TECHNICAL COMMENTARY

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Sleep disturbance

Introduction

People with schizophrenia may show disturbances in the amount, or the quality of sleep they generally receive. Typically sleep follows a characteristic pattern of four stages, where stage 1 is a state of drowsiness and early sleep; stage 2 comprises the largest component of the sleep cycle and is the first complete loss of awareness of the external environment; stage 3 is a deep, slow-wave sleep; and the fourth stage is rapid eye movement (REM) sleep where memorable dreaming and muscle paralysis occurs.

Sleep disturbance can be measured in many ways, including the total sleep time, the sleep latency (the length of time it takes from full wakefulness to sleep), and the sleep efficiency index (the amount of time spent asleep while in bed). Sleep latency can have varying definitions, particularly regarding the definition of “asleep” – some studies define this more strictly as the time from lights out until 10 consecutive minutes of stages 2, 3 or 4, while other studies define the latency more leniently as the time from lights out until the first signs of stage 2 sleep. Chronotype describes sleep-wake and activity timing, involving a preference for either evening hours, intermediate (neither) hours, or morning hours. These preferences can change over time and differ in the peaks of circadian rhythms and the secretion of hormones.

Parasomnias may also be apparent. Parasomnias occurring during non-REM sleep include sleep walking and night terrors, while parasomnias occurring during REM sleep include nightmares, sleep paralysis and dream enactment behaviours.

Method

We have included only systematic reviews with detailed literature search, methodology, and inclusion/exclusion criteria that were published in full text, in English, from the year 2000. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Reviews with pooled data are prioritized for inclusion. Reviews reporting fewer than 50% of items on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA[1]) checklist have been excluded from the library. The evidence was graded guided by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found five systematic reviews that met our inclusion criteria[3-7].

- Moderate quality evidence found medium-sized effects of more total sleep time, more time in bed, and more motor activity in people with schizophrenia than in controls. There were also small effects of more sleep latency, less sleep efficacy, and more time awake after sleep onset in people with schizophrenia. These effects were greater in people with bipolar disorder than in people with schizophrenia. There were no significant differences in the number of awakenings, relative amplitude, interdaily stability or variability of circadian rhythms or acrophose (timing of peak intensity of circadian activity) in either patient group compared to controls.
- Moderate quality evidence finds medium-sized effects of increased stage 1 sleep, decreased stage 4 sleep, decreased slow wave sleep, and decreased REM latency. There were small effects of decreased stage 3 sleep and increased REM duration.
- People recently withdrawn from antipsychotics had shorter total sleep time, longer sleep onset latency, decreased sleep efficacy, longer awake time, increased stage

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1 sleep, decreased stage 2, 3, and 4 sleep, decreased slow wave sleep and shorter REM latency. People on antipsychotics had significantly longer sleep onset latency, increased stage 2 sleep, and decreased total REM sleep.

- Moderate quality evidence finds increased sleep disturbances in general in people at risk of psychosis as measured on the Structured Interview for Prodromal Symptoms. Lower quality evidence also finds increased sleep disturbances in people at risk when measured on the Pittsburgh Sleep Quality Index.
- Moderate to high quality evidence finds people with schizophrenia had more evening type than controls, with no differences between those with schizophrenia or bipolar I disorder.
- Moderate to low quality evidence finds frequent (weekly) nightmares were reported in 9% to 55% of people with schizophrenia. Around 15% reported sleep paralysis and 17% reported sleep-related eating disorders.

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Chan MS, Chung KF, Yung KP, Yeung WF

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

Sleep Medicine Reviews 2017; 32: 69-84

View online review abstract

Comparison	**Sleep disturbances in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, unable to assess precision, direct) finds people with schizophrenia had large effects of shorter total sleep time, more awake time, longer sleep onset latency, and lower sleep efficiency. There were medium-sized effects of increased stage 1 sleep, decreased stage 4 sleep, decreased slow wave sleep, and decreased REM latency. There were small effects of decreased stage 3 sleep and increased REM duration.** **Moderator analyses found medication-naïve patients had shorter total sleep time, longer sleep onset latency, decreased sleep efficacy, and longer awake time. Patients recently withdrawn from antipsychotics had shorter total sleep time, longer sleep onset latency, decreased sleep efficacy, longer awake time, increased stage 1 sleep, decreased stage 2, 3, and 4 sleep, decreased slow wave sleep and shorter REM latency. Patients on antipsychotics had significantly longer sleep onset latency, increased stage 2 sleep, and decreased total REM sleep.**
Sleep variables	
Large, significant effects of; Shorter total sleep time: 29 studies, N = 870, g = -0.76, $p < 0.001$, I^2 = 81%, $p < 0.001$ More awake time: 17 studies, N = 496, g = 0.80, $p < 0.001$, I^2 = 60%, $p < 0.001$ Longer sleep onset latency: 30 studies, N = 913, g = 1.11, $p < 0.001$, I^2 = 80%, $p < 0.001$ Lower sleep efficiency: 25 studies, N = 758, g = -0.96, $p < 0.001$, I^2 = 76%, $p < 0.001$ *Medium-sized, significant effects of;* Increased stage 1 sleep: 25 studies, N = 783, g = 0.49, $p < 0.001$, I^2 = 70%, $p < 0.001$ Decreased stage 4 sleep: 14 studies, N = 395, g = -0.40, $p < 0.01$, I^2 = 43%, $p < 0.05$ Decreased slow wave sleep: 25 studies, N = 784, g = -0.46, $p < 0.001$, I^2 = 64%, $p < 0.001$ Decreased REM latency: 28 studies, N = 775, g = -0.40, $p < 0.01$, I^2 = 65%, $p < 0.001$	

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Small, significant effects of; Decreased stage 3 sleep: 14 studies, N = 395, g = -0.25, $p < 0.05$, I^2 = 0%, $p > 0.05$ Increased REM duration: 17 studies, N = 439, g = -0.28, $p < 0.05$, I^2 = 29%, $p > 0.05$ Moderator analyses found medication-naïve patients had shorter total sleep time, longer sleep onset latency, decreased sleep efficacy, and longer awake time. Patients recently withdrawn from antipsychotics had shorter total sleep time, longer sleep onset latency, decreased sleep efficacy, longer awake time, increased stage 1 sleep, decreased stage 2, 3, and 4 sleep, decreased slow wave sleep and shorter REM latency. Patients on antipsychotics had significantly longer sleep onset latency, increased stage 2 sleep, and decreased total REM sleep. REM latency was shorter only in patients with short duration of illness, whereas slow wave sleep and total REM time were reduced in patients with longer duration of illness.	
Consistency in results	Mostly inconsistent
Precision in results	Unable to assess; no CIs are reported.
Directness of results	Direct

Clarke L, Chisholm K, Cappuccio FP, Tang NKY, Miller MA, Elahi F, Thompson AD

Sleep disturbances and the At Risk Mental State: A systematic review and meta-analysis

Schizophrenia Research 2021; 227: 81-91

View online review abstract

Comparison	**Sleep disturbances in people at risk of psychosis vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, unable to assess precision, direct) finds increased sleep disturbances in people at risk of psychosis as measured on the Structured Interview for Prodromal Symptoms. Lower quality evidence (very small sample) also finds increased sleep disturbances as measured on the Pittsburgh Sleep Quality Index.**
Sleep disturbances	
More sleep disturbances in people at risk of psychosis as measured on the Structured Interview for Prodromal Symptoms (SIPS); 3 studies, N = 1,570, MD = 1.58, 95%CI 0.80 to 2.35, $p < 0.0001$, I^2 = 95% *More sleep disturbances in people at risk of psychosis as measured on the Pittsburgh Sleep Quality*	

Index (PSQI); 2 studies, N = 60, MD = 3.30, 95%CI 1.87 to 4.74, $p < 0.0001$, $I^2 = 0\%$	
Consistency in results	Inconsistent for the SIPS analysis, consistent for the PSQI analysis.
Precision in results	Unable to assess; MDs are not standardised.
Directness of results	Direct

Linke M, Jankowski KS

Chronotype in individuals with schizophrenia: A meta-analysis

Schizophrenia Research 2021; 235: 74-9

View online review abstract

Comparison	**Chronotype in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) finds people with schizophrenia had more evening type than controls, with no differences between those with schizophrenia or bipolar I disorder.**
Chronotype	
A significant, medium-sized effect showed people with schizophrenia had more evening type than healthy controls; 5 studies, N = 1,024, SMD = -0.44, 95%CI -0.65 to -0.23, $p < 0.0001$, $I^2 = 55\%$, $p = 0.07$ The difference was not affected by gender, age, and the type of scale used for assessing chronotype. *There was no significant difference between schizophrenia and bipolar I disorder;* 4 studies, N = 659, SMD = -0.07, 95%CI -0.14 to 0.28, $p = 0.53$, $I^2 = 44\%$, $p = 0.15$	
Consistency in results	Inconsistent for schizophrenia vs. controls, consistent for schizophrenia vs. bipolar disorder.
Precision in results	Precise
Directness of results	Direct

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Meyer N, Faulkner SM, McCutcheon RA, Pillinger T, Dijk DJ, MacCabe JH

Sleep and circadian rhythm disturbance in remitted schizophrenia and bipolar disorder: A systematic review and meta-analysis

Schizophrenia Bulletin 2020; 46: 1126-43

View online review abstract

Comparison	**Sleep and circadian rhythm disturbance in people with schizophrenia vs. people with bipolar disorder.** **Both groups were in a non-acute phase of the illness.**
Summary of evidence	**Moderate quality evidence (large sample, mostly inconsistent and imprecise, direct) found medium-sized effects of more total sleep time, more time in bed, and more motor activity in people with schizophrenia than in controls. There were also small effects of more sleep latency, less sleep efficacy, and more time awake after sleep onset. These effects were greater in people with bipolar disorder compared to controls than in people with schizophrenia compared to controls. There were no significant differences in the number of awakenings, relative amplitude, interdaily stability or variability of circadian rhythms or acrophose (timing of peak intensity of circadian activity) in either patient group compared to controls.**

Sleep disturbance

15 bipolar studies, N = 1,091, 15 schizophrenia studies, N = 679

A large effect of more total sleep time in people with bipolar disorder vs. controls, and a medium-sized effect of more total sleep time in people with schizophrenia vs. controls;

Bipolar disorder vs. controls: SMD = 1.26, 95%CI 0.73 to 1.79, $p < 0.001$

Schizophrenia vs. controls: SMD = 0.46, 95%CI 0.32 to 0.60, $p < 0.001$

These effect sizes were significantly different ($p < 0.001$)

A medium to large effect of more sleep latency in people with bipolar disorder vs. controls, and a small effect of more sleep latency in people with schizophrenia vs. controls;

Bipolar disorder vs. controls: SMD = 0.74, 95%CI 0.34 to 1.14, $p < 0.001$

Schizophrenia vs. controls: SMD = 0.24, 95%CI 0.04 to 0.44, $p < 0.05$

These effect sizes were significantly different ($p = 0.02$)

A large effect of more time awake after sleep onset in people with bipolar disorder vs. controls, and

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a small effect of more time awake after sleep onset in people with schizophrenia vs. controls;
Bipolar disorder vs. controls: SMD = 0.90, 95%CI 0.15 to 1.66, $p < 0.05$
Schizophrenia vs. controls: SMD = 0.24, 95%CI 0.10 to 0.37, $p < 0.001$
These effect sizes were significantly different ($p = 0.002$)
A large effect of more time in bed in people with bipolar disorder vs. controls, and a medium-sized effect of more time in bed in people with schizophrenia vs. controls;
Bipolar disorder vs. controls: SMD = 1.05, 95%CI 0.40 to 1.71, $p < 0.01$
Schizophrenia vs. controls: SMD = 0.65, 95%CI 0.37 to 0.92, $p < 0.001$
These effect sizes were not significantly different ($p > 0.05$)
There were no significant differences in sleep efficacy between people with bipolar disorder and controls, but a small effect of less sleep efficacy in people with schizophrenia vs. controls;
Bipolar disorder vs. controls: SMD = -0.39, 95%CI -0.86 to 0.08, $p > 0.05$
Schizophrenia vs. controls: SMD = -0.16, 95%CI -0.30 to -0.03, $p < 0.05$
These effect sizes were not significantly different ($p > 0.05$)
There were no significant differences in the number of awakenings for either patient group vs. controls;
Bipolar disorder vs. controls: SMD = 0.55, 95%CI -0.32 to 1.42, $p > 0.05$
Schizophrenia vs. controls: SMD = -0.12, 95%CI -0.48 to 0.23, $p > 0.05$
These effect sizes were not significantly different ($p > 0.05$)
Meta-regression showed higher antipsychotic dose was related to longer total sleep time and longer sleep latency. A greater proportion of the sample being prescribed sedative antipsychotics predicted shortened sleep latency.
Circadian rhythm disturbance
A large effect of lower motor activity in people with bipolar disorder vs. controls, and a medium-sized effect in people with schizophrenia vs. controls;
Bipolar disorder vs. controls: SMD = -0.86, 95%CI -1.22 to -0.51, $p < 0.001$
Schizophrenia vs. controls: SMD = -0.75, 95%CI -1.20 to -0.29, $p < 0.01$
These effect sizes were not significantly different ($p > 0.05$)
There were no significant differences in relative amplitude for either patient group vs. controls;
Bipolar disorder vs. controls: SMD = -0.50, 95%CI -1.15 to 0.16, $p > 0.05$
Schizophrenia vs. controls: SMD = -0.25, 95%CI -0.56 to 0.05, $p > 0.05$
These effect sizes were not significantly different ($p > 0.05$)
There were no significant differences in interdaily stability for either patient group vs. controls;

Bipolar disorder vs. controls: SMD = 0.27, 95%CI -0.42 to 0.96, $p > 0.05$ Schizophrenia vs. controls: SMD = -0.10, 95%CI -1.01 to 0.82, $p > 0.05$ These effect sizes were not significantly different ($p > 0.05$) *There were no significant differences in interdaily variability for either patient group vs. controls;* Bipolar disorder vs. controls: SMD = -0.47, 95%CI -1.25 to 0.31, $p > 0.05$ Schizophrenia vs. controls: SMD = 0.30, 95%CI -0.33 to 0.94, $p > 0.05$ These effect sizes were not significantly different ($p > 0.05$) *There were no significant differences in acrophase for either patient group vs. controls;* Bipolar disorder vs. controls: SMD = 0.32, 95%CI -0.01 to 0.65, $p > 0.05$ Schizophrenia vs. controls: SMD = -1.67, 95%CI -4.14 to 0.81, $p > 0.05$ These effect sizes were not significantly different ($p > 0.05$) Increasing age predicted decreasing relative amplitude.

Consistency in results	Authors report some inconsistencies in the analyses
Precision in results	Mostly imprecise
Directness of results	Direct

Waters F, Moretto U, Dang-Vu TT

Psychiatric Illness and Parasomnias: A Systematic Review

Current Psychiatry Reports 2017; 19(7): 37

View online review abstract

Comparison	**Parasomnias in people with schizophrenia.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized samples, unable to assess consistency or precision, direct) finds frequent (weekly) nightmares were reported in 9 to 55% of people with schizophrenia. Around 15% reported sleep paralysis and 17% reported sleep-related eating disorders.**
Parasomnias	
1 study (N = 388) found 9% reported frequent nightmares 1 study (N = 14) found 50% of the sample reported having nightmares that were linked to difficulties	

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falling asleep and phobias about sleep caused by past trauma 1 study (N = 83) found 54% reported bad dreams 1 study (N = 40) found 55% of the sample reported weekly distressing nightmares 1 study (N = 71) found 15% of the sample reported sleep paralysis 1 study (N = 100) found 17% reported sleep-related eating disorders	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no CIs are reported.
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, *g* = Hedges' g standardised mean difference, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), MD = mean difference, N = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), SMD = standardised mean difference, vs. = versus

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Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results, publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[8].

† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) that allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. 0.2 represents a small effect, 0.5 a medium effect, and 0.8 and over represents a large treatment effect[8].

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, an RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. An RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[9]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios

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measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They are an indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the dependent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent substantial heterogeneity and 75% to 100%: considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula;

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed[10].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C that allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

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