Sleep Medicine 66 (2020) 110–118

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Burden of disease in pediatric narcolepsy: a claims-based analysis of health care utilization, costs, and comorbidities

Ginger Carls [a, *], Sheila Reiss Reddy [b], Michael S. Broder [b], Ryan Tieu [b], Kathleen F. Villa [a], Judi Profant [a], Ann C. Halbower [c]

[a] Medical Affairs, Jazz Pharmaceuticals, Inc., 3170 Porter Dr, Palo Alto, CA 94304, USA
[b] Partnership for Health Analytic Research, LLC, 280 South Beverly Dr, Beverly Hills, CA 90212, USA
[c] University of Colorado School of Medicine, 13001 E 17th Pl, Aurora, CO 80045, USA

ARTICLE INFO

Article history:
Received 14 March 2019
Received in revised form
12 August 2019
Accepted 14 August 2019
Available online 26 August 2019

Keywords:
Burden of illness
Comorbid condition
Health care utilization
Health care costs
Narcolepsy
Pediatric

ABSTRACT

Background: This study analyzed a privately insured pediatric population with and without narcolepsy to determine the impact of pediatric narcolepsy on comorbidities, health care utilization, and cost. Additional analyses compared narcolepsy type 1 and type 2.

Methods: This retrospective cross-sectional study identified US patients with narcolepsy <18 years of age with ≥2 claims with a diagnosis code of narcolepsy using Truven MarketScan® data 2011 to 2015. Patients were matched to controls without narcolepsy. Comorbid conditions, health care utilization, and costs were measured by calendar year. *P* values are nominal, and no adjustments for multiplicity or multiple comparisons were made.

Results: A total of 1427 pediatric patients with narcolepsy were identified and matched with 4281 controls from 2011 to 2015. Patients with narcolepsy had more comorbid conditions (mean 5.8 vs 2.4, nominal $P < 0.001$). Respiratory diseases and mood disorders were more common in patients with narcolepsy than controls (57% vs 32% and 56% vs 14%, respectively; both nominal $P < 0.001$). Compared to controls, patients with narcolepsy underwent more diagnostic tests (electroencephalogram, EEG [0.13 vs 0.0053]) and brain computed tomography, CT/magnetic resonance imaging, MRI (0.26 vs 0.022; both nominal $P < 0.001$). Mean annual inpatient days (0.71 vs 0.15), emergency department visits (0.51 vs 0.15), and outpatient office visits (8.6 vs 2.3) were higher for patients with narcolepsy than controls (all nominal $P < 0.001$). Annual mean health care costs were higher for patients with narcolepsy versus controls ($15,797 vs $2449, nominal $P < 0.001$).

Conclusion: Pediatric patients with narcolepsy had greater comorbidity, higher health care utilization, and higher costs than patients without narcolepsy.

1. Introduction

Narcolepsy is a rare, lifelong neurological disorder characterized by excessive daytime sleepiness (EDS) and the inability to regulate sleep–wake cycles [1]. In addition to EDS, the clinical symptoms of narcolepsy include cataplexy, hallucinations during transitions from wakefulness to sleep or sleep to wakefulness, sleep paralysis, and disrupted nighttime sleep [1]. The International Classification of Sleep Disorders, Version 3 and the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition provide detailed diagnostic criteria for narcolepsy [1,2]. However, the diagnostic criteria are not specific to the pediatric population, and little work has been done in pediatric patients to validate the tests upon which the diagnostic criteria rely.

Abbreviations: AHRQ, Agency for Healthcare Research Quality; BOND, Burden of Narcolepsy Disease; CCAE, Commercial Claims and Encounters; CCS, Clinical Classifications Software; CCSM, CCS Multilevel; CSHCN, children with special health care needs; HCUP, Healthcare Cost and Utilization Project; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification.

* Corresponding author. 22 Rue Siggy Vu Letzebuerg, Luxembourg, 1933, Luxembourg.

E-mail addresses: gingercarls@gmail.com (G. Carls), srreddy@pharllc.com (S.R. Reddy), mbroder@pharllc.com (M.S. Broder), ryanstieu@gmail.com (R. Tieu), Kathleen.Villa@jazzpharma.com (K.F. Villa), Judith.Profant@jazzpharma.com (J. Profant), Ann.Halbower@childrenscolorado.org (A.C. Halbower).

https://doi.org/10.1016/j.sleep.2019.08.008
1389-9457/

Only a few epidemiological studies have been conducted in narcolepsy, mostly in small populations. A US population-based study estimated the prevalence of adults with narcolepsy to range from 35.8 to 56.3 per 100,000 people for those with narcolepsy with cataplexy and narcolepsy overall, respectively [3]. A US study of medical and prescription claims estimated the prevalence of narcolepsy in pediatric patients to be 0.7 per 100,000 for patients 0–6 years of age, 6.9 for 7–11 years of age, and 24.0 for 12–17 years of age [4]. Furthermore, the prevalence of US pediatric patients with narcolepsy ≤9 years of age was shown to be 12.7 per 100,000 for females and 85.2 per 100,000 for males [3].

The onset of narcolepsy usually occurs after five years of age and most typically takes place between the ages of 10 and 25 years [1]. Frequently, many years elapse between the onset of narcolepsy symptoms and a diagnosis of narcolepsy [5–8]. Factors contributing to delayed diagnosis include lack of recognition of narcolepsy symptoms by health care providers, school personnel, and parents; partial symptom overlap with more common sleep disorders, such as obstructive sleep apnea (OSA); the lack of a simple diagnostic test that is validated in pediatrics; and a high rate of medical and psychiatric comorbidities in patients with narcolepsy [5–8]. In younger pediatric patients, the presence of behaviors often observed in attention-deficit hyperactivity disorder (ADHD) and the use of ADHD medications may mask narcolepsy symptoms [5]. Pediatric narcolepsy also may be initially misdiagnosed as a neuromuscular disorder, epilepsy, depression, conversion disorder, or psychosis [9,10]. Furthermore, cataplexy may present atypically in pediatric patients initially [11–13], and pediatric patients may be reluctant or unable to describe their symptoms [7,13,14].

Studies have documented considerable economic, clinical, and humanistic burden of disease in the adult and overall population of people with narcolepsy. Narcolepsy often has a negative impact on patients' educational attainment, income, or ability to work [15–17]. Compared to adults without narcolepsy, those with narcolepsy have an increased burden of medical and psychiatric comorbidity, such as OSA and other sleep disorders, mood disorders, anxiety disorders, diabetes, obesity, and headache/migraine [18–20]. Reduced quality of life and significantly higher utilization of health care services and per-patient average costs have been observed in adults with narcolepsy compared to similar patients without narcolepsy [16,17]. Narcolepsy is also a risk factor for accidents [21,22]. Furthermore, adult patients with narcolepsy of all age groups have higher mortality compared to those without the disorder [23].

However, the health care burden of narcolepsy in children has not been comprehensively studied in large US populations. The objective of this study was to examine comorbid conditions, health care utilization, and health care costs in a large sample of pediatric patients with narcolepsy compared with pediatric controls without narcolepsy. A secondary objective was to compare comorbidity, health care utilization, and health care costs in pediatric patients with narcolepsy type 1 and those with narcolepsy type 2.

2. Methods

This was a retrospective cross-sectional study. The primary analysis examined the burden of illness among pediatric patients with narcolepsy compared to patients without narcolepsy of similar age, sex, geographic region, and insurance type in the United States. A subgroup analysis examined burden of illness among patients diagnosed with narcolepsy type 1 compared to patients diagnosed with narcolepsy type 2.

2.1. Data source

This US-based study used data from the Truven Health Analytics MarketScan® Commercial Claims and Encounters (CCAE) database, from 2011 to 2015, which is representative of those with employer-provided health insurance in the United States. The data are deidentified administrative health care claims. The CCAE database includes the health care claims of employees and their dependents of mostly large- and medium-sized, self-insured employers. Coverage is provided under a variety of fee-for-service, fully capitated, and partially capitated health plans, including preferred provider organizations, point-of-service plans, indemnity plans, and health maintenance organizations. The CCAE database includes all benefits received by the patient and covered partially or wholly by the health plan. Data on member enrollment; patient, provider, and hospital demographics; inpatient and outpatient services and costs; diagnoses; medical procedures; and prescription drug use and costs for medications filled through outpatient pharmacies are recorded in the database.

2.2. Patient identification

Over five years, cohorts of patients <18 years of age who had existing or newly diagnosed narcolepsy were identified between January 1, 2011 and December 31, 2015. In each year, narcolepsy was identified on the basis of ≥2 claims with a diagnosis code of narcolepsy, with or without cataplexy (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes: 347.0x, 347.1x; 10th Revision (ICD-10-CM) code: G47.4x). To ensure a confirmatory diagnosis of narcolepsy, the 2 claims must have occurred on separate days and ≥1 claim must have been non-diagnostic (ie, ≥1 claim must not have an indication of multiple sleep latency test [MSLT]/polysomnography [PSG] testing [current procedural terminology (CPT) code: 95805] or other diagnostic testing; Supplementary Table 1).

Patients not continuously enrolled during the entire calendar year were excluded. Patients who met the criteria in ≥1 year (2011–2015) were included in the study. For prevalent patients appearing in multiple calendar years, we randomly selected one year per patient to create a prevalent cohort of unique patients with narcolepsy.

For the comparison of patients with versus without narcolepsy, a control group of pediatric patients who did not have any diagnosis claims for narcolepsy and who were continuously enrolled during the relevant calendar year was drawn from a 5% random sample of commercially insured enrollees. These patients were matched to pediatric patients with narcolepsy, in a 3:1 ratio, by calendar year, age, sex, US census region or census division, and insurance type. Thus, control patients represented a general population of pediatric patients without narcolepsy.

For the subgroup analyses, patients with ≥1 claim for a narcolepsy type 1 diagnosis code (ICD-9-CM code: 347.00; ICD-10-CM code: G47.411) were classified as narcolepsy type 1; patients with no claims for narcolepsy type 1 were classified as narcolepsy type 2.

2.3. Study measures

Comorbid conditions, health care utilization, and health care costs (allowable medical and pharmacy insurance charges) were measured annually.

Specific comorbid conditions were measured using diagnosis codes (ICD-9-CM and ICD-10-CM) to describe the total comorbidity burden. Specific comorbid conditions and autoimmune conditions previously associated with narcolepsy or associated with narcolepsy misdiagnoses in children were selected as comorbid conditions of interest [24,25]. The presence of potential comorbid

conditions was defined based on the presence of ≥1 claim with the diagnosis (ICD-9-CM or ICD-10-CM codes). Comorbid conditions of interest are shown in Supplementary Table 2, and autoimmune conditions are listed in Supplementary Table 3. The Agency for Healthcare Research and Quality/Healthcare Cost and Utilization Project (AHRQ/HCUP) Clinical Classifications Software (CCS) "body system" classification has a range of 0 to 18 systems. A modified CCS scoring system that excluded narcolepsy codes was employed in this study to measure the number of body systems affected by chronic and/or acute comorbid conditions [26].

Inpatient, outpatient medical, and outpatient pharmacy use was also measured. Inpatient utilization was measured by mean annual number of hospitalizations and length of stay. In addition to all-cause utilization, inpatient utilization associated with psychiatric care was measured by mean annual number of psychiatric hospitalizations and length of stay. Outpatient medical utilization was measured by mean annual number of emergency department (ED) visits, non-ED outpatient service visits, diagnostic sleep tests (MSLT and PSG), and radiology/imaging tests (electroencephalography [EEG] and brain computed tomography [CT]/magnetic resonance imaging [MRI]). Outpatient pharmacy utilization was examined by the following measures: the proportion of patients receiving any narcolepsy-related prescription medication (including medications used to treat narcolepsy and other neurological medications); the proportion of patients receiving medications from 1, 2, or ≥3 drug categories; and the mean number of dispensing events with a 30-day supply equivalent (fills of <30 days were considered 1 event). Medications included those presumed to treat narcolepsy symptoms (sleepiness and cataplexy): modafinil, armodafinil, sodium oxybate, methylphenidate, amphetamines, selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants [27]. Other neurological medications that are used to treat potentially comorbid conditions in pediatric patients or misdiagnosed narcolepsy symptoms also were examined: monoamine oxidase inhibitors, other antianxiety medications, anticonvulsants, nonstimulant ADHD medications, and antipsychotics. A complete listing of health care utilization measures is provided in Supplementary Table 4.

Total health care costs and cost by type of service were estimated as a per-patient annual average. All costs were reported as means with standard deviations and inflation adjusted to 2015 US dollars. The analysis of health care costs included: total health care costs (medical and pharmacy costs), medical costs (inpatient hospitalization costs, ED service costs, and non-ED outpatient service costs), and pharmacy costs (total pharmacy costs and narcolepsy-related medications). A complete listing of health care cost measures is provided in Supplementary Table 5.

2.4. Data analysis

Descriptive statistics were calculated, including means and standard deviations for continuous data and relative frequencies and percentages for categorical data. Medians and interquartile ranges were calculated for continuous variables where appropriate. Additionally, statistical tests were performed according to distributional assumptions (eg, *t* test or Wilcoxon test for means and chi-square or Fisher's exact test for proportions). Multiple comparisons were performed without adjustments for multiplicity; as such, nominal *P* values are presented.

Study measures (comorbid conditions, utilization, and costs) were reported for all years combined (2011–2015), stratified by cases versus controls. The study measures also were reported for all years combined among patients with narcolepsy, stratified by narcolepsy type 1 versus narcolepsy type 2. Costs incurred by matched control patients were subtracted from costs experienced by patients diagnosed with narcolepsy in order to calculate burden of illness. Each component of health care costs (eg, inpatient) was also expressed as a share of total costs, separately for cases and controls. This was calculated as the average annual cost per patient for the component (eg, inpatient) divided by the average annual total cost per patient, and expressed as a percentage.

All data transformations and statistical analyses were performed using SAS© version 9.4.

3. Results

A total of 1427 unique pediatric patients with narcolepsy were matched with 4281 controls between 2011 and 2015 (Table 1). Two patients with narcolepsy who were not completely matched with controls were excluded from analysis, except where noted. More than 80% of patients with narcolepsy were 12 to 17 years of age, and 51.9% were male.

3.1. Comorbid conditions

Compared to controls, pediatric patients with narcolepsy had more chronic and acute comorbid conditions, based on the body system index (modified CCS score, Table 2). In patients with narcolepsy versus controls, the mean number of body systems affected by chronic conditions was 2.5 versus 0.6, respectively, and the mean number of body systems affected by chronic and/or acute conditions was 5.8 versus 2.4 (nominal $P < 0.001$ for both comparisons). For 16 of the 18 body systems groups evaluated by CCS, the level of comorbidity was higher in patients with narcolepsy compared to controls. The largest excess prevalence in the narcolepsy group compared with the control group was observed for symptoms, signs, and ill-defined conditions (56.2%), and diseases of the nervous system and sense organs (eg, eyes and ears; 51.9%). Very few patients had claims in the two CCS body systems in which the narcolepsy and control groups did not differ ("complications of pregnancy, childbirth, and the puerperium" and "certain conditions originating in the perinatal period").

Analyses were conducted to identify the frequency of claims for selected conditions known to be associated with pediatric narcolepsy. The frequency of claims with diagnostic codes for 11 of these conditions was higher in patients with narcolepsy compared to patients without narcolepsy (nominal $P < 0.001$ for each comparison). Claims with diagnostic codes for these 11 conditions were identified in >10% of patients with narcolepsy (Fig. 1). These conditions included sleep disorders (circadian rhythm sleep disorders, OSA, sleep-related movement disorders, and insomnia), obesity, allergic or respiratory conditions (asthma, allergic disorders, and upper respiratory infections), anxiety, fatigue, and injury (trauma or burns). Injuries (trauma or burns) and autoimmune disorders were diagnosed in nearly twice as many patients with narcolepsy compared with controls (30.3% vs 16.7%, respectively, for injuries and 2.7% vs 1.1%, respectively, for autoimmune disorders).

Table 1
Patient characteristics.

Characteristic	Narcolepsy (n = 1427)	Control (n = 4281)
Age cohort, n (%)		
≤6 years	38 (2.7)	114 (2.7)
7–11 years	213 (14.9)	639 (14.9)
12–17 years	1176 (82.4)	3528 (82.4)
Sex (female), n (%)	687 (48.1)	2061 (48.1)
Cataplexy present, n (%)[a]	515 (36.0)	NA

NA, not applicable.
[a] Cataplexy was defined as the presence of ≥1 diagnosis for narcolepsy with cataplexy.

Table 2
CCS comorbid conditions among pediatric patients with narcolepsy versus controls.[a]

	Patients with comorbidity		Excess prevalence
	Narcolepsy (n = 1427)	Control (n = 4281)	
Chronic condition indicator (excluding narcolepsy), mean (SD)	2.5 (1.6)	0.6 (1.0)	–
Number of affected body systems (chronic and acute; excluding narcolepsy), mean (SD)	5.8 (2.7)	2.4 (2.4)	–
Infections and parasitic disease, n (%)	310 (21.7)	536 (12.5)	9.2%
Neoplasms, n (%)	87 (6.1)	135 (3.2)	2.9%
Endocrine, nutritional, and metabolic diseases and immunity disorders, n (%)	393 (27.5)	224 (5.2)	22.3%
Diseases of blood and blood-forming organs, n (%)	115 (8.1)	70 (1.6)	6.5%
Mood disorders, n (%)	794 (55.6)	593 (13.9)	41.7%
Diseases of the nervous system and sense organs (excluding narcolepsy), n (%)	1011 (70.8)	807 (18.9)	51.9%
Diseases of the circulatory system, n (%)	163 (11.4)	92 (2.1)	9.3%
Diseases of the respiratory system, n (%)	816 (57.2)	1379 (32.2)	25.0%
Diseases of the digestive system, n (%)	263 (18.4)	277 (6.5)	11.9%
Diseases of the genitourinary system, n (%)	241 (16.9)	330 (7.7)	9.2%
Complications of pregnancy, childbirth, and the puerperium, n (%)	2 (0.1)	11 (0.3)	−0.2%
Diseases of the skin and subcutaneous tissue, n (%)	475 (33.3)	754 (17.6)	15.7%
Diseases of the musculoskeletal system, n (%)	550 (38.5)	802 (18.7)	19.8%
Congenital anomalies, n (%)	115 (8.1)	111 (2.6)	5.5%
Certain conditions originating in the perinatal period, n (%)	1 (0.1)	3 (0.1)	0.0%
Symptoms, signs, and ill-defined conditions, n (%)	1189 (83.3)	1160 (27.1)	56.2%
Injury and poisoning, n (%)	518 (36.3)	808 (18.9)	17.4%
Factors influencing health status and contact with health services, n (%)	1082 (75.8)	2089 (48.8)	27.0%

CCS, Clinical Classifications Software; SD, standard deviation; AHRQ, Agency for Health Research and Quality; HCUP, Healthcare Cost and Utilization Project.
[a] Mean number of body systems affected by chronic and/or acute conditions as measured by the CCS provided by the AHRQ/HCUP. The modified CCS tallies the number of affected body systems based on diagnosis claims and a hierarchical classification system. The number of possible systems ranges from 0 to 18.

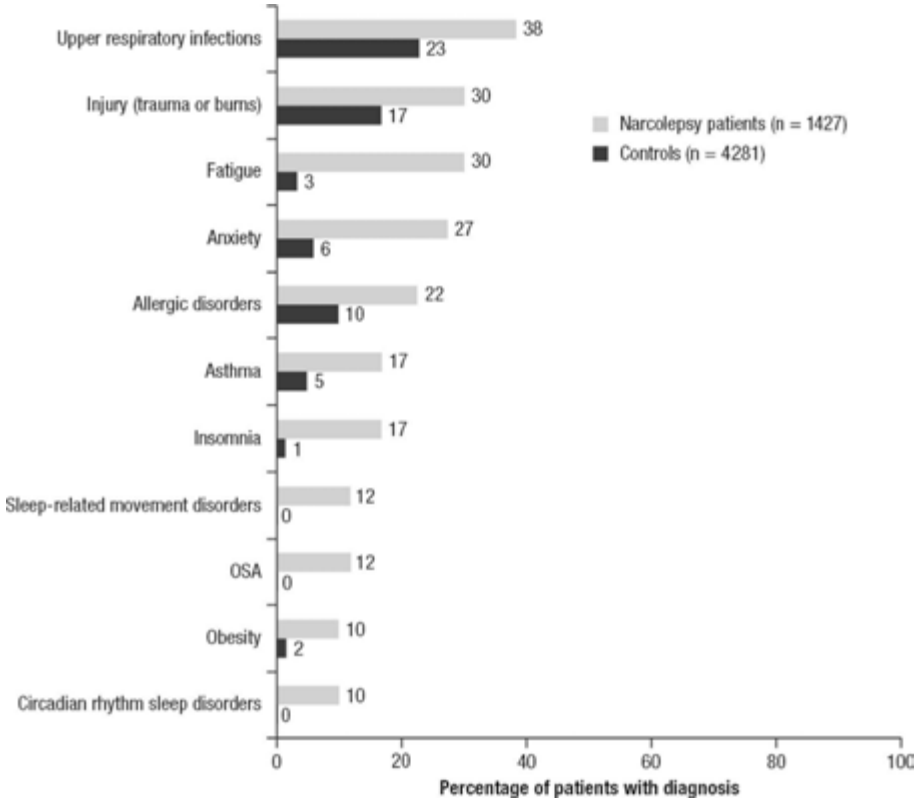

Fig. 1. Selected conditions known to be associated with pediatric narcolepsy that were diagnosed in >10% of patients with narcolepsy. OSA, obstructive sleep apnea. All differences nominal $P < 0.001$.

3.2. Health care utilization

Analysis of annual health care utilization showed that pediatric patients with narcolepsy underwent a higher annual mean number of both MSLT (0.672 vs 0.0007) and PSG tests (0.7834 vs 0.0051; nominal $P < 0.001$ for both comparisons; Fig. 2A) compared with controls. EEG diagnostic tests and brain CT/MRI tests were more frequently conducted in narcolepsy patients, with annual mean numbers of EEG and brain CT/MRI tests of 0.13 and 0.26 for patients with narcolepsy versus 0.0053 and 0.022 for controls (nominal $P < 0.001$ for both comparisons; Fig. 2A). Furthermore, pediatric patients with narcolepsy used outpatient care at higher rates than

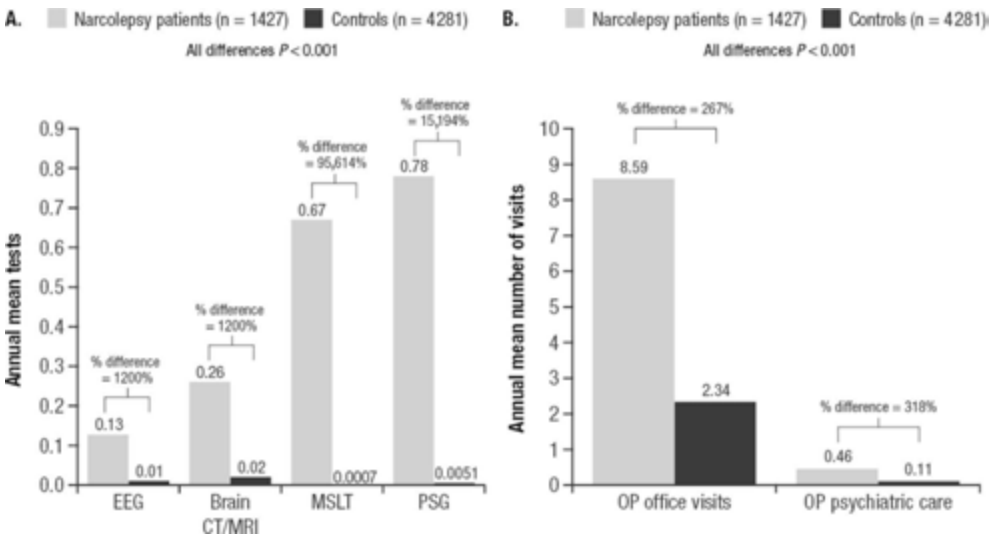

Fig. 2. Utilization rates of outpatient care, including (A) annual tests and (B) annual visits in pediatric patients with narcolepsy compared to controls. EEG, electroencephalography; CT, computed tomography; MRI, magnetic resonance imaging; MSLT, multiple sleep latency test; PSG, polysomnography; OP, outpatient. *P* values are nominal and correspond to the absolute difference.

those without narcolepsy. Compared to controls, patients with narcolepsy had a higher annual mean number of outpatient office visits (8.59 vs 2.34) and outpatient psychiatric visits (0.46 vs 0.11; nominal $P < 0.001$ for both comparisons; Fig. 2B).

Pediatric patients with narcolepsy also used inpatient and emergency care at higher rates than controls. Compared to the control group, the narcolepsy group had more mean all-cause inpatient admissions (0.13 vs 0.02), psychiatric inpatient admissions (0.06 vs 0.01), and ED visits (0.51 vs 0.15; nominal $P < 0.001$ for all comparisons; Fig. 3A). Patients with narcolepsy also had a greater annual mean number of all-cause inpatient days (0.71 vs 0.15) and psychiatric inpatient days (0.41 vs 0.07) than controls (nominal $P < 0.001$ for both comparisons; Fig. 3B).

Analysis of patients who had ≥1 prescription pharmacy claim for narcolepsy-related medications (ie, any prescription medication used to treat narcolepsy symptoms or neurological medications) showed differences in drug utilization patterns in pediatric patients with and without narcolepsy (Supplementary Fig. 1). Among patients in narcolepsy and control groups, respectively, 76% and 10% had pharmacy claims for narcolepsy-related medications, and 72% and 9% had claims for any narcolepsy treatment. The medications most commonly prescribed for patients with narcolepsy were amphetamine, methylphenidate, SSRIs, modafinil, and armodafinil. In patients with narcolepsy and controls, respectively, percentages of patients with ≥1 filled prescription for one of these medications were 26% versus 4% for an amphetamine, 23% versus 3% for methylphenidate, 21% versus 4% for an SSRI, 19% versus 0% for modafinil, and 13% versus 0% for armodafinil (nominal $P < 0.001$ for all comparisons). Percentages of patients with narcolepsy and controls, respectively, who had ≥1 filled prescription for another neurological medication were 9% versus 1% for antipsychotics, 7% versus 2% for a nonstimulant ADHD medication, 7% versus 1% for another anxiety medication, and 3% versus 0% for an anticonvulsant (nominal $P < 0.001$ for all comparisons).

As expected, there were differences in the number of narcolepsy-related prescription medications taken by pediatric patients with

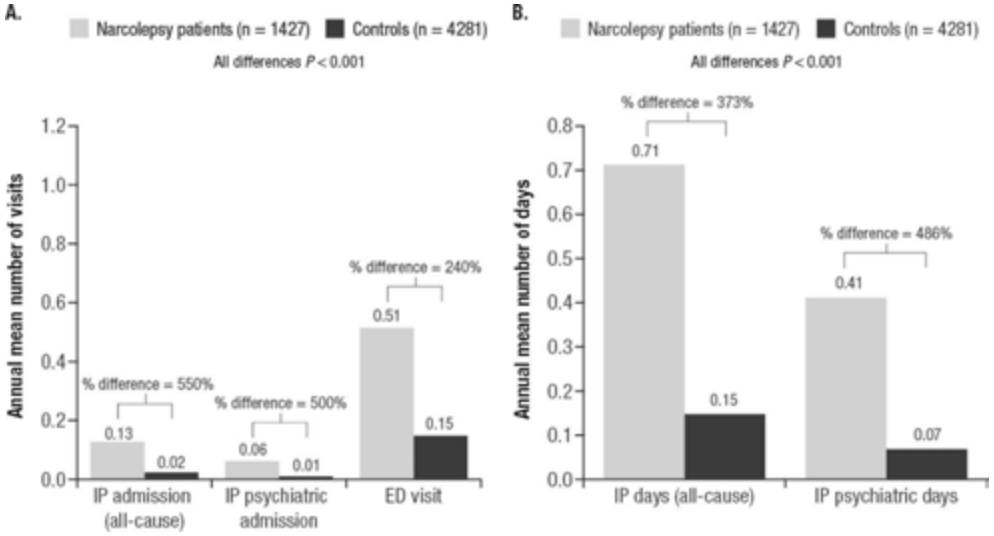

Fig. 3. Utilization rates of inpatient and emergency care, including (A) annual admissions or visits and (B) annual inpatient days, in pediatric patients with narcolepsy compared to controls. IP, inpatient; ED, emergency department. *P* values are nominal and correspond to the absolute difference.

narcolepsy and controls (Supplementary Fig. 2). In the narcolepsy and control groups, respectively, 24% and 90% of patients did not take narcolepsy-related medications, 35% and 7% took 1 medication, 22% and 2% took 2 medications, and 19% and 1% took ≥3 medications. Thus, 41% of the narcolepsy group and 3% of the control group took ≥2 narcolepsy-related medications. The annual mean number of dispensing events for medications dispensed in outpatient pharmacy claims was 18.6 and 4.2 for pediatric patients with narcolepsy and controls, respectively (nominal $P < 0.001$).

3.3. Health care costs

Pediatric patients with narcolepsy had higher health care costs than controls (Table 3). Total annual mean health care costs were $13,348 higher for patients in the narcolepsy group than for those in the control group ($15,797 vs $2449; nominal $P < 0.001$). Diagnostic testing and medical services, including inpatient and outpatient visits, accounted for more than half ($8185) of this cost differential. Outpatient pharmacy costs were $5163 higher for patients with narcolepsy than for controls ($5656 vs $493; nominal $P < 0.001$). Costs of narcolepsy-related medications (including medications used to treat narcolepsy and other neurological medications) accounted for nearly three-quarters ($4351) of the pharmacy cost differential.

3.4. Patients with narcolepsy type 1 versus narcolepsy type 2

Comorbid conditions for which there were differences between patients with narcolepsy type 1 and narcolepsy type 2 are shown in Table 4 (two patients not completely matched with controls are included). Epilepsy/seizures, movement disorders, obesity, schizophrenia, and sleep-related movement disorders were reported more frequently in patients with narcolepsy type 1; while ADHD, allergic disorders, and the CCS Multilevel (CCSM) 5 Mental Illness Categories for attention deficit, conduct, and disruptive behavior disorders and delirium, dementia, and amnestic and other cognitive disorders were more frequent in patients with narcolepsy type 2 (all nominal $P < 0.05$; Table 4).

Table 3
Health care costs in pediatric patients with narcolepsy compared with controls.

	Narcolepsy (n = 1427), $	Control (n = 4281), $	Difference, $
Inpatient admissions	1899	557	1341
ED visit (without admission)	440	116	323
Outpatient physician visit	1139	259	880
Other outpatient	3666	825	2841
Total medical care services	**10,140**	**1956**	**8184**
Outpatient pharmacy	5656	493	5163
Narcolepsy and related Rx	4481	130	4351
Other Rx	1175	364	812
Total costs (medical + pharmacy)	**15,797**	**2449**	**13,348**

ED, emergency department; Rx, prescription.

Although health care utilization was similar across patients with narcolepsy, analyses comparing pediatric patients with narcolepsy type 1 and narcolepsy type 2 identified some differences. A greater proportion of patients with narcolepsy type 1 than patients with narcolepsy type 2 had a brain CT/MRI (23.7% vs 17.8%; $P = 0.008$) and received narcolepsy-related medication (82% vs 72%; nominal $P < 0.001$). In patients with narcolepsy type 1 and narcolepsy type 2, respectively, 18% and 28% of patients did not take narcolepsy-related medications, 33% and 36% took 1 medication, 24% and 20% took 2 medications, and 25% and 16% took ≥3 medications (nominal $P < 0.001$ for comparison). A greater proportion of patients with narcolepsy type 1 than with narcolepsy type 2 had any inpatient hospitalization (10.5% vs 6.7%; nominal $P = 0.011$), but patients with narcolepsy type 1 had a lower number of mean psychiatric hospital days among patients with psychiatric hospitalization than patients with narcolepsy type 2 (7.1 vs 14.4; nominal $P = 0.039$).

Pediatric patients with narcolepsy type 1 had higher health care costs than patients with narcolepsy type 2. Total annual mean health care costs were $5757 higher for patients with narcolepsy type 1 than for those with narcolepsy type 2 ($19,474 vs $13,717; nominal $P < 0.001$). Pharmacy costs were responsible for much of this differential; total mean pharmacy costs were $5479 higher for patients with narcolepsy type 1 than for patients with narcolepsy type 2 ($9155 vs $3676; nominal $P < 0.001$). Costs of narcolepsy-related medications accounted for nearly all ($5310) of this cost differential.

4. Discussion

This retrospective cross-sectional study using the US Truven MarketScan® database compared comorbid conditions, health care utilization, and health care costs in pediatric patients diagnosed with narcolepsy. The key findings of this study indicate that pediatric patients with narcolepsy have more comorbid conditions and higher levels of health care use and costs in the index year compared to pediatric patients without narcolepsy.

Table 4
Comorbid conditions for which there were differences between pediatric patients with narcolepsy type 1 and narcolepsy type 2.

Comorbid condition	Patients with narcolepsy, n (%)			*P* value[b]
	All (n = 1429[a])	Type 1 (n = 515)	Type 2 (n = 914)	
ADHD	82 (5.7)	21 (4.1)	61 (6.7)	0.002
Allergic disorders	320 (22.4)	98 (19.0)	222 (24.3)	0.022
Epilepsy/seizures	78 (5.5)	37 (7.2)	41 (4.5)	0.015
Movement disorders	27 (1.9)	14 (2.7)	13 (1.4)	0.011
Obesity	150 (10.5)	66 (12.8)	84 (9.2)	0.032
Schizophrenia	3 (0.2)	3 (0.6)	0	0.006
Sleep-related movement disorders	167 (11.7)	73 (14.2)	94 (10.3)	0.028
CCSM 5 Mental Illness Categories				
Attention-deficit, conduct, and disruptive behavior disorders[c]	296 (20.7)	81 (15.7)	215 (23.5)	<0.001
Delirium, dementia, and amnestic and other cognitive disorders[d]	32 (2.2)	5 (1.0)	27 (3.0)	0.015

ADHD, attention-deficit hyperactivity disorder; CCSM, Clinical Classifications Software Multilevel.
[a] Includes 2 patients who were not completely matched with control patients.
[b] All nominal *P* values.
[c] CCSM 5 Mental Illness Category 5.3.
[d] CCSM 5 Mental Illness Category 5.4.

Nearly all comorbid conditions examined were more prevalent among patients with narcolepsy than in those without the disorder, although not all comorbid conditions may be truly comorbid, given the extent of misdiagnoses reported prior to the diagnosis of narcolepsy [28]. Future work should examine changes in claims for the treatment of comorbid conditions after the narcolepsy diagnosis in children and adolescents to better understand which conditions are truly comorbid. Notable comorbidity differences between pediatric patients with narcolepsy and controls were observed for allergic disorders, anxiety, asthma, ADHD, depression, upper respiratory infections, injury (trauma or burns), and mean number of affected CCS body systems.

The increases in overall comorbidity burden and prevalence of specific comorbid conditions observed in our study are similar to findings reported in 2017 by Jennum et al. [29]. In this national population-based study that used data from the Danish National Patient Registry, pediatric patients with narcolepsy had a significantly greater comorbidity burden than controls, as measured by the number of main World Health Organization (WHO) group diagnoses [29]. Furthermore, compared to controls, pediatric patients with narcolepsy had a significantly greater prevalence of neoplasms; endocrine, nutritional, and metabolic diseases; mental and psychiatric disorders; nervous system disorders; musculoskeletal system and connective tissue diseases; and abnormal clinical and laboratory findings [29]. Other investigations have also reported high rates of comorbid obesity, other sleep disorders, depression, and anxiety in pediatric patients with narcolepsy [30–33]. The findings of our study also closely parallel those of the Burden of Narcolepsy Disease (BOND) study [16,18,19]. When examining the prevalence of comorbidities using the CCS grouping system, CCS scores tend to be lower in a healthy population without narcolepsy, as reflected by the control group. Furthermore, adult patients with narcolepsy showed significant excess prevalence compared with matched controls for conditions previously reported to be associated with narcolepsy (eg, rapid eye movement behavior disorder and sleep apnea) [18]. An analysis of psychiatric comorbidity found that all categories of mental illness were significantly more prevalent in adult patients with narcolepsy than in controls, with the greatest excess prevalence for anxiety disorders and mood disorders [19]. A retrospective registry-based French study found that 11.1% of pediatric patients with narcolepsy and no controls had an autoimmune disease ($P = 0.01$) [34].

It has previously been shown that for other chronic health conditions (eg, asthma, epilepsy), there is a cost burden for these children with special health care needs (CSHCN) [35,36]. Likewise, the current study has demonstrated that the cost burden of narcolepsy is also substantial, and confirms the importance of assessing health care utilization and costs associated with pediatric narcolepsy. Compared to patients in the control group, patients in the narcolepsy group were more likely to be hospitalized and had more total mean hospital days, ED visits, and physician office visits. Some imaging tests, such as EEG and brain CT/MRI, also were more common among pediatric patients with narcolepsy versus controls. Health care costs, including total costs, inpatient medical costs, outpatient medical costs, and pharmacy costs, were higher among patients with narcolepsy compared to controls. For pediatric patients with narcolepsy, physician office visits and sleep tests made up a substantial portion of outpatient costs, while most drug costs could be attributed to medications used for the treatment of narcolepsy. The greater use of expensive diagnostic tests, increased hospital admissions, and increased outpatient visits in patients with narcolepsy are substantial contributors to the economic burden of narcolepsy. Understanding health care utilization and costs associated with pediatric narcolepsy is critical when assessing a patient's disease outlook in the years following a diagnosis of narcolepsy. To this end, an analysis of claims data from the Truven Health Analytics MarketScan® database demonstrated that health care utilization and the number of comorbid conditions in newly diagnosed pediatric patients generally decreased after diagnosis [37]. Total health care costs remained stable before and after diagnosis, with a decrease in medical services costs and an increase in pharmacy costs in the years following diagnosis [37]. These data suggest that timely diagnosis and treatment decreases utilization and costs prior to diagnosis.

An analysis of health care utilization and costs in the BOND study showed that adults with narcolepsy had significantly higher annual utilization rates compared with their matched controls [16], consistent with the findings in pediatric patients with narcolepsy presented here. For all inpatient and outpatient services analyzed, annual utilization rates in the narcolepsy cohort were generally twice as high as those observed for the control group, and drug utilization was significantly higher in the narcolepsy group [16]. Annualized per-patient costs were also significantly higher in patients with narcolepsy versus controls.

Within the cohort of patients with narcolepsy in our study, outcomes were compared for pediatric patients diagnosed with narcolepsy type 1 and narcolepsy type 2. In contrast to the comparisons between patients with and without narcolepsy, the comparison between patients with narcolepsy type 1 and narcolepsy type 2 revealed fewer and smaller differences in comorbidity, health care utilization, and health care costs. Pediatric patients with narcolepsy type 1 had a higher frequency of some conditions, such as seizures and sleep-related movement disorders, but lower rates of other conditions, such as allergic disorders and ADHD, compared with patients with narcolepsy type 2. Health care utilization was generally similar between patients with narcolepsy type 1 and narcolepsy type 2, but inpatient hospitalization, brain CT/MRI testing, and use of narcolepsy-related medications were more common in patients with narcolepsy type 1. Total health care costs were greater among patients with narcolepsy type 1 compared to those with narcolepsy type 2, and these increased costs were largely attributable to differences in costs for narcolepsy-related medications.

A notable finding of our study is that 18% of pediatric patients with narcolepsy type 1 and 28% of those with narcolepsy type 2 did not appear to be taking a narcolepsy-related prescription medication. Among respondents to the US-based Unite Narcolepsy survey, 92% of whom were adults, 18% were not taking medication prescribed by a health care provider [7]. The results of the current study and others suggest that narcolepsy in pediatric patients may be undertreated. Possible explanations are that some physicians may not recognize the varied symptoms of childhood narcolepsy, may minimize the detrimental impact of sleep disorders, may have limited experience diagnosing or treating pediatric narcolepsy, or may be reluctant to prescribe medications that are not specifically indicated for pediatric patients because of concerns about adverse effects and effectiveness. Additionally, type of provider, types of symptoms that prompt consultation and/or diagnosis, and parental influence are factors that may explain the undertreatment of pediatric narcolepsy. For example, parents or patients may prefer nonpharmacologic management of their narcolepsy symptoms, including scheduled napping [38]. In contrast, some pediatric patients had a high medication burden in our study. Our findings demonstrated that 19% of pediatric patients with narcolepsy type 1 and narcolepsy type 2 received $\geq$3 narcolepsy-related medications, thus adding additional challenges for these patients.

The most important strength of our study is that it includes a large population of geographically dispersed pediatric patients in the United States with narcolepsy type 1 and narcolepsy type 2. Matching pediatric patients with narcolepsy to similar patients without narcolepsy made it possible to characterize differences in patterns of comorbid conditions, health care utilization, and health care costs between the two groups. Representation of large cohorts of pediatric patients with narcolepsy type 1 and narcolepsy type 2 allowed the differentiation of these disorders in terms of their somewhat different comorbidity, health care utilization, and health care cost profiles. To our knowledge, this is the only extensive comparison of patients with narcolepsy type 1 versus narcolepsy type 2 that has been undertaken. Our data suggest that pediatric patients with narcolepsy belong to a category of CSHCN and require more care for their physical, developmental, behavioral, and emotional differences than their typically developing peers. Early recognition and diagnosis of narcolepsy, as well as judicious use of medications that target both sleepiness and cataplexy, may reduce overall diagnostic and treatment health care utilization.

A significant limitation of this study is that the data are taken from a claims database, which only captures diagnoses that are recorded for billing purposes and may not fully capture the undiagnosed and uninsured population. Additionally, it is not possible to determine how rigorous patients' diagnostic processes were, and whether some patients diagnosed with narcolepsy type 2 actually had narcolepsy type 1, given the atypical features of cataplexy in many recently diagnosed pediatric patients. Clinical variables were also not available to determine narcolepsy type 1 in the absence of a diagnosis code. For this analysis, we identified all patients with evidence of narcolepsy type 1 and classified the rest as narcolepsy type 2. Furthermore, patients who were not continuously insured throughout the year for any reason and those insured by Medicaid or not insured at all are not represented. Uninsured children or children with Medicaid represent children of poor socioeconomic status and decreased health care access, who have cost limitations on diagnostic and therapeutic interventions and may experience significant delays in diagnosis or medical care, who have not been examined by this data analysis. Further work is needed to examine the interactions between the number or type of narcolepsy-related medications with outcomes (eg, ER visits, inpatient stays, costs), as well as to understand changes in health care utilization and costs from before to after diagnosis.

The full burden of narcolepsy includes humanistic elements such as high rates of discrepancy between verbal and nonverbal abilities, academic problems, frequent school absenteeism, behavior and adjustment problems, deficient social competence, psychosomatic symptoms, and diminished health-related quality of life [10,14,30,32,34,39]. However, these humanistic elements are beyond the design of the study, which only captures costs to the health care system from a payer perspective. Additional insight into these major consequences of narcolepsy is needed.

In conclusion, our findings demonstrate that insured pediatric patients who are diagnosed with narcolepsy have a greater comorbidity burden, as well as higher health care utilization and health care costs for both medical services, including diagnostic testing, inpatient and outpatient visits, and outpatient pharmacy, compared to a general population of insured pediatric patients without a diagnosis of narcolepsy. Overall, respiratory and mental health comorbidities were more prevalent in patients with narcolepsy, and patients with narcolepsy had higher numbers of diagnostic tests, inpatient days, and medical visits compared with controls. In addition to some differences in comorbidity burden, our analysis identified some differences in health care utilization between pediatric patients with narcolepsy type 1 and narcolepsy type 2. Studies related to other types of narcolepsy-associated burden, such as the psychological impact or the impact on quality of life in pediatric patients, may be worthwhile to investigate in future studies.

Funding source

Research was funded by Jazz Pharmaceuticals. All authors on this paper provided input regarding the study design, analysis, and interpretation of the data. Judi Profant is also employed by Jazz Pharmaceuticals. The authors thank Lauren Fink, PhD, of MedErgy (Yardley, PA, USA) for providing medical writing support, which was funded by Jazz Pharmaceuticals. Although Jazz Pharmaceuticals reviewed the content of this manuscript, the ultimate interpretation and the decision to submit it for publication was made by the authors independently.

Prior presentation

The results of this study have been presented, in part, at the Associated Professional Sleep Societies Annual Meeting 2018; June 2–6, 2018; Baltimore, MD.

Conflicts of interest

GC and KFV are former employees of Jazz Pharmaceuticals, who, in the course of this employment, have received stock options exercisable for, and other stock awards of, ordinary shares of Jazz Pharmaceuticals, plc. SRR, MSB, and RT are employees of Partnership for Health Analytic Research LLC, which received funding from Jazz Pharmaceuticals to conduct this study. JP is a full-time employee of Jazz Pharmaceuticals, who, in the course of this employment, has received stock options exercisable for, and other stock awards of, ordinary shares of Jazz Pharmaceuticals, plc. ACH received funding from the National Science Foundation and serves on medical advisory boards for Avisa Pharma and Jazz Pharmaceuticals.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.08.008.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2019.08.008.

References

[1] American Academy of Sleep Medicine. International classification of sleep disorders. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.
[2] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.
[3] Silber MH, Krahn LE, Olson EJ, et al. The epidemiology of narcolepsy in Olmsted County, Minnesota: a population-based study. Sleep 2002;25:197–202.
[4] Morse AM, Licholai G, Yang M, et al. Prevalence of diagnosed pediatric narcolepsy in the United States. Sleep 2019;42. A306.
[5] Thorpy MJ, Krieger AC. Delayed diagnosis of narcolepsy: characterization and impact. Sleep Med 2014;15:502–7.
[6] Morrish E, King MA, Smith IE, et al. Factors associated with a delay in the diagnosis of narcolepsy. Sleep Med 2004;5:37–41.
[7] Maski K, Steinhart E, Williams D, et al. Listening to the patient voice in narcolepsy: diagnostic delay, disease burden, and treatment efficacy. J Clin Sleep Med 2017;13:419–25.
[8] Kauta SR, Marcus CL. Cases of pediatric narcolepsy after misdiagnoses. Pediatr Neurol 2012;47:362–5.
[9] Thorpy M, Pasta D, Cisternas M, et al. Predictors of time to narcolepsy diagnosis in participants with adult onset of symptoms: results from the Nexus Narcolepsy Registry. Sleep 2018;41:A236.
[10] Shelton AR, Malow B. Correlates to problem behaviors in pediatric narcolepsy: a pilot study. J Clin Sleep Med 2017;13:1435–40.

[11] Plazzi G, Pizza F, Palaia V, et al. Complex movement disorders at disease onset in childhood narcolepsy with cataplexy. Brain 2011;134:3477–89.
[12] Pizza F, Franceschini C, Peltola H, et al. Clinical and polysomnographic course of childhood narcolepsy with cataplexy. Brain 2013;136:3787–95.
[13] Postiglione E, Antelmi E, Pizza F, et al. The clinical spectrum of childhood narcolepsy. Sleep Med Rev 2018;38:70–85.
[14] Dorris L, Zuberi SM, Scott N, et al. Psychosocial and intellectual functioning in childhood narcolepsy. Dev Neurorehabil 2008;11:187–94.
[15] Dodel R, Peter H, Walbert T, et al. The socioeconomic impact of narcolepsy. Sleep 2004;27:1123–8.
[16] Black J, Reaven NL, Funk SE, et al. The Burden of Narcolepsy Disease (BOND) study: health-care utilization and cost findings. Sleep Med 2014;15:522–9.
[17] Flores NM, Villa KF, Black J, et al. The humanistic and economic burden of narcolepsy. J Clin Sleep Med 2016;12:401–7.
[18] Black J, Reaven NL, Funk SE, et al. Medical comorbidity in narcolepsy: findings from the Burden of Narcolepsy Disease (BOND) study. Sleep Med 2017;33:13–8.
[19] Ruoff CM, Reaven NL, Funk SE, et al. High rates of psychiatric comorbidity in narcolepsy: findings from the Burden of Narcolepsy Disease (BOND) study of 9,312 patients in the United States. J Clin Psychiatry 2017;78:171–6.
[20] Jennum P, Ibsen R, Knudsen S, et al. Comorbidity and mortality of narcolepsy: a controlled retro- and prospective national study. Sleep 2013;36:835–40.
[21] Philip P, Sagaspe P, Lagarde E, et al. Sleep disorders and accidental risk in a large group of regular registered highway drivers. Sleep Med 2010;11:973–9.
[22] Smolensky MH, Di Milia L, Ohayon MM, et al. Sleep disorders, medical conditions, and road accident risk. Accid Anal Prev 2011;43:533–48.
[23] Ohayon MM, Black J, Lai C, et al. Increased mortality in narcolepsy. Sleep 2014;37:439–44.
[24] Maski K, Heroux T. Beyond daytime sleepiness: medical, behavioral, psychiatric, and sleep co-morbid conditions associated with pediatric narcolepsy. Curr Sleep Med Rep 2016;2:31–7.
[25] Martinez-Orozco FJ, Vicario JL, De Andres C, et al. Comorbidity of narcolepsy type 1 with autoimmune diseases and other immunopathological disorders: a case-control study. J Clin Med Res 2016;8:495–505.
[26] Agency for Healthcare Research and Quality. HCUP chronic condition indicator. Healthcare Cost and Utilization Project (HCUP); 2015.
[27] Morgenthaler TI, Kapur VK, Brown TM, et al. Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. An American Academy of Sleep Medicine Report. Sleep 2007;30:1705–11.
[28] Taddei RN, Werth E, Poryazova R, et al. Diagnostic delay in narcolepsy type 1: combining the patients' and the doctors' perspectives. J Sleep Res 2016;25:709–15.
[29] Jennum P, Pickering L, Thorstensen EW, et al. Morbidity of childhood onset narcolepsy: a controlled national study. Sleep Med 2017;29:13–7.
[30] Inocente CO, Gustin MP, Lavault S, et al. Depressive feelings in children with narcolepsy. Sleep Med 2014;15:309–14.
[31] Inocente CO, Lavault S, Lecendreux M, et al. Impact of obesity in children with narcolepsy. CNS Neurosci Ther 2013;19:521–8.
[32] Rocca FL, Pizza F, Ricci E, et al. Narcolepsy during childhood: an update. Neuropediatrics 2015;46:181–98.
[33] Wang Z, Wu H, Stone WS, et al. Body weight and basal metabolic rate in childhood narcolepsy: a longitudinal study. Sleep Med 2016;25:139–44.
[34] Inocente CO, Gustin MP, Lavault S, et al. Quality of life in children with narcolepsy. CNS Neurosci Ther 2014;20:763–71.
[35] Sullivan PW, Ghushchyan V, Navaratnam P, et al. The national cost of asthma among school-aged children in the United States. Ann Allergy Asthma Immunol 2017;119:246–252 e1.
[36] Ryan JL, McGrady ME, Guilfoyle SM, et al. Health care charges for youth with newly diagnosed epilepsy. Neurology 2015;85:490–7.
[37] Reddy S, Broder M, Tieu R, et al. Cost and utilization before and after diagnosis in pediatric patients with newly diagnosed narcolepsy: a claims-based analysis. J Manag Care Spec Pharm 2018;24:S56–7.
[38] Thorpy MJ, Dauvilliers Y. Clinical and practical considerations in the pharmacologic management of narcolepsy. Sleep Med 2015;16:9–18.
[39] Posar A, Pizza F, Parmeggiani A, et al. Neuropsychological findings in childhood narcolepsy. J Child Neurol 2014;29:1370–6.