The biopsychosocial effects of restless legs syndrome (RLS)

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Abstract: The symptoms of restless legs syndrome (RLS) are associated with reductions in patients' quality of life (QoL) and mental heath. Sleep disturbance, which is often the most troublesome symptom of RLS, may have a negative impact on patients' daytime cognitive abilities. Research has established a relationship between the symptoms of RLS and mood symptoms, but causality is unclear. Some studies have indicated that the symptoms of RLS precede those of depression or anxiety, and others relate the severity of mood symptoms to the severity of RLS symptoms. Associations between the sleep disturbance produced by RLS and patients' mood symptoms have also been demonstrated. The impact of RLS symptoms and their treatment on QoL, mental health, and cognition are reviewed herein.

Keywords: RLS, depression, anxiety, quality of life, treatment

Introduction

Restless legs syndrome (RLS) is a chronic neurological disorder. Epidemiological studies report that RLS affects about 5%–10% of adults in the general population (Phillips et al 2000; Ulfberg et al 2001a, 2001b). Its four key diagnostic symptoms are (Allen et al 2003):

1. An urge to move the legs, usually accompanied or caused by uncomfortable sensations in the legs.
2. The symptoms begin or worsen during periods of rest or inactivity.
3. The symptoms are partially or totally relieved by movement, at least as long as the activity continues.
4. The symptoms are worsened in the evening or at night, especially at initial presentation.

All four of these symptoms are required to make a diagnosis of RLS. In addition, the presence of periodic leg movements (PLMs) supports the diagnosis, as 80%–90% of patients with RLS experience PLMs (Montplaisir et al 1997). RLS may present as a primary disorder, or secondary to other conditions such as iron deficiency anemia, end-stage renal disease, and normal pregnancy (Allen and Earley 2001).

The etiology of RLS is not proven, but central dopaminergic dysfunction is proposed, based on the benefits of dopamine agonists and exacerbation of RLS symptoms by dopaminergic antagonists. Genetic linkage in familial disease and iron metabolism offer other etiologic areas for exploration. The dopamine agonists have demonstrated efficacy in the management of RLS (see below); indeed, a response to dopaminergic therapy is a supportive clinical feature in the diagnosis of RLS (Allen et al 2003). In addition, the dopamine antagonist risperidone has been reported to induce RLS symptoms (Wetter et al 2002). In studies of potential candidate genes involved in dopaminergic neurotransmission, links to the development of familial RLS have been found on chromosome 12q, suggesting a link to dopamine metabolism for this disorder (Desautels et al 2001, 2002). Finally, studies of CNS iron metabolism

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suggest impact on dopaminergic function, as CNS cellular insufficiency of iron reduces the activity of tyrosine hydroxylase, and may impact the expression of dopamine transporters or receptors (Connor et al 2003).

For 60%–80% of patients with RLS, sleep disturbance is their most distressing symptom, representing the primary reason to seek treatment (Allen et al 2003; Hening et al 2004; Rijsman et al 2004a). Sleep deprivation impacts on daytime functioning; for example, patients report reduced concentration and attention, increased daytime sleepiness, and some mood disturbance (Hening et al 2004; Rijsman et al 2004a). In addition, several studies have demonstrated that RLS has detrimental effects on patients' quality of life (QoL).

Effects of RLS on patients' QoL

Effects in primary RLS

RLS has a detrimental impact on patients' QoL. A large survey of the general populations of six countries identified people with all four diagnostic symptoms of RLS (Allen et al 2005). The survey reported the characteristics of people who experienced symptoms of RLS that caused moderate distress, at least twice-weekly (Allen et al 2005). Most of these people (85%) reported that the symptoms of RLS had a negative impact on their daytime functioning. Most commonly, 51% of patients agreed with the statement "These symptoms have a negative influence on my mood", 48% agreed that "I lack energy when I suffer from these symptoms", and 40% agreed that "My daily activities are disturbed". Smaller proportions of patients (20%–28%) reported that: their social life was affected by symptoms, they were distracted from doing their job, they had a feeling of desperation associated with the symptoms, their partner was kept awake by their symptoms, and their personal relationships were affected. Responses of this same group of RLS sufferers to the Medical Outcomes Study Short Form 36-item (SF-36) questionnaire also indicated that they had lower QoL scores than the general population norms. Moreover, their scores on the SF-36 were similar to those of patients with other chronic medical conditions, such as type-2 diabetes mellitus, depression, and osteoarthritis with hypertension (Allen et al 2005).

Similar results were produced in a survey of 85 patients with diagnosed primary RLS (Abetz et al 2004). These patients showed significantly lower scores (reflecting worse QoL) than the general-population norms on all eight domains of the SF-36 scale. The severity of RLS (assessed using the patient version of the International Restless Legs Scale) affected scores on most of the domains: as severity increased, scores for role–physical, bodily pain, vitality, social functioning, role–emotional, and mental health all decreased (worsened). In addition, the SF-36 scores for these patients with RLS were similar to or worse than those for patients with other medical conditions. Patients with RLS had significantly lower scores on seven of the eight SF-36 domains than patients who had recently experienced a myocardial infarction. In addition, patients' scores on most domains were similar to those for patients with other chronic illnesses, such as type-2 diabetes, depression, chronic obstructive pulmonary disease with hypertension, and osteoarthritis with hypertension (Abetz et al 2004).

Effects in patients with secondary RLS

In a survey of patients undergoing dialysis, 70% reported all four diagnostic symptoms of RLS. The presence of these symptoms was associated with statistically significantly worse QoL on most of the domains of the Kidney Disease QoL questionnaire, which comprises the eight domains of the SF-36 and 11 domains specific to patients with kidney disease (Mucsi et al 2005). Likewise, in a second study of patients undergoing dialysis, those with the symptoms of RLS showed significantly worse scores on the "emotion" domain of the sickness impact profile (SIP) (Rijsman et al 2004b). This difference was even greater when the scores for patients with symptoms of RLS and PLMs in sleep were compared with the scores for patients with none of these symptoms.

Effects of RLS on patients' mental health

Impact on mood

Several studies have shown an association between the symptoms of RLS and worse mental health in comparison with healthy controls. Studies demonstrating an association between the symptoms of RLS and those of depression were recently reviewed by Picchietti and Winkelman (2005). Their review described findings from population-based surveys and studies of patients with RLS. In one survey, people in a representative population who had the diagnostic symptoms of RLS had a higher incidence of depressive symptoms and lower self-reported mental-health scores on the SF-36 (Rothdach et al 2000). In another population-based survey of men, respondents with the symptoms of RLS were more likely to report depressed mood and to complain of decreased libido in comparison with population

norms (Ulfberg et al 2001a). A third, large population-based survey used standard rating scales – the Hamilton Depression Rating scale (HAM-D) and Hamilton Anxiety Rating scale (HAM-A) – to assess depression and anxiety in people reporting the diagnostic symptoms of RLS (Sevim et al 2004). In this survey, people with RLS had statistically significantly higher total scores on the HAM-A and HAM-D than matched controls (even when three questions relating to sleep problems were excluded from the HAM-D, and one question from the HAM-A). Scores on most individual items of the HAM-A and HAM-D were also statistically significantly higher in people with RLS symptoms than in controls. Moreover, scores on these two rating scales were positively correlated with the severity of RLS symptoms, whereas the presence of other comorbid diseases (eg, hypertension, anemia, chronic kidney disease, diabetes mellitus, and migraine) had no effects on anxiety and depression scores. Thus, the authors concluded that the presence of RLS symptoms "was probably the major determining factor for the anxiety and depression scores, with higher scores correlating with more severe RLS" (Sevim et al 2004).

In these population-based surveys, data were obtained from patients who reported the symptoms of RLS but had no formal diagnosis of the disorder. These population-based studies are consistent with studies of patients who received a formal diagnosis of RLS (Picchietti and Winkelman 2005). In a study of 33 patients with RLS, Saletu et al reported statistically significantly more symptoms of depression and anxiety (on the Zung Self-Rating Depression and Anxiety Scales), and a lower quality of life than in healthy controls (Saletu et al 2002a, 2002b). This study also compared EEG changes in RLS patients and healthy controls. RLS patients demonstrated more activity in the frontal, frontopolar, and frontotemporal regions, a trend towards higher activity over the parietal and left temporal regions. The EEG differences were characterized by a significant increase in delta and fast alpha power, a decrease in slow alpha power, acceleration of the dominant frequency in the alpha centroid, and slowing of the delta/theta centroid (Saletu et al 2002b). These changes were similar to those previously reported in patients with major depressive disorder (MDD) (Saletu et al 1996). In addition, the greatest differences between patients with RLS and controls were seen in those EEG measures that have been found (in another group of patients with depression) to be correlated with scores on the HAM-D.

Diagnoses of mood disorders

Although studies have demonstrated an increase in the symptoms of depressed and anxious mood in patients with the symptoms of RLS, symptom severity may not meet the criteria for clinical diagnosis of a mood disorder or of RLS. For example, in the large population survey reported by Sevim et al (2004), mean score for the group of people reporting symptoms consistent with RLS were 8 points on the HAM-A (lower cut-off score for treatment of mild anxiety is 18 points) and 9 points on the HAM-D (a score of 10–13 is considered to reflect mild depression). The authors proposed that the symptoms of depression and anxiety were relatively mild in this survey because it was population-based, and the RLS may have been mild, as only 30% of the people reporting symptoms of RLS had complained about those symptoms to a healthcare practitioner. The authors speculate that patients with a formal diagnosis of RLS might have more severe symptoms, which prompted them to seek treatment, and therefore may also report more severe mood symptoms (Sevim et al 2004).

Two studies have investigated the clinical diagnosis of mood disorders in patients with formally diagnosed RLS. One study of 218 RLS patients investigated retrospectively the diagnoses that patients had been given in the 5 years prior to their referral to a sleep-disorders clinic and their diagnosis with RLS (Banno et al 2000). Nearly half the patients (44% of men and 46% of women) had been diagnosed as having a mood disorder (depression NOS [not otherwise specified] or affective psychosis). These diagnoses were reflected in the drugs used by these patients on presentation at the sleep clinic; antidepressants and benzodiazepines were the most commonly prescribed drugs, along with antihypertensives and analgesics. A second study from Germany investigated the prevalence of anxiety and depression by DSM-IV diagnostic criteria in patients with a diagnosis of RLS (Winkelmann et al 2005). In 130 patients, there were higher 12-month rates of any depressive disorder (18% vs 9%), panic attacks (11% vs 4%), panic disorder (9% vs 2%), and generalized anxiety disorder (GAD; 9% vs 2%), than in controls who had a somatic illness. In most patients, the mood disorder appeared after the onset of RLS, suggesting that the symptoms of RLS might either initiate or aggravate depression and anxiety. Moreover, many patients with RLS attributed problems such as depressed mood and reduced interest to their RLS symptoms. Importantly, a large proportion of patients with concurrent

RLS and depression (35%) reported suicidal thoughts as a result of their RLS symptoms (Winkelmann et al 2005).

Relationship between RLS symptoms and mood disorders

Although the above cited studies have demonstrated that the symptoms of depression and anxiety are often comorbid with RLS, none was designed to demonstrate a causal relationship between RLS and the symptoms of depression and/or anxiety. It is possible that the two sets of symptoms co-exist, as the prevalence of RLS and of mood and anxiety disorders is high. Winkelmann et al from Germany suggested that, as RLS is a highly familial disorder (Winkelmann et al 2000), the increased risk of comorbid mood symptoms and disorders may also have a genetic component (Winkelmann et al 2005). A common CNS mechanism for the symptoms of RLS and depression might also relate to changes in central dopaminergic function (Picchietti and Winkelman 2005). Nevertheless, evidence showing that the mood disorder appeared after the onset of RLS, and attribution of the mood symptoms to RLS, supports the possibility of some causal relationship in at least some patients (Winkelmann et al 2005).

Another confound is the similarity of clinical symptoms or consequences of RLS and mood disorders (Table 1). In particular, patients with RLS, MDD, or GAD may all present with insomnia, daytime tiredness/fatigue, and poor daytime concentration. This overlap in symptomatology may be reflected in the results reported by Banno et al (2000), which showed that many patients with RLS had previously been given a diagnosis of a mood disorder. Some studies have indicated a relationship between the sleep problems associated with RLS and comorbid mood disorder (Kushida et al 2004; Hornyak et al 2005). In addition, in one of these studies, patients with RLS showed elevated item scores on sleep-related symptoms of depression on the Beck Depression Inventory but not on cognitive–affective items. The severity of RLS was correlated with severity of sleep problems, but not with patients' scores for depression, whereas the scores for sleep problems were correlated with scores for depression (Hornyak et al 2005). Thus, one possible reason for the apparent relationship between RLS and mood disorders is that patients with RLS are not actually suffering from a mood disorder, but are simply reporting high scores on sleep-related items of mood inventories. Chronic insomnia alone is considered to be a predictor of later depressive or anxiety disorder (Ford and Kamerow 1989; Breslau et al 1996).

Other studies, however, have indicated that sleep-related symptoms do not account for the increased incidence of mood symptoms and disorders in patients with RLS, as they report higher scores for depression and anxiety even when questions relating to sleep problems are excluded from the rating scales (Sevim et al 2004). In addition, when the presence of RLS as a non-specific stressor is taken into account, an increased prevalence of mood symptoms persists in patients with RLS (Sevim et al 2004; Winkelmann et al 2005). The symptoms and consequences of RLS may have direct detrimental effects on patients' mental health, although the nature of the relationship between RLS, sleep disturbance, and mood disturbance/disorder requires further study.

Cognitive effects of RLS

Few studies have reported the cognitive effects of RLS. In a population-based survey, just under 20% of patients reported that they had difficulty concentrating in either the afternoon or evening (Allen et al 2005). In a small polysomnographic study, patients with RLS showed significant deficits on two tests designed to show prefrontal cortical functioning, when compared with normal controls (Pearson et al 2006). The authors concluded that these deficits were similar to those produced by the loss of a night's sleep, and, therefore, might have been related to the sleep disturbance caused by RLS. An association has also been reported between the symptoms of attention-deficit/hyperactivity disorder (ADHD) and RLS (Wagner et al 2004). Patients with RLS were reported to have a higher incidence of ADHD than those with other sleep disorders (24% vs 3%), and the severity of RLS symptoms was higher in patients who also had symptoms of ADHD than in those who did not. These authors proposed either that the ADHD symptoms of inattention/hyperactivity and reduced concentration may result from the motor symptoms of RLS,

Table 1 Symptoms of depression, generalized anxiety, and RLS

Symptom	MDD	GAD	RLS
Sadness	++++	++	++/–
Insomnia	+++	+++	+++
Sleepiness	+	+/–	+/–
Tiredness/fatigue	+++	++	++
Poor concentration	++	+++	++
Feeling guilt/suicidal	+++	+	+

+ Feature of this disorder (more crosses indicates increased prominence);
– Feature not generally associated with this disorder.
Abbreviations: GAD, generalized anxiety disorder; MDD, major depressive disorder; RLS, restless legs syndrome.

or that the two disorders might share a common dopaminergic etiology (Wagner et al 2004).

Treatment of RLS and impact on biopsychosocial functioning

Several therapeutic classes, particularly those that target dopamine, have demonstrated efficacy on the symptoms of RLS and on its sequelae, such as sleep disturbance. There are also reports that the dopaminergic therapies reduce the biopsychosocial effects of RLS, particularly QoL.

Treatment with ropinirole

The most extensively studied drug for RLS is the dopamine agonist ropinirole. A series of large-scale, placebo-controlled trials has been conducted with this drug, leading to its approval for the treatment of moderate-to-severe primary RLS in adults in eight countries, including the USA, France, Switzerland, Australia, and New Zealand. There were three clinical trials in this program – TREAT RLS 1 and 2 (Therapy with Ropinirole: Efficacy And Tolerability in RLS 1 and 2) and TREAT RLS US – which were multicenter, randomized, double-blind, parallel-group, placebo-controlled trials involving a total of 932 patients with moderate-to-severe RLS, treated for 12 weeks (Trenkwalder et al 2004; Walters et al 2004; Bogan et al 2006). Ropinirole, in comparison with placebo, produced statistically significant improvements in the symptoms of RLS. These studies also demonstrated that ropinirole produced significantly greater improvements than placebo in the validated, disease-specific QoL scale, the RLSQoL questionnaire. In addition, in the TREAT RLS 2 trial only (Walters et al 2004), ropinirole produced a significantly greater improvement in the mental-health domain of the SF-36 than placebo, along with significant improvements in social functioning and vitality. However, there were no significant effects on the other domains of the SF-36 in this trial, and no significant differences between ropinirole and placebo on the SF-36 in the TREAT RLS 1 trial (Trenkwalder et al 2004). The TREAT RLS US trial also included assessments on two other scales, which demonstrated positive effects on mood symptoms (Bogan et al 2006). In subsets of patients with scores on the Hospital Anxiety and Depression Scale that corresponded to at least mildly anxious/depressed mood (≥8 on either subscale), ropinirole produced a statistically significant reduction in the anxiety score, compared with placebo. Ropinirole produced a numerical, but not statistically significant, reduction in patients' depression scores in comparison with placebo. In addition, ropinirole was associated with improvements on the Profile Of Mood States scale, with a statistically significant improvement compared with placebo observed for the "total mood disturbance" and "vigor activity" domains (Bogan et al 2006). The most common adverse event during these clinical trials of ropinirole was nausea; most adverse events were mild or moderate in severity, and their incidence declined over time. In the clinical trials for ropinirole, there were few reports of augmentation of RLS symptoms, although duration of monitoring may have been insufficient to properly assess development of augmentation.

Treatment with pramipexole

Pramipexole has been shown to be effective in treating the symptoms of RLS. However, there are few published data on the effects of pramipexole on QoL measures. One study showed that after 4 weeks of open-label use of pramipexole, patients showed significant improvements in QoL and self-rated depressed mood, compared with baseline, although there were no changes in patients' scores for self-rated anxious mood (Saletu et al 2002c). There are also reports of the efficacy of pramipexole in the treatment of depression in both MDD and bipolar II disorder, albeit at doses higher than those generally used to treat RLS (Corrigan et al 2000; Zarate et al 2004). Pramipexole is best avoided in patients with moderate-to-severe renal disease, since it is cleared from the body through the kidney. In addition, augmentation may also be a complication of pramipexole treatment in patients who are treated for a year or more (Silber et al 2003; Winkelman and Johnston 2004).

Treatment with L-dopa

Studies over 20 years with L-dopa have shown that this drug is effective in the management of the symptoms of RLS (Becker et al 1993; Trenkwalder et al 1995; Benes et al 1999; Collado-Seidel et al 1999); it is licensed for use in the treatment of RLS in Germany. In a double-blind, placebo-controlled, crossover trial, QoL evaluation showed that L-dopa treatment was associated with better life satisfaction for patients (resulting from improvements in activities of daily living and leisure activities) and less burden caused by their symptoms (resulting from less severe fatigue and depressive feelings) than placebo treatment (Benes et al 1999). Similar results were produced in another double-blind, placebo-controlled, crossover trial, which included

some patients with RLS secondary to renal disease, as well as patients with primary RLS (Trenkwalder et al 1995). In this study, L-dopa produced, overall, greater improvements in life satisfaction and negative feelings and complaints than placebo. In contrast, another double-blind, placebo-controlled, crossover trial, using the same QoL assessment, showed no significant positive effects of L-dopa on life satisfaction or burden of symptoms in comparison with placebo (Collado-Seidel et al 1999). An open trial of L-dopa also showed no change in patients' QoL or self-rated depression and anxiety after 4 weeks of treatment (Saletu et al 2003). Thus, current data about QoL appear to be inconclusive for L-dopa therapy. In addition, the potential problems of wearing-off of clinical efficacy at the end of the dose (rebound) and augmentation of symptoms limit the use of this therapy in 40%–80% of patients (Trenkwalder et al 1995; Allen and Earley 1996). Therefore, a recent treatment algorithm for RLS recommended that L-dopa should only be used for the treatment of intermittent RLS, as this infrequent use of L-dopa may carry less risk for the development of augmentation or rebound (Silber et al 2004).

Treatment with pergolide

One short-term, double-blind, placebo-controlled study of pergolide has demonstrated its efficacy in improving the symptoms of RLS and measures of QoL (Wetter et al 1999). Pergolide, in comparison with placebo, produced significantly better scores for life satisfaction and negative feelings and complaints. However, pergolide is an ergot-related dopamine agonist, raising safety concerns typical of ergot derivatives, such as fibrotic changes in the cardiac valves (Pritchett et al 2002; Baseman et al 2004).

Treatment with gabapentin

Gabapentin, an analog of gamma-aminobutyric acid, was compared with L-dopa in a small, open-label study involving patients with RLS secondary to renal disease (Micozkadioglu et al 2004). After 4 weeks, both treatments improved the symptoms of RLS. Gabapentin produced significant improvements compared with baseline on three of the eight SF-36 domains (general health, body pain, and social functioning). L-dopa produced significant improvement only in the body-pain domain. Adverse events were not reported in this study. In a small, double-blind, placebo-controlled study of gabapentin, core RLS symptoms, sleep and periodic limb movements were improved (Garcia-Borreguero et al 2002). Gabapentin produced adverse events of malaise and somnolence; but resulted in no patient withdrawal. No measures of QoL were included in the study.

Treatment approaches for comorbid RLS and mood disorders

There are currently no formal treatment guidelines for the management of comorbid RLS and mood disorders. A practical treatment approach for RLS and depression is suggested by Picchietti and Winkelman (2005). The initial treatment should be based on the severity of depression. In patients with RLS and mild depression, or depression that seems to be a consequence of the RLS, the authors recommend that initial therapy should target the symptoms of RLS, as depression may be alleviated by effective management of RLS symptoms. If MDD is moderate to severe, or present even when the symptoms of RLS have been managed, it should be treated with an antidepressant. The authors recommend the use of bupropion. This choice is partly based on the potential association between the use of other antidepressants, particularly the selective serotonin reuptake inhibitors (SSRIs), and the appearance of RLS. Case histories have reported the development of RLS symptoms in patients treated with antidepressants (Bakshi 1996; Sanz-Fuentenebro et al 1996; Hargrave and Beckley 1998; Agargun et al 2002), although larger studies have failed to find such an association (Brown et al 2005). Nevertheless, bupropion may prove a useful agent in some patients with RLS; three case histories were recently reported in which this drug was effective in improving symptoms of both disorders in patients with comorbid depression and RLS (Kim et al 2005).

Patients with RLS and prominent anxiety symptoms may require treatment with an anxiolytic in addition to dopaminergic therapy for the RLS symptoms. The benzodiazepines, particularly clonazepam, have been used in the treatment of RLS. Their efficacy appears to depend mostly on reducing insomnia, rather than managing the motor and sensory symptoms of RLS (Allen and Earley 2001; Saletu et al 2001). Thus, these drugs may be useful in the management of RLS and anxiety, though there are concerns about the long-term use of these agents and patients require monitoring for dependency and declining efficacy. As with depression, if patients have symptoms of anxiety that are a consequence of RLS, these problems may be ameliorated by the effective management of RLS with dopaminergic agents.

Conclusions

Diminished QoL and mental heath are common in patients with RLS. Sleep disturbance may also produce detrimental effects on daytime cognitive abilities and mood. For some patients, the effects on mental health may be so pronounced as to reach the diagnostic criteria for major depressive disorder or generalized anxiety disorder. In some studies the severity of mood symptoms has been shown to correlate positively with the severity of RLS symptoms. In addition, some studies have indicated an association between the sleep disturbance produced by RLS and these mood symptoms, although sleep disturbance does not appear to account fully for these associated mental-health problems. These problems are important, particularly in patients who suffer severe depressive symptoms and suicidal ideation. It is therefore essential that these mental disorders are treated effectively. There is some evidence from clinical trials that diminished QoL and mood symptoms can be treated by dopamine-agonist therapy, which is also effective in managing the symptoms of RLS.

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