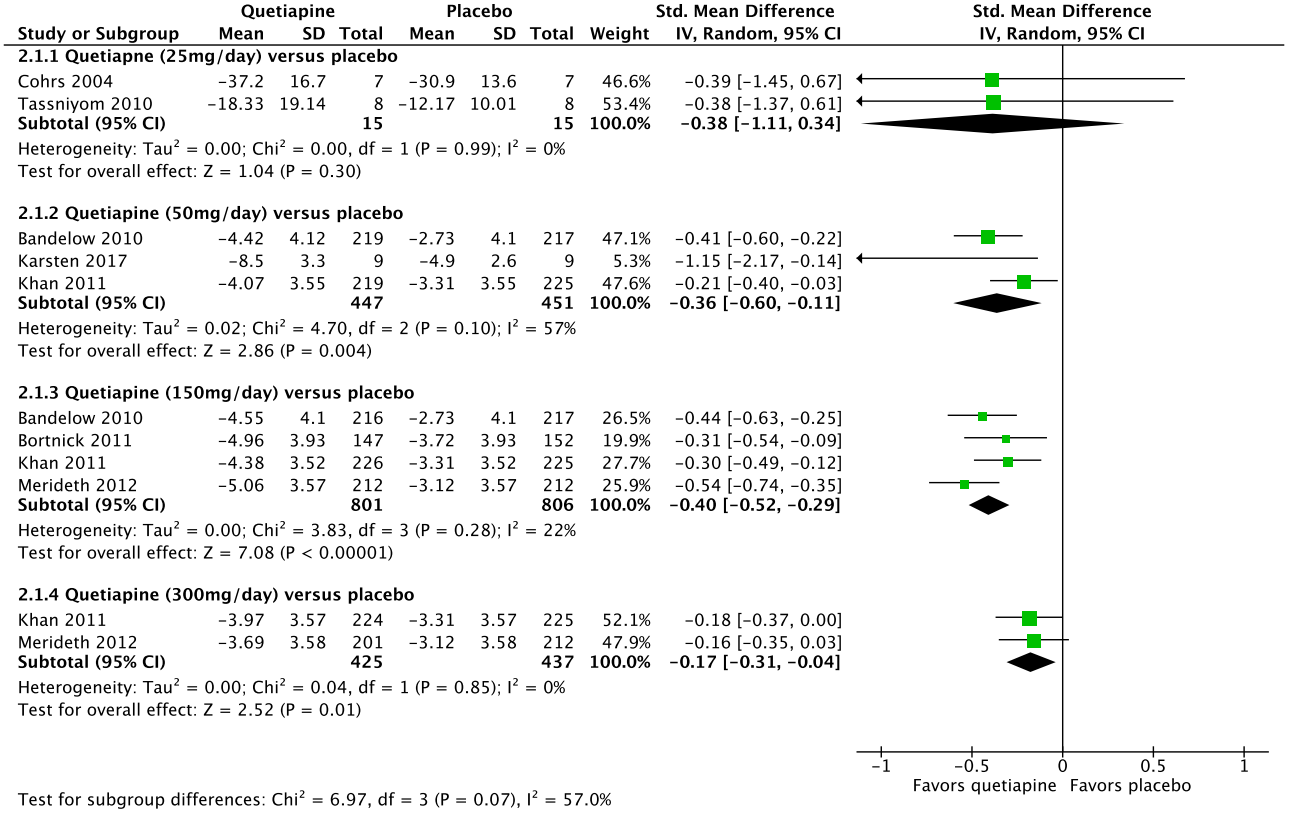

Fig. 6 Forest plot of the comparison between quetiapine and placebo groups in sleep quality in different fixed quetiapine dosage subgroups.

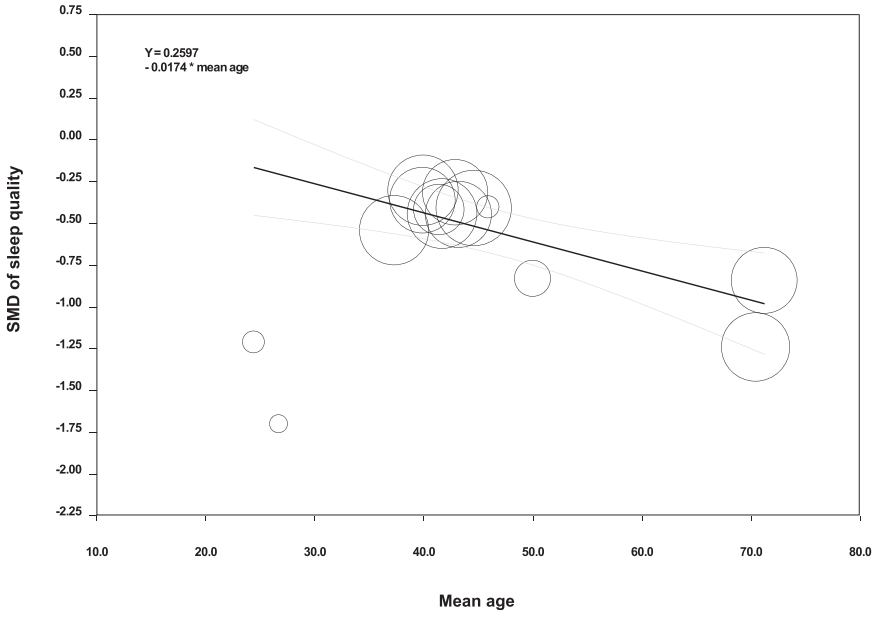

Fig. 7 Meta-regression of standard mean difference (SMD) of sleep quality on mean age.

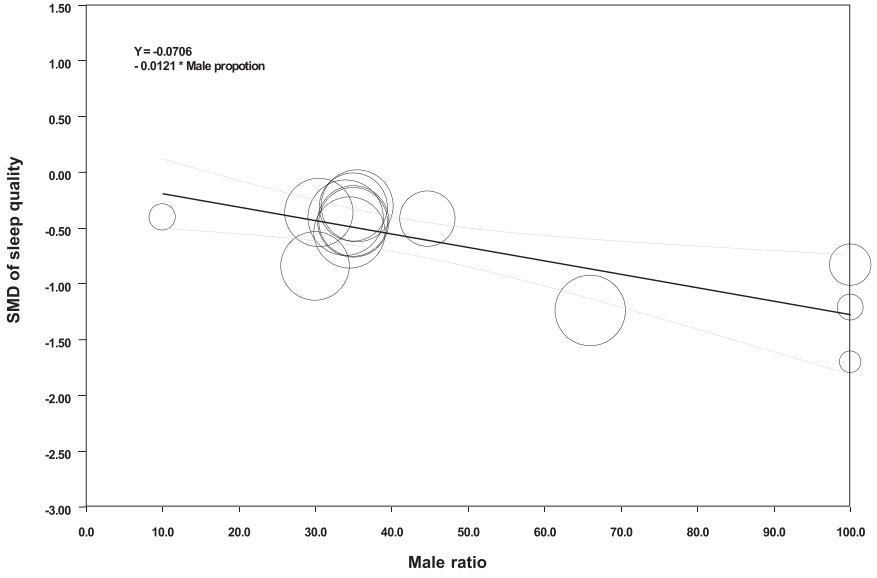

Fig. 8 Meta-regression of standard mean difference (SMD) of sleep quality on male ratio.

3.4.4. Sleep quality – meta-regressions

We included mean age, male ratio, and quetiapine dosage for meta-regression analyses to examine their roles in sleep quality. We extracted the fixed dosage and the ended mean dose of the quetiapine treatment group if the trials had a flexible dosage design. The meta-regression results revealed negative correlations between mean age and SMD of sleep quality (coefficient = -0.0174, P = 0.0001) (Fig. 7) and male ratio and SMD of sleep quality (coefficient = -0.0121, P = 0.0007) (Fig. 8). However, no correlation was found between quetiapine dosage and sleep quality (coefficient: 0.0001, P = 0.973) (Fig. 9).

3.5. Total sleep time

Five trials evaluated quetiapine effects on total sleep time, among which four of them compared quetiapine treatment and placebo (Cohrs et al., 2004; Karsten et al., 2017; Rock et al., 2016; Tassniyom et al., 2010) and two trials compared quetiapine treatment and other psychiatric drugs (antipsychotic haloperidol and antidepressant mirtazapine) (Karsten et al., 2017; Maneeton et al., 2013). Among them, two crossover trials used polysomnography (Cohrs et al., 2004; Karsten et al., 2017); the other three trials used actigraphy (Rock et al., 2016), investigator recorded to-

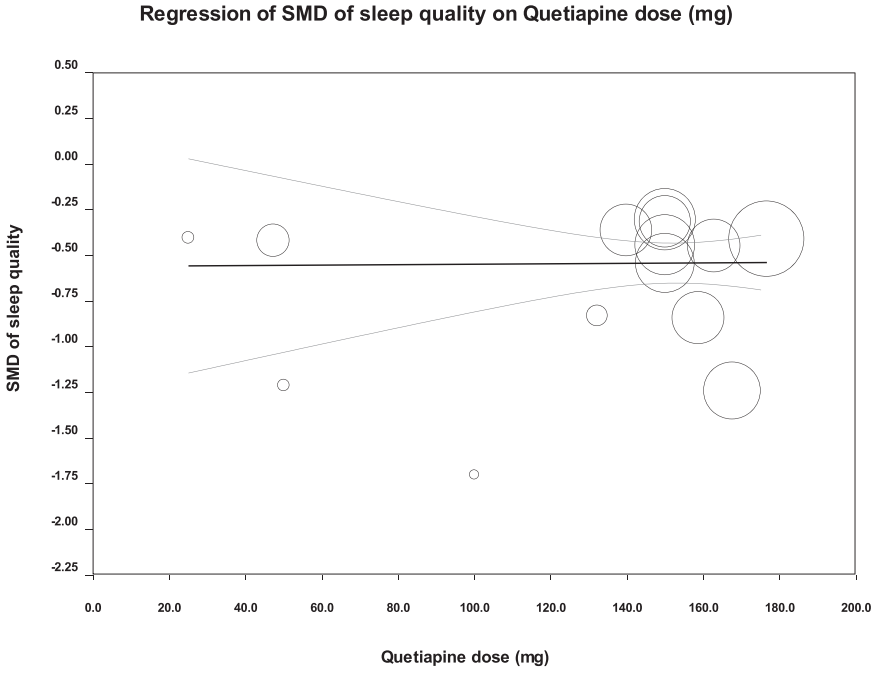

Fig. 9 Meta-regression of standard mean difference (SMD) of sleep quality on quetiapine dosage (mg).

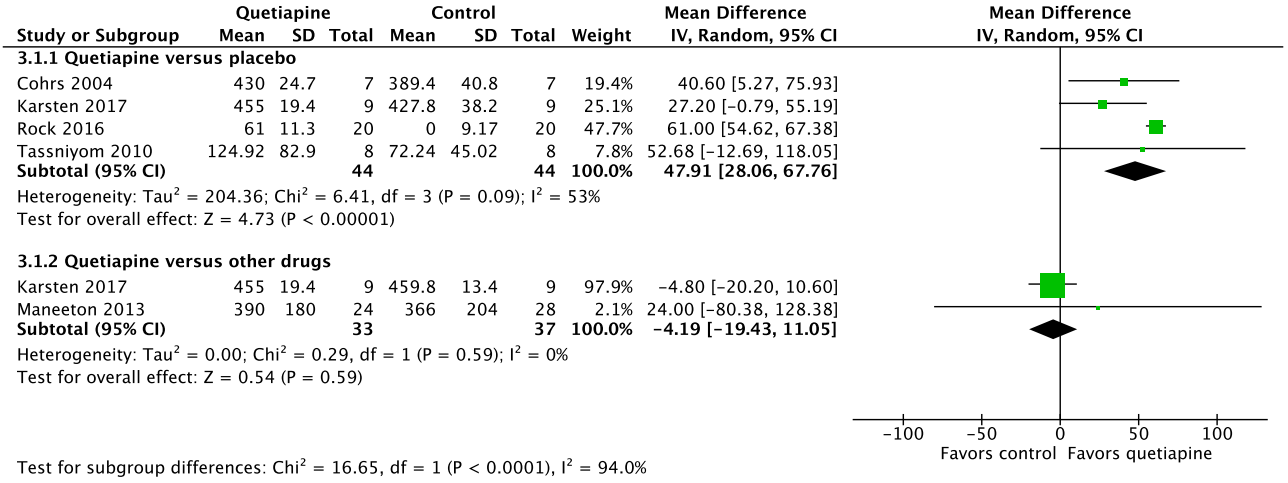

Fig. 10 Forest plot of the comparison between quetiapine and placebo group and other psychiatric drug group in total sleep time.

tal sleep time (Maneeton et al., 2013), and self sleep log (Tassniyom et al., 2010), respectively. We pooled the trials according to their control types (Fig. 10). Quetiapine group demonstrated an increase in total sleep time compared with placebo (MD: 47.91 [95%CI: 28.06, 67.76]), with a moderate heterogeneity across trials ($I^2 = 53\%$, $P = 0.09$). No difference was found between quetiapine group and other psychiatric drugs (MD: -4.19 [95%CI: -19.43, 11.05]) and no heterogeneity across trials was observed ($I^2 = 0\%$, $P = 0.59$).

3.6. Antidepressant and anxiolytic effects

Supplementary Materials 3 summarizes the results of quetiapine treatment compared with placebo in depression and anxiety levels. In brief, quetiapine group had a significant reduction of the change score of least-squares mean of the Clinical Global Impression-Severity scale (CGI-S), Hamilton Anxiety Rating Scale (HAM-A), and Montgomery-Åsberg Depression Rating Scale (MADRS) than in the placebo group. The same comparison in the MDD subgroup revealed a significant reduction of CGI-S and HAM-A in the quetiapine group compared with the placebo, but not in MADRS.

3.7. Adverse effects and discontinuation

Supplementary Materials 4 summarizes the results of meta-analyses between the quetiapine group and placebo. In

brief, the pooled results showed a quetiapine use increased the risk of most but not all AEs reported and the discontinuation rate due to AEs compared with the placebo.

4. Discussion

The current study found that quetiapine treatment improved sleep quality significantly in GAD, MDD, and healthy subjects. Dosage analysis indicated that the effective dose was 50 mg/day, 150 mg/day, and 300 mg/day, but not 25 mg/day. Further meta-regressions revealed that older age and male sex are factors of better responses, but not the dosage. Quetiapine treatment significantly increased the total sleep time compared with control but not with other psychiatric drugs. Also, quetiapine treatment increased the risk of most of the AEs reported. The previous systemic review of case reports and controlled studies revealed that quetiapine is effective as a sleep-helping drug, from 12.5 mg/day to 800 mg/day (Wine et al., 2009). The present study has amended evidence supporting a narrower effective range of quetiapine as a sleep-helping drug.

Due to the widespread prescription of quetiapine for sleep disorders and the risk of side effects, some researchers have been warning against prescribing quetiapine for sleep (Debernard et al., 2019). Because of the commonness of AEs in quetiapine treatment, official guidelines have only recommended drug use for patients with specific comorbid psychiatric disorders (Anderson and Vande Griend, 2014). Our study found a higher risk of several side effects, including weight gain and hypertriglyceridemia but not cholesterol levels that came along with quetiapine treatment. These seem to be short-term side effects that many other factors affect. A pragmatic clinical trial in drug-naïve patients with a first-episode of non-affective psychosis has shown significant increments in insulin resistance and total cholesterol and LDL-cholesterol levels after one year of quetiapine treatment (Vázquez-Bourgon et al., 2018). A recent cohort study also reported that total cholesterol and LDL cholesterol increased after a 3-month low-dose treatment (<150 mg/day) (Dubath et al., 2021). According to Katzman et al., who investigated long-term quetiapine effects in GAD patients, 86.9% of the participants developed common AEs during the open-label period, and 19.4% discontinued the treatment because of the AEs (Katzman et al., 2011), posing a worry of compliance in the clinical practice in a specific group of GAD patients. Furthermore, because trials or studies observing the long-term efficacy, safety, and AEs of quetiapine treatment in insomnia in the general population are scants, quetiapine should be used cautiously and with appropriate monitoring for adverse effects and abuse (Modesto-Lowe et al., 2021). More studies with longer follow-up duration are required to confirm whether quetiapine causes metabolic changes in the low dose range.

A direct thought for maintaining efficacy while reducing AEs is to use quetiapine at a lower dose effective for insomnia treatment. Our meta-analysis demonstrated a wide effective range from 50 mg/day to 300 mg/day, with no apparent dose-response pattern. The pooled results of 50 mg/day and 150 mg/day offer a relatively solid picture of efficacy in terms of effect size and heterogeneity and thus may be considered an ideal starting dosage range. Another interesting issue observed from the pooled results is the sensitivity analyses. Excluding the two trials recruiting elderly patients treated with quetiapine XR 50-300 mg and showing more remarkable improvement in sleep quality reduced the heterogeneity dramatically, suggesting that the elderly might respond better than younger adults. While our meta-regressions suggested that older age and male sex contribute to a better quetiapine response (a negative SMD implies a larger improvement of sleep quality in the quetiapine group compared with placebo), the actual mechanisms are probably more complex than simply age and sex. While Dziurkowska and Wesołowski (2020) found higher saliva quetiapine levels in man than in women, the analysis of a large therapeutic drugs database by Castberg et al. (2017) revealed a generally higher dose-adjusted quetiapine plasma concentrations in females than in males, which was not apparent before menopause but increased after menopause, suggesting that complex interacting biochemical pathways related to sex and aging are involved. Also, considering that the mean age of patients participating in most included trials in our study were under 50 years old, the positive correlation between male sex and sleep quality in our study might not be sufficient to explain the aging influences on drug responses. For other evidence supporting a role of older age in a better drug response, Castberg et al. (2017) found that age dose-adjusted serum quetiapine concentration increased with age. The reciprocal influences between treatment effects on anxiety and depression symptoms and sleep quality should be considered. Indeed, among the trials included in the current study, those which recruited subjects with GAD and MDD patients demonstrated narrower confidence intervals, while trials that recruited fibromyalgia, primary insomnia, and healthy subjects in the meta-analysis of sleep quality and dosage demonstrated wider confidence intervals. This picture implies that the GAD and MDD patients responded more consistently than those with other primary health problems or healthy subjects. Reverse causation, i.e., insomnia is an expression of GAD and MDD, may explain the consistency of quetiapine response in GAD and MDD patients compared to the non-GAD and non-MDD subjects. This is partially supported by a recent time-series analysis that longer rather than shorter bedtimes were associated with more depression core symptoms in MDD patients (Lorenz et al., 2020). Another concern is that the included trials used subjective measurements to assess sleep quality, posing a question of mixed judgment of sleep hours and sleep depth. Nevertheless, one of our included trials has shown that quetiapine increases explicitly the duration of stage N2 of non-rapid eye movement sleep in healthy subjects (Karsten et al., 2017). More studies should be conducted to clarify the observations.

There was heterogeneity in our meta-analyses arising from clinical variations and result formats. First, the diagnoses and health conditions of included trials varied from GAD, MDD, fibromyalgia, delirium, primary insomnia, to healthy subjects. Second, different formulations, dosages, and intervention duration were adopted in different trials. Third, participants in each trial ranged from younger adults to the elderly. As mentioned previously, sensitiv-

ity analyses indicated that the elderly might respond better to quetiapine treatment. Fourth, the insomnia baseline of some included trials was unknown. Finally, different measuring tools and result formats for sleep quality were used. The main limitation of the current study is that many of included trials were funded by a patent-holding company for quetiapine (Bandelow et al., 2010; Bauer et al., 2009; Bortnick et al., 2011; Calandre et al., 2014; Cohrs et al., 2004; Cutler et al., 2009; El-Khalili et al., 2010; Katila et al., 2013; Katzman et al., 2011; Khan et al., 2011; Liebowitz et al., 2010; Merideth et al., 2012; Mezhebovsky et al., 2013; Potvin et al., 2012; Wang et al., 2014; Weisler et al., 2009), posing a potential bias in reporting of the results. Further independent trials are required.

5. Conclusion

A nice sleep is essential for a better health and performance. Our study indicates that quetiapine below the therapeutic dose for schizophrenia and acute manic episodes is effective in insomnia management as well as a antidepressant and an anxiolytic drug. However, its long-term efficacy and safety remain to be investigated, especially in non-psychiatric subjects. Because of the popularity of quetiapine use in insomnia management, we recommend a start from a dose range of 50-150 mg/day with priority consideration for elderly with GAD or MDD, while monitoring its potential AEs. More rigorous trials that investigate the long-term effects of quetiapine treatment in insomnia are warranted.

Contributors

CYL designed the study and wrote the protocol. CYL and CHC managed the literature searches and analyses and wrote the first draft of the manuscript. MCMT and KWT provided methodological and statistical advises on the study. EWL supervised the study and edited the manuscript. All authors contributed to and have approved the final manuscript.

Role of the funding source

None.

Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2022.11.008.

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