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Title: Sleep in schizophrenia: a systematic review and meta-analysis of polysomnographic findings in case-control studies

Short title: Sleep in schizophrenia

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Abbreviations

Abbreviation	In full
AASM	American academy of sleep medicine manual for the scoring of sleep and associated events
CI	Confidence interval
CINAHL	Cumulative index to nursing and allied health literature
D&T	Duval and Tweedie's trim and fill test
EEG	Electroencephalogram
EMBASE	Excerpta medica database
EMG	Electromyogram
EOG	Electrooculogram
NREM	Non-rapid eye movement sleep
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PSG	Polysomnography
REM	Rapid eye movement sleep
REMD	Rapid eye movement sleep density
REML	Rapid eye movement sleep latency
S1-4	Stage 1, 2, 3 and 4 sleep
SD	Standard deviation
SE	Sleep efficiency
SOL	Sleep onset latency
SWS	Slow wave sleep
TAT	Total awake time
TST	Total sleep time

Summary

Polysomnographic studies have been performed to examine the sleep abnormalities in schizophrenia, but the results are inconsistent. An updated systematic review, meta-analysis, and moderator analysis was conducted. Major databases were searched without language restriction from 1968 to January 2014. Data was analyzed using the random-effects model and summarized using the Hedges's g. Thirty-one studies with 574 patients and 515 healthy controls were evaluated. Limited by the number of studies and a lack of patient-level data, moderator analysis was restricted to medication status, duration of medication withdrawal, and illness duration. We showed that patients with schizophrenia have significantly shorter total sleep time, longer sleep onset latency, more wake time after sleep onset, lower sleep efficiency, and decreased stage 4 sleep, slow wave sleep, and in the duration and latency of rapid eye movement sleep compared to healthy controls. The findings on delta waves and sleep spindles were inconsistent. Moderator analysis could not find any abnormalities in sleep architecture in medication-naïve patients. Patients with antipsychotic withdrawal for longer than eight weeks were shown to have less sleep architectural abnormalities, compared to shorter duration of withdrawal, but the abnormalities in sleep continuity were similar. Slow wave sleep deficit was found in patients with schizophrenia for more than three years, while sleep onset latency was increased in medication-naïve, medication-withdrawn, and medicated patients. Our study showed that polysomnographic abnormalities are present in schizophrenia. Illness duration, medication status, and duration of medication withdrawal are several of the clinical factors that contribute to the heterogeneity between studies.

Introduction

Schizophrenia is a complex and devastating neurodevelopmental disorder caused by a combination of genetic and environmental factors [1]. For the diagnosis of schizophrenia, the diagnostic and statistical manual of mental disorders, fifth edition, requires the presence of two or more active-phase symptoms, including delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms that are associated with impairment in personal, social, or occupational functioning for at least one month as well as continuous signs of disturbance, including periods of prodromal or residual symptoms for at least six months [2]. Depending on the severity of illness, sleep disturbance occurs in 30-80% of patients with schizophrenia, and is associated with positive and negative symptoms, cognitive deficits, poorer outcome, and impaired quality of life [3-6]. The assessment of sleep disturbance includes face-to-face interview, self-report questionnaire, sleep diary, actigraphy, and polysomnography (PSG). PSG is an objective method to derive quantitative sleep measures and records electroencephalogram (EEG), electrooculogram (EOG) and electromyogram (EMG). The Rechtschaffen and Kales (R&K) [7] system for scoring distinguishes two sleep stages: non rapid eye movement (NREM) sleep, which is further divided into stages 1-4 (S1-4), and rapid eye movement (REM) sleep. In the past 50 years, many studies using PSG have been done to help understand the neurobiology of schizophrenia. Disturbances in sleep continuity have been shown in patients with schizophrenia [8]. The early hypothesis that psychotic symptoms are due to an intrusion of REM sleep into alertness led to a number of investigations on REM sleep disturbance in schizophrenia; however, according to recent reviews, the findings were mixed [9-11]. A few studies found that REM latency (REML) was shortened in patients with schizophrenia [12, 13]; while some researchers argued that this finding might be due to heterogeneity in the

study sample and the effect of medications [6, 14-16]. Deficit in slow wave sleep (SWS), or S3 and S4 sleep, was first observed in patients recently withdrawn from antipsychotic medications [6, 17, 18]. Further studies in drug-naïve patients found that the reduction in SWS was not always present [14, 19, 20]. As delta waves and cortical slow oscillations are mediated by thalamocortical circuits [21], some researchers suggested that SWS deficits are indicative of thalamocortical dysfunction and thus cognitive deficits in schizophrenia [22]. The interest in thalamocortical dysfunction and cognitive deficits has led to recent studies on the relevance of sleep spindles in schizophrenia. Several studies found a reduction in sleep spindles activity in patients with schizophrenia, compared to patients with depression and healthy controls [23]; furthermore, the reduction in sleep spindles activity was associated with a failure of sleep-dependent motor learning [24, 25]. These previous studies indicate that many aspects of sleep disturbance have been examined in patients with schizophrenia. There is an urgent need to systematically review and summarize the findings. Variations in study results could be due to heterogeneity in demographic and illness characteristics, medication status, and PSG methodology.

In the last two decades, two meta-analyses on PSG abnormalities in schizophrenia have been published. The first meta-analysis was published in 1992 and included 12 studies and 239 participants [26]. The only significant finding was a decrease in REML in patients with schizophrenia, compared to healthy controls. The second meta-analysis was published in 2004 and included 652 participants [8]. Eighteen studies were identified by literature search up to 2001. A published study in 2003 by the authors was also included. The major findings were increased sleep onset latency (SOL), decreased total sleep time (TST), and decreased sleep efficiency (SE) in patients with schizophrenia, compared to healthy controls. For neuroleptic-naïve patients, an increase in total awake time (TAT) and a reduction in S2% were found. Given that the last meta-analysis was performed more than 10 years ago, our

study aimed to cover new findings, identify moderators that could explain the heterogeneity between studies, and provide insight for better understanding of the neurobiology of schizophrenia. To provide an objective evaluation of the sleep disturbance in schizophrenia, this review covered case-control studies that used PSG. We hypothesized that there are differences in sleep continuity and PSG characteristics in patients with schizophrenia, compared to healthy controls and that clinical and methodological variations are the moderators of heterogeneity between studies.

Methods

This meta-analysis was conducted with reference to the Preferred reporting items for systematic reviews and meta-analyses (PRISMA) [27]. The protocol was registered at the International prospective register of systematic reviews (CRD42014008782). The MEDLINE, PsycINFO, Excerpta medica database (EMBASE), Cumulative index to nursing and allied health literature (CINAHL), and Dissertations and thesis A&I from January 1968 through 25 January 2014 were searched without language restriction using the search terms: (schizophreni* OR psychosis OR "psychotic disorder") AND (sleep OR polysomnogra* OR PSG OR electroencephalogra* OR EEG) in titles or abstracts or as keywords. The year 1968 was taken as a starting point, as in this year the R&K criteria was published and from this year onwards, studies were more likely to use this standardized scoring system. Reference lists of the included studies and several reviews were examined for additional articles. As a forward search, we used the MEDLINE to identify articles that cited the included studies. Figure 1 presents the flowchart of the systematic review.

By title and abstract screening, we excluded: 1) animal studies; 2) case reports, case series, guidelines, statements, and comments; 3) reviews unrelated to sleep or psychiatry; 4)

studies unrelated to schizophrenia; and 5) studies in which it was clearly stated in the abstract that no PSG was done and no healthy control group was investigated. By full text screening, we excluded studies: 1) with diagnosis of schizophrenia not based on standardized diagnostic criteria; 2) using a mixed diagnostic group; 3) with participants having past or current comorbid psychiatric or neurological illnesses; 4) not using healthy subjects as control; 5) not using the R&K or the American academy of sleep medicine (AASM) criteria for PSG scoring; 6) not having an all-night un-manipulated PSG record; 7) with no information on the outcomes of interest; and 8) that we could not contact the corresponding author by multiple emails or mails over three months for essential data.

Study selection

Two investigators (MC and KY) selected relevant publications independently according to the eligibility criteria. Any disagreement was resolved by thorough discussion and consultation with the senior author (KC). When a study had more than one patient group of interest (e.g. one group of patients taking typical antipsychotics and another group taking atypical antipsychotics), we considered it twice as two different comparisons and divided the control group based on the ratio of the number of subjects in the two patient groups. When the same group of authors published more than one article using data from the same group of subjects, we considered it as one set of comparison and used the most comprehensive dataset that was available. The name of the corresponding author, method of recruitment, methodology, demographics, clinical parameters, and PSG data were used to detect sample duplication. When multiple arms were included in one study, data from schizophrenia and control arms were used. When patients received multiple nights of PSG but the controls only had one night, only the night when the controls were investigated was selected for case-control comparison. Commercial translation companies were commissioned to translate

languages other than English and Chinese into English. Two translators with relevant experience translated the articles independently.

Data collection process

Two investigators (MC and PC) extracted the data independently using a pre-designed form. Disagreements were resolved by thorough discussion and consultation with the senior author (KC). Data was obtained from the original articles and by contacting the corresponding authors when necessary. With no clear answers from the corresponding authors after three months, the particular item or procedure was considered missing or not performed.

Sleep continuity variables extracted for meta-analysis included TST, SOL, % or duration of TAT, and SE. Sleep architecture variables included % of S1, S2, S3, and S4. REM sleep variables included % of REM, REM density (REMD), and duration of REML and the first REM period. Additional PSG variables included measures on sleep spindles, k complexes, and delta waves.

Demographic variables extracted included the number of subjects and their age and gender. When detailed information was given only for one of the two groups, but it was reported that the other group was age- and sex-matched, the same mean and standard deviation (SD) were used for participants of both groups.

Illness variables included age of onset, source of recruitment, diagnostic subtype, duration of illness, scores of standardized symptom scales, diagnostic procedure, and the type, duration, and dosage of psychotropic medications.

Procedural variables included the number of adaptation nights, bed time and wake up time, EEG, EMG and EOG parameters, definition of EEG waveforms and PSG variables, the number and any blinding of personnel involved in PSG scoring, and any screening for specific sleep disorders.

Risk of bias in individual studies

There has been no standardized tool to assess the risk of bias in case-control studies. The U.S. agency for healthcare research and quality recommended five systems out of 12 that can be used to assess observational studies [28]. The Scottish intercolleagiate guidelines network system was one of the recommended systems [29] and was used in our study because it is relatively simple and easy-to-rate. The internal validity section of the Scottish system has 11 items that are used to assess subject selection, exposure status, confounding factors, and statistical analysis. Each item can be rated as well covered, adequately addressed, poorly addressed, not addressed, not reported, or not applicable. The overall assessment section contains three questions which can be rated as ++, +, or –. For the potential sources of bias and confounders in PSG studies of schizophrenia, our assessment scale was based on an article by Thaker et al. [30] (Supplementary Table 1). Two independent raters (MC and PC) assessed the risk of bias of each study. Any disagreement was resolved by discussion and consultation with the senior author (KC).

Statistical analysis

All statistical analyses were performed using the Comprehensive meta-analysis software version 3.0. The summary measure was the effect size, calculated as Hedges's g and its 95% confidence interval (CI), between patients with schizophrenia and healthy controls. Due to differences in demographic characteristics and inclusion and exclusion criteria between studies, it was expected that there was heterogeneity *a priori*; hence the sleep-wake parameters varied more than chance. Therefore, the random-effects model [31] and inverse-variance method were employed to calculate summary estimates.

Variations in the definitions of PSG parameters were expected. A previous meta-analysis [8] tried to take into account the differences in definition of SOL and REML by subgroup analysis, but the heterogeneity was not reduced. In this project, this variation was

statistically accounted for by using standardized mean difference instead of raw mean difference.

Heterogeneity between studies was evaluated using the Cochran's Q statistic, with p-value less than 0.10 indicating significant heterogeneity [32]. The I^2 statistic was computed as a compliment to the Q statistic. As suggested by Higgins et al. [33], I^2 values of 0%, 25%, 50%, and 75% indicate no, low, moderate, and high heterogeneity.

Publication bias was examined by visual inspection of a funnel plot. Publication bias was suspected when the funnel plot was asymmetrical. The Duval and Tweedie's trim and fill test (D&T) method was used to adjust the effect size for publication bias [34]. Sensitivity analysis was performed using the leave-one-out method in order to investigate the influence of each study on the synthesized effect size in the random effects model [33].

Moderator analysis was carried out to analyze the factors that were associated with heterogeneity. The following pre-defined moderators were planned for investigation: 1) age and gender; 2) subtype of schizophrenia, duration of illness, and severity of positive, negative and cognitive symptoms; 3) medication status, including medication-naïve, medication-withdrawn, or medicated; 4) duration of antipsychotic withdrawal; and 5) the use of first or second generation antipsychotics and the dosage of antipsychotics. As recommended by Borenstein et al. [36], one moderator analysis was conducted for each 10 studies included and a minimum of three studies were required for subgroup analysis. To make sure that all participants were under the effect of the moderator, the range of the distribution was examined, instead of the mean. The presence of between-group difference was measured by testing the heterogeneity between groups.

Results

Study selection

A total of 35 studies [6, 13-20, 24, 25, 37-60] were included in our systematic review (Table 1), but only 31 of the 35 studies were included in meta-analysis. The other four studies [42, 52, 54, 60] examined specific PSG parameters. Twenty of the 35 studies were published after the last meta-analysis [8]. Three studies [20, 39, 59] contributed more than one dataset and some authors published their data more than once (Supplementary Table 2). One article was written in Chinese [18], one in Turkish [39], and one in Japanese [46], while the other articles were in English.

Description of the included studies

There were 574 patients with schizophrenia and 515 healthy controls. Patients' mean age was 29.3 years, compared to 27.8 years in the control group. Patients' gender was reported in 28 studies. Males constituted 80.0% of the patient group and 78.6% in the control group. Duration of illness was reported in 18 studies and the mean duration was 7.0 years. The mean age of onset was 21.9 years (number of studies = 11), mean Brief psychiatric rating scale score was 44.9 (n = 16), implying moderate illness severity [61], and mean Positive and negative syndrome scale score was 75.7 (n = 6), which is equivalent to moderate illness severity [62]. The diagnostic system used, subtype of schizophrenia, medication status, PSG nights used for analysis, and PSG procedure were presented in Table 1.

Risk of bias of individual studies

None of the included studies scored a minus in the overall assessment section of the Scottish system, suggesting that there was low risk of bias in the included case-controlled studies (Supplementary Table 1). Except for the fact that little attention was paid to non-participants, other areas were rated as "well covered" or "adequately addressed". There were various sources of bias or confounders related to PSG studies of schizophrenia, but in

general, the methodological quality was satisfactory. Ten of the 35 studies did not report whether the PSG technologists were blinded to subject group, while eight studies did not describe any use of adaptation nights (Supplementary Table 1). There were five studies with the highest methodological quality [6, 16, 38, 45, 56].

Comparison between schizophrenia and healthy controls

Table 2 presents a summary of the meta-analytic results. There were significant differences between schizophrenia and healthy controls in most of the PSG variables, except S2% and duration of the first REM period. Funnel plots detected publication bias in SE, but the direction of effect size did not change when publication bias was taken into account by the D&T test (Hedge's g after six studies to the left of the mean were trimmed = -0.67, CI = -0.99 to -0.34). There were significant heterogeneities in almost all variables, except S3%, REMD, and duration of the first REM period, as indicated by the Cochran's Q statistic and I^2 values. The leave-one-out sensitivity analysis found that the significant findings in REMD disappeared when outlying studies were removed.

Moderator analysis

As only 31 studies were available for meta-analysis, according to our *a priori* plan, only three moderator analyses were performed. The three most relevant moderators with patient-level data, including medication status, duration of medication withdrawal, and duration of illness, were chosen (Tables 3-5).

Medication status

Medication-naïve. Four to seven datasets were analyzed depending on the PSG parameters. Medication-naïve patients had significantly shorter TST, longer SOL, decreased SE, and longer TAT, compared to healthy controls, but there was no significant difference in sleep architecture. Within-group heterogeneity was absent or low, except for REM%, which had moderate heterogeneity (I^2 = 49.2).

Medication-withdrawn. Eight to 17 datasets were analyzed. Patients with schizophrenia recently withdrawn from antipsychotics had significantly shorter TST, longer SOL, decreased SE, longer TAT, higher S1%, lower S2%, S3%, S4%, SWS%, and shorter REML, compared to healthy controls. Within-group heterogeneity was significant for all PSG variables.

Medicated. Three to six datasets were analyzed. Patients on antipsychotics had significantly longer SOL, greater S2%, and lower REM%, compared to healthy controls. Within-group heterogeneity was found for SOL, S1%, S2%, and SWS%, based on the Q statistic and I^2 value.

Comparison between patients that are medication-naïve, medication-withdrawn, and medicated. There were significant between-group differences in TST, SE, TAT, S2%, and REML. Medication-naïve and medication-withdrawn patients had shorter TST, longer TAT, lower SE and S2%, and shorter REML, compared to medicated patients.

Duration of antipsychotic withdrawal

Subgroup analysis was carried out according to antipsychotic withdrawal for two weeks or less, three to seven weeks, and eight weeks or longer (**錯誤! 找不到參照來源。**4). The cut-offs were chosen because previous studies have shown that withdrawal of phenothiazines can induce a dopaminergic supersensitivity that lasts for more than three weeks [62, 63], while butyrophenones continue to act on the central dopaminergic neurons for at least seven weeks after withdrawal [65, 66], and thioridazine could still be detected in the plasma up to seven weeks after withdrawal [66]. We found significant differences between patients with antipsychotic withdrawal for two weeks or less and healthy controls in TST, SOL, SE, TAT, and REML. In patients with antipsychotic withdrawal for three to seven weeks, there were significant differences in TST, SOL, SE, TAT, S1%, S2%, and REML, as compared to healthy controls. For those who had antipsychotic withdrawal for eight weeks or

longer, the differences in TST, SOL, SE, and TAT, compared to healthy controls, were still present. There were within-group heterogeneities in most of the analyzed variables in all three groups, but no significant between-group differences were detected.

Duration of illness. Only 12 studies provided the range of the duration of illness and were included in moderator analysis. The cut-off for short and long duration of illness was three years, because the first three years of illness are commonly targeted for early intervention of psychosis. Common to patients with short and long duration of illness, there were significant differences in SOL, SE, and S1%, compared to healthy controls; however, REML was significantly shorter only in patients with short duration of illness, whereas SWS% and REM% were significantly reduced in those with longer duration. There were no significant differences in all PSG parameters between patients with short and long duration of illness. Within-group heterogeneities were observed in most of the analyzed sleep-wake variables in both groups (Table 5).

Descriptive summary of the PSG variables that are not feasible for meta-analysis

Ten studies examined delta waves by various quantitative methods, and the results were conflicting (**錯誤! 找不到參照來源。**6). Two studies [47, 49] suggested a reduction in the number of delta waves, but four [14, 48, 56, 57] did not. Two studies [47, 56] suggested a reduction in delta wave amplitude, but one [57] did not. Two studies [24, 42] showed a reduction in delta power, but two [52, 54] did not.

Six studies, consisting of five datasets, examined sleep spindles by various quantitative methods (**錯誤! 找不到參照來源。**7). Sleep spindles parameters were reduced in medicated patients compared to healthy controls in two studies [24, 60] that employed power analysis and one study that used 256-channel EEG [57], but in two studies that examined medication-naïve patients using visual scoring, no significant reduction was found [19, 53]. None of the studies provided data on k complexes.

Discussion

Key results

Compared to healthy controls, patients with schizophrenia were shown to have significantly lower TST and SE, longer SOL and TAT, increased S1, reduced S3, S4, SWS and REM sleep, shorter REML, and increased REMD. Our findings are different from two previous meta-analyses [8, 26]. Only a decrease in REML was found in the first meta-analysis [26], perhaps due to antipsychotic withdrawal effects. The second meta-analysis conducted 10 years ago [8] found increased SOL and decreased TST and SE; besides these findings, our systematic review, which had 11 additional studies and increased statistical power, showed that apart from sleep continuity, sleep architecture was also disturbed in patients with schizophrenia. There was no obvious publication bias identified in our review, but significant heterogeneity between studies was present, which may be another reason to account for the different findings between systematic reviews. On moderator analyses, medication-naïve patients were shown to have disrupted sleep, but no abnormality in sleep architecture, when compared to healthy controls. Both sleep continuity and sleep architecture were disturbed in medication-withdrawn patients, but for medicated patients, the differences when compared to healthy controls were longer SOL, more S2, and less REM sleep. Our study showed that disturbances in sleep continuity remained apparent eight weeks or longer after antipsychotics withdrawal, but the withdrawal effects on sleep stages and REML disappeared after eight weeks. Regarding the relationship of sleep and the duration of illness, we found that as schizophrenia illness progresses REML tends to normalize, but deficits in SWS become evident. Our analysis on the quantitative measures of delta sleep and sleep

spindles showed that there were great variations in methodology between studies and the results were conflicting.

PSG abnormalities in schizophrenia

Our systematic review showed that sleep continuity and sleep architecture are disturbed in patients with schizophrenia. It is important to ask whether the PSG abnormalities in schizophrenia are unique in comparison to major depressive disorder and primary insomnia, which are often associated with sleep disturbances. Although all three conditions have disrupted sleep, it seems that they differ in terms of REM sleep and SWS. Compared to healthy controls, people with major depressive disorder have increased REM sleep and REMD, but reduced REML [67]. In primary insomnia, REM sleep is decreased, but there is no change in REML [68]. For schizophrenia, our findings suggested that there is a decrease in REM sleep and REML and an increase in REMD, albeit possible influence by antipsychotics and antipsychotic withdrawal. The abnormalities in REM sleep appear to be different in schizophrenia, major depressive disorder, and primary insomnia, suggesting that the underlying mechanisms may be different. The increase in REM sleep in depressive disorder is often normalized following remission, implying that it is a state phenomenon [67]. There has been no longitudinal data in schizophrenia to show whether the decrease in REM sleep is a state or trait phenomenon or solely a medication effect.

Regarding SWS, patients with schizophrenia have reduced S3, S4 and SWS, while people with major depressive disorder and primary insomnia are also associated with a decrease in SWS [67, 68]. In depression, the reduction of SWS persists during remission and is present in high-risk probands, suggesting that it is more likely to be a trait phenomenon [67]. In high-risk probands of patients with schizophrenia, SWS deficit was reported in one study [69] but was not observed in two other studies [37, 70]. Additional studies in high-risk probands of schizophrenia and on the state-trait changes in REM sleep and SWS are needed.

Medication-naïve patients

Similar to Chouinard et al.'s review [8], the sleep of medication-naïve patients are disrupted compared to healthy controls. A moderator analysis on the impact of psychotic symptoms on sleep was not possible; hence it is unsure whether the sleep disruption was due to acute symptoms of schizophrenia or the underlying neurobiological abnormalities. We found no significant difference in sleep architecture between medication-naïve patients and healthy controls, which is consistent with Chouinard et al.'s review, except a reduced S2% reported in their review that was based on a smaller number of studies. Our meta-analytic findings are in line with early observations that SWS deficit in schizophrenia is a result of antipsychotic withdrawal and should not be present in medication-naïve cases [45, 53]. SWS deficit has been found to correlate with negative symptoms [49], cognitive impairment [6, 19], and reduced ventricular size [71], but these features may not be predominant in medication-naïve cases. We believe more studies on medication-naïve patients with ratings of their negative and cognitive symptoms and ventricular size will be useful.

Medication-withdrawn patients

In addition to the findings in the previous review [8] which showed that patients recently withdrawn from antipsychotics have increased SOL and decreased TST and SE compared to healthy controls, our meta-analysis found that they also have increased TAT and S1, decreased S2, S4, and SWS, and shorter REML. Similar to the previous review, heterogeneity between studies was statistically significant for all PSG parameters, suggesting that the number, type, and dosage of antipsychotics and the duration of withdrawal may determine the changes in sleep upon antipsychotic withdrawal. There have only been studies examining the withdrawal effects of haloperidol, one of the many antipsychotics, which showed that TST, SWS, REM sleep, and REMD were reduced, but the changes returned to baseline in two to six weeks [72, 73]. As the mechanisms of action are different between

antipsychotics, the findings in haloperidol cannot be applied to other antipsychotics. Our moderator analysis by the number of weeks of antipsychotics withdrawal showed that abnormalities in sleep architecture normalized with duration of withdrawal for eight weeks or longer. Based on our findings, we suggest the duration of antipsychotic withdrawal should be at least eight weeks for studies of sleep architecture in drug-free patients with schizophrenia, but for studies of sleep continuity, a longer duration of withdrawal is needed.

Medicated patients

On behavioral changes, our findings of improved sleep continuity in medicated patients are in line with previous studies on both first generation and second generation antipsychotics [74]. Different from actigraphy studies [e.g. 75], which observed an increase in TST in patients with schizophrenia, we could not detect any changes in TST in polysomnographic studies, perhaps due to the fixed bedtime schedule in sleep laboratory. We also found that SOL was lengthened in medicated patients compared to healthy controls. Previous studies have shown that both risperidone and paliperidone can shorten SOL, but the effects of clozapine, olanzapine, chlorpromazine, and haloperidol are inconsistent, while promethazine and trifluoperazine are not associated with reduced SOL [74]. We anticipate that enforcement of early bed time and wake time in sleep laboratory may lead to an over-estimation of SOL. However, a recent study comparing the sleep-wake habits of medicated patients with schizophrenia and healthy controls over one month [76] found that SOL was significantly longer in schizophrenia, suggesting that the sleep laboratory setting cannot fully account for the prolonged SOL in schizophrenia. The authors suggested that the results may be accounted by circadian rhythm disturbances in schizophrenia. Recent studies have also suggested that circadian rhythm disturbances are common in schizophrenia [77] and are associated with cognitive impairment in patients with schizophrenia [78]. Our finding of prolonged SOL in medicated patients may reflect circadian rhythm disturbances that are not

improved with antipsychotics. A recent study has shown that cognitive-behavioral factors, common in people with insomnia, can be another contributing factor for the lengthening of SOL in schizophrenia [79].

On sleep architectural changes, we found that a decrease in REM sleep was detected in medicated patients, compared to healthy controls, but not in medication-naïve or medication-withdrawn patients. The findings suggest that the decrease in REM sleep may be a medication effect; hence, in future studies of REM sleep in schizophrenia, it is important to control for the confounding effects of antipsychotic medications.

Duration of illness

There have been limited data addressing the relationship between sleep and the duration of illness in schizophrenia. Our moderator analysis found that SWS deficit becomes evident as illness progresses; however, the finding should be interpreted with caution, as there were significant heterogeneities on SWS% in relation to medication status and the duration of antipsychotic withdrawal. It has been shown that a deteriorating course of illness with the presence of negative and cognitive symptoms occurs in more than half of the patients with schizophrenia [80]. SWS deficit has been shown to have a close relationship with the neurobiological mechanisms underlying executive function deficits and negative symptoms in schizophrenia [81, 82]. A magnetic resonance imaging study found a significant negative correlation between the duration of illness and thalamic volume [83]. As the thalamus is involved in the thalamocortical circuits which are essential for the generation of delta sleep [21], it is possible that the thalamocortical circuits are impaired as illness progresses. This circuit impairment may be reflected by SWS deficit, in addition to executive function impairment and negative symptoms.

Another finding in our study is that patients with illness shorter than three years have shortened REML, compared to healthy controls, but REML normalizes as illness progresses.

A shortening in REML is found in depressive disorder [67] but not in primary insomnia [68], suggesting that shortened REML may be associated with depressive symptoms, but not caused by sleep disruption. Depressive symptoms are common in the early stage of schizophrenia [84], while patients with long duration of illness are more likely to have negative symptoms, including affective flattening, which may explain the normalization of REML during the progression of illness.

A decrease in REM sleep was also detected in patients with duration of illness longer than three years, compared to healthy controls, but there were not enough studies to examine whether REM sleep was also affected in patients with shorter duration of illness. Further studies on the relationship between REM sleep and the duration of illness are needed.

Quantification of delta sleep and sleep spindles

The conflicting result of delta waves quantitative analysis is in line with the significant heterogeneity of the SWS findings in this study. Another finding is that sleep spindles deficit was only noted by computerized method in medicated patients, but not by visual scoring in medication-naïve patients. A previous study showed that the duration, amplitude, and number of sleep spindles were reduced in patients with schizophrenia who were taking antipsychotics, but the reduction was not present in patients with other psychiatric conditions who were also taking antipsychotics [57], suggesting that sleep spindles deficit may be a feature of schizophrenia but not a medication effect. There is another study published in October 2014 using a computerized method, which showed that sleep spindles deficit was present in antipsychotic-naïve early-course schizophrenia [85]. The conflicting findings highlight that further studies are needed on sleep spindles deficit and its relationship with various aspects of schizophrenia. A recent paper on an impairment of trans-thalamic cortico-cortical interactions as an explanation of the source monitoring deficits in schizophrenia has been written to support the sleep spindles deficit findings [86]. Another

study which showed a reduction in thalamic nuclei volume in patients with schizophrenia [87] is also in line with sleep spindles and SWS deficits in schizophrenia.

Strengths of the study

We have conducted a comprehensive literature search without language restriction and repeated backward and forward manual search to assure all relevant studies have been included. Despite expert recommendations of the importance of comprehensive search and an exclusion of study duplications [88], a previous study found that these steps were either not reported or not performed in many systematic reviews and meta-analyses [89].

Study limitations

*Unexplained heterogeneity***.** Some moderators, including symptom severity, subtype of schizophrenia, and the type and dosage of antipsychotics may explain the heterogeneity between studies, but they were not analyzed in this study due to a lack of patient-level data. Future studies should recruit homogenous samples with reference to the potential moderators.

*Risk of bias in the included studies***.** Apart from clinical variables, there are methodological issues that may explain the heterogeneity between studies. These include sampling bias, variations in bedtime schedule, and differences in the definition of PSG parameters, scoring method, the number of adaptation nights, and the number of PSG. Although the methodological quality varied between studies, most of the included studies were rated to have satisfactory quality; hence we used an all-inclusive approach in meta-analysis. However, future studies with better methodological quality are needed to accurately determine the relevance of sleep in schizophrenia.

Moderator analyses. It must be noted that the groupings of the duration of antipsychotic withdrawal and duration of illness are arbitrary; hence the results of our moderator analyses are only good for hypothesis generation. Further studies with specific study design are needed to examine the effects of antipsychotic withdrawal and illness

duration on sleep in schizophrenia. Another limitation is that the included studies did not specify the type of concomitant psychotropic medications that were used prior to withdrawal and in studies of medicated patients, a small proportion of them received other psychotropic medications. In view of the complex medication effect, for instance, some antidepressants (e.g. fluoxetine) have REM-suppressing effects, while others (e.g. bupropion) have no effect or REM-enhancing effects [90], the contribution of concomitant medications to the study findings is uncertain, especially in patients with short medication withdrawal period. Women have been shown to have a higher delta power than men, but there have been mixed findings regarding SWS% [91, 92]. Whether gender can be a moderator is uncertain since the reviewed studies have either male only samples or mixed-sex samples of which separate data regarding gender is not available. The gender difference in SWS% is around 1-3%; hence the difference in SWS% between schizophrenia and controls is unlikely to be affected by floor effect. Lastly, the number of studies may be too small to detect between-group differences in moderator analyses.

Generalizability. Studies usually recruited patients without comorbid conditions, but in real-world settings, patients with schizophrenia may have abuse of substances and alcohol, leading to sleep disruption and changes in REM and NREM sleep [93]. For instance, alcohol increases NREM sleep and decreases REM sleep in the first few hours following use, but REM rebound will occur upon alcohol withdrawal at the end of the night. Patients with schizophrenia may have obstructive sleep apnea, periodic leg movement disorder, restless leg syndrome, antipsychotic-induced akathisia, comorbid psychiatric condition, or are taking multiple psychotropic medications, which will affect sleep architecture. Patients with narcolepsy type 1, a condition with REM sleep dysregulation, may present with psychotic-like symptoms and are sometimes misdiagnosed as schizophrenia [94, 95]. In essence, the

polysomnographic findings summarized in this article may not reflect clinical variations in day-to-day practice.

Clinical and research implications

PSG studies are not routinely performed in patients with schizophrenia, but our findings provide useful information to help clinicians understand the patients' behavioral sleep problems and the effects of antipsychotics and chronicity on their sleep. On research implications, PSG measures, amongst other neurophysiological parameters, are hopeful candidates for a better understanding of the neurobiology of schizophrenia.

Our study showed that there are unique abnormalities in sleep continuity and sleep architecture in schizophrenia. Increased SOL and the underlying circadian rhythm disturbances may be important in relation to outcomes and clinical management. SWS deficits, negative symptoms, and cognitive impairment are features indicative of illness progression and are potential targets for therapeutic intervention. A shortened REML in patients with illness for less than three years suggests that further examination of the affective symptoms in the early stage of schizophrenia may be important. It is too soon to conclude the significance of delta waves, sleep spindles, and k complexes deficits in schizophrenia. Lastly, our study has highlighted various important areas and methodological issues that need to be addressed in future studies.

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Practice points

1. Sleep continuity and sleep architecture are disturbed in patients with schizophrenia compared to healthy controls.
2. Medication-naïve patients have disrupted sleep continuity but not sleep architecture; both sleep continuity and sleep architecture are affected in medication-withdrawn patients, and medicated patients have prolonged sleep onset latency, more stage 2 sleep, and reduced rapid eye movement sleep.
3. Sleep onset latency is prolonged in schizophrenia and is not improved with antipsychotic medications, suggesting an underlying circadian rhythm disturbance and dysfunctional cognitive-behavioral factors that warrant separate interventions.
4. Slow wave sleep deficit becomes evident as illness progresses, and is associated with negative and cognitive symptoms.
5. Rapid eye movement sleep latency is shortened in schizophrenia with less than three years of illness. Despite the possible confounding effects of antipsychotic withdrawal, this abnormality may be related to depressive symptoms in the early course of schizophrenia.
6. Findings on delta waves and sleep spindles are inconsistent.

Research agenda

1. Further studies in high-risk probands of schizophrenia and on the state-trait changes in rapid eye movement sleep and slow wave sleep are necessary.
2. There is a need to examine the sleep of medication-naïve patients and its relationship with psychopathology and structural and functional abnormalities of the brain.
3. Study design should take into consideration various potential moderators and methodological issues.
4. Further quantitative studies on delta waves, sleep spindles, and k-complexes and their relationship with various aspects of schizophrenia are needed.

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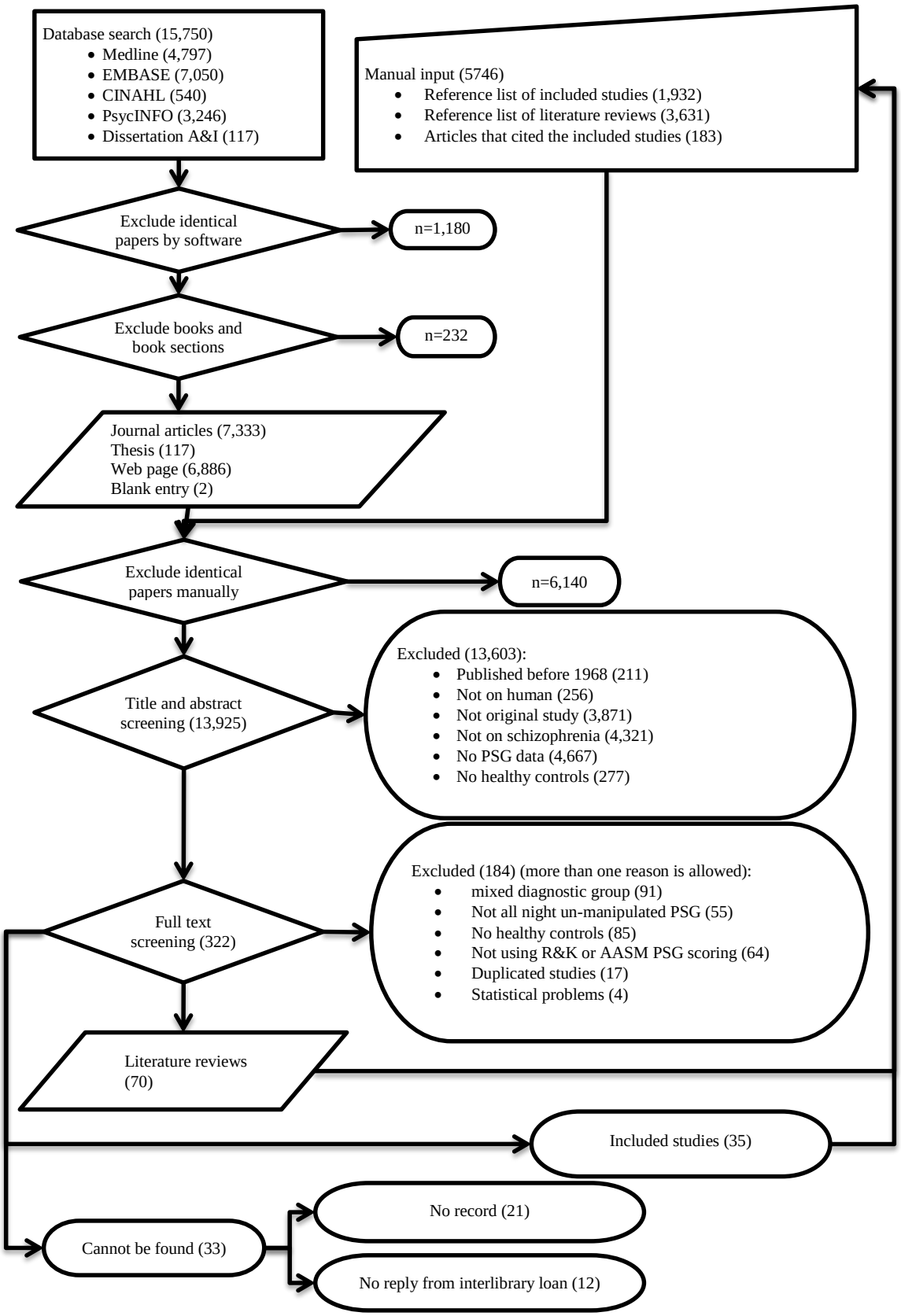

Figure 1. Flow diagram of study selection
Abbreviations: AASM, American academy of sleep medicine manual for the scoring of sleep and associated events; PSG, polysomnography; R&K, Rechtschaffen and Kales (1968) system for scoring sleep stages

Table 1. Study characteristics

1st author, yr	Ref	No. (S/C)	Age in yr (mean±SD)	% of male (S/C)	Diagnostic system	Subtype (% of total)	Duration of illness in yr (mean±SD) or category (% of total)	Symptom score (scale: mean±SD)	Medication status (% of total)	PSG nights used for analysis	Bedtime schedule	PSG scoring (scoring system/no. of rater/blinding of rater)
Chen XS, 2006	18	25/44	S:29±8 C:28±8	52/52	CCMD-3	NR	1.0±0.7	NR	4-week drug-withdrawn	2nd	2100-0630	R&K/NR/NR
Ferrarelli F, 2010	57	49/44	S:38.2±10.6 C:36.7±7.8	67/66	DSM-IV	Paranoid (72) Disorganized (10) Undifferentiated (10) Residual (8)	15±8	PANSS: 88.5±12.7 PANSS +ve: 21.5±4.2 PANSS –ve: 22.3±4.8 PANSS GP: 45.2±6.9	Chlorpromazine equivalent 570±430 mg/day	1st	NR	AASM/2/yes
Forest G, 2007	19	8/8	S:31.0±19.9 C:21.4±4.9	75/75	DSM-IV-TR	NR	Acute (100)	PANSS: 85.6±NR PANSS +ve: 21±NR PANSS –ve 23.3±NR	Drug-naive	2nd	NR	R&K/2/NR
Ganguli R, 1987	14	8/16	S:21.5±4.0 C:22.8±2.9	75/38	DSM-III, RDC	NR	Range 0.06-5	BPRS: 45.9±9.5 BPRS +ve: 19.9±5.8	Drug-naive	Average of 1st and 2nd	NR	R&K/>1/yes
Goder R, 2006	42	16/17	S:31 (22-44) C:31 (24-43)	56/59	ICD-10	Paranoid (88) Hebephrenic (6) Undifferentiated (6)	NR	PANSS: 77 (52-112)	Stable dose of Amisulpride 600mg (100-800mg)	2nd	Bed time: 2200-2400 Wake time: 0645	R&K/1/yes
Hoffmann R, 2000	56	13/13	S:33.5±8.8 C:31.3±5.1	100/100	DSM-III-R	Paranoid (62) Disorganized (7) Undifferentiated (31)	0.9±0.6	BPRS: 41.3±5.1 SAPS: 48±19.2 SANS: 41.7±21.6	4-week drug-withdrawn	2nd	Free	R&K/NR/yes
Hudson JI, 1993	13	8/19	S:27.9±6.8 C:24.5±3.2	NR	DSM-III-R	NR	6.1±4.6	BPRS: 48.7±13.7	4 weeks drug-withdrawn	Average of 1st-4th	NR	R&K/1/NR
Kajimura N, 1995	47	6/6	S:31.8±6.8 C:27.3±NR	100/100	DSM-III-R	Disorganized (67) Undifferentiated (33)	10.3±4.3	NR	8 weeks stable dose of neuroleptics and BZD	2nd	2200-0700	R&K/NR/NR
Kempenaers C, 1988	15	9/9	S:25.6±2.6 C:25.1±3.0	100/100	RDC	Paranoid (100)	Subacute (11) Subchronic (44) Chronic (44)	BPRS: range 43-77	4 weeks drug-withdrawn	Average of 3th-5th	Free	R&K/1/yes
Lauer CJ, 1997	45	22/20	S:32.7±8.6 C:30.7±6.7	64/65	DSM-III-R	Paranoid (100)	2.8±3.4	BPRS: 54.5±11.2 BPRS +ve: 18.1±3.5 BPRS –ve: 3.3±1.4	Drug-naive	2nd	2300-0700	R&K/>1/yes
Lee JH, 2001	41	5/5	S:33.0±5.1 C:32.4±7.4	100/100	DSM-III-R	Paranoid (80) Undifferentiated (20)	12.6±6.4	BPRS: 40.8±3.35	2 weeks drug withdrawn	2nd	2300-0700	R&K/1/NR
Lusignan FA, 2009/2010	50/ 51	14/15	S:25.5±3.2 C:22.3±4.2	93/80	DSM-IV-TR	NR	NR	NR	Medicated: risperidone (14), quetiapine (22), olanzapine (50), clozapine (14)	Average of 2nd and 3rd	Free	R&K/NR/NR

Manoach DS, 2010	24	14/15	S:41±7 C:42±6	79/73	DSM-IV	Paranoid (72) Disorganized (7) Undifferentiated (7) Residual (14)	16±8	PANSS: 57.2±17.6 PANSS +ve: 15±7 PANSS –ve: 15±5 PANSS GP: 29.25±9.33 BPRS: 18±12 SANS: 39±17	6 weeks stable dose of typical (7), atypical (86), or typical and atypical antipsychotics (7). Diverse adjunctive medications for anxiety, agitation, and/or concurrent mood disturbance (71)	Average of 1st-4th	2200-0700	R&K/1/yes
Poulin J, 2000	54	6/6	S:37.7±7.4 C:23.5±4.7	67/67	DSM-IV	NR	Acute (100)	NR	Drug-naive	2nd	NR	R&K/NR/NR
Poulin J, 2003/2008	52/ 53	11/11	S:29.6±15.8 C:25.3±11.3	55/73	DSM-IV, DSM-IV-TR	NR	Acute (100)	BPRS: 48.4±5 BPRS +ve: 10.1±2.3 BPRS –ve: 8.9±4.7	Drug-naive	Average of 1st and 2nd	Free	R&K/2/NR
Rafael JS, 2004	38	18/21	S:32.9±10.9 C:29.9±9.4	43/48	DSM-IV	NR	NR	NR	2 weeks drug withdrawn	3rd	2300-0700	R&K/1/yes
Riemann D, 1995	44	10/10	S:15.8±1.8 C:16.6±1.9	40/70	ICD-10 DSM-III-R	NR	0.9±1.0	NR	1 week drug withdrawn	2nd or average of 2nd and 3rd	Bed time: 2030-2300 Wake time: 0600-0800	R&K/>1/yes
Roschke J, 1995	43	13/13	S:28±5 C:28±4	92/92	DSM-III-R	Paranoid (77) Disorganized (23)	Subchronic (24) Chronic (7) Acute on chronic (15) Unspecified (54)	BPRS: 46±6 SAPS: 38±15 SANS: 59±29	12 weeks drug withdrawn	2nd	2300-0700	R&K/2/NR
Sarkar S, 2010	37	20/20	S:26.6±5.3 C:29.25±10.1	100/100	ICD-10	Paranoid (65) Non-paranoid (35)	2.9±2.8	PANSS: 74.4±8.01 PANSS +ve: 26.1±6.58 PANSS –ve: 14.9±5.86 PANSS GP: 33.45±4.47 BPRS: 56.55±8.19	16 weeks drug withdrawn	1st	Free	R&K/NR/NR
Sekimoto M, 2007	48	11/12	S:30.6±7.8 C:30.3±7.4	100/00	DSM-IV	Disorganized (73) Undifferentiated (27)	10.7±6.3	NR	8 weeks stable dose of typical antipsychotics	NR	Bedtime: 2200-2300 Wake time: 0700	R&K/>1/yes
Sekimoto M, 2011	49	17/18	S:30.4±7.2 C:28.5±7.3	100/100	DSM-IV	Disorganized (76) Undifferentiated (24)	11.4±6.3	BPRS: 31.7±NR BPRS +ve: 5.1±3.2 BPRS –ve: 6.2±2.8	Neuroleptic-naïve (18), 4 weeks drug withdrawn (12), 8 weeks typical antipsychotics stable dose (70)	2nd	Bedtime: 2200-2300 Wake time: 0700	R&K/>1/yes

Tandon R, 1991	55	12/10	18-45 yr, age and sex matched		DSM-III-R	NR	NR	NR	2 weeks drug withdrawn	2nd	2300-0630	R&K/>1/yes
Tandon R, 1992 (naïve/withdrawn/ control)	20	20/20/ 15	26.8±7.1/ 29.8±7.7/ 25.6±5.3	60/70/67	DSM-III-R	NR	3.5±2.2/ 6.9±4.4	BPRS: 46±9.3/ 49.4±7.5 BPRS +ve: 14.1±3.4/ 15.2±2.4	Withdrawn group: 2 weeks drug withdrawn	2nd	NR	R&K/>1/yes
Tandon R, 1997 (drug-free/typical/ clozapine/risperidone/ control)	59	40/20/ 10/7/20	NR	NR	RDC, DSM-III-R	NR	NR	NR	Drug-free (52) 2 weeks stable dose of: typical antipsychotics (26), clozapine (13), or risperidone (9)	2nd	NR	R&K/>1/yes
Tandon R, 1999	58	24/20	S:28±8, C:27±7	63/70	RDC, DSM-III-R	NR	7±6	NR	2 weeks drug withdrawn	Average of 2nd and 3rd	NR	R&K/>1/yes
Tekell JL. 2005	16	17/17	S:35.5±9.7 C:30.3±4.0	82/82	DSM-III-R	NR	NR	BPRS: 41.2±6 SAPS: 48.4±18.1 SANS: 45.1±20.5	4 weeks drug withdrawn	2nd	Free	R&K/1/yes
Uchimura N, 2006	46	6/6	S:26.7±4.0 C:25.7±9.0	33/33	DSM-IV	Paranoid (67) Disorganized (33)	7.5±8.8	BPRS: 66.5±5.4 BPRS +ve:21.2±NR BPRS –ve:9.3±NR	Drug-naïve	1st	2230-0630	R&K/NR/NR
Van C, 1991	40	9/9	S: 28.3±6.3 C:29.7±5.4	100/100	RDC	Paranoid (67) Disorganized (11) Undifferentiated (22)	Subchronic (55) Chronic (45)	BPRS: 59.7±14.6	9 weeks drug withdrawn	4 continuous nights of PSG were performed	Bed time no later than 0000	R&K/NR/NR
Wamsley EJ, 2012/ Bartsch U, 2013	25/ 60	21/17	S:34±9 C:36±7	81/82	DSM-IV	NR	10±8	PANSS: 54±16.9 PANSS +ve: 12±5 PANSS –ve: 15±5 PANSS GP: 28±10	6 weeks stable dose of olanzapine (14), quetiapine (5), aripiprazole (43), clozapine (43), or risperidone consta (14)	Average of 2nd-4th	Fixed	R&K/1/yes
Yang C, 2006	6	15/15	S:40.6±3.7 C:40.2±4.1	100/100	DSM-IV	Undifferentiated (100)	17.3±3.7	PANSS: 94.5±18.2	2 weeks drug withdrawn	2nd	Free	R&K/1/yes
Yetkin S, 2011	39	13/13	S:24.4±5.9 C:25.3±5.0	100/100	DSM-IV	Undifferentiated (100)	4.6±5.2	BPRS: 32.2±6.6 SAPS: 29.8±18.3 SANS: 44.4±20.9	Drug-naïve (46) 8 weeks drug withdrawn (54)	2nd	Wake time: 0700	R&K/>1/yes
Zarcone VP, 1987	17	12/18	S:26.3±4.3 C:30.3±7.6	100/100	RDC	Paranoid (75) Undifferentiated (25)	Chronic	BPRS: 49±NR (10 cases)	2-week drug withdrawn	Average of 2nd-6th	NR	R&K/NR/NR

Abbreviations: %, percentage; +ve, positive; -ve, negative; AASM, American academy of sleep medicine manual for the scoring of sleep and associated events; BPRS, brief psychiatric rating scale; C, control; CCMD-3, Chinese classification of mental disorder version 3; DSM-III/DSM-III-R/DSM-IV/DSM-IV-TR/DSM-V, third/third revised/fourth/fourth text revised/fifth edition of the diagnostic and statistical manual of mental disorders; ICD-8/ICD-9/ICD-10, eighth/ninth/tenth revision of the international classification of diseases; no., number; NR, not reported; PANSS, positive and negative syndrome scale; pts, patients; R&K, Rechtschaffen and Kales system for scoring sleep stages; Ref, reference number; S, schizophrenia; SD, standard deviation; yr, year.

Table 2. Summary of meta-analyses

	No. of datasets	No. of S/C	Mean of S	Mean of C	Hedges's g	Q	I^2
TST min	29	447/423	378.94	421.39	-0.76***	144.74***	80.66
SOL min	30	467/446	46.54	15.67	1.11***	141.97***	79.57
SE%	25	376/382	80.82	91.44	-0.96***	98.07***	75.53
TAT min	17	243/253	53.61	23.57	0.80***	40.05***	60.05
TAT%	8	106/105	10.18	4.88	0.59***	10.57	33.75
S1%	25	387/396	12.72	8.90	0.49***	78.65***	69.49
S2%	25	387/396	54.35	55.06	-0.01	85.17***	71.82
S3%	14	205/190	6.95	7.84	-0.25*	7.96	0.00
S4%	14	205/190	4.64	6.40	-0.40**	22.82*	43.03
SWS%	25	406/378	12.14	15.12	-0.46***	66.26***	63.78
REM%	27	413/375	19.14	20.53	-0.26*	52.18**	50.17
REML min	28	395/380	83.79	95.90	-0.40**	76.38***	64.65
REMD	17	241/198	38.12	37.11	0.28*	22.62	29.26
1st REM min	7	108/89	14.02	14.92	-0.12	1.78	0.00

* p< .05, ** p< .01, *** p< .001

Abbreviations: %, percentage; min, minutes; Q, Cochran's Q statistic; REM, rapid eye movement sleep, REMD, rapid eye movement sleep density; REML, rapid eye movement sleep latency; S/C, schizophrenia/control; S1, stage 1; S2, stage 2; S3, stage 3; S4, stage 4; SE, sleep efficiency; SOL, sleep onset latency; SWS, slow wave sleep; TAT, total awake time; TST, total sleep time.

Table 3. Moderator analyses by medication status

	TST	SOL	SE%	TAT	S1%	S2%	S4%	SWS%	REM%	REML
Medication-naïve										
No. of datasets	7	6	6	4	6	6	6	4	5	6
S/C	81/74	73/66	73/66	40/35	75/68	75/68	75/68	47/53	53/48	73/66
Hedges's g	-0.98***	1.24**	-1.32***	1.03***	0.35	-0.18	-0.20	-0.17	-0.17	-0.47
Q	3.87	8.26	7.85	1.03	0.70	7.95	4.64	2.58	7.88	5.25
I^2	0.00	39.49	36.32	0.00	0.00	37.11	0.00	0.00	49.24	4.79
Medication-withdrawn										
No. of datasets	14	16	13	10	13	13	8	12	14	17
S/C	197/ 217	225/ 248	171/ 189	140/ 156	180/ 201	180/ 201	116/ 107	164/ 193	191/ 195	237/ 258
Hedges's g	-1.15***	1.10***	-1.27***	1.05***	0.71***	-0.31*	-0.50**	-0.48*	-0.13	-0.57***
Q	71.84***	42.99***	28.22**	18.55*	46.05***	25.06*	15.44*	34.36***	37.85***	44.59***
I^2	81.90	65.11	57.47	51.47	73.94	52.11	54.68	67.98	65.65	64.12
Medicated										
No. of datasets	6	6	6	3	5	5	1	5	6	3
S/C	115/109	115/109	115/109	46/44	66/65	66/65	14/15	101/94	115/109	31/33
Hedges's g	0.10	1.33***	-0.04	0.08	0.12	0.57**	NA	-0.52	-0.51*	0.50
Q	6.29	83.61***	4.17	0.59	11.11*	10.59	NA	19.25***	2.11	0.37
I^2	20.50	94.02	0.00	0.00	54.99	52.79	NA	79.22	0.00	0.00
Between-group difference										
Q	12.60**	0.28	25.07***	10.81**	4.04	11.76**	1.14	0.73	1.99	7.48*

* p< .05, ** p< .01, *** p< .001.

Abbreviations: %, percentage; no., number; Q, Cochran's Q statistic; REM, rapid eye movement sleep, REML, rapid eye movement sleep latency; S/C, schizophrenia / control; S1, stage 1; S2, stage 2; S4, stage 4; SE, sleep efficiency; SOL, sleep onset latency; SWS, slow wave sleep; TAT, total awake time; TST, total sleep time.

Table 4. Moderator analyses by the duration of antipsychotic withdrawal

	TST	SOL	SE	TAT	S1%	S2%	S4%	SWS%	REM%	REML
					≤ 2 weeks					
No. of datasets	5	7	4	5	5	5	4	6	7	8
S/C	54/56	93/93	39/34	59/63	57/55	57/55	52/50	81/75	93/93	105/103
Hedges's g	-1.24**	1.40***	-1.63***	1.21***	0.66	-0.26	-0.57	-0.45	0.11	-0.55*
Q	13.73**	10.94	6.93	4.96	7.99	16.75**	8.17*	10.84	17.37**	7.12
I^2	70.86	45.14	56.73	19.36	49.93	76.12	63.28	53.89	65.45	1.66
					3-7 weeks					
No. of datasets	6	6	6	3	6	6	3	6	5	6
S/C	83/106	83/106	83/106	45/57	83/106	83/106	37/30	83/106	58/62	83/106
Hedges's g	-1.18**	0.95***	-1.21***	1.00**	1.00**	-0.54*	-0.16	-0.38	-0.31	-0.84**
Q	52.53***	3.84	3.29	8.76*	20.26**	2.69	1.80	27.18***	9.30	23.12***
I^2	90.48	0.00	0.00	77.17	75.32	0.00	0.00	81.60	56.99	78.37
					≥ 8 weeks					
No. of datasets	4	4	4	3	3	3	2	2	3	4
S/C	49/49	49/49	49/49	36/36	40/40	40/40	NA	NA	40/40	49/49
Hedges's g	-1.07*	0.66*	-1.14***	0.68*	0.12	-0.05	NA	NA	-0.28	-0.24
Q	5.28	15.16**	14.16**	1.05	8.11*	3.31	NA	NA	9.64*	7.50
I^2	43.12	80.22	78.81	0.00	75.33	39.54	NA	NA	79.26	60.01
					Between-group difference					
Q	0.06	3.81	1.11	1.51	2.75	1.61	0.80	0.02	1.19	2.13

Parameters with less than three studies were not analyzed.
* $p < .05$, ** $p < .01$, *** $p < .001$.
Abbreviations: %, percentage; no., number; Q, Cochran's Q statistic; REM, rapid eye movement sleep, REML, rapid eye movement sleep latency; S/C, schizophrenia / control; S1, stage 1; S2, stage 2; S4, stage 4; SE, sleep efficiency; SOL, sleep onset latency; SWS, slow wave sleep; TAT, total awake time; TST, total sleep time.

Table 5. Moderator analyses by the duration of illness

	TST	SOL	SE%	TAT	S1%	S2%	SWS%	REM%	REML
					≤ 3 years				
No. of datasets	3	4	4	2	3	3	3	2	4
S/C	44/63	54/73	54/73	NA	48/67	48/67	48/67	NA	54/73
Hedges's g	-1.30	1.18***	-1.16**	NA	1.11**	-0.38	-0.76	NA	-1.01**
Q	43.94***	8.77*	2.65	NA	15.07**	0.64	13.89***	NA	15.59**
I^2	95.45	65.81	0.00	NA	86.73	0.00	85.60	NA	80.76
					> 3 years				
No. of datasets	6	6	6	5	6	6	6	6	5
S/C	68/71	68/71	68/71	62/65	68/71	68/71	68/71	68/71	54/56
Hedges's g	-0.42	0.82***	-0.90**	0.60	0.73*	0.51	-0.99**	-0.42*	0.34
Q	9.86	5.96	19.89**	15.20**	8.94	22.73***	16.05**	3.13	2.17
I^2	49.31	16.13	74.86	73.68	44.06	78.01	68.84	0.00	0.00
					Between-group difference				
Q	1.12	0.91	0.32	NA	0.50	3.02	0.14	NA	9.10

Parameters with less than three studies were not analyzed.
* p < .05, ** p< .01, *** p< .001.
Abbreviations: %, percentage; no., number; Q, Cochran's Q statistic; REM, rapid eye movement sleep, REML, rapid eye movement sleep latency; S/C, schizophrenia / control; S1, stage 1; S2, stage 2; S4, stage 4; SE, sleep efficiency; SOL, sleep onset latency; SWS, slow wave sleep; TAT, total awake time; TST, total sleep time.

Table 6. Summary of studies on quantification of delta waves

Ref	Quantitative measures		Patients	Controls	p value
47	No. of delta half-waves with freq 0.5-2.0 Hz and ampl ≥ 31μV		2311.5 ± 634.4	6162.7 ± 632.0	< .01
	Average ampl and freq of delta half-waves	Ampl (μV)	13.9 ± 0.8	17.7 ± 0.7	< .01
		Freq (Hz)	0.97 ± 0.08	1.09 ± 0.05	NS
49	No. of delta half-waves with ampl ≥5μV and dur 0.167-1.52s in frontal, central, parietal, and occipital regions		Delta wave counts were significantly reduced in patients than controls in frontal (<.0001) and central (< .001) regions.		
48	No. of delta half-waves with ampl ≥31μV and freq 0.5-20.Hz				NS
	The asym index of delta wave counts at the L and R frontal regions, calculated as (L-R)/(L+R)				< .05
24	Power in delta bands (1-4Hz) via Welch's method using a Hanning window with 50% overlap		47% reduction at L occipital leads		< .05
56	Incid and ampl (uV^2) of delta waves in the first 3 NREM periods.				
	NREM1	Incid	68.1 ± 9.4	71.8 ± 6.8	NS
		Ampl	880.9 ± 216.6	1091.1 ± 132.4	< .0007
	NREM2	Incid	59.8 ± 9.7	67.0 ± 7.7	NS
		Ampl	700.7 ± 260.1	879.4 ± 191.7	NS
	NREM3	Incid	54.1 ± 11.5	62.7 ± 4.7	NS
		Ampl	524.8 ± 211.6	714.2 ± 183.3	< .02
42	Log-transf absolute power of delta waves at EEG sites. Only sig results shown.				
	T5		63.6 (61.6-65.6)	64.3 (62.3-66.1)	.049
	T6		63.2 (61.3-65.3)	64.0 (62.2-65.9)	.02
	O1		63.3 (61.7-66.3)	64.6 (62.7-66.5)	.04
	O2		63.4 (61.5-66.1)	64.6 (62.7-66.7)	.03
57	Incid, negative peak ampl, and average slope of slow waves				NS
14	Automated delta-wave counts per min				
	NREM1		21.5	33.5	NS
	NREM2		12.6	22.5	NS
	NREM3		7.9	10.8	NS
	NREM4		4.5	8.5	NS
	Averaged counts, raw				< .05
	Averaged counts, age adjusted				NS
54	Spectral analysis of delta band (0.75-3.75Hz)				NS
52	Spectral analysis of delta band (0.75-3.75Hz)				NS

Values are expressed in mean, mean ± SD, or mean (95% confidence interval).
Abbreviations: Ampl, amplitude; asym, asymmetry; dur, duration; freq, frequency; incid, incidence; L, left; R, right; Ref, reference number; transf, transformed.

Table 7. Summary of studies on quantification of sleep spindles

Ref	Quantitative measures		Patients	Controls	p value
19	Visual scoring of 12-15Hz that lasts 0.5-2.0s at C3 or C4.		71.7 ± 11.3	95.9 ± 24.3	NS
24	Power analysis of 12-15Hz during S2 at q4	power at C4 (%)	1.61 ± 1.22	2.91 ± 2.06	NS
		power at C4-C3 (%)	-0.02 ± 0.29	0.49 ± 2.19	NS
		density at C4 (min^{-1})	0.34 ± 0.31	0.60 ± 0.36	NS
57	High-density EEG using 256-lead.	12-16Hz	Spindle power reduction, $p < .05$		
	Dur, ampl, no. and integrated spindle act in 11-16Hz NREM epochs using non-parametric mapping	12-16Hz	Spindle parameters reduction, $p < .0004$		
		12-14Hz	Dur, no. and integrated act deficits in prefrontal region, $p< .001$		
		14-16Hz	Deficits in prefrontal spindle dur, centroparietal spindle ampl, no. and integrated act in prefrontal, centroparietal and L temporal region, $p < .001$		
25	Power spectral density by FFT to successive 3s epochs at S2	Power at 12-13.5Hz ($\mu V^2/Hz$)	0.043 ± 0.02	0.074 ± 0.06	p <.05
		Power at 13.5-15Hz ($\mu V^2/Hz$)	0.034 ± 0.02	0.043 ± 0.03	NS
	Spindle defined as wavelet signal > 4.5 times the mean signal ampl of all artifact-free epochs > 400ms	Spindle no.	308 ± 144	485 ± 122	p < .001
		Spindle density (min^{-1})	1.3 ± 0.5	2.1 ± 0.6	p < .001
	Max voltage following 12-15Hz band pass filtering	Ampl (μV)	16.8 ± 3.4	17.3 ± 5.0	NS
	Spectral peak of spindle following FFT decomposition	Freq (Hz)	12.9 ± 1.5	13.0 ± 1.8	NS
	Mean FFT-derived power spectral density at 12-15Hz range	Sigma power ($\mu V^2/Hz$)	0.31 ± 0.13	0.35 ± 0.19	NS
	Spindle dur	Dur (s)	1.01 ± 0.16	1.04 ± 0.05	NS
60	Compared local SW triggered spindle power by moving window multi-taper spectrograms		Spindle power was strongly modulated by SW in controls, but markedly modulated in patients (no p values provided)		
	Coupling of frontal to parietal and central to occipital regions during SW by SW triggered coherograms		Strong spindle coherence after SW in controls which was sig increased after learning, but sig attenuated in patients		
53	Visual scoring of spindles at C3 or C4 as 12-14 Hz bursts 0.5-2.0s with no ampl criteria by 2 judges with blinding.		2.9 ± 1.5	2.6 ± 1.6	NS

Values are expressed in mean ± SD. Abbreviations: Act, activity; coh, coherence; FFT, Fast Fourier transform; inc, increased; L, left; q4, the forth NREM-REM cycle; max, maximum; redu, reduced; R, right; Ref, reference number; sig, significantly; SW, slow waves.

Supplementary Table 1. Sources of bias in polysomnography (PSG) case-control studies of schizophrenia.

Scottish intercolleagiate guidelines network system		
Internal validity section (11 items)	No. of studies rated as "well covered" or "adequately addressed"	Reference number
The study addresses an appropriate and clearly focused question	35	6, 13-20, 24, 25, 37-60
The cases and controls are taken from comparable populations	35	6, 13-20, 24, 25, 37-60
The same exclusion criteria are used for both cases and controls	33	6, 13-20, 24, 25, 37-45, 47-53, 55-60
More than 70% of each group (cases and controls) participated in the study	32	13, 15-20, 24, 25, 37-44, 46-60
Comparison is made between participants and non-participants to establish their similarities or differences	0	
Cases are clearly defined and differentiated from controls	34	6, 13-20, 24, 37-60
It is clearly established that controls are non-cases	34	6, 13-20, 24, 25, 37-53, 55-60
Measures have been taken to prevent knowledge of primary exposure influencing case ascertainment	20	6, 14-16, 20, 24, 25, 38, 39, 42, 44, 45, 48, 49, 55-60
Exposure status is measured in a standard, valid, and reliable way	35	6, 13-20, 24, 25, 37-60
The main potential confounders are identified and taken into account in the design and analysis	34	6, 13-20, 24, 25, 37-46, 48-60
Confidence intervals are provided	35	6, 13-20, 24, 25, 37-60
Overall assessment section (3 items)	No. of studies with + or ++	
How well was the study done to minimize the risk of bias or confounders?	35	6, 13-20, 24, 25, 37-60
Taking into account the methodology and statistical power, are you certain that the overall effect is due to the exposure being investigated?	35	6, 13-20, 24, 25, 37-60
Are the results directly applicable to the patient group targeted by this guideline?	35	6, 13-20, 24, 25, 37-60
Items from Thaker et al.[30]		
Source of bias or confounders	No. of studies that addressed the item	Reference number
Daily activity level is specified 1) Free bed and wake time	10	6, 15, 16, 37, 50-53, 56, 57
2) Exclusion of activities that affect sleep-wake pattern, e.g. daytime nap, shift work	15	6, 15, 16, 20, 24, 37, 38, 40, 45, 50-53, 56, 58
Standardized PSG scoring technique is used, either R&K or AASM	35	6, 13-20, 24, 25, 37-60
Definitions of PSG parameters are reported	31	6, 13-15, 17-20, 24, 25, 37-45, 48-56, 58-60

Adaptation night is used	26	6, 15-20, 25, 38, 39, 41-45, 47-51, 54-56, 58-60
Medication status is reported	35	6, 13-20, 24, 25, 37-60
Duration of medication withdrawal is reported (not applicable to articles [14, 24, 25, 42, 45-54, 57, 59, 60])	18	6, 13, 15-20, 37-41, 43, 44, 55, 56, 58
Symptomatic status is reported based on standardized tools, e.g. PANSS, BPRS	27	6, 13-17, 19, 20, 24, 25, 37-43, 45, 46, 48, 49, 52, 53, 56, 57, 59, 60
Symptom stability within drug withdrawal interval is reported (not applicable to articles [14, 25, 42, 45-54, 57, 59, 60, 97])	5	15, 20, 38, 43, 56
Presence or absence of tardive dyskinesia is reported	2	6, 20
Caffeine consumption is restricted	10	6, 19, 37, 39, 43, 45, 50-53
Nicotine consumption is restricted	3	6, 37, 39
Screening of specific sleep disorders is done	29	6, 13, 15-20, 24, 25, 37-39, 41, 43-46, 48-53, 55-60

Supplementary Table 2. Publications using the same dataset

Repeating author	Articles analyzed	Articles analyzed in pairs	Duplicated articles	Articles included qualitatively	Reasons
Zarcone VP Jr	17[a]		96		Same group of patients was studied twice. Only median and inter-quartile range was presented in article 96.
Roschke J	43		97, 98		Same group of patients was studied thrice. Two more patients were included in article 43.
Tandon R	59	20			The medication-free subjects in article 59 were the same as those in article 20. The 15 healthy controls in article 20 overlapped with the 20 healthy controls in article 59.
Godbout R	51	50			Same group of patients was studied twice. PSG data in the two articles had no duplication except REML. The mean and SD of REML in the two studies were different. The author replied that the REML published in article 51 was the correct one.
Godbout R	53			52	Same group of patients was studied twice. Results of spectral analysis was presented in article 52.
Manoach DS	25			60	Same group of patients was studied twice. Analysis of sleep spindle oscillations was presented in article 60.

[a] The numbers refer to reference numbers.