REVIEW

Socioeconomic impact of restless legs syndrome and inadequate restless legs syndrome management across European settings

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Restless legs syndrome (RLS) is one of the most common neurological disorders. It describes an irresistible urge to move the legs, mostly manifested in the evening and at night, which can lead to severe sleep disturbance. As part of the European Brain Council (EBC)-led Value-of-Treatment project, this study aimed at capturing the socioeconomic impact of RLS related to the inadequate diagnosis and treatment across different European healthcare settings. The economic burden of RLS was estimated using the published EBC framework of analysis in three separate European Union healthcare systems (France, Germany, and Italy). The RLS care pathway was mapped to identify the unmet needs of patients. Based on specific patient stories, the economic impact of correctly diagnosing RLS and changing between inadequate and target treatment was calculated using appropriate scenario analysis. RLS proved to be a significant personal and social burden, when epidemiological data, high prevalence of RLS, and its need for treatment are combined. By looking at the savings emerging from the provision of optimal care management (timely and correct diagnosis, evidence-based therapy, avoidance of therapy-related complications such as augmentation), the authors foresee substantial economic savings with the achievement of adequate diagnosis and treatment of RLS. Education about RLS is urgently needed for all subspecialties involved in RLS patient care as well as the general public. Equally important, the search for new causal treatment strategies should be intensified to reduce suffering and substantial societal cost.

Introduction

Restless legs syndrome (RLS) is a common neurological disease that is characterized by an irresistible and compelling urge to move the legs (or arms and sometimes other body parts as well), usually accompanied by highly uncomfortable sensations in the affected limbs [1]. RLS is a common condition that has a substantial impact on daily activities and quality of life. The circadian variation of RLS symptoms, with major complaints in the evening and at night, leads to severe sleep disturbance and deprivation and has a substantial impact on normal daily activities and the lives of

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sufferers and their families. It influences and interacts with many comorbidities [2], and it also causes loss of work, loss of social networks, and even early and premature retirement.

The diagnosis is primarily set by a clinical history (essential questions) that can be taken by any physician independent of the discipline. Misdiagnoses and none or incorrect treatment regimens occur due to lack of knowledge and expertise at both the primary and secondary care levels and, as a consequence, lead to wrong routing of the patient. As a result, diagnosis and correct management of RLS is delayed for many patients. Access to specialized RLS care is rarely available across Europe. The currently available medications provide symptom reduction only, and side effects of the medicines have created new and serious problems such as augmentation of RLS symptoms [3,4].

Estimates of the prevalence of RLS have varied widely, depending on the patient population and the diagnostic criteria studied. The publication of standardized criteria for the diagnosis of RLS [1,5] has facilitated comparisons between studies, yielding reliable estimates of the prevalence of RLS in the general population. Population-based studies using these criteria suggest that RLS symptoms of any frequency or severity are present in 5% to 10% of the general population in Western industrialized countries [6,7] and in a lower proportion in Asian populations [8,9]. According to recent data from the Study of Health in Pomerania study, the prevalence of RLS in the adult German population is 6% to 9%, including all levels of severity [10]. In addition, Allen *et al* [11] report that about 2.7% of the European population suffer from moderate to severe RLS. It has been suggested that RLS with an early onset (before age 45 years) tends to progress slowly, whereas RLS of later onset generally progresses rapidly until the severity reaches a plateau. As a result, the greatest burden of morbidity is seen amongst middle-aged to elderly patients [12]. A majority of studies have reported that the prevalence of RLS is approximately twice as high in women as in men [13], with an increase of prevalence with age among both genders [13]. In addition, there is evidence from the Dortmund Health Study in Germany that approximately 1.6% of the population was both affected by RLS and wished for treatment for RLS [14]. Given its high prevalence in the general population and how it affects the patients' lives, it is necessary to evaluate the socioeconomic impact of RLS and the inadequate RLS diagnosis and treatment across different European Union (EU) healthcare systems.

The aims of this study were: (i) to present an analysis of the socioeconomic impact of RLS as a disease across a series of EU settings, (ii) to describe the RLS patient's pathway and key treatment gaps, and (iii) to evaluate the economic impact of filling the key treatment gaps identified looking at specific EU case studies. For each of the three aims, both methods and key results are reported. The final scope was to discuss the overall findings of the studies and report on the policy recommendations emerging from them, in alignment with the overall European Brain Council (EBC)-led Value-of-Treatment (VoT) project [15].

The socioeconomic impact of RLS as a disease in Europe

Methods

The economic burden of RLS was estimated for the first time across EU settings by using the published framework adopted by the EBC in "The Economic Cost of Brain Disorders in Europe 2010" [16]. The analysis was performed for three separate healthcare systems, France, Germany, and Italy, as examples of EU nations with different healthcare systems with regard to delivery of services, financing, and coverage. Details on the methodology applied are described elsewhere [16]. One-year prevalence and annual cost per person of RLS were based on best estimates derived from the literature reviews by panels of working-group experts [17] and 2016 gross domestic product per capita (http://www.tradingeconomics.com/) [18,19]). The estimates included healthcare costs as well as indirect costs to society, such as lost productivity due to reduced ability to work (including sick days) or to work at full capacity. The socioeconomic impact of RLS in France, Germany, and Italy was provided; the yearly total costs were presented for the three country settings. Two separate scenarios were considered. First, we calculated the economic impact of RLS when assuming a prevalence of the disease with a treatment wish, equal to 1.6% [14]. Second, in the next calculation, we considered a more relaxed scenario with a prevalence of 2.7% RLS [11].

Results

When considering the overall economic impact of RLS in the EU sample given by the three countries (France, Germany, and Italy as pooled data; Fig. 1), RLS with prevalence 1.6% (scenario 1) reported a

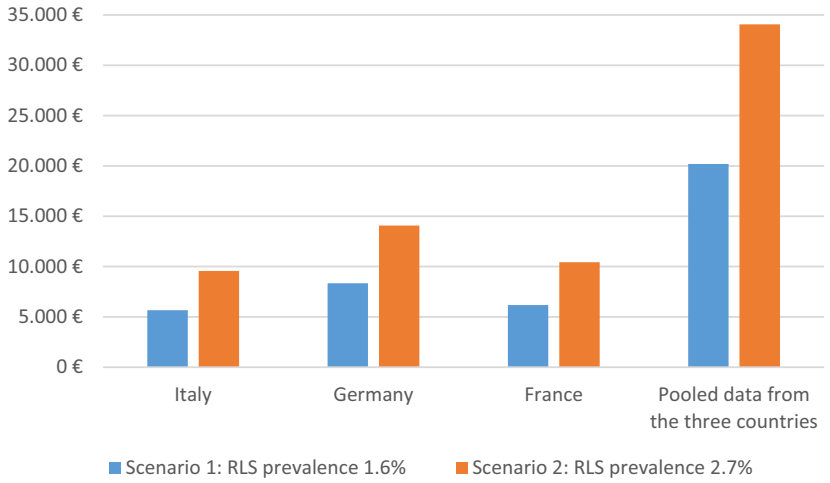

Figure 1 Socioeconomic impact of restless legs syndrome (RLS) in France, Germany, and Italy. Yearly total costs according to different prevalence assumptions are presented for the three country settings (millions euros, 2016). Scenario 1 relates to the prevalence of RLS patients who wish therapy in a city in Germany [14]. Scenario 2 relates to the overall prevalence of RLS in the United States from Allen*et al*[11]. [Colour figure can be viewed at wileyonlinelibrary.com]

total yearly cost of €20,188.68 million (including €6181.07 million for France, €8339.28 million for Germany, and €5668.33 million for Italy). Costing estimates produced when using different assumption for RLS prevalence are presented in Fig. 1.

The RLS care pathway and key treatment gaps

Methods

The RLS care pathway was mapped looking at the patient experience and treatment gaps to describe patients' needs and issues along the whole care process and identify the critical unmet needs of patients as well as the underlying causal factors. The results of the analysis were built based on available evidence-based diagnosis and treatment guidelines in Europe [3] as well as national guidance in France (La Société Française de Neurologie; http://www.sf-neuro.org/), Germany (Deutsche Gesellschaft für Neurologie; https://www.dgn.org/) and Italy (Societa' Italiana di Neurologia; http://www.neuro.it/), and expert and patient opinions. The group set out to identify the typical stages in the patient journey. Diagnostic delay, access to good care, the cost of nontreatment, sick leave, loss of income/job, proportion of drug-resistant patients, awareness of RLS among medical professionals, available medicines or lack of medicines, and importantly, incorrect application and dosages that cause adverse reactions, possible prevention, screening/prodroma, early intervention, and overall disease management were all mapped using the framework provided by the EBC (Fig. 2). Recommendations were proposed on how these shortcomings can be improved.

Three experts, one for each country (Y.D. for France, C.T. for Germany, R.F. for Italy), considered a specific treatment gap emerging from the care pathway analyses and individually selected a typical patient story that would describe the impact of suboptimal treatment in the patient's life. Each case of suboptimal treatment (baseline scenario) was then matched with a target scenario to describe what would happen to the same patient in case that patient received appropriate care.

Results

The major gaps identified alongside the patient pathway included delayed diagnosis, insufficient response, and augmentation as a result of treatment complication. They were described in terms of typical patient cases.

Augmentation is a severe adverse reaction of long-term dopaminergic therapy of RLS [20]. With high doses of levodopa/dopamine decarboxylase inhibitor or dopamine agonists, RLS symptoms become much worse and spread over the entire body during many hours per day. A significant aspect of augmentation is often a misinterpretation of this phenomenon: when symptoms get worse, the treating physician will assume loss of efficacy and increase the dosage. This results in even more severe augmentation. More is not better in RLS treatment. As a result, a drug holiday is often advised, an almost impossible journey for the

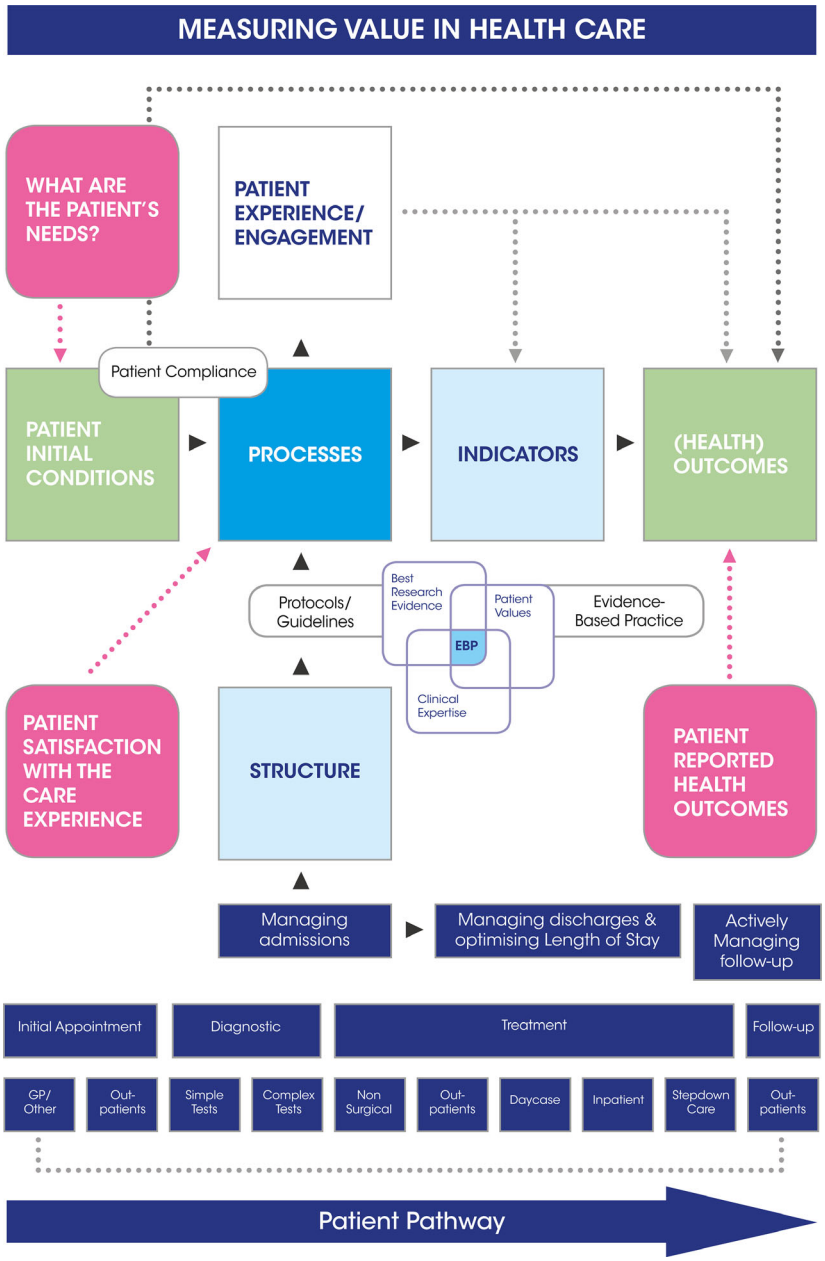

Figure 2 Measuring value in healthcare by achieved outcomes, starting with defining the patient's needs (inpatient care pathway; from the European Brain Council, 2017). [Colour figure can be viewed at wileyonlinelibrary.com]

patient due to extreme withdrawal symptoms and no sleep for many days.

The economic impact of closing the key treatment gaps

Methods

The analyses for the VoT project were built on previously published research in the field, particularly where it generated evidence on effectiveness, and used methods successfully employed in published studies to explore the economic case for closing treatment gaps in brain disorders. Depending the quality and type of the evidence available, economic modeling techniques were used to build a series of analytical models to evaluate the cost-effectiveness of closing the treatment gap and explore the impact of transitioning from sub-optimal patient pathway to what can be considered as target treatment according to clinical guidance [15]. In

Table 1 Missed or delayed diagnosis: assumptions, unit costs and sources of information per country settings

(a) Inadequate treatment

				France			Germany			Italy		
Healthcare services	Assumption	Frequency	Unit	Unit costs (euros, FR)	Payer (FR)	Source	Unit costs (euros, GER)	Payer (GR)	Source	Unit costs (euros, Italy)	Payer (Italy)	Source
VISITS - referral to a psychiatrist (specialist visit)		1 visit per month during 6 years from age 33 to 39 years	Consultation	52.00	Health care system	Statutory health insurance	95	Statutory health insurance	EXPERT OPINION	20.66	Healthcare system	GAZZETTA UFFICIALE 2013
VISITS- follow up referrals with various specialists	Consultation of cardiologist, pneumologist for chest pain, short breathing.	5 per year during 5 years (age 34 to 39)	Consultation	42.00	Health care system	Statutory health insurance	95	Statutory health insurance	EXPERT OPINION	20.66	Healthcare system	GAZZETTA UFFICIALE 2013
MEDICINES - antidepressants	Venlafaxine 75 mg	Venlafaxine 75 mg per day druing 5 years	1 cps	0.30	Patient	http://www.vidal-dis.com/	1.11	Statutory health insurance	EXPERT OPINION	0.4	Healthcare system	Federfarma.it
VISITS - referral to a psychiatrist (specialist visit)	Outpatient consultation with psychiatrist	6 times per year for 5 years	Consultation	52.00	Health care system	Statutory health insurance	95	Statutory health insurance	EXPERT OPINION	20.66	Healthcare system	GAZZETTA UFFICIALE 2013
MEDICINES – pramipexole		Pramipexole 0.18 mg 1 cp per day during 3 months, then 2 per day druing 3 months then 3 per day during 6 months from 39 to 40 years	1 cps	0.18	Patient	http://www.vidal-dis.com/	1	Statutory health insurance	EXPERT OPINION	0.166667	Healthcare system	Federfarma.it
MEDICINES - pramipexole increased dosages		Pramipexole 0.7 mg from 41 to 43 years, then 2 capsules at 0.7 mg per day from 43 to 45 years, then 3 capsules at 0.7 mg till 47 years old	1 cps	0.76	Patient	http://www.vidal-dis.com/	1.5	Statutory health insurance	EXPERT OPINION	0.6	Healthcare system	Federfarma.it
INPATIENT HOSPITAL STAY	One night of polysomnography in hospital		1 inpatient hospitalstay	1376.43	Health care system	Statutory health insurance	2405	Statutory health insurance	DRG	2850	Healthcare system	GAZZETTA UFFICIALE 2013
MEDICINES - between hospitalisations	3 capsules of pramipexole 0.7 mg per day and venlafaxine 75 mg per day	Until the second hospitalisation	Daily dosage	2.57	PATIENT	http://www.vidal-dis.com/	4.11	Statutory health insurance	EXPERT OPINION	2.2	Healthcare system	Federfarma.it

(continued)

Table 1 *(Continued)*

(a) Inadequate treatment

Healthcare services	Assumption	Frequency	Unit	France			Germany			Italy		
				Unit costs (euros, FR)	Payer (FR)	Source	Unit costs (euros, GER)	Payer (GR)	Source	Unit costs (euros, Italy)	Payer (Italy)	Source
SECOND INPATIENT HOSPITAL STAY		Age 51, 3 nights in hospital to start the withdrawal of all medications progressively over 10 days,	1 inpatient hospitalstay	1376.43	Health care system	Statutory health insurance	2405	Statutory health insurance	DRG	2850	Healthcare system	GAZZETTA UFFICIALE 2013
MEDICINES - rotigotine		Age 51 till now age 67: one patch of rotigotine 2 mg per day	1 patch	1.88	Patient	http://www.vidal-dis.com/	2	Statutory health insurance	EXPERT OPINION	3.610714	Healthcare system	Federfarma.it
MEDICINES - oxycodone		Age 51 till now age 67: one oxycodone at 20 mg LP per day	1 LP day	0.79	Patient	http://www.vidal-dis.com/	3	Statutory health insurance	EXPERT OPINION	0.606071	Healthcare system	Federfarma.it
MEDICINES – clonazepam		Age 51 till now age 67: clonazepam 1 cp at 2 mg per day	1 cps	0.05	Patient	Statutory health insurance	0.1	Statutory health insurance	EXPERT OPINION	0.0725	Healthcare system	Federfarma.it

Indirect costs	Assumption	Frequency	Unit	Unit costs (€, France)	Payer (France)	Source	Unit costs (€, Germany)	Payer (Germany)	Source	Unit costs (€, Italy)	Payer (Italy)	Source
Absenteeism - monthly wages to be provided	She was a primary school teacher	30 days per year between 35 to 60 years old	Per month	2625	Society	https://www.ssa.gov/policy/docs/progdesc/ssptw/2012-2013/europe/index.html	3855	Society	http://www.wageindicator.org	1959	Society	http://www.wageindicator.org

(b) Target treatment

Healthcare services	Assumption	Frequency	France			Germany			Italy		
			Unit costs (euros, FR)	Payer (FR)	Source	Unit costs (euros, GER)	Payer (GR)	Source of information	Unit costs (euros, Italy)	Payer (Italy)	Source
VISITS - diagnosis of RLS (specialist visit)	Young child 11 years old	1	42	Health care system	Statutory health insurance	95	Statutory health insurance	EXPERT OPINION	20.66	Healthcare system	GAZZETTA UFFICIALE 2013

(continued)

Table 1 *(Continued)*

(b) Target treatment

			France			Germany			Italy		
Healthcare services	Assumption	Frequency	Unit costs (euros, FR)	Payer (FR)	Source	Unit costs (euros, GER)	Payer (GR)	Source of information	Unit costs (euros, Italy)	Payer (Italy)	Source
VISITS - follow-up visits (specialist visit)	Consultation of RLS specialist: , 2 per year since the diagnosis	2 per year	42	Health care system	Statutory health insurance	95	Statutory health insurance	EXPERT OPINION	20.66	Healthcare system	GAZZETTA UFFICIALE 2013,
VISITS- follow up referrals with specialists	No requirement		42	Health care system	Statutory health insurance	95	Statutory health insurance	EXPERT OPINION	20.66	Healthcare system	GAZZETTA UFFICIALE 2013,
MEDICINES - pramipexole	Pramipexole 0.18 mg	1 cp per day during 3 months, then 2 per day druing 3 months from 39 to 40 years -from the diagnosis	0.177667	Patient	http://www.vidal-dis.com/	1	Statutory health insurance	EXPERT OPINION	0.166667	Healthcare system	http://www.federfarma.it/Farmaci-e-farmacie/Cerca-un-farmaco.aspx
FIRST INPATIENT HOSPITAL STAY	No requirement				Statutory health insurance	2405	Statutory health insurance	DRG	2850	Healthcare system	GAZZETTA UFFICIALE 2013
SECOND INPATIENT HOSPITAL STAY	No requirement				Statutory health insurance	2405	Statutory health insurance	DRG	2850	Healthcare system	GAZZETTA UFFICIALE 2013
Indirect costs	Assumption	Frequency									
Absenteism	Absenteism	15 days per year between 35 to 60 years old	2625	Society	https://www.ssa.gov/policy/docs/progdesc/ssptw/2012-2013/europe/index.html	3855		http://www.wageindicator.org	1959	Society	http://www.wageindicator.org/main/salary/Salarycheckers

This Table contains the statement on the unit cost of a one night inpatient hospital stay for polysomnography. At present the figures are calculated as if every RLS patient would receive this diagnostic procedure. As in reality this is not the case, therefore we calculated the scenario about the costs in the three different countries, if only 10%, 20% ,30 % or 100 % of the RLS patients asking for therapy would undergo this first step. The differences in the overall savings as calculated with the different proportions of RLS patients undergoing inpatient hospital stay polysomnography range between 2 and 6 % (see Table 2 for calculation of savings for the three different countries). Cp, capsule; cps, capsules; DRG, disease related groups.

Table 2 Calculation of savings for the healthcare systems with different proportions of RLS outpatients receiving a polysomnography

	10% PSG outpatient procedure costs 10%	20% PSG outpatient procedure costs 20%	30% PSG outpatient procedure costs 30%	100% PSG outpatient procedure costs 100%
France				
Saving for healthcare system (compared with worst case management)	7302	7285	7269	7155
Germany				
Saving for healthcare system (compared with worst case management)	3805	3781	3756	3586
Italy				
Saving for healthcare system (compared with worst case management)	7930	7919	7908	7831

For the purpose of our sensitivity analyses we assumed one PSG outpatient procedure and zero MRI. We consider four different options for PSG outpatient procedure costs (10%, 20%, 30%, 100%). The overall cost estimates for the worst case management remain unchanged. The total saving for healthcare related costs (compared with worst case management) are reported in this Table. PSG, polysomnography.

the case of RLS, only a single article [17]—an outpatient scenario in Germany—on the economic evidence was available, and effectiveness data were very limited. Given the challenges experienced in sourcing relevant evidence to populate the economic modeling framework (EBC, 2017), the working group agreed to consider a scenario analysis using three typical patients to illustrate cases of suboptimal treatment as presented by the care pathway analyses. The three country experts (Y.D., C.T., and R.F.) gathered their personal opinions on the use of resources in the different scenarios and provided a source of unit cost from their local country's public tariff and their personal practice data. Costs related to absenteeism from work were calculated looking at country wages for the specific case-study jobs. The timeframe varied according to the personal life story described in the three case studies. Cost estimates included those for the one person described in the case study and covered those incurred by the healthcare provider or society, depending on the individual cases. A discount rate of 3.5% was applied as appropriate. Details on the assumptions made as well as the unit costs and sources of information across country settings are reported in Tables 1 to 4.

For the purpose of our sensitivity analyses we assumed one polysomnography (PSG) outpatient procedure and zero MRI. We consider four different options for PSG outpatient procedure costs (10%, 20%, 30%, 100%). The overall cost estimates for the worst case management remain unchanged. The total saving for healthcare related costs (compared with worst case management) are reported below.

Results

The case reports on the economic savings across healthcare systems were detailed when closing the three treatment gaps illustrated by the typical patients' stories. The economic savings were calculated when changing from suboptimal to target treatment (Fig. 3).

Delayed diagnosis

When calculating the difference in direct costs for the healthcare provider, adequate treatment provides a cost savings of €1600 to €33,300 over a period of 54 years across the three healthcare systems. When healthcare and productivity costs incurred by the whole society are considered, adequate treatment provides cost savings at a level of €35,000 to €50,500 per patient case.

Table 3 Insufficient response: assumptions, unit costs and sources of information per country settings. (a) Inadequate treatment. (b) Target treatment

(a) Inadequate treatment

				France			Germany			Italy		
Healthcare services	Assumption	Frequency	Unit	Euro - average unit costs for FR	PAYER FR	Source	Euro - average unit costs for GER	PAYER GER	Source	Euro - average unit costs for Italy	Payer	Source
VISITS - sleep doctor (specialist visits)		3 per year	One visit	42	Health care system	42 euros per visit	17	Health care System	EXPERT DATA	20.66	Health care System	GAZZETTA UFFICIALE 2013
INPATIENT HOSPITAL STAY (sleep center) including PSG Diagnosis: RLS with PLMS		3 days (full DRG)	One full DRG	2605	Health care system	2605 euros for 3 nights	2400	Health care System	EXPERT DATA	2850	Health care System	GAZZETTA UFFICIALE 2013
MEDICINES – clonazepam		Bedtime	1 day dosage	0.048214	Patient	Clonazepam 1,35 euros for 28 cp	0.1	Health care System	EXPERT DATA	0.0705	Health care System	Federfarma.it
MEDICINES - pramipexole with increasing dosage		Bedtime (average dosage 0.56 used)	1 day dosage	0.533	Patient	Pramipexole 0.18 mg 1 cp per day (30 cp = 5,33 euros)	0.7	Health care System	EXPERT DATA	0.715	Health care System	Federfarma.it
INPATIENT HOSPITAL STAY (sleep center) including PSG		3 days (full DRG)	1 day dosage	2605	Health care system	2605 euros for 3 nights	2.4	Health care System	EXPERT DATA	2850	Health care System	GAZZETTA UFFICIALE 2013
MEDICINES - pramipexole 0.7 mg		Bedtime (1.5 years)	1 day dosage	0.758	Patient	Pramipexole 0.7 mg (1 month = 30 cp = 22,74 euros	1	Health care System	EXPERT DATA	0.855	Health care System	Federfarma.it
MEDICINES -and oxycodone/naloxone 5/2.5 mg		Bedtime (1.5 years)	1 day dosage	0.002413	Patient	Oxycodone 5 mg 5,74 euros of 28 cp (no oxycodone + naloxone available in France)	1.2	Health care System	EXPERT DATA	0.946	Health care System	Federfarma.it
INPATIENT HOSPITAL STAY (sleep center) including MRI		3 days (full DRG)	One full DRG	2605	Health care system	2600 euros for 3 nights (no more cost for MRI for inpatients...	2400	Health care System	EXPERT DATA	2850	Health care System	GAZZETTA UFFICIALE 2013
MEDICINES – bromazepam		Bedtime (2.5 years)	1 day dosage	0.052	Patient	Bromazepam 1,56 euros for 30 cp	0.3	Health care System	EXPERT DATA	0.368	Health care System	

(continued)

Table 3 *(Continued)*

(b) Target Treatment

				France			Germany			Italy		
Healthcare services	Assumption	Frequency	Unit	average unit costs for FR-Euro	PAYER	source	average unit costs for GER-Euro	PAYER	source	average unit costs for Italy-Euro	PAYER	Source
PSG as outpatient (exclusion of sleep comorbidities)			One PSG outpatient procedure	200.07	Health care system		300	Health care System	EXPERT DATA	139.44	Health care System	GAZZETTA UFFICIALE 2013
VISITS - Sleep specialist/Neurologist			One visit	42	Health care system		17	Health care System	EXPERT DATA	20.66	Health care System	GAZZETTA UFFICIALE 2013
MEDICINES - clonazepam/ pramipexole/oxycodone-naloxone (rotation as needed/avoid augmentation)	Daily cost: average of the three treatments	Bedtime (2 mg/ 0.7 mg/ 5-2.5 mg)	Daily dosage	0	No reimbursement, patient payed!		1	Health care System	EXPERT DATA	0.624	Health care System	Federfarma.it
VISITS - GP (diagnosis plus follow up visits - 3/4 per year)	From 2005	3 TO 4 A YEAR	ONE GP's ambulatory visit	23	Health care system		17	Health care System	EXPERT DATA	40	Health care System	http://www.lettera43.it/it/guide/economia/2015/06/30/quanto-guadagna-un-medico-di-base/21599/

This Table contains the statement of the unit cost of three times for a "3-day inpatient hospital stay (sleep center) including the performance of a PSG and an MRI". This means during altogether 9 days of inpatient hospital stay two PSGs and one MRI are - if considered necessary - performed. In this case the unit costs contain (per definition of the health system reimbursement - for example in the DRG system) the expenses for these two diagnostic steps - i.e. the costs remain the same independently whether one or two PSGs and/or one MRI are actually performed. In case we would be able to disentangle the actual costs attributable directly to the costs of two PSGs (2 × 300 Euros for Germany) and MRI procedure (300 Euros for Germany), the overall „full DRG expenses" of a three times "3 day inpatient hospital stay" (9 × 2.400 = 21.600 Euros minus 900 Euros = 20.700; difference is 4.14 %) would be reduced by a saving of <5%. In case only two times "3-day inpatient hospital stay" are required - with two PSGs and no MRI - the difference would be 4.17 % . In case the costs for one PSG were higher (i.e. 1000 Euros) the (theoretical) figures for the calculated costs (no PSG and no MRI) would be reduced by about 10 %. cp, capsule/capsules; DRG, disease related groups; GP, general practitioner; MRI, magnetic resonance imaging; PLMS, periodic leg movements during sleep; PSG, polysomnography; RLS, restless legs syndrome.

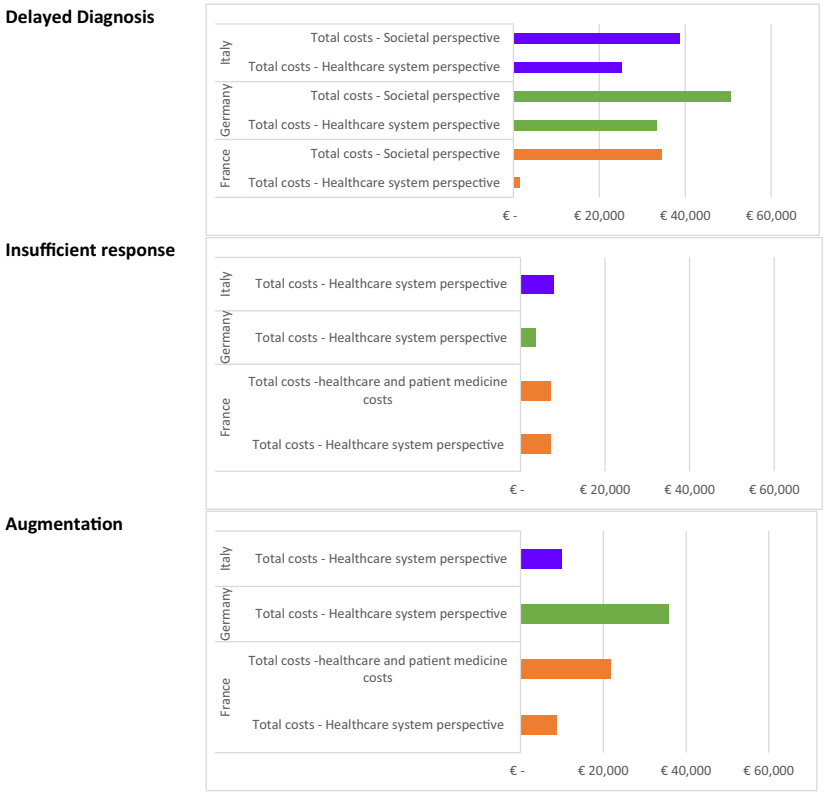

Figure 3 Economic savings when closing restless legs syndrome (RLS) treatment gaps (changing from inadequate to target treatment). Total period of time covered in the modeling: 56 years (delayed diagnosis), 11 years (insufficient response), and 4 years (augmentation). The perspectives adopted were as follows: France—The healthcare costs incurred by the healthcare system include visits, hospital stays, and tests, as there is no reimbursement of any RLS medicine (neither dopa agonist nor oxycodone–naloxone). The healthcare costs incurred by the society cover all patient costs for medicines plus healthcare costs incurred by the healthcare system (i.e., visits, hospital stays, and tests). In addition, we included the productivity loss (due to absenteeism from work). Germany and Italy—The healthcare costs incurred by the healthcare system include visits, hospital stays, tests, and RLS medicines. In the two countries the societal perspectives include both the healthcare costs covered by the national healthcare system (i.e., visits, hospital stays, tests, and RLS medicines), plus the productivity loss (due to absenteeism from work). GP, general practitioner. [Colour figure can be viewed at wileyonlinelibrary.com]

Insufficient response

On an 11-year time horizon, adequate treatment brings a cost saving of €3600 to €7800 per patient case.

Augmentation

When calculating the difference in indirect costs for the healthcare provider, adequate treatment would provide a cost savings of €8900 to €36,000 euros per patient case in a 4-year time horizon. The variation in estimates across the three countries may be attributable to differences in health delivery practices, coverage, and care payment systems.

Estimates on the savings per country are reported in Figure 3. More details on the total costs attached to the baseline and target scenarios for the three patients' stories are reported in Tables 1 to 4.

Discussion

For the first time, results from our cost of illness analysis on RLS, based on the robust framework developed as part of the EBC 2010 report [16], allowed us to provide the economic impact of RLS with specific application to a selection of EU healthcare systems. The study presents not only differences with respect to their financing and service provision arrangements, but also with respect to the underlying governance mechanisms. It showed that RLS economic impact varies between €20,188.68 million per year, when the prevalence of RLS patients wishing for treatment is assumed to be 1.6% of the population, to €34,068.41 million per year, when the prevalence of RLS patients is assumed to be 2.7% of the population for the three EU countries (France, Germany, and Italy) combined.

Table 4 Augmentation: assumptions, unit costs and sources of information per country settings. (a) Inadequate treatment. (b) Target treatment

(a) Inadequate treatment

				France			Germany			Italy		
Healthcare services	Assumption	Frequency	Unit	Unit costs (euros, FR)	Payer (FR)	Source	Unit costs (euros, GR	Payer (G)	Source	Unit costs (euros, Italy)	Payer (Italy)	Source
DIAGNOSIS - hospitalisation for obstructive sleep apnoea	Inpatient hospital stay, 3 full days	ONE (NOVEMBER 2012)	Hospitalisation period	2605	Health care system		2405	Statutory health insurance	DRG System	2850	Healthcare system	GAZZETTA UFFICIALE 2013
CPAP therapy	From diagnosis up to the end - consider the unit cost of one device (one for the whole period) plus unit cost for a pack of n disposables (mask, filter - one each every day)	Daily therapy for 4 years	One CPAP	1105	Health care system		2332.7	Statutory health insurance	Rote Liste; sleep lab, 3 days 432,70 Euro; CPAP machine 800-3000,- €,	600	Healthcare system	Expert
			Yearly cost perishables (mask, fliter)	204		Average from other countries	204	Statutory health insurance	Masc 80-250 €, filter 28-50 €.	180	Healthcare system	Expert
VISITS - sleep doctor (specialist visits)	Every 6 months until the end	2 visits every year until the end	One visit	42	Health care system		95	Statutory health insurance		20.66	Healthcare system	GAZZETTA UFFICIALE 2013
VISITS - neurologist (specialist visit)	After 6 months (MAY 2013) AND after 3 years (MAY 2016)	2 visits	One visit	42	Health care system		95	Statutory health insurance		20.66	Healthcare system	GAZZETTA UFFICIALE 2013
MEDICINES - l-DOPA 100 mg at night	On L dopa from CPAP therapy (november 2012) until first visit to neurologist (April 2013). The first 3 months on L dopa 100 mg, following 3 months on Ldopa 200 mg	November 2012 to April 2013	One tablet 100 mg	0.129	Patient	7.74 euros 60 cp	0.26	Statutory health insurance	Rote Liste	0.5786	Healthcare system	Federfarma.it

(continued)

Table 4 *(Continued)*

(a) Inadequate treatment

Healthcare services	Assumption	Frequency	Unit	France			Germany			Italy		
				Unit costs (euros, FR)	Payer (FR)	Source	Unit costs (euros, GR	Payer (G)	Source	Unit costs (euros, Italy)	Payer (Italy)	Source
MEDICINES - l-DOPA 200 mg	On L dopa from CPAP therapy (november 2012) until first visit to neurologist (April 2013). The first 3 months on L dopa 100 mg, following 3 months on Ldopa 200 mg	November 2012 to April 2013	One tablet 200 mg	0.169	Patient	10,14 euros for 60 cp	0.4	Statutory health insurance	Rote Liste	0.5786	Healthcare system	Federfarma.it
MEDICINES - ropinirole 4 mg a night	On ropinirole from CPAP therapy (november 2012) until first visit to neurologist (April 2013). The first 3 months on 4 mg a night, following 3 months 8 mg (2 × 4 mg, evening and at night)	November 2012 to April 2013	One daily dose 4 mg	0.477143	Patient	13,36 euros for 28 cp	2.97	Statutory health insurance	Rote Liste	0.642857	Healthcare system	Federfarma.it
MEDICINES - ropinirole 8 mg (2 × 4 mg, evening and at night)	On ropinirole from CPAP therapy (november 2012) until first visit to neurologist (April 2013). The first 3 months on 4 mg a night, following 3 months 8 mg (2 × 4 mg, evening and at night)	November 2012 to April 2013	One daily dose 8 mg	0.954286	Patient	26,72 euros for 28 cp	5.32	Statutory health insurance	Rote Liste	1.178571	Healthcare system	Federfarma.it
MEDICINES - ropinirole higher dosage up to 32 mg	From the first to the second visit to the neurologist (3 years): ropinirole average dosage of 18 mg (range from 8 mg to 32 mg)	From MAY 2013 to MAY 2016	One daily dose	3.817143	Patient	4 * 26,72 euros for 28 cp	21.28	Statutory health insurance	Rote Liste	2.946429	Healthcare system	Federfarma.it
MEDICINES - L-DOPA from 100 mg up to 800 mg	From the first to the second visit to the neurologist (3 years): L dopa average dosage of 450 mg (range from 100 to 800 mg)	From MAY 2013 to MAY 2016	One daily dose	0.676	Patient	4 * 10,14 euros for 60 cp	3.2	Statutory health insurance	Rote Liste	2.6037	Healthcare system	Federfarma.it

(continued)

Table 4 *(Continued)*

(b) Target Treatment

				France			Germany			Italy		
Healthcare services	Assumption	Frequency	Unit	Unit costs (euros, FR)	Payer (FR)	Source	Unit costs (euros, GR)	Payer (GR)	Source	Unit costs (euros, Italy)	Payer (Italy)	Source
INPATIENT HOSPITAL STAY – special RLS center	NOVEMBER 2016 - how many days? 12 days	One inpatient hospital stay , DRG, including PSG	1376.43	Health care system	1376,43 for one night	2405	Statutory health insurance	DRG System	2850	Healthcare system	GAZZETTA UFFICIALE 2013	INPATIENT HOSPITAL STAY – special RLS center
DIAGNOSIS - obstructive sleep apnoea	One hospitalisation	ONE (NOVEMBER 2012)	Hospitalisation period	1376.43	Health care system		2405	Statutory health insurance	Not RLS related costs	2850	Healthcare system	GAZZETTA UFFICIALE 2013
CPAP therapy	From diagnosis up to the end - consider the unit cost of one device (one for the whole period) plus unit cost for perishables (mask, filter - one each every day)	Daily therapy for 4 years	One CPAP	1105	Health care system		2332.7	Statutory health insurance	Not RLS related costs	600	Healthcare system	Expert
					Health care system		204	Statutory health insurance	Masc 80-250 €, filter 28-50 €.	180	Healthcare system	
VISITS - sleep doctor (specialist visits)	Every 6 months until the end	2 visits every year until the end	One visit	42	Health care system		17	Statutory health insurance:	KV (the allied Health insurance system)	20.66	Healthcare system	GAZZETTA UFFICIALE 2013
VISITS - neurologist (specialist visit)	One VISIT only - after 6 months (MAY 2013)	One visit	One visit	42	Health care system		17	Statutory health insurance	KV	20.66	Healthcare system	GAZZETTA UFFICIALE 2013
MEDICINES - clonazepam/ pramipexole/ oxycodone-naloxone (rotation as needed/avoid augmentation)	Daily cost: average of the three treatments bedtime (2 mg/ 0.7 mg/5-2.5 mg respectively)	From May 2013 until the end	daily dosage	0	Patient		2	Statutory health insurance	RotePSG, polysomnography; R Liste	0.624	Healthcare system	Federfarma.it

CPAP, Continuous positive airway pressure; PSG, polysomnography; RLS, restless legs syndrome.

Due to delayed diagnosis and inadequate treatment, RLS cases resulted in severe treatment complications with significant impact on both direct and indirect healthcare costs. When considering closing current treatment gaps with a change from suboptimal (in terms of delayed diagnosis, insufficient response, or augmentation) to optimal care, we confirmed substantial economic savings with the achievement of adequate diagnosis and treatment of RLS. Crucially, the RLS epidemiological studies define RLS only according to a three-question set used in epidemiological surveys [11,13,21,22], but not along the need of treatment, and therefore our estimates should be considered a rough estimate of the overall RLS impact. The wish for treatment is an essential driver of costs in RLS [14] as well as severity of the disease [17].

This study offers also a first attempt at measuring the economic benefits of addressing three major treatment gaps in RLS care pathways looking into a selection of real case studies. Economic case study analyses are increasingly widely used to contribute to an early assessment of the economic case for specific interventions/services where there is a lack of evidence of the wider impacts in the literature and no economic and epidemiological data are available to build appropriate economic modeling. Economic cases have already been used to inform health policy, and practical examples can be found elsewhere with application to a series of long-term conditions and multiple comorbidities ([23]; National Health Service England, 2017).

There are several limitations of the current case studies: the three cases have been selected by RLS experts arbitrarily, no formal selection process has been used, and they are single cases following individual treatment models or failures of these, although experts were advised to select typical, characteristic, and frequently occurring cases. Sources on the three different countries varied across the three cases, and different perspectives were adopted depending on the type of resources. Therefore, the economic data produced by the case study analyses can only be examples for the single country and the individual expert. The calculated costs are based on the assumption that 100% of RLS patients undergo an inpatient hospital stay, polysomnographic diagnostic procedure, and an MRI. The authors, however, do not by any means imply that every RLS patient may need polysomnography and/or diagnostic magnetic resonance imaging. For the respective calculations assuming that only a small proportion (10%–30%) of RLS patients receive these investigations, we refer to the footnotes of Tables 1, 2 and 3.

When translating RLS costs and the consequences of RLS inadequate treatment, to the general population we foresee substantial economic impacts well beyond what may be anticipated from current epidemiological figures in the literature. Unfortunately, the economic evidence, deriving from both the cost of illness and cases studies analyses, is limited to three specific EU settings. More quality data and randomized case studies should be performed to map the impact of RLS across multiple countries, including both developed and emerging national economies.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Informed consent

The corresponding author (J.J.) affirms that this is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained. All authors had access to the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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