Sleep in Untreated Patients With Schizophrenia: A Meta-Analysis

by Sylvie Chouinard, Julie Poulin, Emmanuel Stip, and Roger Godbout

Abstract

The present meta-analysis investigated the characteristics of sleep in patients with schizophrenia without neuroleptic treatment at the time of sleep recording. The 20 selected studies included 652 participants (321 patients with schizophrenia and 331 healthy subjects). Effect sizes were evaluated using *d* values for the following sleep variables: sleep latency (SL), total sleep time (TST), sleep efficiency index (SEI), total awake time (TAT), stage 2 percentage (S2%), stage 4 percentage, slow-wave-sleep percentage, rapid-eye-movement (REM) percentage, and REM latency. The initial meta-analysis revealed that patients with schizophrenia have the following sleep disorders: increased SL, decreased TST, and decreased SEI. A moderator analysis revealed that these sleep disorders were worse for the neuroleptic-withdrawal group relative to the never-treated group. However, only never-treated patients showed significantly increased TAT and diminished S2%. These results confirm that patients with schizophrenia have sleep disorders that are not necessarily a consequence of neuroleptic treatments, suggesting that sleep disorders are an intrinsic feature of schizophrenia. However, it must be noted that some sleep disorders may be amplified by residual effects of neuroleptic withdrawal, while others appear to be dampened by neuroleptic treatment.

Keywords: Schizophrenia, sleep, electroencephalogram, meta-analysis, neuroleptic drug-free.

***Schizophrenia Bulletin*, 30(4):957–967, 2004.**

The most prominent sleep abnormalities reported in patients with schizophrenia are increased sleep latency (SL) (Jus et al. 1973; Benson et al. 1991, 1996; Van Cauter et al. 1991), decreased total sleep time (TST) (Feinberg and Hiatt 1978; Lauer et al. 1997; Poulin et al. 2003), decreased sleep efficiency index (SEI) (Benson and Zarcone 1993; Hudson et al. 1993; Nishino et al. 1998), increased total awake time (TAT) (Benson et al. 1991, 1996; Keshavan et al. 1998), and shortened rapid-eye-movement latency (REML) (Kupfer et al. 1970; Ganguli et al. 1987; Benson et al. 1991). However, some studies did not confirm these findings in SL (Gaillard et al. 1984; Röschke et al. 1998), TST (Jus et al. 1973; Kempenaers et al. 1988), SEI (Ganguli et al. 1987; Poulin et al. 2003), TAT (Van Cauter et al. 1991; Nishino et al. 1998), and REML (Riemann et al. 1995; Keshavan et al. 1998). Moreover, it appears that inconsistencies remain regarding certain characteristics of sleep in patients with schizophrenia, especially increased TAT and shortened REML. One possible explanation is that neuroleptic withdrawal itself has residual effects not present in never-treated patients.

The aim of the present meta-analysis was to enhance the understanding of the results of previous studies evaluating sleep in untreated patients with schizophrenia. The meta-analytic method permits the integration of all results from comparable studies and identifies differences between experimental and control groups. Meta-analysis can further identify moderator variables that explain the variability between the results of different studies (e.g., some studies with never-treated patients and others with neuroleptic-withdrawal patients), providing an objective basis for possible explanations.

Benca et al. (1992) performed a meta-analysis on sleep in nine psychiatric disorders, including schizophrenia. They reviewed 11 studies on sleep in patients with schizophrenia without neuroleptic treatment at the polysomnographic sleep recording. They found only three studies in which sleep parameters in patients with schizophrenia were compared to those of healthy individuals. The meta-analytic results based on these three studies revealed that the group with schizophrenia had increased

Send reprint requests to Dr. Roger Godbout, Centre de recherche Fernand-Seguin, Hôpital Louis-H. Lafontaine, 7331 Hochelaga, Montréal (Québec) Canada H1N 3V2; e-mail: roger.godbout@umontreal.ca.

SL, decreased TST, and decreased slow-wave-sleep time. In this meta-analysis, the high number of variables studied and the very small number of studies comparing sleep in schizophrenia to healthy controls reduced the power of the results. Moreover, since then, additional studies involving patients with schizophrenia and healthy participants have been published. Thus, a larger meta-analysis is required.

The present report has two goals: (1) to provide a systematic overview of studies' results on sleep abnormalities in untreated patients with schizophrenia as compared to healthy subjects; and (2) to explore the effect of the drug-free condition (i.e., some studies recorded never-treated patients, while others recorded neuroleptic-withdrawal patients) on the variability of the results of those studies.

Methods and Materials

Selection of Studies. A MEDLINE search (1965–June 2001) and a PsychINFO search (1927–June 2001) were made using the National Library of Medicine (NLM Gateway: http:// gateway.nlm.gov/gw/cmd). Other articles were added using the bibliography of the articles obtained in this manner, and we included our own recent contribution (Poulin et al. 2003). The search terms *sleep* and *schizophrenia* were employed, producing 1,489 reports. Two reviewers independently read each abstract from the reports generated to identify relevant studies according to a set of criteria. First, studies were selected if sleep was recorded in a sleep laboratory; 219 eligible reports were identified at this step. These selected studies then had to meet a set of criteria, including (1) use of the classical method of Rechtschaffen and Kales (1968) to score sleep records (6 studies did not record sleep with this method); (2) inclusion of a control group of healthy subjects (159 studies did not have such a control group); (3) drug-free or never-treated condition at sleep recording (114 studies had medicated patients); and (4) presentation of statistical results or means and standard deviations (SDs) for both groups (6 studies did not present sufficient data). Some studies did not meet more than one criterion. In several cases, results representing the same patients were presented in multiple articles; in such cases, only the most comprehensive article was included in the meta-analysis. The final set of references consisted of 20 studies.

Study Coding. Results were computed in an Excel spreadsheet. Author names and dates of publication were used for report identification. In each study, the number of subjects, mean, and SD for the following variables were computed independently for the schizophrenia and control groups: age, SL, TST, SEI, TAT, stage 2 percentage (S2%), stage 4 percentage (S4%), slow-wave-sleep (stage 3 + 4) percentage (SWS%), REM sleep percentage (REM%), and REM sleep latency (REML). The following additional descriptive variables were computed: diagnosis method, diagnosis subtype, clinical scale scores (mean ± SD), severity of illness, duration of illness (mean ± SD), naps (excluded or not), comorbid sleep disorders (exclusion of sleep apnea and sleep-related periodic limb movements or not), imposed versus free bedtime period, SL strict definition (from lights off to 10 consecutive minutes of stage 2, 3, or 4) and lenient definition (from lights off to first S2 epoch), REML strict definition (from sleep onset to first 3 minutes of REM sleep minus wake time between sleep onset and REM onset) and lenient definition (from sleep onset to first epoch of REM sleep including wake time between sleep onset and REM sleep onset), and duration of neuroleptic-withdrawal period.

Effect Sizes. The effect size used was *d* values (Hunter and Schmidt 1990). This statistic represents the difference of means between the two measured groups, divided by the pooled SD. Effect size was calculated on each sleep variable described in table 1. In some studies, the F value or *t* value were not available and the effect size was then calculated based on the means and SDs. The mean differences were corrected for bias of sample size. A weighted mean effect size was calculated for each sleep variable by pooling all separate *d* values. A positive effect size indicates that the schizophrenia group had higher values than the control group, and a negative effect size has the reverse meaning. The variance between the studies and the specificity report (which indicated the percentage of the variance not explained by sample error) were also calculated. The confidence interval (CI) indicated whether mean effect sizes were statistically significant; this was the case when the CI did not include zero.

Moderator Variables. To explain the variability obtained in effect sizes and large CIs, we searched for the presence of moderator variables that exerted an influence on the dependent variable. For a moderator analysis to be performed, each group must include at least three studies that limit the number of moderator variables analyzed. The first moderator variable analysis verified whether the presence of previous neuroleptic treatment in itself caused variance between the studies compared to never-treated studies. Thus, the studies were divided into two groups of patients: never treated (G1) and neuroleptic withdrawal (G2). The complete meta-analysis was processed on these two distinct groups. A second moderator variable (i.e., duration of neuroleptic withdrawal) was evaluated. The studies of G2 were thus divided into two additional new groups: interruption of treatment for 2 weeks or less (G3)

Table 1. Definition of sleep variables

Sleep variable	Acronym	Definition
Sleep latency	SL	From lights off to consecutive 10 minutes of stage 2, 3, or 4 (minutes)
Strict definition	S–SL	
Lenient definition	L–SL	From lights off to first S2 epoch (minutes)
Total sleep time	TST	Minutes of sleep during recording of sleep
Sleep efficiency index	SEI	Percentage of total recording period spent asleep
Total awake time	TAT	Minutes awake during sleep recording
Stage 2 percentage	S2%	Ratio of stage 2 time to TST
Stage 4 percentage	S4%	Ratio of stage 4 time to TST
Slow-wave-sleep percentage	SWS%	Ratio of stage SWS time to TST
Rapid-eye-movement sleep percentage	REM%	Ratio of REM time to TST
Rapid-eye-movement sleep latency	REML	
Strict definition	S–REML	From sleep onset to first 3 minutes of REM sleep minus wake time between sleep onset and REM onset
Lenient definition	L–REML	From sleep onset to first epoch of REM sleep including wake time between sleep onset and REM onset

and interruption of treatment for more than 2 weeks (G4). Because some studies contain patients with heterogeneous neuroleptic-withdrawal durations, including never-treated patients, we tested the G2, G3, and G4 groups with and without those studies. The second and third moderator variables we tested are based on SL and REML definitions. SL definition studies were divided into two groups: strict and lenient definition of SL. We tested the effect of this moderator variable on SL, TST, and REML because SL definition may affect their outcome. For REML definitions, studies were also divided into two groups: strict and lenient definition. We tested this moderator variable on only REML because it does not influence other sleep variables. It should be noted that moderator variables such as age as well as imposed bedtime (participant goes to sleep and wakes up at a moment determined by investigators) versus free bedtime (participant goes to sleep and wakes up at his or her habitual time) were also evaluated. The results, however, were not conclusive, as the variance was not diminished, and these moderator variables were thus discarded.

Some interesting variables could not be included as moderator variables in the present meta-analysis because of lack of information. For example, duration of illness, chronicity, diagnosis subtype, scale symptoms (positive and negative symptoms), and subtypes of neuroleptic treatment were found to be heterogeneous *within* most of the studies themselves, so they could not be used with the present meta-analytic method. Still, these variables could serve as estimates to describe participating groups. Some of the studies did not allow naps before sleep and did not include participants with comorbid sleep disorders (e.g., sleep apnea, sleep-related periodic limb movements), but others did.

Results

General Description of Studies. A total of 20 publications on 652 participants (321 patients with schizophrenia and 331 healthy subjects) were included in the meta-analysis. One study had two sets of data, as it had two group of patients with schizophrenia (i.e., a drug-free group and a neuroleptic-withdrawal group) (Tandon et al. 1992). Thus, this publication generated two independent studies. At least one adaptation night was performed prior to data collection in each of the 21 studies. The mean age of both groups (among 20 studies) was 31. Gaillard et al. (1984) did not present the ages of the participants, indicating only the interval age of each group: 19–36 for the schizophrenia group and 16–43 for the control group. The average percentage of males (among 20 studies) was 76 percent for the schizophrenia group and 72 percent for the control group. Hoffmann et al. (2000) did not present participants' gender. The mean duration of the illness was 6.74 years, which was calculated using the eight studies that provided this information. The patients included in the present meta-analysis were 65 percent chronic, 22 percent subchronic, 9 percent subacute, and 4 percent acute; diagnosis subtypes were 51 percent paranoid, 25 percent residual, 16 percent undifferentiated, 5 percent catatonic,

and 3 percent disorganized. Only four studies did not present this information (Jus et al. 1973; Tandon et al. 1992; Nishino et al. 1998; Poulin et al. 2003). Brief Psychiatric Rating Scale mean total score was 47.7 (14 studies provided this information), positive symptoms score was 12.6, and negative symptoms score was 7.6 (6 studies provided positive and negative symptoms scores). Results of each study included in the meta-analysis are presented in table 2. The number of subjects in both groups and the significance of the results are indicated for each study.

Composite Effect Size (Initial Meta-Analysis). The significant effect sizes revealed differences between the patients with schizophrenia and healthy subjects on the SL, TST, and SEI variables. The results revealed a high magnitude of the effect size on these sleep variables. However, the results did not show any significant effect size between the two groups on the other sleep variables: TAT, S2%, S4%, SWS%, REM%, and REML (table 3). All sleep variables showed high variability between studies. The high specificity report on every sleep variable indicated that the variance was not explained by sample error. The high variances and the large CI on every sleep variable suggest an influence of moderator variables.

Moderator Analysis

Presence of previous neuroleptic treatment. The studies were grouped according to the presence of previous neuroleptic treatment: never treated (G1) and neuroleptic withdrawal (G2). The effect sizes for G1 revealed that never-treated patients with schizophrenia were significantly different from healthy participants on SL, TST, SEI, TAT, and S2% (table 4). Effect sizes were not significant for G1 on S4%, SWS%, REM%, and REML. The variance between the studies decreased on each sleep variable for G1 (table 4) in comparison to initial meta-analysis (table 3), and the variance did not further decrease when we tested G2 without studies including never-treated patients.

In contrast, the effect sizes for G2 revealed that neuroleptic-withdrawal patients with schizophrenia were significantly different from healthy participants on only the sleep variables already identified in the initial meta-analysis (i.e., SL, TST, and SEI; see table 3). Effect sizes were not significant for the other sleep variables: TAT, S2%, S4%, SWS%, REM%, and REML (table 4). In G2, the variances decreased (table 4) in comparison to the initial meta-analysis (table 3) on TST, S2%, and S4%; they remained constant on SEI and TAT; and they increased on SL, S4%, REM%, and REML. This increase suggests the influence of other moderator variables within the group of neuroleptic-withdrawal patients. The specificity reports were high on every sleep variable in both groups. Mean effect sizes were greater in G2 than in G1 on SL, TST, SEI, S4%, and REM% (figure 1). In contrast, the mean effect size was greater in never-treated patients than in neuroleptic-withdrawal patients for TAT.

Duration of neuroleptic withdrawal. In the second moderator analysis, G2 was divided into two groups according to the duration of neuroleptic withdrawal: 2 weeks or less (G3), or more than 2 weeks (G4). S4% was not analyzed in G3 and G4 because of a lack of studies on this variable. The effect sizes for G3 revealed that patients with schizophrenia were significantly different from healthy participants on SL, TST, and SEI. However, G3 did not reveal significant effect sizes for the other sleep variables: TAT, S2%, SWS%, REM%, and REML (table 5). The variance between studies for G3 (table 5) decreased in comparison to G2 (table 4) on all sleep variables, except for TAT, which increased. In G3, the specificity reports were high on almost all sleep variables, except for SEI, which was very low. G4 indicated significant effect sizes on SL and SEI. The effect sizes were not significant on the other sleep variables analyzed: TAT, S2%, SWS%, REM%, and REML (table 5). For G4 in comparison to G2, the variances between studies decreased for SEI and TAT, they increased for SL, TST, SWS%, and REM%, and they remained stable for REML. The specificity reports were high on each sleep variable for this group. The variance did not further decrease when we tested groups G3 and G4 without studies including never-treated patients or patients who were withdrawn from neuroleptics for a longer period of time than that specified by our criteria.

Effect of SL definition. From all studies, two groups were formed according to the definition of SL used: strict (S–SL) or lenient (L–SL). Compared to the initial meta-analysis (table 3), the variance for S–SL slightly decreased on SL, TST, and REML (table 6). As shown in the initial meta-analysis, the effect sizes for S–SL revealed that patients with schizophrenia were significantly different from healthy participants on SL and TST and not different on REML. The specificity reports for S–SL were high, except for TST. Compared to the initial meta-analysis, the variance for L–SL increased for SL and decreased for TST and REML. TAT could not be analyzed because it includes fewer than three studies. The effect sizes revealed the same significant differences as for the initial meta-analysis (table 6). The specificity reports for L–SL were low for TST and REML.

Effect of REML definition. From all studies again, two groups were formed according to the definition of REML used: strict (S–REML) or lenient (L–REML). Both groups revealed a slightly decreased variance on the REML variable compared to the initial meta-analysis (table 3). As shown in the initial meta-analysis, the effect

Table 2. Description of the 20 studies included in the meta-analysis

Study	*n* schizophrenia	*n* control	SL	TST	TAT	SEI	S2%	S4%	SWS%	REM%	REML
Benson et al. 1991[2]	20	15	+	–	NA	NA	*ns*	–	NA	*ns*	–
Benson et al. 1996[3]	14	14	+	–	+	NA	*ns*	–	NA	*ns*	NA
Benson and Zarcone 1993[2]	18	13	+	–	+	–	*ns*	–	NA	*ns*	–
Gaillard et al. 1984[2]	8	16	*ns*	–	+	NA	NA	NA	NA	NA	*ns*
Ganguli et al. 1987[1]	8	16	*ns*	*ns*	*ns*	*ns*	*ns*	*ns*	*ns*	*ns*	*ns*
Hoffmann et al. 2000[3]	13	13	+	*ns*	NA	–	*ns*	*ns*	*ns*	–	*ns*
Hudson et al. 1993[2]	8	19	*ns*	–	NA	–	*ns*	NA	*ns*	*ns*	–
Jus et al. 1973[1]	11	10	+	*ns*	*ns*	NA	*ns*	*ns*	NA	*ns*	–
Kempenaers et al. 1988[3]	9	9	+	*ns*	*ns*	*ns*	*ns*	*ns*	*ns*	*ns*	*ns*
Keshavan et al. 1998[2]	30	30	+	–	+	–	NA	NA	*ns*	*ns*	*ns*
Lauer et al. 1997[1]	22	20	+	–	NA	–	–	*ns*	*ns*	NA	*ns*
Nishino et al. 1998[3]	14	14	+	–	*ns*	–	*ns*	NA	+	*ns*	*ns*
Poulin et al. 2000[31]	7	10	+	–	NA	*ns*	*ns*	–	*ns*	*ns*	–
Riemann et al. 1991[2]	11	11	NA	NA	NA	NA	NA	NA	NA	NA	*ns*
Riemann et al. 1994[2]	36	43	+	NA	NA	–	–	NA	+	+	–
Riemann et al. 1995[2]	20	10	*ns*	NA	NA	–	*ns*	*ns*	*ns*	*ns*	*ns*
Röschke et al. 1998[3]	11	11	*ns*	*ns*	NA	NA	*ns*	NA	*ns*	NA	–
Tandon et al. 1992 (a) [1]	20	15	+	–	+	–	*ns*	*ns*	*ns*	*ns*	–
Tandon et al. 1992 (b)[2]	20	15	+	–	*ns*	–	–	*ns*	*ns*	*ns*	–
Van Cauter et al. 1991[3]	9	9	+	*ns*	*ns*	–	NA	NA	NA	NA	*ns*
Zarcone et al. 1987[2]	12	18	+	–	NA	NA	NA	NA	NA	*ns*	–

Note.—+ = significantly more in schizophrenia patients than in controls; – = significantly less in schizophrenia patients than in controls; NA = not available; *ns* = nonsignificant.

[1]Never-treated patients.

[2]Neuroleptic-withdrawal patients with interruption of treatment for 2 weeks or less.

[3]Neuroleptic-withdrawal patients with interruption of treatment for more than 2 weeks.

Table 3. Initial meta-analysis on sleep variables

	SL*	TST*	SEI*	TAT	S2%	S4%	SWS%	REM%	REML
Effect size *d*	1.34	–1.50	–1.58	0.77	–0.47	–0.34	0.01	0.11	–0.58
n study	19	17	14	11	16	10	13	17	21
n subject	542	496	410	350	489	278	433	537	643
Variance	0.21	0.26	0.18	0.18	0.12	0.32	0.10	0.39	0.22
SR	0.90	0.84	0.70	0.97	0.86	0.92	0.77	0.93	0.94
95% CI –	0.44	–2.47	–2.41	–0.07	–1.14	–1.45	–0.63	–1.11	–1.50
95% CI +	2.24	–0.49	–0.74	1.60	0.20	0.77	0.60	1.33	0.35

Note.—CI = confidence interval; REM% = rapid-eye-movement percentage; REML = REM latency; S2% = stage 2 percentage; S4% = stage 4 percentage; SEI = sleep efficiency index; SL = sleep latency; SR = specificity report; SWS% = slow-wave-sleep percentage; TAT = total awake time; TST = total sleep time.

* Significantly different.

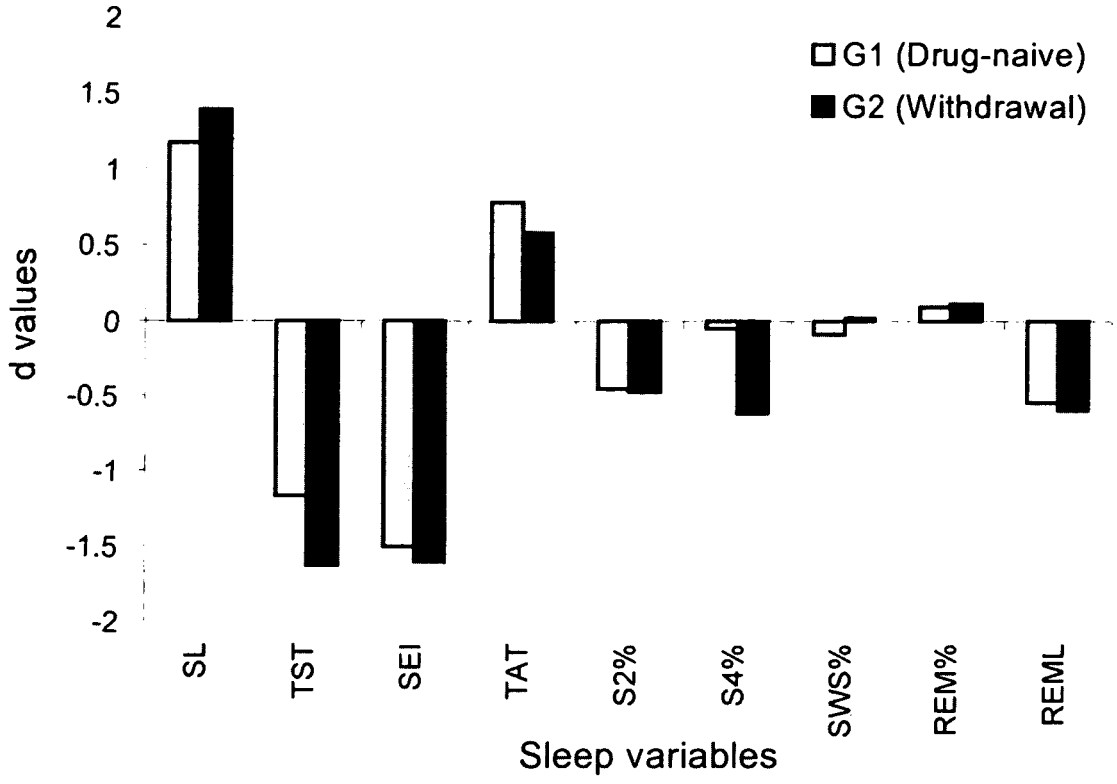
Table 4. Moderator analysis of neuroleptic withdrawal on the sleep variables

		SL*	TST*	SEI*	TAT*	S2%*	S4%	SWS%	REM%	REML
G1	Effect size *d*	1.17	–1.17	–1.51	0.78	–0.46	–0.05	–0.09	0.09	–0.55
	n study	5	5	4	3	5	5	4	4	5
	n subject	139	139	118	80	139	139	118	97	139
	Variance	0.07	0.17	0.12	0.09	0.02	0.14	0.04	0.13	0.14
	SR	0.94	0.97	0.68	0.94	0.52	0.79	0.55	0.76	0.89
	95% CI –	0.64	–1.96	–2.17	0.20	–0.77	–0.78	–0.49	–0.61	–1.28
	95% CI +	1.70	–0.37	–0.84	1.36	–0.15	0.67	0.30	0.79	0.19
		SL*	**TST***	**SEI***	**TAT**	**S2%**	**S4%**	**SWS%**	**REM%**	**REML**
G2	Effect size *d*	1.39	–1.63	–1.60	0.58	–0.48	–0.62	0.02	0.11	–0.60
	n study	14	12	10	8	11	5	9	13	16
	n subject	403	357	292	350	350	139	315	440	504
	Variance	0.25	0.20	0.21	0.19	0.15	0.35	0.12	0.44	0.25
	SR	0.89	0.68	0.72	0.93	0.89	0.96	0.81	0.94	0.95
	95% CI –	0.42	–2.50	–2.49	–0.28	–1.24	–1.78	–0.66	–1.19	–1.59
	95% CI +	2.37	–0.76	–0.70	1.44	0.29	0.55	0.69	1.42	0.39

Note.—CI = confidence interval; G1= never-treated patients; G2 = neuroleptic-withdrawal patients; REM% = rapid-eye-movement percentage; REML = REM latency; S2% = stage 2 percentage; S4% = stage 4 percentage; SEI = sleep efficiency index; SL = sleep latency; SR = specificity report; SWS% = slow-wave-sleep percentage; TAT = total awake time; TST = total sleep time.

* Significantly different.

Figure 1. Moderator variable analysis of presence of previous exposure to neuroleptic treatment in schizophrenia[1]



Note.—REM% = rapid-eye-movement percentage; REML = REM latency; S2% = stage 2 percentage; S4% = stage 4 percentage; SEI = sleep efficiency index; SL = sleep latency; SWS% = slow-wave-sleep percentage; TAT = total awake time; TST = total sleep time.

[1]Mean effect sizes *d* are greater in neuroleptic-withdrawal patients than in never-treated patients for SL, TST, SEI, S4%, and REM% but smaller for TAT.

sizes revealed that patients with schizophrenia were not significantly different on REML. The specificity reports for S-REML were high for both groups (table 7).

Discussion

We found that sleep disorders were consistently present in untreated patients with schizophrenia as compared to healthy participants, including increased SL, decreased TST, and diminished SEI. This is consistent with several studies that demonstrated this phenomenon (see above). To some extent, the initial analysis (table 3) revealed no difference on the other sleep variables: TAT, S2%, S4%, SWS%, REM%, and REML. A high-specificity report showed that the variance between studies was not explained by sampling error. This supports the work of Tandon et al. (1992), who suggested that variance can be caused by interruption of neuroleptic treatment. We found that patients who stopped taking neuroleptics prior to recordings had more severe sleep disorders than never-treated patients on SL, TST, and SEI. The never-treated patients were more disturbed on different sleep variables: they showed more TAT and less S2% than the healthy subjects.

Most drug-free studies demonstrated augmentation of TAT in schizophrenia (Gaillard et al. 1984; Benson and Zarcone 1993; Keshavan et al. 1998), but some did not (Ganguli et al. 1987; Nishino et al. 1998), and some studies reported diminution in S2% in patients with schizophrenia (Tandon et al. 1992; Lauer et al. 1997), while others did not (Ganguli et al. 1987; Poulin et al. 2003). Tandon et al. (1992) found a decrease in S2% in patients treated previously as compared to healthy subjects and never-treated patients. Our initial meta-analysis including all patients did not find a difference in TAT and S2% compared to healthy participants (table 3). However, a moder-

Table 5. Moderator analysis of duration of neuroleptic withdrawal on sleep variables

		SL*	TST*	SEI*	TAT	S2%	SWS%	REM%	REML
G3	Effect size *d*	1.45	−1.72	−1.57	0.95	−0.50	0.04	0.37	−0.64
	n study	8	7	5	4	6	5	8	10
	n subject	262	242	173	149	257	251	317	363
	Variance	0.19	0	0.003	0.27	0.14	0.04	0.21	0.23
	SR	0.84	—	0.04	0.99	0.91	0.67	0.92	0.96
	95% CI −	0.60	−1.72	−1.67	−0.06	−1.22	−0.35	−0.53	−1.58
	95% CI +	2.30	−1.72	−1.46	1.97	0.22	0.44	1.28	0.30
		SL*	**TST**	**SEI***	**TAT**	**S2%**	**SWS%**	**REM%**	**REML**
G4	Effect size *d*	1.29	−1.45	−1.66	0.64	−0.31	−0.06	−0.56	−0.43
	n study	6	5	5	4	5	4	5	6
	n subject	141	115	119	93	123	94	123	141
	Variance	0.34	0.66	0.49	0.11	0.11	0.28	0.44	0.23
	SR	0.95	0.93	0.79	0.89	0.77	0.87	0.96	0.89
	95% CI −	0.15	−3.05	−3.03	−0.01	−0.96	−1.09	−1.86	−1.38
	95% CI +	2.43	0.14	−0.28	1.29	0.33	0.98	0.73	0.51

Note.—CI = confidence interval; G3 = without neuroleptic treatment for 2 weeks or less; G4 = without neuroleptic treatment for more than 2 weeks; REM% = rapid-eye-movement percentage; REML = REM latency; S2% = stage 2 percentage; SEI = sleep efficiency index; SL = sleep latency; SR = specificity report; SWS% = slow-wave-sleep percentage; TAT = total awake time; TST = total sleep time.

*Significantly different.

Table 6. Moderator analysis of SL definition on sleep variables

		SL*	TST*	SEI*	TAT*	REML
S–SL	Effect size *d*	1.40	−1.58	−1.63	0.78	−0.76
	n study	10	10	7	7	10
	n subject	334	334	247	246	334
	Variance	0.18	0.17	0.12	0.11	0.16
	SR	0.77	0.59	3.78	0.94	0.93
	95% CI −	2.23	−0.78	−0.94	0.14	0.03
	95% CI +	0.57	−2.38	−2.32	1.43	−1.54
		SL*	**TST***	**SEI***	**TAT**	**REML**
L–SL	Effect size *d*	1.28	−1.30	−1.58	—	−0.17
	n study	5	4	5	2	7
	n subject	115	95	115	—	216
	Variance	0.26	0.01	0.42	—	0.05
	SR	0.79	0.20	0.60	—	0.36
	95% CI −	2.27	−1.06	−0.32	—	0.27
	95% CI +	0.29	−1.53	−2.85	—	−0.62

Note.—CI = confidence interval; REML = rapid-eye-movement latency; SEI = sleep efficiency index; SL = sleep latency (L = lenient; S = strict); SR = specificity report; TAT = total awake time; TST = total sleep time.

* Significantly different.

Table 7. Moderator analysis of REML definition on sleep variables

		REML
S–REML	Effect size *d*	–0.69
	n study	10
	n subject	354
	Variance	0.16
	SR	0.91
	95% CI –	0.09
	95% CI +	–1.48
		REML
L–REML	Effect size *d*	–0.13
	n study	6
	n subject	174
	Variance	0.14
	SR	0.80
	95% CI –	0.59
	95% CI +	–0.86

Note.—CI = confidence interval; REML = rapid-eye-movement latency (L = lenient; S = strict); SR = specificity report.

ator analysis revealed that never-treated patients have more TAT and less S2% than healthy participants. These results suggest that augmentation of TAT and diminution of S2% are a basic sleep disorder in schizophrenia. These findings suggest that neuroleptic treatments alter sleep architecture, particularly TAT and S2%, as the neuroleptic-withdrawal group did not show differences on these variables compared to the control group. This finding may indicate that previous neuroleptic treatments could induce a long-term normalization of awakenings and stage 2 in patients with schizophrenia.

Some studies also showed a diminution in S4% in patients with schizophrenia compared to healthy individuals (Benson et al. 1991; Poulin et al. 2003; Röschke et al. 1998), whereas others did not (Kempenaers et al. 1988; Tandon et al. 1992). Curiously, most studies of sleep in schizophrenia did not reveal a diminution in SWS% (stage 3 + stage 4). The present meta-analysis did not reveal any difference in S4%, or in SWS%, independent of previous neuroleptic treatments (tables 3 and 4). It is possible that another moderator variable not identified in the present study (e.g., chronicity, symptomatology) has an influence on SWS in schizophrenia (Keshavan et al. 1995, 1996).

REML also showed a different sensitivity to group effect across studies. Some studies revealed a shortened REML (Jus et al. 1973; Zarcone et al. 1987; Hudson et al. 1993; Poulin et al. 2003), and others did not (Ganguli et al. 1987; Kempenaers et al. 1988). The results of the present meta-analysis did not reveal any significant mean effect size between patients with schizophrenia and healthy participants on REML. The definition of REML cannot be considered responsible for the divergence between studies as shown by the analysis. In almost all studies, REML is defined as minutes from sleep onset to the first appearance of REM sleep minus wake time (Ganguli et al. 1987; Benson et al. 1991, 1996; Tandon et al. 1992; Benson and Zarcone 1993; Lauer et al. 1997; Keshavan et al. 1998). However, some authors did include wake time (Zarcone et al. 1987; Kempenaers et al. 1988; Van Cauter et al. 1991; Poulin et al. 2003). Tandon et al. (1992) showed that the duration of the neuroleptic-free period affects REM sleep in schizophrenia. They found that previously treated patients withdrawn for 2 to 4 weeks had a shorter REML and greater REM% in comparison to patients withdrawn for more than 4 weeks. Such a comparison was not possible with our data set. Another explanation of the discrepancies between studies on REM sleep may concern the small number of females included in almost every study in the present meta-analysis, with more than 76 percent of the subjects being male. It has been suggested that male and female patients with schizophrenia have different pathophysiological mechanisms underlying REML (Goldman et al. 1996). These authors found a significant relation between reduced REML and poor outcome in females but not in males. Gender differences could thus explain why the present meta-analysis did not reveal any significant results for REML (and possibly other sleep variables).

It is hypothesized that the main contributing factors to variability between studies of sleep in patients with schizophrenia are methodological differences (Tandon et al. 1992). One such difference consists of the fact that almost all studies have focused on patients treated previously and withdrawn from neuroleptics before sleep recording, omitting never-treated patients with schizophrenia. The sleep of never-treated patients is more likely to reflect the fundamental sleep pattern in schizophrenia, and we have shown here that neuroleptic treatment and its withdrawal affect sleep parameters. Indeed, it is known that neuroleptics have a residual effect on sleep, even after a washout period of 6 weeks (Neylan et al. 1992). When studies were subdivided into two groups according to treatment status (i.e., never treated and neuroleptic withdrawal), variance decreased for each sleep variable in the never-treated group and for only certain sleep variables in the neuroleptic-withdrawal group (table 4). This

shows that never-treated patients have more homogeneous sleep architecture than neuroleptic-withdrawal patients. Treatment subtypes and duration of previous neuroleptic treatment may explain in part the variance in the neuroleptic-withdrawal patients. Some studies showed that different neuroleptics have different effects on sleep patterns in patients with schizophrenia (Wetter et al. 1996; Dursun et al. 1999). Another meta-analysis is needed to characterize sleep in patients with schizophrenia treated with different antipsychotic drugs.

SWS% and REML are often used to propose hypotheses about the pathophysiology of schizophrenia. The evidence as to whether reduced SWS% and shortened REML exist in never-treated patients is still inconsistent. There are five studies evaluating the sleep of never-treated patients with schizophrenia, and there are discrepancies among those studies (table 2) (Lauer et al. 1997). The present meta-analysis did not reveal significant results on SWS% and REML. It is possible that other variables such as chronicity, severity, or diagnosis subtype play a role in the discrepancies between studies, but a lack of available information did not permit us to examine this issue. It is recognized that sleep parameters differ among different subtype diagnoses (Van Kammen et al. 1988), but almost all studies included patients with mixed subtypes. In future publications on sleep in schizophrenia, researchers should describe or control for the following components: duration of illness, severity of symptoms (e.g., Brief Psychiatric Rating Scale or Positive and Negative Syndrome Scale), and subtype of diagnosis.

In sum, our meta-analysis confirms that patients with schizophrenia have sleep disorders, whether they are never treated or withdrawn from neuroleptic treatment. Moderator analyses further indicate that neuroleptic withdrawal has residual effects that amplify some sleep disorders and normalize others. Many hypotheses about the pathophysiology of schizophrenia were prompted by sleep abnormalities observed in this disease. If these hypotheses are based on results contaminated by previous neuroleptic treatment, then they explain not the disease itself but the state related to the treated or untreated conditions. Whether sleep disorders in persons with schizophrenia reflect an intrinsic feature or a reaction to the illness is still debatable, and each publication has its own merit given that methodological issues are discussed accordingly. Furthermore, beyond physiopathological concerns, such studies are bound to have a considerable impact, as they could be used as an additional tool to track treatment response.

References

Benca, R.M.; Obermeyer, W.H.; Thisted, R.A.; and Gillin, J. Sleep and psychiatric disorders: A meta-analysis. *Archives of General Psychiatry,* 49:651–668, 1992.

Benson, K.L.; Faull, K.L.; and Zarcone, V.P., Jr. Evidence for the role of serotonin in the regulation of slow wave sleep in schizophrenia. *Sleep,* 14:133–139, 1991.

Benson, K.L.; Sullivan, E.V.; Lim, K.O.; Lauriello, V.P., Jr.; and Pfefferbaum, A. Slow wave sleep and computed tomographic measures of brain morphology in schizophrenia. *Psychiatry Research,* 60:25–134, 1996.

Benson, K.L., and Zarcone, V.P. Rapid eye movement sleep eye movements in schizophrenia and depression. *Archives of General Psychiatry,* 50:474–483, 1993.

Dursun, S.M.; Patel, J.K.; Burke, J.G.; and Reveley, M.A. Effects of typical antipsychotic drugs and risperidone on the quality of sleep of patients with schizophrenia: A pilot study. *Journal of Psychiatry & Neuroscience,* 24:333–337, 1999.

Feinberg, I., and Hiatt, J.F. Sleep patterns in schizophrenia: A selective review. In: Williams, R.L., and Karacan, I., ed. *Sleep Disorders: Diagnosis and Treatment.* New York, NY: Wiley, 1978. pp. 205–231.

Gaillard, J.M.; Iorio, G.; Campajola, P.; and Kemali, D. Temporal organisation of sleep in schizophrenics and patients with obsessive-compulsive disorder. *Advances in Biological Psychiatry,* 15:76–83, 1984.

Ganguli, R.; Reynolds, F.; and Kupfer, D.J. Electroencephalographic sleep in young never-medicated schizophrenics. *Archives of General Psychiatry,* 44:36–44, 1987.

Goldman, M.; Tandon, R.; DeQuardo, J.R.; Taylor, S.F.; Goodson, J.; and McGrath, M. Biological predictors of 1-year outcome in schizophrenia in males and females. *Schizophrenia Research,* 21:65–73, 1996.

Hoffmann, R.; Hendricke, W.; Rush, A.J.; and Armitage, R. Slow-wave activity during non-REM sleep in men with schizophrenia and major depressive disorders. *Psychiatry Research,* 95:215–225, 2000.

Hudson, J.I.; Lipinski, J.F.; Keck, P.E., Jr.; Aizley, H.G.; Vuckovic, A.; Zierk, K.C.; and Pope, H.G., Jr. Polysomnographic characteristics of schizophrenia in comparison with mania and depression. *Biological Psychiatry,* 34:191–193, 1993.

Hunter, J.E., and Schmidt, F.L. *Methods of Meta-analysis.* Thousand Oaks, CA: Sage Publications, 1990.

Jus, K.; Bouchard, M.; Jus, A.K.; Villeneuve, A.; and Lachance, R. Sleep EEG studies in untreated, long-term schizophrenic patients. *Archives of General Psychiatry,* 29:386–390, 1973.

Kempenaers, C.; Kerkhofs, M.; Linkowski, P.; and Mendlewicz, J. Sleep EEG variables in young schizophrenic and depressive patients. *Biological Psychiatry,* 24:828–833, 1988.

Keshavan, M.S.; Miewald, J.; Haas, G.; Sweeney, J.; Ganguli, R.; and Reynolds, C.F. Slow-wave sleep and symptomatology in schizophrenia and related disorders. *Journal of Psychiatric Research,* 57:303–314, 1995.

Keshavan, M.S.; Reynolds, C.F., 3rd; Miewald, J.M.; and Montrose, D.M. A longitudinal study of EEG sleep in schizophrenia. *Psychiatry Research,* 59:203–211, 1996.

Keshavan, M.S.; Reynolds, C.F., 3rd; Miewald, J.M.; Montrose, D.M.; Sweeney, J.A.; Vasko, R.C., Jr.; and Kupfer, D.J. Delta sleep deficits in schizophrenia. *Archives of General Psychiatry,* 55:443–448, 1998.

Kupfer, D.J.; Wyatt, R.J.; Scott, J.; and Snyder, F. Sleep disturbance in acute schizophrenic patients. *American Journal of Psychiatry,* 126:1213–1223, 1970.

Lauer, C.J.; Schreiber, W.; Pollmächer, T.; Holsboer, F.; and Krieg, J.C. Sleep in schizophrenia: A polysomnographic study on drug-naive patients. *Neuropsychopharmacology,* 16:51–60, 1997.

Neylan, T.C.; Van Kammen, D.P.; Kelley, M.E.; and Peters, J.L. Sleep in schizophrenic patients on and off haloperidol therapy: Clinically stable vs relapsed patients. *Archives of General Psychiatry,* 49:643–649, 1992.

Nishino, S.; Mignot, E.; Benson, K.L.; and Zarcone, V.P., Jr. Cerebrospinal fluid prostaglandins and corticotropin releasing factor in schizophrenics and controls: Relationship to sleep architecture. *Psychiatry Research,* 78:141–150, 1998.

Poulin, J.; Daoust, A.M.; Forest, G.; Stip, E.; and Godbout, G. Sleep architecture, phasic activities and their clinical correlates in drug-naive schizophrenic patients. *Schizophrenia research,* 62:147–153, 2003.

Rechtschaffen, A., and Kales, A. *A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects.* NIH Publication No. 204. Washington, DC: Public Health Service, U.S. Government Printing Office, 1968.

Riemann, D.; Gann, H.; Fleckenstein, P.; Hohagen, F.; Olbrich, R.; and Berger, M. Effect of RS 86 on REM latency in schizophrenia. *Psychiatry Research,* 38:89–92, 1991.

Riemann, D.; Hohagen, F.; Krieger, S.; Gann, H.; Müller, W.E.; Olbrich, R.; Wark, H.J.; Bohus, M.; Low, H.; and Berger, M. Cholinergic REM induction test: Muscarinic supersensitivity underlies polysomnographic findings in both depression and schizophrenia. *Journal of Psychiatric Research,* 28:195–210, 1994.

Riemann, D.; Kammerer, J.; Löw, H.; and Schmidt, M.H. Sleep in adolescents with primary major depression and schizophrenia: A pilot study. *Journal of Child Psychology and Psychiatry, and Allied Disciplines,* 36:313–326, 1995.

Röschke, J.; Wagner, P.; Mann, K.; Prentice-Cuntz, T.; and Frank, C. An analysis of the brain's transfer properties in schizophrenia: Amplitude frequency characteristics and evoked potentials during sleep. *Biological Psychiatry,* 43:503–510, 1998.

Tandon, R.; Shipley, J.E.; Taylor, S.; Greden, J.F.; Eiser, A.; DeQuardo, J.; and Goodson, J. Electro-encephalographic sleep abnormalities in schizophrenia. *Archives of General Psychiatry,* 49:185–194, 1992.

Van Cauter, E.V.; Linkowski, P.; Kerkhofs, M.; Hubain, P.; L'hermite-Balériaux, M.; Leclercq, R.; Brasseur, M.; Copinschi, G.; and Mendlewick, J. Circadian and sleep-related endocrine rhythms in schizophrenia. *Archives of General Psychiatry,* 48:348–356, 1991.

Van Kammen, D.P.; Van Kammen, W.B.; Peters, J.; Goetz, K.; and Neylan, T. Decreased slow-wave sleep and enlarged lateral ventricles in schizophrenia. *Neuropsychopharmacology,* 1:265–271, 1988.

Wetter, T.C.; Lauer, C.J.; Gillich, G.; and Pollmacher, T. The electroencephalographic sleep pattern in schizophrenic patients treated with clozapine or classical antipsychotic drugs. *Journal of Psychiatric Research,* 30:411–419, 1996.

Zarcone, V.P., Jr.; Benson, K.; and Berger, P.A. Abnormal rapid eye movement latencies in schizophrenia. *Archives of General Psychiatry,* 44:45–49, 1987.

Acknowledgments

This research was made possible by grants from the Canadian Institutes of Health Research, the Natural Science and Engineering Research Council of Canada, and the Fonds de la Recherche en Santé du Québec.

The Authors

Sylvie Chouinard, M.Sc., is Ph.D. candidate, Université du Québec à Montréal, and Centre de Recherche Fernand-Seguin, Hôpital Louis-H. Lafontaine, Montréal, Québec. Julie Poulin, M.Sc., is M.D.-Ph.D. candidate, Université de Montréal, and Centre de Recherche Fernand-Seguin, Hôpital Louis-H. Lafontaine. Emmanuel Stip, M.D., M.Sc., is Clinical Associate Professor, Department of Psychiatry, Université de Montréal, and Centre de Recherche Fernand-Seguin, Hôpital Louis-H. Lafontaine. Roger Godbout, Ph.D., is Full Professor, Department of Psychiatry, Université de Montréal, and Centre de Recherche Fernand-Seguin, Hôpital Louis-H. Lafontaine.