

Impact of Sleep-Related Complaints on Depressive Symptoms in Patients With Restless Legs Syndrome

Magdolna Hornyak, M.D.; Marta Kopasz, M.A.Psych.; Mathias Berger, M.D.; Dieter Riemann, Ph.D.; and Ulrich Voderholzer, M.D.

Received Dec. 17, 2004; accepted May 3, 2005. From the Department of Psychiatry and Psychotherapy, University Hospital, Freiburg, Germany.

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Corresponding author and reprints: Magdolna Hornyak, M.D., Department of Psychiatry and Psychotherapy, University Hospital Freiburg, Hauptstrasse 5, D-79104 Freiburg, Germany (e-mail: magdolna_hornyak@psyallg.ukl.uni-freiburg.de).

Objective: Restless legs syndrome (RLS) is a distressing sensorimotor disorder with a 5% to 10% prevalence in the United States and Western Europe. The nocturnal occurrence of symptoms often leads to severe sleep disturbances. RLS has been reported to be associated with depression and anxiety. The aim of the present study was to investigate the relationship between RLS symptom severity, sleep disturbances, and depressive symptoms.

Method: Questionnaire data from 100 consecutive patients with idiopathic RLS who had been investigated in our Sleep Disorders Unit from April 1999 to December 2004 were evaluated. Patients were untreated regarding RLS, depression, or sleep disturbances. Severity of RLS was assessed with the International RLS Study Group rating scale (IRLS). Depressive symptoms and subjective sleep quality were determined using the Beck Depression Inventory (BDI) and the Pittsburgh Sleep Quality Index (PSQI), respectively.

Results: IRLS scores indicated moderate-to-severe RLS symptoms in the population studied (mean \pm SD IRLS score = 23.6 ± 6.7). The mean \pm SD BDI score was 9.3 ± 5.6 , with highest values on the "reduced sleep," "loss of energy," and "work difficulties" items, indicating predominating somatic symptoms of depression. Fourteen patients had a BDI score of 15 to 20 ("mild depression"), and 3 patients had a BDI score of 20 to 30 ("mild to moderate depression"). Overall, patients estimated their sleep quality as moderately impaired (mean \pm SD PSQI score = 10.9 ± 3.7). Severity of RLS correlated with the impairment of subjective sleep quality ($r = 0.281$, $p = .007$) but not with self-rated depressive symptoms ($r = 0.119$, $p = .237$).

Conclusion: RLS patients scored high on the somatic items of the BDI, particularly on those related to sleep disturbance, but not on the other items that mostly address cognitive symptoms. Our results indicate that RLS might be associated with some features of depression but not with the full spectrum of a depressive disorder. The relationship between the 2 disorders should be investigated in further studies.

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Restless legs syndrome (RLS) is a distressing sensorimotor disorder occurring with a 5% to 10% prevalence in the United States and in Western European countries.^{1–5} Clinical diagnostic criteria were outlined by the International RLS Study Group in 1995 and revised in 2003.^{6,7} According to the 4 minimal diagnostic criteria, RLS is characterized by (1) an urge to move accompanied by unpleasant feelings in the legs, often referred to as pain by the patients, and symptoms that (2) occur most prevalently in the evening and at night, (3) worsen during periods of rest, and (4) are relieved by movement. Although the legs are usually most severely afflicted, other parts of the body such as the arms may also be involved. Restless legs syndrome is often accompanied by severe sleep disturbances due to the nocturnal occurrence of symptoms. Sleep interruption and daytime fatigue are the complaints that disturb patients to the greatest degree and are, in most cases, also the reason for consulting a physician.⁵ Restless legs syndrome still is an underdiagnosed disorder, often called "the most common disorder you never heard of." Patients, on average, have been seeking medical advice for at least 2 years before the correct diagnosis is made.⁸ Restless legs syndrome patients often complain about symptoms indicating depression. In a retrospective evaluation, 45% of RLS patients were reported to be diagnosed as having psychological/psychiatric disorders (most often depression) before being given the diagnosis of RLS.⁹

An association between RLS symptoms and depressive mood,¹⁰ tension state,¹¹ and elevated scores for depressive symptoms^{12,13} has been observed in earlier studies. Actual epidemiological surveys applying valid diagnostic criteria demonstrated self-reported deterioration of mental health,¹ self-reported depressed mood, and social isolation in RLS patients.³ Furthermore, assessments of quality of life indicate diminished well-being in patients with RLS.^{4,14} Evaluation of depressive symptoms

Table 1. Studies Assessing Prevalence or Severity of Depressive Symptoms in Patients With Restless Legs Syndrome (RLS)

Study	No. of RLS Patients	Method of Assessing Depressive Symptoms	Mean Score for the Assessed Depressive Symptoms		Cutoff Value	Remarks
			RLS Patients	Controls		
Rothdach et al, 2000 ²	36	CES-D	11.6	7.8	Scores > 16 are commonly considered indicative of depression	Expert-rating scale
Banno et al, 2000 ⁹	218	Diagnosis of affective disorder according to ICD-9	NA	NA	Diagnostic criteria fulfilled or not	45% of the RLS patients were registered in a database with the diagnosis of a comorbid mood disorder (depression or affective psychosis) Number of days within the past 30 days with mental health considered to be "not good"
Phillips et al, 2000 ¹	170	Self-reported mental health "not good"	9.76 (days)	4.98 (days)	NA	Assessed by the question, "Are you affected by depressed mood without any recognizable reason?" Answer: yes/no
Ulfberg et al, 2001 ³	231	Likelihood of self-reported depressiveness	Adjusted odds ratio: 2.6	NA	NA	Self-rating scale
Saletu et al, 2002 ¹⁶	33	Zung Self-Rating Depression Scale (SDS)	SDS index: 49.8 ± 10.6 ^b	SDS index: 37.0 ± 5.8 ^b	SDS index (raw score × 1.25); > 50	Expert-rating scale
Sevim et al, 2004 ¹⁵	103	Hamilton Rating Scale for Depression	9.27 ± 5.03 ^b	5.88 ± 4.99 ^b	< 10 consistent with normal mood	Expert-rating scale
Vandeputte and de Weerd, 2003 ¹⁷	154 ^a	Beck Depression Inventory	11.88 ± 0.65 ^b	NA	10–14; on the border of depression; > 15: mild depression	Self-rating scale. Patients with RLS and with PLMD were evaluated. Treated and untreated patients were not separated
Winkelmann et al, 2005 ¹⁸	130	Diagnosis according to DSM-IV (CID)	Adjusted odds ratio for major depression: 2.6	NA	NA	Structured diagnostic telephone interview. 82% of patients evaluated were treated for RLS

^aTotal includes PLMD patients.^bMean ± SD score.

Abbreviations: CES-D = Center for Epidemiologic Studies Depression Scale, CID-I = Composite International Diagnostic Interview, NA = not applicable, PLMD = periodic limb movement disorder.

with validated expert-rating scales revealed slightly though significantly elevated scores in various studies (Table 1). Two studies used expert-rating scales in RLS subjects: one study² used the Center of Epidemiologic Studies Depression Scale, and another study¹⁵ used the Hamilton Rating Scale for Depression. Another 2 studies assessed depressive symptoms in RLS by means of validated self-rating questionnaires. One study¹⁶ used the Zung Self-Rating Depression Scale and demonstrated a mean score on the border of depression in untreated RLS patients. The other study¹⁷ used the Beck Depression Inventory (BDI), which yielded scores in the upper normal range in a mixed group of treated and untreated patients with RLS or periodic leg movement disorder, which is characterized by insomnia or daytime sleepiness related to the presence of periodic leg movements in sleep.¹⁹ Up to now, the only study using a structured diagnostic interview found a 12-month prevalence of a depressive episode in 17.7% of patients (lifetime prevalence = 36.9%) and dysthymia in 5.3% of patients (lifetime prevalence = 5.3%) according to DSM-IV criteria.¹⁸ In that study, the majority of RLS patients interviewed (82%) received pharmacologic treatment for their RLS.

Since sleep disturbances are considered a relevant symptom for the diagnosis of depression and are also assessed in expert-rating and self-rating depression questionnaires, one can assume that the high prevalence of depressive symptoms in RLS may, at least partly, be related to the sleep complaints reported by RLS patients. If so, this relationship would have clinical implications, as one would expect that treatment of RLS ought to resolve the depressive symptoms to some extent. To explore the relationship between depressive symptoms and sleep disturbances in RLS, we retrospectively evaluated completed self-rating scales of untreated patients with idiopathic RLS investigated in the Sleep Disorders Unit of our department. We postulated that sleep-related complaints would have an impact on the frequency and severity of self-reported depressive symptoms.

METHOD

Patients

Patients were diagnosed as having RLS according to established diagnostic criteria.^{6,7} Records of all RLS patients investigated in our

Sleep Disorders Unit from April 1999 (the first time we used the RLS Severity Scale when participating in the study validating it²⁰) to December 2004 were inspected. As the study was a retrospective evaluation, Institutional Review Board approval was not needed. Only those 172 patients were considered for the study for whom completed questionnaires assessing RLS severity and depressive symptoms (BDI²¹) were available. Of these, only patients who had idiopathic RLS and were not taking any medication potentially influencing RLS were included. Patients were excluded from the evaluation for the following reasons: ongoing treatment of RLS with any type of substance (18 patients); withdrawal of substances influencing RLS or sleep during the last 2 weeks before investigation (8 patients taking benzodiazepines, 5 patients taking opiates, 1 patient taking methylphenidate); treatment with corticosteroids (2 patients); treatment with antidepressants or other psychoactive substances (24 patients); comorbidity with sleep apnea syndrome (4 patients untreated, 7 patients treated with continuous positive airway pressure), human immunodeficiency virus (2 patients), narcolepsy (1 patient), or Parkinson's disease (1 patient); and RLS secondary to another condition (1 patient, due to iron deficiency). The use of herbal extracts as sleeping aids was not an exclusion criterion. One hundred patients were included in the final evaluation. Most (95%) of the included patients were de novo RLS patients. The diagnostic procedure comprised a semistructured interview to ascertain history of sleep disturbance, physical and psychiatric examination, and obtaining of laboratory data and polysomnography findings.

Rating Scales

Severity of RLS was assessed by the International RLS Study Group rating scale (IRLS), a validated questionnaire developed by the International RLS Study Group.²⁰ The IRLS is a brief, patient-completed instrument that can be used to assess RLS severity for purposes of clinical assessment, research, or therapeutic trials. It comprises 10 questions addressing symptoms of RLS and their impact on the patient's life. Each question is to be answered on a scale of 5 points (0–4), higher scores indicating greater severity of symptoms. A total score of 0 to 10 points indicates mildly severe RLS; 10 to 20 points, moderately severe RLS; 20 to 30 points, severe RLS; and 30 to 40 points, very severe RLS.

Depressive symptoms were assessed by the BDI.²¹ The BDI is a commonly used validated questionnaire for assessing self-estimated severity of depressive symptoms. The BDI comprises 21 questions, each offering 4 possible answers (0–3). Higher scores indicate greater severity of symptoms. Depending on the total score, the grade of depressive symptoms is classified as follows: 0 to 9 points, no or minimal depression; 10 to 14 points, on the border of depression; 15 to 20 points, mild depression; 21 to 30

points, mild to moderate depression; 31 to 40 points, moderate to severe depression; 41 to 63 points, severe depression.

The Pittsburgh Sleep Quality Index (PSQI)²² was designed to measure sleep quality in clinical populations. It is a validated self-rating questionnaire that assesses sleep quality and disturbances over a 1-month time period. We used a slightly modified version assessing the same questions over a 2-week interval.²³ The PSQI comprises 19 items that generate 7 component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. The sum of these component scores yields 1 global score. The global score of the PSQI ranges from 0, indicating no impairment of sleep at all, to 21, indicating severe subjective impairment of sleep. Fully completed PSQI questionnaires were available from 92 of the 100 patients included in the study.

Both the BDI and the PSQI are routinely used questionnaires in our Sleep Disorders Unit. Patients filled in the questionnaires the day before the polysomnography investigation.

Statistics

Since the data points did not follow a normal distribution, correlations were calculated according to Spearman. The level of significance (2-tailed) was set at $p \leq .05$. Values are reported as mean \pm SD.

Since both the IRLS and the BDI have items addressing sleep disturbances (item 4 in the IRLS and item 16 in the BDI), we used the method of prorating for statistical purposes. In doing that, we removed the overlap items assessing the severity of sleep disturbances from both scales and obtained the prorated sum score by multiplying the sum of the remaining items by 10/9 for the IRLS and by 21/20 for the BDI.

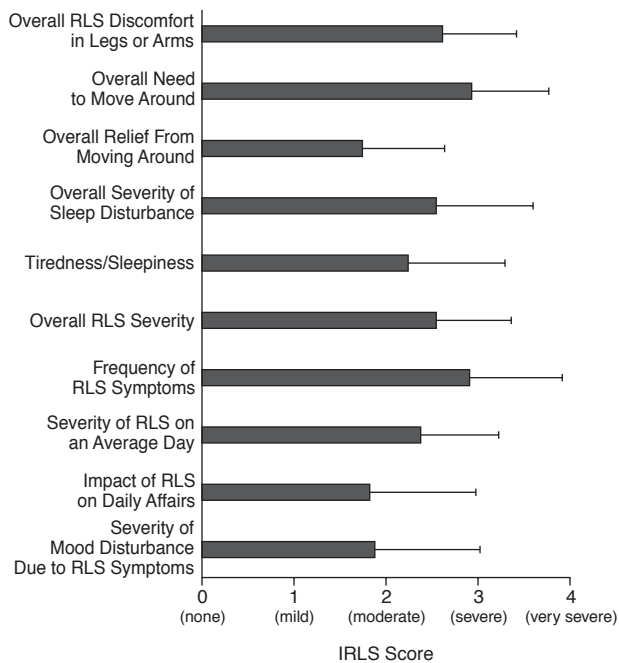
RESULTS

One hundred patients were included in the study, 65 women (mean \pm SD age = 55 \pm 13 years) and 35 men (mean \pm SD age = 55 \pm 12 years). Most patients were moderately to severely afflicted with RLS (mean \pm SD IRLS score = 23.6 \pm 6.7 points). Mean scores for the 10 items assessed by the IRLS are shown in Figure 1. Items indicating symptom severity ("symptom" factor)²⁴ were scored higher than those indicating the impact of the disorder ("impact" factor).²⁴

Depressive Symptoms Assessed by the Beck Depression Inventory

The mean \pm SD overall score on the BDI was 9.3 \pm 5.6 points. Patients scored the highest on the "reduced sleep," "loss of energy," and "work difficulties" items, items indicating physical symptoms of depression. Items typical for

Figure 1. Mean (SD) Item Scores on the IRLS in 100 Patients With Restless Legs Syndrome (RLS)



Abbreviation: IRLS = International RLS Study Group rating scale.

cognitive-affective symptoms such as “depressed mood,” “feelings of failure,” “guilt,” “feelings of punishment,” “self-contempt,” and “self-reproach” received low scores (Figure 2). Of the 100 patients, 83 (51 women, 32 men) had a BDI score < 15 (no depression or on the border of depression), 14 patients (12 women, 2 men) had a BDI score of 15 to 20 (mild depression), and 3 patients (2 women, 1 man) had a BDI score of 21 to 30 points (mild to moderate depression). The distribution of item frequency in the 17 patients expressing mild to moderate depressive symptoms (BDI score ≥ 15) was similar to that in the total RLS population, with the highest scores for “reduced sleep” (2.1 ± 0.7 points) followed by “loss of energy” (1.7 ± 0.8 points), “irritability” (1.4 ± 0.8 points), and “work difficulties” (1.4 ± 0.7 points). The mean \pm SD IRLS score in this subset of patients was 25.5 ± 6.2 points.

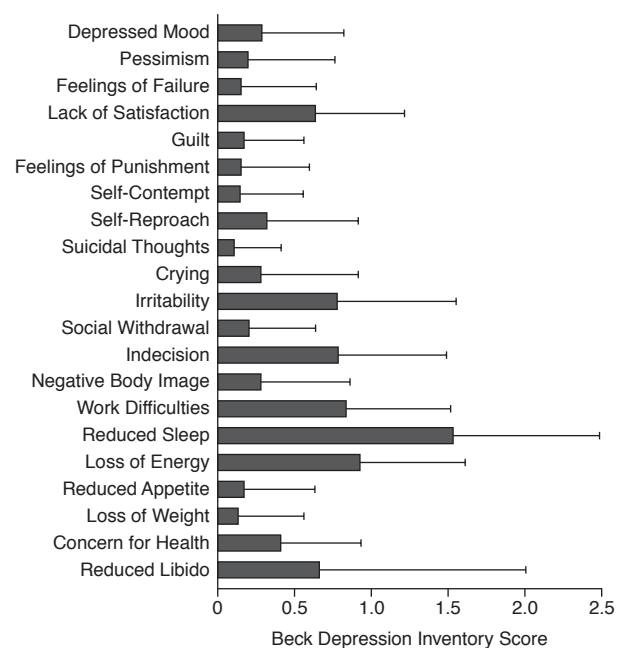
Subjective Sleep Quality Assessed by the Pittsburgh Sleep Quality Index

Patients estimated their sleep quality as slightly to moderately impaired (10.9 ± 3.7 points). The components indicating difficulties in falling asleep or maintaining sleep reached the highest scores (Figure 3).

Relationship Between Severity of RLS, Depressive Symptoms, and Subjective Sleep Quality

Severity of RLS correlated with the impairment of subjective sleep quality (IRLS score vs. PSQI score;

Figure 2. Mean (SD) Item Scores on the Beck Depression Inventory in 100 Patients With Restless Legs Syndrome^a



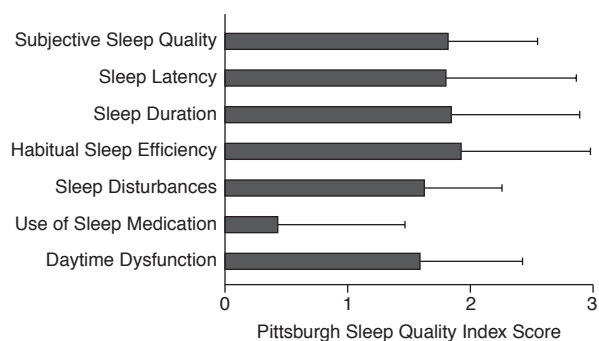
^aHigher scores indicate greater severity of symptoms.

$r = 0.281$, $p = .007$) but not with self-estimated depressive symptoms (IRLS score vs. BDI score; $r = 0.119$, $p = .237$). However, a higher degree of sleep impairment was correlated with higher depression scores (PSQI score vs. BDI score; $r = 0.329$, $p = .001$). Score on item 10 of the IRLS addressing the severity of mood disturbance (“How severe is your mood disturbance from your RLS symptoms—for example angry, depressed, sad, anxious, or irritable?”) correlated significantly with scores on the BDI items “work difficulties” ($p = .003$), “suicidal thoughts” ($p = .007$), “lack of satisfaction” ($p = .011$), “depressed mood” ($p = .012$), “loss of energy” ($p = .018$), and “indecision” ($p = .041$) and also with the global BDI score ($r = 0.213$, $p = .034$). Score on item 4 of the IRLS addressing severity of sleep disturbance (“Overall, how severe is your sleep disturbance from your RLS symptoms?”) showed a strong correlation with the global PSQI score ($r = 0.371$; $p = .000$) and with the PSQI component scores “subjective sleep quality” ($p = .024$), “sleep duration” ($p = .003$), “sleep efficiency” ($p = .009$), and “daytime dysfunction” ($p = .031$) and showed a tendency with “sleep disturbances” ($p = .063$).

DISCUSSION

Our study yields 2 main findings. First, 17% of patients with moderate to severe RLS symptoms had slightly elevated scores on the BDI, indicating a possible

Figure 3. Mean (SD) Component Scores on the Pittsburgh Sleep Quality Index in 100 Patients With Restless Legs Syndrome^a



^aHigher scores indicate greater impairment of the subjects on the component scales.

mild or mild to moderate depressive syndrome. In these patients in particular, but also in the whole patient population, elevated item scores were mainly recorded on sleep-related symptoms (reduced sleep, loss of energy) and the consequences thereof (irritability, work difficulties). Second, depressive symptoms in patients with RLS seem to be related to the impairment of sleep rather than to the severity of RLS symptoms. Thus, RLS seems to be associated with only a part of the spectrum of depressive symptoms and not with all of them.

Results of our study regarding the occurrence of depressive symptoms are in line with previous investigations (see Table 1). Both expert-rating and self-rating depression scales demonstrated elevated depression scores in RLS patients with mean values in the upper normal range.^{2,15,16,17} Similarly, the lifetime and 12-month prevalence of depressive disorders was found to be increased in RLS compared to non-RLS subjects¹⁸ when using the Composite International Diagnostic Interview^{25,26} according to DSM-IV.

The increased incidence of depressive symptoms in RLS patients found in previous studies as well as in our study may be interpreted from different angles, as depression and sleep disturbances are mutual confounds and sleep-related symptoms are relevant contributors to the diagnosis of a depressive disorder. Studies evaluating the relationship of sleep disturbances and psychiatric disorders showed that subjects with chronic insomnia are at a high risk of developing major depressive disorder (MDD) later on.^{27,28} The elevated rate of MDD in RLS patients¹⁸ comes as no surprise from this viewpoint, as most RLS patients suffer from insomnia for a long time before being diagnosed with and treated for RLS.⁵ In line with this consideration, a previous study reported a modulating effect of RLS-related sleep disturbances on the association of RLS severity with emotional distress.²⁹ On the other hand,

difficulties in maintaining sleep are frequent in affective disorders. DSM-IV diagnostic criteria for MDD³⁰ are based on 9 characteristic symptoms, of which any 5 must be present for confirming the diagnosis. It is noteworthy that at least 5 symptoms can arise directly from or indirectly as the consequence of a sleep disturbance (insomnia or hypersomnia, fatigue or loss of energy, diminished ability to concentrate, mental/physical sluggishness or agitation, and diminished interests or pleasure in all activities). The high impact of sleep-related complaints on depressive symptoms in RLS as it was shown in our study may, at least partly, account for the high number of patients fulfilling the diagnostic criteria for MDD in previous studies.

Insomnia, found to be the most frequently reported symptom of MDD in our patients with RLS, has also been found to be a prevailing symptom of MDD in patients with other somatic disorders, such as chronic painful physical conditions (CPPCs).^{31,32} In CPPC, physical symptoms of depression such as sleep disturbances, fatigue, psychomotor retardation or agitation, and difficulties with concentration are prominent and may be directly related to the chronic pain. On the other hand, it has been shown that patients with chronic pain tend to attribute their depressive physical symptoms to their painful physical condition.^{33,34} Because of the complex relationship between pain and depressive symptoms, it has been suggested that depression should be assessed differently in subjects with physical pain.³⁴ This proposal was made in support of the recommendation of DSM-IV that symptoms clearly related to a physical condition should be discarded from diagnostic criteria. Similar considerations may also be relevant in the case of RLS patients, and the exclusion of sleep-related symptoms in the diagnosis of MDD might give a different rate of depressive disorders in patients with RLS. However, this approach would be based merely on an assumption that sleep disturbances are fully accounted for by symptoms of RLS. Adding to this problem is the fact that, to date, we have no data on the course of depressive symptoms in patients with sufficient treatment of RLS.

To date, one can only speculate on the relationship between RLS and depression. On the one hand, the comorbidity may simply reflect an association of both disorders, as is known to exist for depression with other somatic diseases such as stroke,³⁵ diabetes,³⁶ coronary artery disease,³⁷ or renal failure.³⁸ On the other hand, however, a genuine comorbidity of RLS and depressive disorders cannot be excluded either. A common pathway of RLS and depression may be delineated from the involvement of the dopaminergic system in both disorders. The dopaminergic system is thought to be involved both in the pathophysiology of depression³⁹ and in the pathophysiology of RLS,⁴⁰ and dopaminergic substances are regarded as the first choice of treatment in RLS.⁴¹ Furthermore, one

should also consider the third possibility that RLS is associated with only some depressive symptoms but not with the full spectrum of a depressive disorder. As we have shown, RLS patients score high on the somatic items of the BDI, particularly on those related to sleep disturbance, but not on the items that mostly address cognitive symptoms. The association of RLS and depression therefore might not necessarily indicate a common biological basis for both conditions, but could instead be a consequence of symptom overlap producing some of the symptoms we recognize as depression. If so, RLS engenders some depressive symptoms but is most likely not directly associated with what we consider a major depressive disorder.

The study presented here has some limitations due to the method of assessing depressive symptoms and due to patient selection. We retrospectively evaluated scores on the BDI. The BDI is the most commonly used self-rating instrument for depressive symptoms. The power of resolution of the BDI has been reported to be satisfactory in many studies comparing different diagnostic groups with one another and with controls.⁴²⁻⁴⁴ Compared to expert-rating scales, the BDI appeared to be biased in having a relatively larger number of variables concerning depressive cognitive attitudes, in contrast to variables reflecting functional impairment or somatic symptoms.⁴⁵ Therefore, our study may still underestimate the impact of disturbed sleep on depressive symptoms, as RLS patients had low scores on items reflecting maladaptive cognitive-affective symptoms and attitudes. The results of the present study also may be influenced by the way patients were selected. In contrast to epidemiological studies, our patients represent a subset of affected patients, who usually suffer more intensely than patients not seeking medical help. Additionally, we did not include RLS patients receiving antidepressant medication since it has been reported that some antidepressants trigger or worsen symptoms of RLS.^{46,47} By not including these patients, we might have excluded the RLS patients suffering the most from depression. A further, methodological objection may be seen in the relatively low variance of the correlating scales (BDI vs. IRLS and BDI vs. PSQI). However, the high significance of their correlation (small p values) supports the assumption of an authentic relationship between these parameters. The investigation of a larger patient population could further clarify this issue. For the problem of overlapping items addressing sleep disturbances, we had to prorate scores of the items addressing sleep on both the BDI and the IRLS. This problem may be circumvented by the use of a control group in future studies.

In conclusion, untreated RLS patients with moderate to severe RLS had slightly elevated BDI scores, with the major contribution coming from sleep-related symptoms (reduced sleep, loss of energy) and their consequences (irritability, work difficulties). Restless legs syndrome might therefore be associated with some depressive

symptoms but not with the full spectrum of a depressive disorder. Longitudinal studies exploring the relationship of depressive symptoms to RLS in untreated and treated patients may shed light on the relationship between the 2 conditions.

Drug name: methylphenidate (Ritalin, Metadate, and others).

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