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Chapter

A Meta-Analysis of Sleep Disturbances in Panic Disorder

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Abstract

The nature and prevalence of sleep disturbances in panic disorder (PD) have been often discussed but remain unclear. The objective of this systematic review and meta-analysis is to document sleep disturbances in PD. Systematic database search and standardized extraction were conducted. Meta-analysis was computed on self-report (subjective) and polysomnographic (PSG) (objective) data and on prevalence rates of nocturnal panic attacks (NPA). Of the 1262 publications retrieved, 31 were included. PD patients were compared to healthy controls on subjective and objective measures. Patients had higher Pittsburgh sleep quality index (PSQI) global scores (hedges' g = 1.306, 95% CI [0.532, 2.081]), longer PSG sleep latency (hedges' g = 0.81, 95% CI [0.576, 1.035]), poorer PSG sleep efficiency (hedges' g = −0.79, 95% CI [−1.124, −0.432]), and shorter stage 2 (hedges' g = 0.70, 95% CI [−1.231, −0.120]) and total sleep time (hedges' g = −0.739, 95% CI [−1.127, −0.351]). Among patients, 52.1% (95% CI [0.464, 0.577]) reported NPA (≥1/lifetime). Patients with PD demonstrate subjective and objective sleep alterations. More than half have experienced NPA. These sleep disturbances could have a significant role in maintaining PD symptoms.

Keywords: panic disorder, nocturnal panic attacks, insomnia, sleep, sleep disturbances, meta-analysis

1. Introduction

Panic disorder (PD) is a common anxiety disorder, with a prevalence rate of 3.7% in the general population [1]. It is characterized by sudden and recurrent surges of anxiety known as panic attacks, apprehensiveness about panic, and avoidance of potential future panic attacks [2]. In PD, as in many anxiety disorders [3], sleep may be affected. The existing literature describes two primary types of sleep problems in patients with PD: insomnia and nocturnal panic attacks (NPA).

1.1 Insomnia in patients with PD

DSM-IV-TR defines insomnia as difficulty initiating or maintaining sleep, early awakening, or non-restorative sleep [4]. Symptoms must be present at least three times per week for at least 1 month and must be the source of significant distress or dysfunction [4]. Compared to DSM-IV-TR, DSM-5 added new criteria for insomnia, including early awakening and dissatisfaction with sleep quality [2]. Furthermore, the minimum duration of symptoms was increased to 3 months [2]. Insomnia is assessed using a wide variety of measures that can be generally classified as subjective or objective. The former uses self-report questionnaires and diaries or

clinician-rated assessments; the latter uses physiological measures such as polysomnography or actigraphy [5].

1.2 Nocturnal panic attacks

NPA are paroxysmal events characterized by abrupt awakening in a state of intense anxiety and discomfort [6]. In contrast with panic attacks that begin after waking, individuals experiencing NPA wake up in a state of panic [2]. Nocturnal panic attacks generally occur between stage 2 and stage 3 sleep and are not associated with the content of a nightmare [6]. In the majority of cases, daytime panic attacks are more frequent than NPA. However, a minority of patients primarily experience nocturnal panic attacks [7], and cases of individuals with exclusively nocturnal panic attacks have been reported [8]. Nocturnal panic attacks can be assessed using the NPA appendix from the anxiety disorders interview schedule for DSM-IV. This clinician-administered interview thoroughly assesses NPA and includes questions relating to NPA frequency, apprehensiveness about future NPA, and avoidance behaviors.

1.3 Why study sleep in panic disorder?

Disturbed sleep in patients with PD is associated with greater PD severity [9]. In a recent study, researchers found that there was a significantly higher prevalence of insomnia (insomnia severity index > 8) in patients with severe or moderate PD symptoms than in patients with mild symptoms [9]. In addition to being associated with symptom severity, sleep disturbances, specifically NPA, are associated with suicidal behavior [10].

Not only are sleep disturbances (insomnia and NPA) associated with greater PD severity and with suicidal behavior, they are also hypothesized to perpetuate panic symptoms. Researchers have proposed that insomnia, NPA, and panic interact and reinforce one another in a vicious cycle [11]. Studies of individuals from the general population revealed that one night of sleep deprivation increases general anxiety and physiological activation [12]. In a similar experiment with patients with PD, researchers observed panic attacks in 40% of patients after one night of sleep deprivation, although none of the participants had experienced a panic attack in the prior week [13]. In the same study, none of the control participants (healthy controls or patients with obsessive-compulsive disorder) reported a panic attack the following day [13]. Although the experience of insomnia is distinct from the experience of sleep deprivation, patients with chronic insomnia can develop a sleep deficit [14]. Some researchers have therefore hypothesized that the effect of chronic insomnia could be comparable (although less intense) to the effect of sleep deprivation, resulting in increased general activation and triggering panic attacks [11]. When an individual also experiences NPA, they may develop apprehensiveness about going to sleep [15]. Apprehensiveness can result in a delayed bedtime, thereby compounding lack of sleep, increasing general activation, and potentially triggering panic [11]. Furthermore, some patients with PD tend to experience distress and even panic attacks in states of relaxation or states of decreased vigilance [16, 17]. It is hypothesized that such a reaction may occur immediately prior to sleep in some patients and may disturb sleep onset.

1.4 Unresolved issues related to insomnia in patients with PD

1.4.1 Subjective sleep data

Numerous studies have reported subjective sleep data from patients with PD, collected using a wide variety of psychometric tools. For example, many studies

have used the Pittsburgh sleep quality index and report a general sleep quality index [18–21]. The Hamilton depression scale (HAM-D) is another frequently used scale that assesses difficulty initiating and maintaining sleep, as well as early awakenings [22–25]. Moreover, some studies measure variables that are not included in the definition of insomnia, such as sleep duration [23]. This diversity of variables and measures complexifies comparison between studies and precludes a clear portrait of sleep alterations in PD.

1.4.2 Objective sleep data

In contrast to subjective sleep data, objective data is collected in a standardized fashion, generating results that are comparable across studies. However, despite greater uniformity in assessment, the literature on objective sleep data has yielded contradictory results. For example, some authors have reported poorer sleep efficiency in patients with PD in comparison to healthy controls [19, 26], whereas others report no difference between groups [27]. Similarly, inconsistent results have been published about slow-wave sleep (stages 3 and 4) and REM sleep latency [6, 22, 26–31]. The wealth of conflicting data is confusing and can lead to erroneous conclusions. For example, if two studies report a difference between PD and control groups in a given variable and two others report no difference, readers tend to conclude that no substantial difference exists, which may not be the case [32]. Among possible explanations, inconsistencies may be partly attributable to a lack of statistical power: indeed, polysomnographic studies tend to have small sample sizes due to their costly and complex nature.

1.5 Unresolved issues concerning the prevalence of NPA in patients with PD

The results of NPA prevalence studies vary significantly. For example, Schredl et al. [33] reported an NPA prevalence rate of 37%, whereas Stein et al. [20] reported a figure almost twice as high (68%). Moreover, different authors use different frequency criteria, ranging from "at least one lifetime NPA" [34–36], to "two to four NPA per year" [33], to "a minimum of four NPA per month" [37], or to "many times per week" [33]. A summary of the data is indicated in order to gain clarity on the rate of NPA in patients with PD.

1.6 The need for a systematic literature review and meta-analysis

The unanswered questions described above indicate a clear need for a more precise portrait of sleep disturbances in PD. A systematic review of the existing literature is warranted. Some authors have undertaken the effort in recent decades [38–41], but contradictory results from objective data and variations in the reporting of subjective data resulted in questions remaining about sleep alterations in the population. Lack of uniformity in NPA prevalence measurement and reporting yielded significant variability in prevalence rate estimates. Meta-analytic methodology involves pooling all samples into one group to conduct a quantitative analysis of data from previous research, with greater statistical power than when analyzing each study's data alone. This method would likely allow for a clearer interpretation of the current literature on the subject.

The present study was designed to systematically review the existing literature on sleep disturbances in PD. More precisely, the objectives were (1) to compare sleep in patients with PD to sleep in healthy controls and (2) to assess the prevalence rate of NPA in patients with PD. We hypothesized that the sleep of patients with PD would be significantly different from that of healthy controls.

2. Method

The preferred reporting items for systematic reviews and meta-analysis (PRISMA) checklist was used to design the study and to report results based on best practices in the field of literature reviews and meta-analyses [42].

2.1 Literature research

We conducted a literature review in these databases: PsycNet, MedLine, ProQuest, Web of Knowledge, Cochrane, and Psychology and Behavioral Sciences Collection. Search terms used in PsycNet were "panic disorder" OR "panic attack" OR panic AND sleep OR "sleep disorders" OR insomnia OR "nocturnal panic" OR "sleep deprivation." Search terms used in MedLine, Web of Knowledge, and Cochrane were panic OR "panic disorder" AND sleep OR "sleep initiation and maintenance disorders" OR dyssomnia OR "sleep deprivation." Publication date was 1980 (DSM-III year of publication) to May 2016 inclusive.

To retrieve gray literature (i.e., unpublished work or studies that are published outside widely available journals) [43], reference lists of selected articles were searched for potentially eligible articles regarding sleep in PD. The Laval University library was searched for book chapters addressing sleep in PD. Reference lists were screened for articles of interest. Inclusion of ProQuest and Web of Knowledge databases helped retrieve gray literature, as these sources contain theses, symposia, and convention papers, in addition to journal articles.

2.2 Article selection

The following inclusion criteria were used: (a) studies had to be published in English, French, or Spanish; (b) minimum participant age was 18 years; (c) to ensure population representativeness, studies including participants with comorbidities were accepted if PD was the primary diagnosis for at least one subgroup; (d) studies had to report quantitative group data for at least one sleep variable; (e) data on sleep disturbances had to include means, standard deviations, and group sizes for PD and control groups; (f) prevalence of NPA had to be reported in percentage or number of participants, and total sample size had to be included; (g) data had to be issued from self-report questionnaires, clinician-administered interviews, sleep diaries, polysomnography, or actigraphy; and (h) for subjective and objective sleep data, patients with PD had to be compared to a group of healthy controls (for the prevalence of nocturnal panic, no comparison group was necessary).

Studies that met the following criterion were excluded: (a) studies in which all patients with PD reported a physical disease or one of the following comorbid psychiatric disorders, schizophrenia, bipolar disorder, and alcohol or drug abuse or dependence, and (b) studies in which no data could be grouped using the following procedure:

Studies were classified and grouped on the basis of the measure they reported. For example, all studies reporting results on the Pittsburgh sleep quality index (PSQI) were grouped together, the same was done for the Hamilton rating scale (HAM-D), polysomnography, etc. For articles reporting NPA, grouping was carried out on the basis of the frequency criteria used. For example, all studies reporting the prevalence of patients who had at least one NPA in their lifetime were grouped together, all articles reporting the prevalence of patients having at least one NPA/month were grouped together, etc. Some articles reported data from specific sleep measures or NPA frequency criteria that were not repeated elsewhere.

Studies reporting data that could not be grouped with other data from at least one additional study were excluded.

2.3 Data extraction

Once reference retrieval was complete, each of the selected papers was reviewed, and data was extracted using a standardized rating form and coding manual. Extracted variables included information about the sample and sampling method, general methodology, and sleep characteristics (self-report sleep data, polysomnographic/actigraphic data, and prevalence of NPA).

2.4 Inter-rater agreement

2.4.1 Article selection

To reduce selection bias, a second trained judge independently rated the eligibility of 30% of the retrieved literature. The results of the two judges' ratings were compared, and cases of disagreement were discussed to reach consensus.

2.4.2 Data extraction

Five raters participated in data extraction. Four of the judges were undergraduate psychology students, and one was a graduate psychology student (AP). A pilot coding was conducted, wherein all judges used the coding manual to rate the same

Item	Percentage inter-rater agreement
Study description	
PD group sample size	100.0
Control group sample size	100.0
Mean age	88.2
Gender	73.1
Medication permitted or not	96.2
Percentage of participants taking medication	84.6
Psychometric instrument used to diagnose PD	82.7
Psychometric instrument used to assess sleep	100.0
Self-report data	
Sleep variable—PD group	88.9
Sleep variable—control group	88.9
Polysomnographic data	
Sleep variable—PD group	100.0
Sleep variable—control group	98.8
NPA	
Percentage of sample reporting NPA	46.7
NPA frequency criterion	66.7

Note: NPA = nocturnal panic attack; PD = panic disorder.

Table 1.
Inter-rater agreement.

four studies. When training was complete, studies were randomly assigned to one of the four undergraduate judges. The graduate student acted as second judge and independently coded all studies. Regular meetings were held to review discrepancies and reach consensus. In total, 29 of the 31 studies (93.5%) included in the meta-analysis were independently rated by two judges. The percentages of inter-rater agreement were between 70 and 100% for the majority of coded variables (see details in **Table 1**). Lower agreement rates were observed on variables related to NPA, a finding that can be explained by a lack of precision in reports of NPA prevalence.

2.5 Data analysis

Results were analyzed using the comprehensive meta-analysis software, version 3. Since the studies included in this review varied widely, a random effects model was used. Many of the studies had small sample sizes, in particular polysomnographic studies. Hedges' g was consequently chosen for effect size because of its correction for small samples [32]. Q and I^2 were used to assess heterogeneity. For each analysis of significant results including three studies or more, Orwin's fail-safe N was used to investigate publication bias. In these cases, a funnel plot was visually examined.

3. Results

A total of 1229 articles were screened for eligibility (**Figure 1**). Of the 1229,80 initially met inclusion criteria. Forty-nine were subsequently excluded. A total of 31 studies were selected for review. The majority of studies with self-report or polysomnographic data reported no significant differences in age or gender ratio

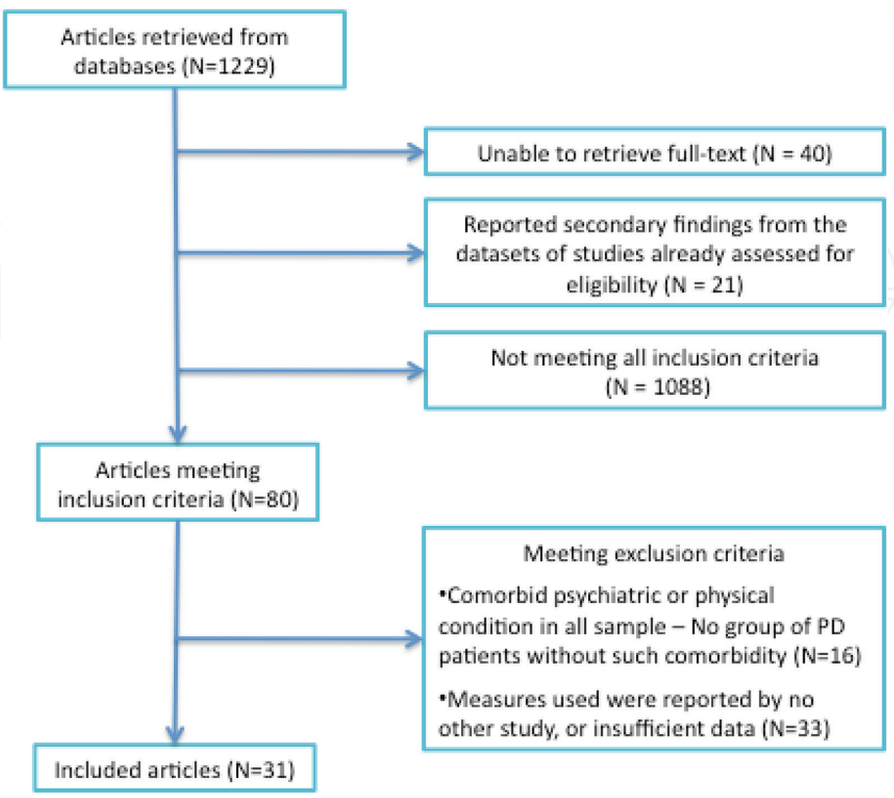


Figure 1.
Study selection flow chart.

between PD and control groups. Of the 31 studies analyzed, seven included participants taking medication. Participants were medication-free in all but one of the polysomnographic studies. In all studies, PD diagnoses were made using validated diagnostic interviews. The majority of patient samples were recruited in clinics/hospitals or were referred by a health professional. Control participants were mostly recruited through local media.

3.1 Self-report sleep data

Of the 31 selected articles, seven reported self-report data. All seven studies used the PSQI. The component scales of subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, daytime dysfunction, and the PSQI global score were analyzed. The sixth PSQI scale (medication use) was not analyzed because the variable was outside the scope of the present study. Pooled PD group size ranged from 47 to 182 participants (average = 94 participants). Pooled control groups ranged from 15,151 to 15,238 participants (average = 15,163 participants) (**Table 2**). The wide difference between average group size in PD and control groups was due to the presence of one study whose control group was 15,117 participants. When this study was removed from calculations of the average sample size, average control group size was 46 participants.

Analyses revealed that patients with PD had significantly greater scores than healthy controls for the PSQI scales of sleep quality, sleep latency, sleep disturbances, daily dysfunction, and global score. This means that patients with PD reported worse sleep quality, longer sleep latency, more sleep disturbances, and more daily dysfunction. All effect sizes were large as per Cohen's criteria [44]. There were no significant differences between groups on PSQI sleep efficiency and sleep duration scales.

Variable	Effect size (Hedges' g)	95% CI	Standard error	Variance	Q	I^2	Number of studies	PD group sample size	Control group sample size
PSQI subjective sleep quality	1.76*	[1.26, 2.31]	0.28	0.08	—	—	2	89	15,151
PSQI sleep latency	1.31*	[0.42, 2.21]	0.46	0.21	—	—	2	89	15,151
PSQI sleep duration	−0.18	[−1.33, 0.98]	0.59	0.35	—	—	2	89	15,151
PSQI sleep efficiency	0.81	[−0.08, 1.70]	0.45	0.21	—	—	2	89	15,151
PSQI sleep disturbances	1.56*	[0.65, 2.47]	0.46	0.22	—	—	2	89	15,151
PSQI daily dysfunction	1.71*	[1.38, 2.04]	0.17	0.03	—	—	2	89	15,151
PSQI global score	1.31*	[0.53, 2.08]	0.40	0.16	69.38**	92.79	6	182	15,238

Note: PSQI = Pittsburgh sleep quality index; — = insufficient number of studies to report heterogeneity; CI = confidence interval.
**= Significant differences between groups, $p < 0.05$.*
***= Significant heterogeneity, $p < 0.05$.*

Table 2.
Meta-analysis results for self-report data.

To evaluate the consistency of data across studies, heterogeneity tests were performed on data for PSQI global score. The results indicated the presence of significant heterogeneity. Estimated variance in true effects (I^2) was 92.8%. The small number of effect sizes precluded subgroup or meta-regression analyses that may have explained the heterogeneity of results.

Among subjective sleep variables, the impact of publication bias was assessed for PSQI global score. Results of Orwin's fail-safe N indicated that 48 unpublished studies with no effect would be required to lower the combined effect for PSQI global score to 0.2 (criterion for trivial effect). Moreover, the analysis of the funnel plot revealed an uneven distribution of studies, the majority of which were below the mean Hedges' g value. That is, both Orwin's fail-safe N and funnel plot analysis suggest the possibility of publication bias due to a "file drawer effect" (i.e., fewer studies with unsignificant results are published). The results must therefore be interpreted with caution.

3.2 Polysomnographic sleep data

Of the 31 included studies, 15 reported polysomnographic or actigraphic data. Meta-analysis was performed with 18 variables: sleep latency, sleep efficiency, number of awakenings, total sleep time, total wake time, REM sleep characteristics (duration, density, percentage, latency, number of REM periods), slow-wave sleep characteristics (duration, percentage), duration of stage 1 and stage 2 sleep, and percentage of stages 1–4 sleep. Pooled samples sizes varied between 19 and 209 participants for PD groups (average = 115 participants) and between 19 and 164 participants for control groups (average = 86 participants) (**Table 3**).

Significant differences between PD and control groups were demonstrated for four variables. PD participants had longer sleep latency, lower sleep efficiency, and shorter total sleep time than healthy controls. Duration of stage 2 sleep was also shorter. Analyses for the 14 other sleep variables did not show statistical significance.

To evaluate the consistency of data across studies, heterogeneity tests were performed on data for sleep latency, sleep efficiency, and total sleep time. The results indicated the presence of significant heterogeneity for sleep efficiency and for total sleep time. For the former, estimated variance in true effects (I^2) was 52%. For the latter, estimated variance in true effects (I^2) was 68%. There was no significant heterogeneity among sleep latency effect sizes. The small number of effect sizes precluded subgroup or meta-regression analyses that may have explained the heterogeneity of results.

We assessed the possibility of publication bias for the following variables: sleep latency, sleep efficiency, and total sleep time. For sleep latency, Orwin's fail-safe N was 31 (criterion for trivial Hedges' g = 0.2). This statistic indicates that it would take 31 studies with no effect to decrease the effect size to 0.2 or lower. Similar analysis yielded Orwin's fail-safe N of 26 for sleep efficiency and 24 for total sleep time. The results indicated that total effect size for each variable could be affected by publication bias. However, analysis of funnel plots, which are relatively well-balanced, indicated a lower probability of publication bias. When Orwin's fail-safe N and funnel plot analysis are combined, the possibility of publication bias cannot be excluded.

3.3 Prevalence of NPA

Thirteen studies were included in the analysis of the prevalence of NPA in patients with PD. Data was classified into three distinct categories according to

Variable	Effect size (Hedges' g)	Confidence interval (95%)	Standard error	Variance	Q	I^2	Number of studies	PD group sample size	Control group sample size
Sleep latency	0.81*	[0.58, 1.04]	0.12	0.01	7.95	0.00	10	168	147
Sleep efficiency	−0.78*	[−1.12, −0.43]	0.18	0.03	16.20**	50.62	9	186	118
Number of awakenings	0.07	[−0.25, 0.40]	0.17	0.03	2.35	0.00	4	80	66
Total sleep time	−0.74*	[−1.13, −0.35]	0.20	0.04	31.06**	67.80	11	209	164
Total wake time	0.58	[−0.20, 1.36]	0.40	0.16	27.02**	81.49	6	88	68
REM sleep duration	−0.12	[−0.75, 0.50]	0.32	0.10	4.15	51.76	4	65	51
REM sleep density	−0.04	[−0.41, 0.32]	0.19	0.03	1.73	0.00	4	64	52
% REM sleep	−0.01	[−0.22, 0.20]	0.11	0.01	6.98	0.00	10	181	134
REM latency	−0.25	[−0.73, 0.24]	0.25	0.06	33.48**	76.10	9	187	140
Number of REM periods	0.04	[−0.60, 0.67]	0.32	0.11	3.60	44.38	3	40	30
Slow-wave sleep duration	0.03	[−0.51, 0.57]	0.28	0.08	—	—	2	27	23
% slow-wave sleep	−0.07	[−0.42, 0.28]	0.18	0.03	22.53**	60.05	10	174	132
Stage 1 duration	0.25	[−0.36, 0.87]	0.31	0.10	—	—	2	19	19
Stage 2 duration	−0.68*	[−1.23, −0.12]	0.28	0.08	—	—	2	27	23
% stage 1 sleep	0.13	[−0.11, 0.36]	0.12	0.01	3.71	0.00	9	164	137
% stage 2 sleep	0.19	[−0.30, 0.67]	0.25	0.06	39.89**	77.44	10	190	153
% stage 3 sleep	0.31	[−0.38, 1.00]	0.35	0.12	10.43**	71.24	4	97	54
% stage 4 sleep	−0.31	[−1.10, 0.47]	0.40	0.16	13.28**	77.41	4	97	54

Note: Q = weighted sum of squares, indicates total dispersion; I^2 = proportion of variance due to real differences in effect size; PD = panic disorder; REM sleep = rapid eye movement sleep; slow-wave sleep = stages 3 and 4 sleep; — = insufficient number of studies to report heterogeneity; CI = confidence interval.
**= Significant differences between groups, $p < 0.05$.*
***= Significant heterogeneity, $p < 0.05$.*

Table 3.
Meta-analysis results for polysomnographic and actigraphic data.

reported NPA frequency: at least one lifetime NPA, one or more NPA in the past month, and two NPA per month or per 2 months with apprehensiveness about possible future NPA. For the latter criterion, the intensity of apprehensiveness about NPA had to be a minimum of four on a scale of 1–8. Finally, both NPA and

Frequency criteria	Event rate (prevalence %)	Confidence interval (95%)	Q	I^2	Number of studies	Sample size
1 or more lifetime NPA	52.1	[46.4, 57.7]	36.51*	75.34	10	1647
1 NPA in the last month	27.0	[17.9, 38.6]	8.47*	64.59	4	224
2 NPA/month or /2 months with apprehensiveness 4/8, lasting at least 6 months	40.9	[18.1, 68.5]	—	—	2	221

Note: Q = weighted sum of squares, indicates total dispersion; I^2 = proportion of variance due to real differences in effect size; PD = panic disorder; NPA = nocturnal panic attack; — = insufficient number of studies to report heterogeneity; CI = confidence interval.
**= Significant heterogeneity, $p < 0.05$.*

Table 4.
Meta-analysis results for NPA prevalence.

apprehensiveness had to be present for at least the prior 6 months. A meta-analysis was performed for each of the three categories, with frequency of NPA in patients with PD and PD group sample size as input data. Results indicated that, among the pooled sample of patients with PD, an average of 52.1% (95% CI [46.4, 57.7]) reported at least one lifetime NPA (**Table 4**). The heterogeneity test revealed significant heterogeneity between studies and indicated that 73% of observed variance was attributed to true effects. The prevalence rate of one or more NPA in the past month was 27.0% (95% CI [17.9, 38.6]), and the heterogeneity test was significant. Sixty-five percent of observed variance was attributed to true effects. For recurrent NPA (2/month or/2 months with apprehensiveness about possible future NPA, intensity of apprehensiveness of minimally four on a scale of 1–8.), the mean prevalence rate was 40.9% (95% CI [18.1, 68.5]). As analyses included only two studies, heterogeneity was not calculated.

4. Discussion

This study was designed to use meta-analytic methodology to draw a detailed portrait of sleep disturbances in PD. More specifically, the primary objective was to compare sleep in this population to sleep in healthy controls. Results from subjective and objective data analysis confirmed the hypothesis that sleep quality in the former group is significantly poorer than in the latter group. Furthermore, in comparison to controls, patients with PD take longer to fall asleep and have more sleep disturbances and more difficulty with daytime functioning secondary to sleep problems. Analysis of objective sleep data revealed differences between patients with PD and healthy controls in sleep continuity parameters: patients with PD take longer to fall asleep, have a shorter sleep duration, and demonstrate poorer sleep efficiency. For the majority of sleep architecture parameters, no differences were noted between patients with PD and control participants, with the exception of stage 2 duration, which was shorter in patients with PD.

4.1 Self-report data

To date, some literature reviews have explored subjective sleep complaints in PD [3, 38–40]. They reported conclusions that are consistent with the data reported here, indicating that patients with PD report significant subjective sleep alterations. However, most reviews did not detail the nature of these complaints. For example, Mellman [39] reported that there was subjective insomnia in patients with

PD, but without further specifying if there was a problem with sleep onset, sleep maintenance, or early awakenings. Only one recent systematic literature review has provided greater precision on subjective sleep complaints by reporting the results of nine previous studies in a structured manner [3]. This study reports a wide range of measures such as the sleep-wake experience list [45], the PSQI [18, 21, 46, 47], and the Goldberg depression and anxiety scales [48]. This unites useful and diverse information about the sleep of patients with PD. However, equivalence of measures and results synthesis remains difficult to judge. The statistical procedures of meta-analysis that we used allowed us to carry out the said synthesis and provided easily understandable summary indicators (size effects) of the results.

The elevated level of heterogeneity in PSQI global scores constitutes one critical point for consideration in our analysis of subjective sleep data. Variation in effect sizes is significant, and the majority of variance (92.8%) is attributable to differences in true effects. The observed elevated level of heterogeneity may be attributable to hidden covariates that moderate the differences between patients with PD and healthy controls. Previous research has identified subgroups of patients with PD in which insomnia might be more prevalent, including patients reporting NPA, depression [45], and greater anxiety sensitivity [18]. Effect sizes reported in each individual study may vary according to whether participants from these subgroups were included. Unfortunately, the number of studies reporting PSQI global scores was too low to permit the investigation of the impact of such variables via meta-regression [32]. Further research addressing the impact of covariates such as NPA, depression, and anxiety sensitivity on sleep quality in PD patients is warranted.

4.2 Objective data

Among objective sleep variables, previous literature reviews reported impairments in sleep continuity parameters. Reports of sleep onset latency, sleep efficiency, and total sleep time alterations were the most cited and robust [3, 39, 40]. Some authors also mentioned that patients with PD have difficulty maintaining sleep [39], with higher percentage of wake time [40]. Combined effect sizes from our findings indeed confirm that patients with PD have shorter sleep, take longer to fall asleep, and have poorer sleep efficiency. However, they do not confirm previous findings regarding sleep maintenance, since total wake time and number of awakenings were similar in PD and control groups. Based on these results, the nature of sleep difficulties in PD seems to be restricted to sleep onset and early awakenings, rather than sleep maintenance.

Previous reviews highlighted the existing inconsistencies in sleep architecture data. Overall, they report that there is as much evidence showing that the sleep architecture of patients with PD and of healthy controls is different as there is evidence that they are not [3, 40]. The narrative nature of previous reviews limited the conclusions that could be drawn from such data. Given this limit, the present study used meta-analysis to synthesize conflicting data. Results showed no difference between the sleep of patients with PD and the sleep of healthy control participants on the percentages of stage 1 and stage 2 sleep, of slow-wave sleep, and of REM sleep. Also, there were no differences between groups for the number of REM periods, REM sleep density and duration, stages 1 and 2 sleep duration, slow-wave sleep duration, and percentages of stage 3 and of stage 4 sleep. However, the latter results were less reliable due to the small number of studies that were included (two to four studies for each variable). Therefore, confirmation of the results is needed.

In sum, there is reliable evidence that, in comparison to healthy controls, patients with PD demonstrate alterations in objective sleep latency, sleep efficiency, and total sleep time. Also, it is plausible that percentages of REM sleep, of delta sleep, and of

stage 1 and stage 2 sleep do not differ between patients with PD and controls. For other variables, further research is required to confirm existing results.

4.3 Why is sleep altered in PD?

A recent literature review highlighted the need for studies to go beyond mere descriptions of sleep disturbances and to investigate the role of sleep disturbances in the development and maintenance of PD [3]. Research on the impact of cognitive activity on sleep yielded important insights into the onset of insomnia in PD. Studies of the possible links between repetitive thought (e.g., worry or rumination) and various sleep characteristics in college students indicated that repetitive thoughts impact sleep [49]. Since patients with PD often worry about having panic attacks, it is possible that reported sleep alterations could be associated with repetitive worry about future panic. This hypothesis is consistent with Harvey's [14] cognitive model of insomnia, which proposes that excess negative cognitive activity plays a central role in the maintenance of insomnia.

In patients with PD, the content of repetitive thinking often relates to possible panic attacks and their consequences. Patients develop a fear of anxiety itself, i.e., anxiety sensitivity [18, 50]. Researchers have found that, in patients with PD, anxiety sensitivity is linked to insomnia and, in particular, to longer sleep latency [18]. Authors hypothesized that anxiety sensitivity makes patients monitor their anxiety signs and symptoms and could increase levels of cognitive, emotional, and physiological activation [18]. This state of activation could disrupt the healthy course of sleep [18].

Sleep impairment caused by activation could be the beginning of a cycle where anxiety and insomnia mutually feed each other. Evidence suggests that sleep deprivation induces activation and anxiety in the general population [12] and increases the risk of panic in patients with PD [13]. Therefore, it is hypothesized that a sleep deficit could increase the risk of panic by inducing activation and anxiety. Indeed, since patients with PD fear signs of anxiety, the activation and anxiety caused by the sleep deficit trigger more anxiety that can culminate into panic attacks. These panic attacks could further disrupt sleep because of the activation state they caused and apprehensiveness. Future research should aim at verifying the hypothesis of the vicious cycle between panic and insomnia in order to better understand the cognitive, behavioral, and emotional mechanisms behind the sleep disturbances identified in the present study.

The majority of the results issued from objective data were consistent with cognitive models of insomnia and PD. In contrast, the finding that patients with PD have shorter stage 2 sleep is not intuitive. One possible explanation for this result is the inclusion of patients with NPA. Since NPA usually occur between stage 2 and stage 3 sleep, there may be a relationship between the presence of NPA and decreased stage 2 sleep. An alternative explanation is that shorter stage 2 sleep is an artifact of overall shorter sleep time. Since stage 2 sleep is the longest stage over the course of a night's sleep (i.e., 45–55% of total sleep time; [51]), the changes in sleep continuity observed in our study (longer sleep latency, lower sleep efficiency, and shorter total sleep time) may be attributable to shorter sleep in all three stages. Since stage 2 occupies the majority of the night, it may be the only stage for which the change can be statistically detected. Indeed, the fact that the percentage of stage 2 sleep observed in patients with PD does not differ significantly from that observed in control subjects supports this hypothesis.

Gathering detailed data on the nature of subjective and objective insomnia is a first step toward a greater understanding of the mechanisms (e.g., cognitions, anxiety sensitivity, repetitive thinking, etc.) through which insomnia could

maintain panic symptoms and vice versa. Nevertheless, the present review does not permit further inferences about interactions between sleep and PD. Considering that analyses of PSQI component scales, stages 1 and 2 sleep duration, slow-wave sleep (duration of slow-wave sleep, percentage of stages 3 and 4), and REM sleep (duration, density, number of REM periods) are based on a small number of studies (between two and four), further research is required to confirm the specific nature of sleep alterations, particularly regarding sleep architecture.

4.4 Nocturnal panic attacks

This study's secondary aim was to estimate the prevalence rate of NPA. Results indicated that, among patients with PD, 52.1% (95% CI [46.4, 57.7]) experienced at least one lifetime NPA and 27.0% (95% CI [17.9, 38.6]) experienced at least one panic attack in the past month. Furthermore, 40.9% (95% CI [18.1, 68.5]) of patients with PD reported recurrent NPA (at least 1–2/month in the past 6 months) with apprehensiveness about possible future nocturnal attacks. Of the three estimates, the lifetime prevalence obtained here is the most precise and reliable, with a confidence interval ranging from 46.4 to 57.7%. This represents an improvement compared to previously reported estimates: 44–71% in Lee and Douglass [38], 18–69% in Mellman [39], and 33–71% in Papadimitriou and Linkowski [40]. The two other NPA prevalence estimates calculated in our meta-analysis have wider confidence intervals, indicating poorer reliability. The poorer reliability may explain why the prevalence rate is higher using a more restrictive criterion (1/month or/2 months, with apprehensiveness, present since 6 months; 40.9%) than using a less restrictive criterion (one NPA in the past month; 27.0%). These results may be attributable to measurement error rather than to real differences in prevalence.

Some authors have proposed that NPA could be linked to abnormalities in breathing regulation and patterns [52]. Previous research has suggested that patients with PD have chronic hyperventilation [53], which would cause CO_2 depletion in the blood [54]. The metabolism would then adapt and become more sensitive to small increases of CO_2 in the blood [52]. Since non-REM sleep stages imply a reduced breathing rate and, therefore, a rise in CO_2, authors propose that they could be sufficient to induce the physiological reactions and physical sensations that are feared by people with PD [54, 55]. Considering that there have been reports linking nocturnal panic to sleep apnea [56], we could hypothesize that sleep apnea could induce even stronger physiological sensations in people with CO_2 hypersensitivity. Therefore, they would be more at risk of having NPA. However, the abnormalities in breathing regulation cannot totally explain the presence of NPA. Cognitive components such as beliefs about physiological sensations and interoceptive conditioning still have to be present in order for NPA to occur.

4.5 Limitations

Interpretation of the present findings should take into account the following limitations. Some variables were reported by very few studies. For example, only two studies reported data on PSQI subscales, slow-wave sleep, and stage 1 and stage 2 sleep duration. On the one hand, the limited data increases the risk of biased results, as there is no guarantee that the two included effect sizes are representative of the entire distribution of true effects [32]. On the other hand, a risk inherent to not running the analyses also exists, as it allows for the possibility of vote-counting, which is even more biased [32]. For example, Papadimitriou and Linkowski [40] discussed conflicting results about self-reported sleep efficiency. With only results of individual studies available, the authors could not draw concrete conclusions.

Our meta-analysis did not provide a clear conclusion either, but allowed us to contribute to the knowledge in this area by statistically synthesizing the data, taking into consideration the relative weight of each study, and providing a confidence interval for a true effect.

A significant number of studies with subjective sleep data could not be used because they used diverse self-report questionnaires. For example, a study by Batterham et al. in 2012 [48] was the only one to use the Goldberg depression and anxiety scale questions about sleep. While some of the data could have been merged into a single analysis designed to answer the question "Is there a significant difference in subjective sleep between patients with PD and healthy controls?", such an analysis would not have provided information about specific sleep disturbances.

The majority of studies using PSQI did not report scores for the seven subscales. The inclusion of this data would have permitted a better comparison of subjective and objective sleep data. Previous research indicates that there is a misperception of sleep in some subjects with insomnia, who overestimate sleep onset latency and underestimate total sleep time [57, 58]. Conversely, other subjects tend to overestimate their total sleep time [58]. It would have been interesting to compare the results of the meta-analysis for subjective and objective sleep data. Future research should emphasize precision in reports of subjective sleep complaints.

The absence of standards in NPA reporting complicated study comparison, with the result that many studies were excluded from our estimates. Moreover, few authors specified whether or not apprehensiveness about possible future NPA was present. As discussed previously, the presence of apprehensiveness is important because it is hypothesized to increase arousal and maintain insomnia. In the absence of apprehensiveness, interactions between NPA, insomnia, and PD are less clear. We therefore suggest the use of standardized frequency criteria for NPA prevalence that include apprehensiveness about future NPA. The criterion used by Craske et al. [59] and Albert et al. [60] constitutes a good example. The use of a standardized measure of NPA (e.g., the appendix to ADIS-IV for NPA) would contribute to the generation of standardized data. This section of the ADIS-IV is clinician-administered; developing a self-report version could also make standardized evaluation of NPA more accessible. However, since ADIS-IV has been updated to ADIS-5, an update of the appendix to DSM-5 criteria is needed before any other developments take place.

5. Conclusion

In conclusion, this systematic literature review confirms the presence of both subjective and objective insomnia in patients with PD. The results indicate that sporadic NPA are common in this population, i.e., more than one in every two patients with PD (52.1%) report at least one lifetime NPA. Recurrent NPA with apprehensiveness about future episodes seems to be slightly less common (40.9%) and is hypothesized to trigger and maintain insomnia. However the reliability of this last prevalence is low and needs confirming in future research.

We would like to emphasize the importance of using standardized psychometric tools such as the PSQI when reporting research data about sleep in patients with PD. Moreover, reporting results for subscales could give a better and more complete idea of the type of sleep alterations patients are experiencing. Also, research in this area would benefit from greater standardization in reports of subjective sleep and NP, and from particular attention in detailing subscales and information about diverse sleep variables (e.g., sleep latency, sleep efficiency, awakenings, etc.).

Finally, we would like to highlight the need for new research reporting polysomnographic data from patients with PD. Indeed, many of the studies included in our review were completed over 20 years ago. With the publication of DSM-5, the need for current data is even greater. Such studies could also be designed to help understand the cognitive processes by which insomnia is generated and maintained. Polysomnographic studies could also help understand the role of sleep-disordered breathing in NPA. Further study of sleep in patients with PD is particularly important because sleep problems are associated with poorer outcomes in individuals presenting psychopathology [61, 62]. Given the link between PD and sleep disturbances, such research could yield significant benefits for clinical evaluation and treatment of patients with PD.

Conflict of interest

The authors have no conflict of interest to declare.

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