Clinical, Economic, and Humanistic Burden Associated With Narcolepsy: Results From a Systematic Literature Review

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INTRODUCTION

- Narcolepsy is a rare, chronic neurological disorder that affects the brain's ability to regulate sleep-wake cycles, resulting in excessive daytime sleepiness (EDS) among other symptoms[1,2]
- There are 2 types of narcolepsy: narcolepsy type 1 (NT1), which includes cataplexy, and narcolepsy type 2 (NT2), which does not include cataplexy[3]
  - Cataplexy is a sudden, spontaneous, and temporary loss of muscle tone, often triggered by emotional stimuli such as fear, anger, laughter, or stress[3,4]
- While studies have demonstrated that narcolepsy is associated with negative impacts to patients' lives, including clinical (eg, comorbidities), economic (eg, increased medical costs), and humanistic (eg, impaired health-related quality of life [HRQoL]) burden, there is a need to summarize results across studies[5-8]

OBJECTIVE

- To comprehensively summarize the burden of illness (BOI) in narcolepsy by systematically reviewing 10 years of published research, with outcomes that include:
  - Clinical burden (eg, journey to diagnosis, comorbidities, healthcare resource utilization, and mortality)
  - Economic burden (eg, costs to patients, caregivers, employers, and/or health systems)
  - Humanistic burden (eg, impacts on HRQoL)

METHODS

SEARCH OF PEER-REVIEWED ARTICLES AND CONFERENCE ABSTRACTS

- Structured searches of PubMed identified relevant peer-reviewed journal articles
  - Search strings were developed according to a population/patient/problem, interest, context (PICOS) framework
  - Preselected criteria: English-language studies published between 2012 and 2022 that included information related to clinical, economic, and/or humanistic BOI in human patients with narcolepsy
- Searches of abstracts were conducted from relevant conference databases published between 2020 and 2022 that met selection criteria detailed above

SELECTION PROCESS FOR FULL-TEXT REVIEW

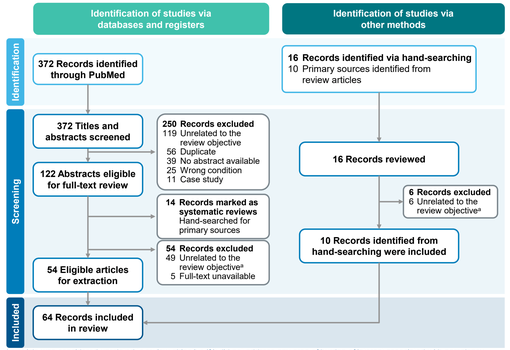
- All records identified from the PubMed search were reviewed in 2 rounds:
  - Title/abstract screening: Full-text articles were retrieved if the record met the selection criteria, presented insufficient information for a determination about whether it met the selection criteria, and/or was a review article suspected to contain information on additional relevant articles
  - A second round of review was then performed on the retrieved full-text articles
- Data were collected if the article contained clinical, economic, and/or humanistic outcomes
- Following data extraction, all economic data were converted into 2022 US dollars using an inflation factor calculated using the United States Department of Labor Statistics Consumer Price Index
- Hand-searches of systematic review articles were conducted by reviewing the references within these reviews, identifying and obtaining potentially relevant articles, and conducting a full-text review of the article(s) following the same extraction protocol described above

RESULTS

NUMBER OF ARTICLES INCLUDED IN THE SYSTEMATIC LITERATURE REVIEW

- A total of 372 articles were retrieved from PubMed using the search strings and an additional 16 articles were retrieved through hand-searching (see Methods)
- After applying inclusion/exclusion criteria, 64 records were included for final data extraction (**Figure 1**): 53 articles (83%) summarized data related to clinical burden, 8 articles (13%) for economic burden, and 27 articles (42%) for humanistic burden
- The greatest percentage of articles (42%) included both types of narcolepsy; a majority of articles (51%) described studies of adults with narcolepsy

FIGURE 1: PRISMA Diagram



[a]An article was considered unrelated to review objective if it did not address any area of burden of interest associated with narcolepsy. Six conference abstracts were identified from databases, which included SLEEP Meeting, World Sleep Congress, American Psychiatric Association, International Society for Pharmacoeconomics and Outcomes Research, Academy of Managed Care Pharmacy (AMCP), and AMCP Nexus.

CLINICAL BURDEN OF NARCOLEPSY

Journey to Diagnosis

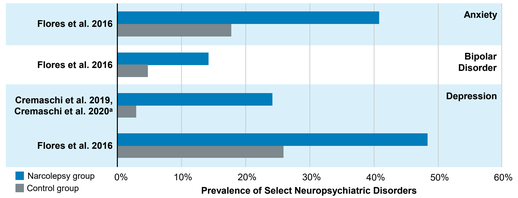
- Mean time from symptom onset to diagnosis ranged from 8.7 to 14.6 years, reflecting significantly delayed time to diagnosis[7,9-11] (**Figure 2**)
  - No significant difference was found between NT1 and NT2 for diagnostic delay[9]
- Early age of symptom onset generally predicted greater diagnostic delays[6,9]
- Symptoms and impacts of narcolepsy, beyond EDS and cataplexy that might lead to misdiagnosis and diagnostic delays, include cognitive difficulties, fatigue, depression, and anxiety, which overlap those of psychiatric disorders

FIGURE 2: Mean Time From Symptom Onset to Narcolepsy Diagnosis

Comorbidities and Mortality Associated With Narcolepsy

- Compared with controls, patients with narcolepsy presented with higher rates of neuropsychiatric and physical comorbidities
- Patients with narcolepsy demonstrated significantly greater odds of having attention-deficit hyperactivity disorder, major depressive disorder, bipolar disorder, and a broad range of anxiety disorders (eg, agoraphobia, panic disorder, social anxiety disorder, and obsessive-compulsive disorder)[5,12-18] (**Figure 3**)

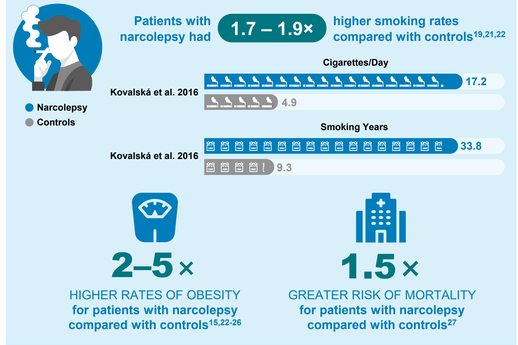
FIGURE 3: Comparing the Prevalence of Select Neuropsychiatric Disorders Between Patients With Narcolepsy and Matched Controls



[a]Depression rate reported for NT2. Patients with NT2 had significantly higher prevalence of depression compared to controls and NT1.

- There was evidence of greater tobacco use in patients with narcolepsy (**Figure 4**)
  - Patients with narcolepsy had higher smoking rates, smoked significantly more, and for significantly longer than controls[19-22] (**Figure 4**)

FIGURE 4: Tobacco Smoking, Obesity, and Mortality Rates Among Patients With Narcolepsy Versus Controls

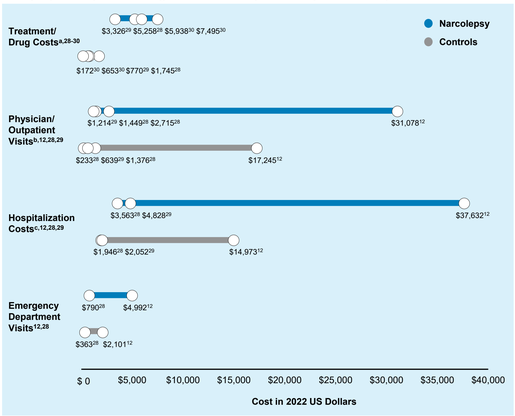


- Ohayon et al. (2013) found that narcolepsy significantly increased the odds of having heart diseases (adjusted odds ratio [AOR] = 2.07), hypercholesterolemia (AOR = 1.51), hypertension (AOR = 1.32), diseases of the digestive system (AOR = 3.27), and upper respiratory tract diseases (AOR = 2.52) (all $P < 0.05$) versus the general population[5]
- Overall, the mortality rate of patients with narcolepsy was approximately 1.5 times greater than those without ($P < 0.001$); mortality rates were higher regardless of sex or age[27]
  - Mortality rates for patients with narcolepsy peaked in the 25–34 and 35–44 age groups, suggesting a possible link between increased rates of depression and suicide with symptom onset[27]

ECONOMIC BURDEN OF NARCOLEPSY

- Based on a large, population-based study, the annual utilization rates of medical services was 2 times greater in patients with narcolepsy relative to healthy matched controls, regardless of the type of narcolepsy[28]
  - Emergency department visits, inpatient and outpatient visits and services, and drug utilization were all significantly higher in patients with narcolepsy ($P < 0.01$)[28]
- Patients with narcolepsy reported higher annual direct costs associated with more frequent emergency department visits (narcolepsy up to $4,992 vs controls up to $2,101), hospitalizations (narcolepsy up to $37,632 vs controls up to $14,973), outpatient care (narcolepsy up to $31,078 vs controls up to $17,245), and higher medication costs (narcolepsy up to $7,495 vs controls up to $1,745)[12,28-30] (**Figure 5**)
- In one study of pediatric patients diagnosed with narcolepsy, mean annual healthcare costs for narcolepsy were over 6 times higher than controls ($20,932 vs $3,245)[30]

FIGURE 5: Comparison of Annual Direct Costs Between Narcolepsy and Control Groups (bars represent range and circles represent reported costs)



[a]Defined as drug costs,[28] medication costs,[29] and pharmacy costs for pediatric patients.[30] [b]Defined as physician visits and outpatient services,[28] healthcare professional visit,[12] and outpatient treatment costs.[29] [c]Defined as inpatient hospitalizations,[12] hospitalization costs,[28] and inpatient treatment annual costs.[29]

- Regarding indirect economic impacts, narcolepsy was associated with a greater frequency of missed workdays (7.6 vs 3 days/employee/year, $P < 0.01$) and short-term disability incidents (0.15 vs 0.07 incidents/employee/year, $P < 0.01$), and higher annual costs associated with absenteeism ($17,479 vs $10,389) and presenteeism ($9,548 vs $6,789) versus matched controls, respectively[12,28]
  - Further, patients with narcolepsy reported nearly twice as many "economically inactive years" across the lifespan compared with controls (18.63 vs 9.43 years)[20]

HUMANISTIC BURDEN OF NARCOLEPSY

- Patients with narcolepsy exhibited lower HRQoL, with demonstrated impairments in several domains, including role-emotional functioning, vitality, and social functioning[23]
- There were also functional limitations associated with narcolepsy, including the inability to care for children[31,32]
- Education and employment were significantly impacted by narcolepsy due to absenteeism, lack of productivity, and attention deficits[31,32]
- There was significantly more health-related social stigma in patients with narcolepsy than in controls across domains that captured social rejection, financial insecurity, social isolation, and internalized shame[32]

STUDY LIMITATIONS

- This systematic review included studies that were published in English between 2012 and 2022, and therefore relevant studies outside this time range were excluded from review. While this review describes the current burden of narcolepsy, it is unclear how clinical, economic, and humanistic outcomes have changed over time
- Similar to other systematic reviews, this review may be subject to publication biases
  - While attempts were made to include elements of the grey literature, searches of relevant conference databases did not yield any records that were eligible for inclusion in the review

CONCLUSIONS

- The diagnostic journey for those with narcolepsy is challenging, and patients often experience symptoms for years before they are diagnosed
  - Physical and mental health comorbidities may further complicate the diagnostic process
- Narcolepsy is associated with an increased risk of obesity and smoking behaviors, and higher rates of mortality compared with those without narcolepsy
- Narcolepsy is also associated with impaired HRQoL and functional limitations, reduced work productivity, and increased use of healthcare resources and medical costs
- Future research is needed to understand clinical, economic, and humanistic outcomes in subgroups (eg, narcolepsy subtype, age of symptom onset, and treatment status)

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Key contributors

MJD contributed to conceptualization, methodology, writing – reviewing and editing, visualization, and supervision. **ML-C**, **GH**, and **KM** contributed to project administration, methodology, data curation, formal analysis, validation, investigation, writing – reviewing and editing, and visualization.

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MJD is an employee and stockholder of Alkermes, Inc. **ML-C**, **GH**, and **KM** are employees of QualityMetric, an IQVIA business.

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