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The Real Burden of Restless Legs Syndrome: Clinical and Economic Outcomes

Rachel E. Salas, MD; and Anthony B. Kwan [Order Reprints]

Restless legs syndrome (RLS) is a highly prevalent and substantially underdiagnosed sensorimotor disorder. Only relatively recently have the large impact on patient quality of life (QoL) and the economic burden associated with RLS become more widely recognized. QoL in patients with RLS has been shown to be worse than that of many other chronic conditions, including type 2 diabetes, clinical depression, and osteoarthritis. Sleep disturbance, a cardinal feature of RLS, is the most common and most destructive of its symptoms. More than two-thirds of RLS patients experience serious insomnia, and waking up several times per night is typical for this patient population. Moreover, RLS disrupts rest during waking hours, such as when the patient is sitting or relaxing. Thus, whether awake or asleep, the RLS patient finds little opportunity for the general restorative behaviors necessary for healthy human functioning, resulting in high rates of comorbidities including depression, anxiety, and hypertension. The direct and indirect costs related to RLS have been evaluated in a few studies. Although the cost studies are associated with certain limitations (eg, use of questionnaires), the results show that costs related to RLS are substantial. Healthcare utilization, primarily in the form of doctor visits, constitutes the largest proportion of direct expenditures for RLS in the United States. Indirect costs are also large, primarily due to productivity losses, which are as high as 20% in RLS patients. Effective treatment of RLS is necessary to limit the negative effects of RLS on QoL and to reduce costs associated with the condition.

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Restless legs syndrome (RLS) is a highly prevalent sensorimotor disorder with the potential to exert a very substantial negative impact on the quality of life (QoL) of those affected.[1,2] The 4 standard diagnostic criteria for RLS are: 1) an urge to move the legs, 2) such an urge, or unpleasant feelings, while in a state of rest or inactivity, 3) relief of the urge and unpleasant feeling through movement, and 4) experience or intensification of the urge/unpleasant feelings during the evening or night hours.[3,4]

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The pathophysiology of RLS is not fully understood; however, dopaminergic dysfunction and brain iron deficiency are thought to play a role. RLS is categorized as either primary or secondary. Primary RLS is idiopathic, with no known cause. Secondary RLS is associated with particular medical conditions, for example iron deficiency or chronic renal failure, or the use of certain medications.[5]

Reports regarding the epidemiology of RLS provide somewhat variable prevalence estimates based on the particular countries in which prevalence is measured, and how RLS is reported visà-vis the threshold of symptom severity. The REST General Population study, which included interviews with 15,391 adults in the United States (n = 6014), France, Italy, Spain, and the United Kingdom, found that 7.2% of the total study population met all 4 diagnostic criteria with "any frequency" of symptoms, while 5% experienced symptoms at least once per week, and 2.7% were designated RLS "sufferers," meaning they experienced moderately or severely distressing symptoms at least twice per week. Data from the United States showed that 7.6% experienced the 4 diagnostic symptoms of RLS with any frequency, 5.8% experienced the 4 symptoms once or more per week, and 3.1% were designated RLS sufferers.[2]

A recent systematic review by Innes et al of RLS epidemiology studies from North America and Western Europe—which included 34 papers comprising over 230,000 participants— found prevalence rates in adults ranging from 4% to 29%.[6] The RLS Epidemiology, Symptoms, and Treatment (REST) General Population study found the prevalence of RLS approximately 2 to 3 times more common in women—depending on severity of symptoms—which was roughly consistent with the Innes findings.[2,6] Other demographic risk factors for RLS have been identified in epidemiologic studies. A study published in 2012, for example, examined demographic and socioeconomic risk factors for RLS based on the results of 2 population-based cohort studies conducted in Germany. One of the studies included was conducted in Dortmund and included 1312 participants; the other study was conducted in Pomerania and included 4308 participants. The authors found that risk factors for RLS in the Pomeranian study, which had a mean follow-up of 5.2 years, included female gender, being retired, and being unemployed. The study from Dortmund, which had a mean 2.2 year follow-up, observed slightly different risk factors: being retired, not having an education

beyond primary school, being unemployed, having a low income, and doing shift work. Both studies also found that increased age and having an overall lower socioeconomic status were both associated with elevated RLS risk.[7]

Underdiagnosis of RLS is common, with only 41% of those requiring medical treatment actually receiving an RLS diagnosis; less than one-third of those experiencing frequent RLS symptoms receive an appropriate diagnosis.[1] In addition to underdiagnosis, misdiagnosis is common. Hening et al noted a high risk for confounding symptoms ("mimics") in RLS and conducted a study that examined the risk of being misdiagnosed with RLS despite qualifying for a diagnosis based on the 4 standard diagnostic criteria.[3] Of the 1232 participants in the Hening study, 126 were found not to have RLS and yet reported experiencing symptoms that were consistent with the 4 diagnostic criteria.[3] The authors further identified 6 mimics that sufficiently resembled 1 or more of the 4 diagnostic criteria so as to provoke misdiagnosis. These 6 mimics were: leg cramps, peripheral neuropathy, radiculopathy, arthritic pain, positional discomfort (ie, a particular seated/lying position causing RLS-like symptoms rather than urge/discomfort while being at rest per se), and pronounced or frequent unconscious movement of the feet or legs (eg, foot tapping, hypnic jerks).[3]

RLS has, in recent years, become the subject of intensifying study as the prevalence of RLS and the seriousness of an RLS diagnosis are becoming better recognized. The purpose of the present article is to examine the clinical and QoL burdens experienced by those who live with RLS symptoms as well as the economic burden borne by managed care organizations (MCOs) and the public at large.

Quality of Life

The burden on patient QoL arising from RLS can be severe, as has been observed in numerous QoL studies. Kushida et al, employing the SF-36 instrument for measuring QoL, found that across all 8 domains addressed by SF-36—including physical functioning, physical role functioning, bodily pain, general health perceptions, vitality, social role functioning, emotional role functioning, and mental health—participants with RLS scored significantly worse than published norms for the general US population. The authors also compared SF-36 scores for RLS with those scores observed in patients with type 2 diabetes, clinical depression, and osteoarthritis, and found that RLS patients had lower scores in nearly every domain, both physical and mental, compared with those other patient populations.[8]

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These results are consistent with a study conducted by Abetz et al, which also employed the SF-36 and which also found significantly worse scores in each of the SF-36 domains for RLS patients compared with the general population. Similarly to the Kushida study, the study authors compared QoL scores in RLS participants with those of people with type 2 diabetes, clinical depression, chronic obstructive pulmonary disease (COPD) with hypertension, and osteoarthritis with hypertension. RLS patients were found to experience worse QoL scores for role-physical, bodily pain, and vitality compared with the other 4 groups, and worse scores for social function, role-emotional, and mental health than all but those with clinical depression. RLS patients also fared worse for general health compared with the type 2 diabetes and osteoarthritis groups.[9]

Sleep Disturbance

The burden of RLS on QoL can manifest in numerous ways, but much of the burden arises from the disturbance of sleep that the condition engenders. Sleep-related symptoms were by far the most commonly reported troublesome symptom experienced by patients with RLS in the REST Primary Care study, which included data from 23,052 patients in primary care centers in the United States and Western Europe (**Figure**).[10] More than two-thirds (68.6%) of REST study participants required more than 30 minutes to fall asleep (diagnostic for insomnia), while 60.1% stated that they awoke at least 3 times every night, and the same percentage described difficulty sitting or relaxing.[10,11] In addition, 57.2% of respondents reported that their activities of daily living (ADLs) were disturbed by RLS and 53.9% described depressive symptoms. When asked about the overall effect of RLS on their QoL, more than one-third of the study participants said that RLS had a high negative impact on their lives, and the remainder reported that it had some degree of negative impact.[10]

In the REST General Population study, which involved face-to-face or telephone interviews, more than three-fourths of study participants designated as RLS sufferers reported sleeprelated symptoms, 55.5% reported disturbance of daytime functioning, -59.4% reported pain associated with their RLS symptoms, and 26.2% reported mood disturbance (tendency to become depressed or "low"). The authors of a German study of patients with RLS diagnosed at movement disorder or neurological clinics observed that it took participants an average of 82.5 minutes to fall asleep and that patients averaged 4.3 awakenings per night.[12]

Sleep disturbance due to RLS has a negative impact on patient QoL, including performance. Many participants in the REST study reported

daytime sleepiness and difficulty concentrating the next day, presumably due to sleep disturbance.[2]

Other Common Comorbidities in Patients With RLS

A variety of comorbidities are associated with RLS, including renal disease, iron deficiency, anemia, neuropathy, sleep apnea, pregnancy, and attention deficit disorder.[13,14] It has been observed that people with Parkinson's disease often have RLS, although this connection is not observed in untreated Parkinson's; it is hypothesized that RLS in patients with Parkinson's disease may be a consequence of treatment with certain drugs rather than the result of a direct pathological relationship.[15]

The psychological distress experienced by people with RLS can be quite severe, as RLS is a chronic condition in which rest, in both awake and sleeping states, is repeatedly and indefinitely disrupted. The extent and varieties of psychological distress associated with RLS were the subject of a recent study by Scholz et al. Psychological abnormalities commonly observed among the RLS participants were somatization (ie, the emergence of medical symptoms without a discernable organic cause), anxiety, compulsivity, and depression, all of which occurred at significantly higher rates than in members of the general population. In addition, a significant correlation was observed between psychological issues and disease severity.[16]

RLS is relatively common in patients with renal disease. The form of RLS observed in this patient population, uremic RLS, may be associated with greater symptom severity and different patterns of patient age at onset.[17] An Italian study of patients with end-stage renal disease undergoing hemodialysis found an RLS prevalence rate of 18.4% in this patient population, and notably severe symptoms: 41% described moderate symptoms, 31% had severe symptoms, and 16% had very severe symptoms. Only 12% of study participants reported a mild form of RLS symptoms, which comprises a much smaller proportion than typical participants with idiopathic RLS.[17] These results are consistent with a recent Greek study, which observed an RLS prevalence of 42% in 70 patients undergoing hemodialysis, and also found an average symptom score, for all participants with RLS, that met or exceeded the threshold for categorization as severe.[18] The Greek study also observed that RLS patients undergoing hemodialysis showed evidence of significant muscle atrophy in the legs, a clinical manifestation not observed in patients undergoing hemodialysis who did not have RLS.[18]

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The Real Burden of Restless Legs Syndrome: Clinical and Economic Outcomes - Page 3

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Restless legs syndrome (RLS) is a highly prevalent and substantially underdiagnosed sensorimotor disorder. Only relatively recently have the large impact on patient quality of life (QoL) and the economic burden associated with RLS become more widely recognized. QoL in patients with RLS has been shown to be worse than that of many other chronic conditions, including type 2 diabetes, clinical depression, and osteoarthritis. Sleep disturbance, a cardinal feature of RLS, is the most common and most destructive of its symptoms. More than two-thirds of RLS patients experience serious insomnia, and waking up several times per night is typical for this patient population. Moreover, RLS disrupts rest during waking hours, such as when the patient is sitting or relaxing. Thus, whether awake or asleep, the RLS patient finds little opportunity for the general restorative behaviors necessary for healthy human functioning, resulting in high rates of comorbidities including depression, anxiety, and hypertension. The direct and indirect costs related to RLS have been evaluated in a few studies. Although the cost studies are associated with certain limitations (eg, use of questionnaires), the results show that costs related to RLS are substantial. Healthcare utilization, primarily in the form of doctor visits, constitutes the largest proportion of direct expenditures for RLS in the United States. Indirect costs are also large, primarily due to productivity losses, which are as high as 20% in RLS patients. Effective treatment of RLS is necessary to limit the negative effects of RLS on QoL and to reduce costs associated with the condition.

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Hypertension is another comorbidity strongly associated with RLS, as shown by data from the Nurses Health Study II, one of the largest prospective studies ever conducted. The participants included in the RLS/hypertension study were, in fact, a subpopulation of the larger study, and consisted of 65,544 middle-aged women (aged 41-58 years), among whom 2475 experienced RLS symptoms 5 to 14 times per month, and 1748 of whom experienced RLS symptoms at least 15 times per month. Within the more frequent symptoms group, the rate of hypertension was 33%, compared with 26% in the less frequent symptom group and 21.4% among participants without RLS. The age-adjusted odds ratio (OR) for hypertension in the more frequent and less frequent symptom groups compared with the non-RLS group was 1.73 and 1.24, respectively (P <.0001 for trend). The multivariate-adjusted OR was 1.41 for the more frequent symptom group and 1.06 for the less frequent symptom group (P <.0001 for trend).[19]

Studies of patients with fibromyalgia also reveal a high prevalence of RLS. A US study of 172 fibromyalgia patients observed an age- and gender-adjusted RLS prevalence of 33% versus 3% in 63 matched controls (P <.01).[20] In a Swedish study of women with diagnosed fibromyalgia, researchers mailed questionnaires to 266 patients who attended a fibromyalgia rehabilitation clinic; 232 patients (87%) responded. Of these responders, 64% were reported to have fulfilled the standard criteria for an RLS diagnosis.[21] A small recent study involving participants with irritable bowel syndrome (IBS) also observed RLS to be very common in those with diarrhea-predominant IBS (62%), but less prevalent in those with constipation-predominant IBS (4%) or mixed-symptom IBS (33%).[22]

Economic Burden

The economic impact of RLS has been somewhat, if not extensively, studied; unfortunately, few such studies have been undertaken in the United States. One such US study, conducted by Allen et al and published in 2011, gathered data regarding lost productivity, healthcare resource use, and expenditures as reported by patients in 2007. These patient-reported data, while revealing, are somewhat less rigorous in their sourcing compared with a study that, for example, employs insurance claims data to determine disease-related expenditures.

Beginning with a large pool of possible candidates (over 300,000 individuals), the study authors identified and recruited 251 participants with "primary" RLS; that is, RLS without a recognizable secondary cause. Within this group, a subgroup of 131 RLS "sufferers" was also

identified, ie, participants whose RLS severity required medical intervention based on symptoms that occurred at least twice per week and that were regarded by the participant as moderate or severely distressing.[1] Half of those with primary RLS were employed during the course of the study: 36% worked full time and 15% worked part time. An additional 15% participated in volunteer work. Participants with primary RLS worked an average of 30.4 hours per week. Absenteeism associated with primary RLS was found to be 1.1% (0.3 hours per week), while on-the-job effectiveness was decreased by 13.5% in participants with primary RLS ("presenteeism"). Overall workplace productivity loss due to primary RLS was 14.1%, or 5.6 hours per 40-hour work week.1 RLS sufferers experienced similar, if somewhat worse, rates of productivity loss. The absenteeism rate was 1.9%, the presenteeism rate was 18.9%, and the overall productivity loss was 19.9%, or 1 day per 40-hour week.[1] Disease severity was strongly correlated with loss of productivity in both groups: $r = 0.54$ for primary RLS and $r = 0.53$ for RLS sufferers (both $P < .0001$).[1]

Healthcare resource use reported in the Allen study included medical treatment received by participants during the 3 months preceding their recruitment. During that 3-month period, 57.6% of participants with primary RLS reported making at least 1 visit to a primary care/general practitioner; 36.4% of the visits were RLS related. By comparison, 64.1% of RLS sufferers had at least 1 primary care/ general practitioner visit, of which 44% were RLS related. In addition, 29.8% of participants with primary RLS undertook specialist visits (31.2% RLS related) versus 36.6% of RLS sufferers (37.5% RLS related). The emergency department was used by 7.8% of participants with primary RLS (12.5% RLS related) over the course of the 3-month pre-study period compared with 9.2% (16.7% RLS related) of RLS sufferers. With regard to medication use, 44.4% of participants with primary RLS and 54.2% of RLS sufferers were receiving at least 1 medication, with ropinirole being the most common (7.3% primary RLS vs 11.5% RLS sufferers), hydrocodone the second-most common (6.8% primary RLS vs 8.4% RLS sufferers), and pramipexole being the third-most common (primary RLS 5.4% vs 7.6% RLS sufferers).[1] Annualized direct expenditures based on these 3-month data, for RLS specific healthcare resources only, were estimated to be $350 for participants with primary RLS ($187 medical visits, $129 medications) and $490 for RLS sufferers ($274 medical visits, $171 medications). Both medication and healthcare resource use costs related to RLS were significantly associated with symptom severity.[1]

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A study from Philipps-University Marburg in Germany, published in 2010, utilized expenditure figures from a relatively transparent public/private insurance system. It should be noted that the study included data collected via a validated questionnaire given to 519 participants with RLS at various disease stages who were being seen at 5 different treatment centers. Direct and indirect costs were calculated for a 3-month period of observation. Costs were reported in 2006 Euros, and are converted here at a rate of 1.25 dollars per Euro, which was the average exchange rate in 2006 and is the approximate exchange rate in September 2012.[23] Total 3-month costs were found to be $2613, of which 37% was attributed to direct costs. Three-month direct medical and non-medical costs for the health insurance provider were $974. The largest proportion of this cost, $443, was attributable to hospitalization, which was necessary in 32 patients who had an average length of stay of 1 day. Mean drug costs, which amounted to $374, comprised the second-largest direct cost category. Physician/outpatient services accounted for another $63, and physical therapy, $57. Indirect cost calculations were based on 3 categories—working days lost, productivity lost, and early retirement costs— and amounted to a total of $1635 during the 3-month period. Both direct and indirect costs were found to be significantly associated with disease severity (P <.01).[23]

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A separate cost-of-illness study from Germany employed the Markov model to estimate annual RLS-related expenditures. The annual direct costs to a "sickness fund" (a type of non-profit health insurance provider which most Germans are obliged to join) were estimated to be $1237, while $1607 in costs were incurred outside the sickness fund system. Drug costs represented roughly two-thirds of expenditures.[24] It should be noted that treatment costs, and to some extent drug costs, are typically lower in Germany than in the United States.

RLS expenditures, while not extraordinarily high, certainly represent meaningful expenditures both directly and indirectly. This was confirmed by a systematic review of cost studies in RLS, which, although heterogeneous in design and results, was consistent in observing higher rates of expenditure for third-party payers for patients with RLS compared with average patients without RLS in the primary care setting. The review also found that pharmacologic treatment of RLS was consistently cost-effective across therapies.[25]

The full economic impact of not treating RLS has not been satisfactorily evaluated at present. Nevertheless, it seems highly likely that certain costs—for example, lost productivity, which already comprises a very substantial part of the total costs related to RLS—will increase when patients experience greater disease severity. It may also be the case that failure to treat RLS exacerbates comorbidities, requiring additional

expenditures and healthcare resource utilization that might not otherwise be necessary.

Conclusions

RLS is an underdiagnosed condition with a relatively high prevalence and a negative effect on QoL. The deleterious impact of RLS on QoL is perhaps surprisingly large for a condition that may not appear particularly serious to those unfamiliar with it. The effects of RLS can be very serious indeed, and QoL among its sufferers is generally worse than that of other chronic diseases such as type 2 diabetes, depression, and osteoarthritis. Sleep disturbance, perhaps more than any other feature of RLS, is responsible for a large proportion of the deterioration in QoL associated with the condition and represents a cardinal feature of RLS. RLS is also associated with a spectrum of comorbidities, including renal disease, hypertension, and fibromyalgia. The costs, both direct and indirect, attributable to RLS are substantial, and although recent analyses of the economic impact of RLS do not address nationwide costs, they are likely to be significant considering both the measurable costs on an individual basis and the extent of the prevalence of RLS. Greater awareness among clinicians and managed care professionals about RLS has the potential to help improve rates of diagnosis and treatment, which will potentially reduce the impact of RLS on patient QoL and healthcare expenditures.

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