High Rates of Psychiatric Comorbidity in Narcolepsy: Findings From the Burden of Narcolepsy Disease (BOND) Study of 9,312 Patients in the United States

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ABSTRACT

Objective: To evaluate psychiatric comorbidity patterns in patients with a narcolepsy diagnosis in the United States.

Methods: Truven Health Analytics MarketScan Research Databases were accessed to identify individuals ≥ 18 years of age with ≥ 1 *ICD-9* diagnosis code(s) for narcolepsy continuously insured between 2006 and 2010 and non-narcolepsy controls matched 5:1 (age, gender, region, payer). Extensive subanalyses were conducted to confirm the validity of narcolepsy definitions. Narcolepsy subjects and controls were compared for frequency of psychiatric comorbid conditions (based on *ICD-9* codes/Clinical Classification Software [CCS] level 2 categories) and psychiatric medication use.

Results: The final population included 9,312 narcolepsy subjects and 46,559 controls (each group, mean age = 46.1 years; 59% female). All categories of mental illness were significantly more prevalent in patients with narcolepsy versus controls, with the highest excess prevalence noted for CCS 5.8 Mood disorders (37.9% vs 13.8%; odds ratio [OR] = 4.0; 95% CI, 3.8–4.2), CCS 5.8.2 Depressive disorders (35.8% vs 13.0%; OR = 3.9; 95% CI, 3.7–4.1), and CCS 5.2 Anxiety disorders (25.1% vs 11.9%; OR = 2.5; 95% CI, 2.4–2.7). Excess prevalence of anxiety and mood disorders (narcolepsy vs controls) was higher in younger age groups versus older age groups. Psychiatric medication usage was higher in the narcolepsy group versus controls in the following categories: selective serotonin reuptake inhibitors (36% vs 17%), anxiolytic benzodiazepines (34% vs 19%), hypnotics (29% vs 13%), serotonin-norepinephrine reuptake inhibitors (21% vs 6%), and tricyclic antidepressants (13% vs 4%) (all *P* values < .0001).

Conclusions: Narcolepsy is associated with significant comorbid psychiatric illness burden and higher psychiatric medication usage compared with the non-narcolepsy population.

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Narcolepsy is a disabling sleep disorder that is reported to have a prevalence of approximately 1 in 2,000 people worldwide.[1] Patients with narcolepsy typically complain of excessive daytime sleepiness and frequent overwhelming urges to sleep or inadvertent daytime lapses into sleep, as well as disrupted nighttime sleep.[1–4] A definitive, but not universal, symptom is cataplexy, a sudden, involuntary loss of skeletal muscle tone lasting from seconds to 1 or 2 minutes, most commonly triggered by positive emotions.[5,6] Other characteristic symptoms include sleep paralysis and hallucinations, both at sleep onset and upon awakening.[2,3]

Although most patients with narcolepsy develop symptoms in late adolescence or early adulthood,[4,7] delays in diagnosis for a decade or longer are common.[8,9] Causes of delayed diagnosis include physicians' general lack of familiarity with narcolepsy, wide-ranging clinical manifestations of narcolepsy that may be confused with the symptoms of other diseases, lack of patient access to laboratory-based sleep testing, and the broad variety of both medical and psychiatric comorbidities associated with narcolepsy, including obesity, other sleep disorders, and psychiatric illnesses such as depression and anxiety.[10–14]

It is not uncommon for narcolepsy patients with comorbid psychiatric conditions to have their psychiatric illness recognized and treated, but have their narcolepsy condition go undiagnosed and untreated. Moreover, the sleepiness and fatigue of patients with narcolepsy without psychiatric conditions are often mistakenly diagnosed as being caused by a psychiatric illness, resulting in the mistreatment or undertreatment of the narcolepsy itself.[15–19]

The potential excess prevalence of psychiatric comorbidities in patients with diagnosed narcolepsy, while previously suggested, has not been thoroughly evaluated using adequate datasets, and there have been no large, US population-based analyses examining this issue. This study was conducted to more fully characterize the patterns of psychiatric comorbidities in patients diagnosed with narcolepsy. To do this, 5-year data on 9,312 narcolepsy patients identified from a US claims database of more than 7 million continuously enrolled patients were extensively analyzed.

METHODS

The Burden of Narcolepsy Disease (BOND) study accessed the Truven Health Analytics MarketScan Research Databases to identify individuals ≥ 18 years of age with at least 1 diagnosis code for narcolepsy with or without cataplexy (*ICD-9* 347.0, 347.00,

Table 1. Demographics of the Study Population

Variable	Narcolepsy (n = 9,312)	Matched Controls (n = 46,559)
Age,[a] mean (SD), y	46.1 (13.3)	46.1 (13.3)
Range, y	18–93	18–93
Age category, n (%)		
18–24 y	354 (3.8)	1,770 (3.8)
25–34 y	1,564 (16.8)	7,814 (16.8)
35–44 y	2,296 (24.7)	11,494 (24.7)
45–54 y	2,834 (30.4)	14,163 (30.4)
55–74 y	1,963 (21.1)	9,813 (21.1)
75+ y	301 (3.2)	1,505 (3.2)
Female, n (%)	5,513 (59.2)	27,564 (59.2)
Payer, n (%)		
Commercial	8,357 (89.7)	41,774 (89.7)
Medicare	955 (10.3)	4,785 (10.3)

[a]As of January 1, 2006.

347.01, 347.1, 347.10, or 347.11) continuously insured between 2006 and 2010. Controls without narcolepsy were matched 5:1 on age, gender, region, and payer type. Truven Health Analytics databases are de-identified in compliance with the Health Insurance Portability and Accountability Act Standards for Privacy of Individually Identifiable Health Information. Given the anonymized nature of the data, the need for full protocol review was waived by a local institutional review board.

Comorbid conditions were defined by *ICD-9* diagnosis code and were grouped using single-level and multilevel Clinical Classifications Software (CCS) for *ICD-9* developed for the Healthcare Cost and Utilization Project (HCUP), sponsored by the US Agency for Healthcare Research and Quality (AHRQ).[20] Narcolepsy subjects and controls were compared for frequencies of psychiatric conditions, identified by the appearance of ≥ 1 psychiatric diagnosis code(s) mapped to a CCS level 2 category (5.1–5.15, excluding 5.6 [disorders usually diagnosed in infancy, childhood, or adolescence] and 5.14 [screening and history of mental health and substance abuse]) any time during the study period; specific subcategories of bipolar disorders (5.8.1) and depressive disorders (5.8.2) were also analyzed.

A condition was considered "present" if a patient's health insurance claim(s) included 1 or more diagnosis code(s) in the category during the 5-year study period, irrespective of the timing relative to the narcolepsy diagnosis code(s). Excess prevalence with narcolepsy was measured by subtracting prevalence within the dataset among control patients from prevalence within the dataset among narcolepsy patients. Outcomes relative to controls were analyzed for the entire narcolepsy population and for narcolepsy subgroups according to gender and age demographics. Psychiatric drug usage patterns were also compared. As described elsewhere,[21] extensive analyses were performed to confirm the validity of the narcolepsy population as defined according to the presence of a minimum of 1 narcolepsy diagnosis code. Further validation analyses concluded that differences in comorbidity rates were not primarily attributable to the presence of a possible care-seeking behavior bias.

Clinical Points

- This is the first large-scale US study to investigate and demonstrate a high rate of psychiatric comorbidity in patients with narcolepsy.
- Patients with unrecognized and untreated narcolepsy may respond poorly to psychiatric treatment.
- Differential diagnosis of mood and anxiety disorders should include the consideration of narcolepsy, particularly in patients with fatigue/daytime sleepiness and those who seem unresponsive to standard treatment approaches.

Comparisons of comorbidity prevalence within groups were performed with a conditional χ^2 test, accounting for matching (conditional logit analysis). This analysis allowed the block-out variability to be removed, so that the comparisons of interest (controls to narcolepsy) were more precise. An analysis controlling for the presence of sleep-related breathing disturbance conditions was performed, which identified no differences from the noncontrolled data; therefore, this analysis was not included in this report. *P* values < .05 were considered significant. The Bonferroni step-down *P* value adjustment procedure of Holm was used to control the family-wise error rate at .05. All statistical analyses were carried out using SAS/STAT software, version 9.2 (SAS Institute, Inc). The term *prevalence* is used throughout this article to refer to prevalence within this large database and is not intended to imply prevalence in the general population.

RESULTS

A total of 55,871 subjects (59% female) met analysis inclusion criteria, including 9,312 in the narcolepsy cohort and 46,559 matched controls. The subjects' demographic and baseline characteristics are presented in Table 1.

Psychiatric Comorbidity by Narcolepsy Status

Subjects in the narcolepsy cohort had claims evidence in the 5-year study period suggesting substantially higher psychiatric comorbidity burden compared to controls. Prevalence rates of specific psychiatric comorbidities for all narcolepsy patients and controls are presented in Table 2. All categories of mental illness were significantly more prevalent in patients with narcolepsy than in controls. The greatest excess prevalences among narcolepsy patients were found for anxiety disorders (25.1% vs 11.9% in narcolepsy and controls, respectively) and mood disorders (37.9% vs 13.8% in narcolepsy and controls, respectively).

Psychiatric Comorbidity Patterns by Gender and Age

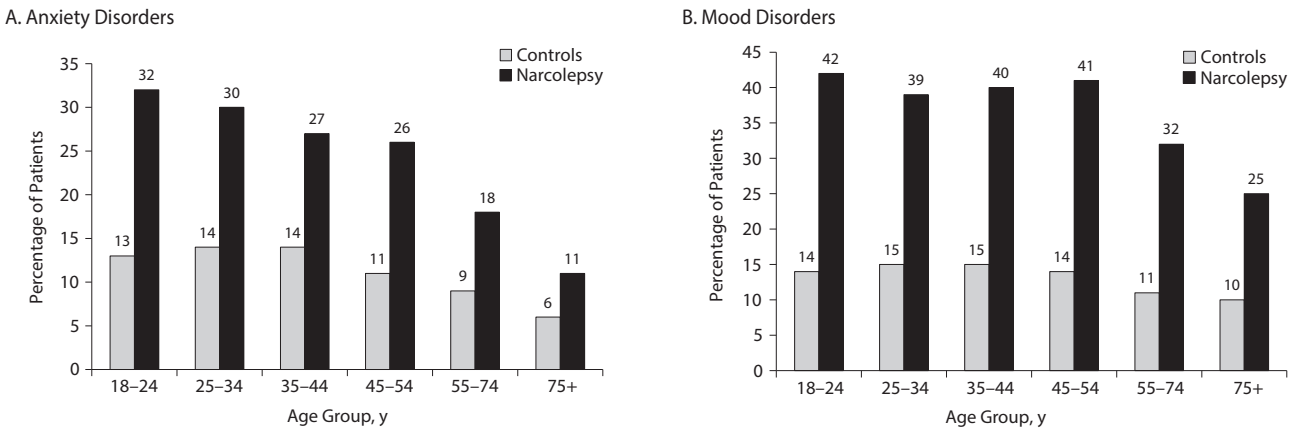
Mood and anxiety disorder patterns were further analyzed with regard to patient age and gender. The observed general pattern of increased psychiatric comorbidity prevalence in narcolepsy patients compared to controls was maintained regardless of patient gender (data not shown) or age. When psychiatric comorbidity prevalence was analyzed according

Table 2. Psychiatric Comorbidity Prevalence (CCSM Level 2 Categories)[a] and Selected Subcategories for Patients With a Narcolepsy Diagnosis Versus Matched Controls

	Patients With Comorbidity		
CCSM 5 Mental Illness Categories	Controls (n = 46,559)	Narcolepsy (n = 9,312)	OR (95% CI)[b]
5.1 Adjustment disorders	5.4%	11.2%	2.3 (2.1–2.4)
5.2 Anxiety disorders	11.9%	25.1%	2.5 (2.4–2.7)
5.3 Attention deficit, conduct, and disruptive behavior disorders	1.3%	7.3%	6.2 (5.6–7.0)
5.4 Delirium, dementia, and amnestic and other cognitive disorders	1.5%	4.6%	3.8 (3.3–4.3)
5.7 Impulse control disorders not elsewhere classified	0.1%	0.2%	1.9 (1.1–3.2)
5.8 Mood disorders	13.8%	37.9%	4.0 (3.8–4.2)
5.8.1 Bipolar disorders	2.1%	8.3%	4.4 (3.9–4.8)
5.8.2 Depressive disorders	13.0%	35.8%	3.9 (3.7–4.1)
5.9 Personality disorders	0.2%	1.1%	5.8 (4.3–7.7)
5.10 Schizophrenia and other psychotic disorders	0.9%	3.4%	3.8 (3.3–4.4)
5.11 Alcohol-related disorders	1.3%	1.9%	1.4 (1.2–1.7)
5.12 Substance-related disorders	1.2%	4.0%	3.5 (3.0–4.0)
5.13 Suicide and intentional self-inflicted injury[c]	0.2%	1.0%	4.1 (3.1–5.4)
5.15 Other miscellaneous mental disorders	4.0%	14.5%	4.1 (3.8–4.4)

[a]CCSM categories 5.5 (developmental disorders) and 5.6 (disorders usually diagnosed in infancy, childhood, or adolescence) and 5.14 (screening and history of mental health and substance abuse codes) were excluded.
[b]All χ^2 *P* values < .0001 except for CCSM categories 5.7 (*P* = .02379) and 5.11 (*P* = .00021); all *P* values have been adjusted to account for multiple testing using the Bonferroni correction.
[c]Includes unsuccessful suicide attempts only, because continuous insurance coverage was required for study inclusion.
Abbreviations: CCSM = Clinical Classification Software for *ICD-9* diagnosis codes, multilevel; OR = odds ratio.

Figure 1. Population Prevalence, Within Age Categories, of Anxiety Disorders (A) and Mood Disorders (B)



to age category, the highest excess prevalence for anxiety and mood disorders was identified in the younger age groups (Figure 1).

Psychiatric Drug Usage: Narcolepsy Versus Controls

As expected, patients with narcolepsy showed greater use of a wide range of psychiatric drugs commonly used for the treatment of narcolepsy (Table 3). However, even among the subset of patients with psychiatric diagnoses, patients with narcolepsy used psychiatric drugs at higher rates than did their similarly diagnosed controls across all studied categories of medications.

DISCUSSION

This study of psychiatric comorbidity in narcolepsy is the first to evaluate a large claims-based dataset. This robust dataset included a validated population of 9,312 narcolepsy subjects and 46,559 highly matched controls. Compared with findings for non-narcoleptic controls, narcolepsy was associated with significantly higher rates of almost all categories of mental illness and a particularly high burden of anxiety and depression. While many of the comorbid findings were not unexpected, the range of increased prevalence across the whole spectrum of psychiatric classifications was surprising, as were some of the individual categories such as delirium and dementia. The higher rates of psychiatric comorbidities were paralleled by the high use of psychiatric medications observed among patients with narcolepsy compared to controls with diagnosed psychiatric conditions. The observed medication usage patterns suggest that the severity of psychiatric illness in patients with narcolepsy is at least similar, if not greater in magnitude, compared with the non-narcolepsy psychiatric population.

Table 3. Psychiatric Drug Exposure in All Narcolepsy Patients Versus Their Matched Controls and in the Subgroups of Controls and Narcolepsy Patients Having at Least 1 Psychiatric Diagnosis[a]

	Total Study Population			Patients With a Psychiatric Diagnosis		
Drug Category	Controls (N = 46,559) n (%)	Narcolepsy (N = 9,312) n (%)	OR (95% CI)[b] Narcolepsy vs Controls	Controls (n = 12,454) n (%)	Narcolepsy (n = 5,420) n (%)	OR (95% CI)[b] Narcolepsy vs Controls, Within Subset
Anxiolytic benzodiazepines	8,799 (18.9)	3,170 (34.0)	2.3 (2.2–2.4)	4,780 (38.4)	2,425 (44.7)	1.3 (1.2–1.4)
Hypnotics[c]	6,157 (13.2)	2,734 (29.4)	2.8 (2.7–3.0)	3,337 (26.8)	2,048 (37.8)	1.7 (1.6–1.8)
SNRIs	2,728 (5.9)	1,925 (20.7)	4.4 (4.1–4.7)	1,957 (15.7)	1,591 (29.4)	2.2 (2.1–2.4)
SSRIs	7,933 (17.0)	3,356 (36.0)	2.9 (2.8–3.1)	5,344 (42.9)	2,669 (49.2)	1.3 (1.2–1.4)
Stimulants	1,383 (3.0)	5,034 (54.1)	41.8 (38.3–45.7)	963 (7.7)	3,084 (56.9)	15.8 (14.5–17.2)
TCAs	1,959 (4.2)	1,205 (12.9)	3.5 (3.2–3.7)	1,017 (8.2)	857 (15.8)	2.1 (1.9–2.3)

[a]Data represent percentage of patients who filled at least 1 prescription for a drug in the category during the 5-year study period.
[b]ORs are narcolepsy versus controls; all comparisons narcolepsy versus controls $P < .0001$, with Bonferroni adjustment to account for multiple testing.
[c]Hypnotics include hypnotic benzodiazepines, miscellaneous sedative hypnotics, and nonbenzodiazepine sedative hypnotics.
Abbreviations: OR = odds ratio, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

The rate of suicide attempt and intentional self-injury was 5-fold greater in patients with a narcolepsy diagnosis compared with controls. Ohayon[22] and Ohayon and colleagues[23] recently reported >7-fold increased suicide-related mortality in a longitudinal study of 322 patients with narcolepsy. While suicide risk in narcolepsy has not been rigorously evaluated until recently, sleep disturbances in general have been previously linked with suicidal ideations and events[24–26] as well as self-harm behaviors.[27]

In both the narcolepsy and control populations, the prevalence distributions of mood and anxiety disorders showed general patterns reflecting highest prevalence rates in younger age groups, with a decline in prevalence noted around the fourth and fifth decades of life. While these patterns are consistent with overall population epidemiology of psychiatric disease,[28–30] our data demonstrated the greatest excess in mood and anxiety disorders between narcolepsy patients and their controls in the youngest age group (18–24 years), suggesting a particular burden in this population.

Within the database population, there was a 4-fold greater rate of schizophrenia and other psychotic disorders among patients with a narcolepsy diagnosis compared with controls, an association that has been reported previously[31–40] but is not completely understood. Such cases can present particular diagnostic and therapeutic challenges, often demonstrating a high severity of schizophrenic symptomatology and poor treatment response.[31,37–39] A further complication to the diagnosis and management of schizophrenia symptoms in patients with narcolepsy is a potential association between stimulants and amphetamine-like drugs with the development of psychotic symptoms[41]; these drug classes are commonly used for the treatment of narcolepsy and were evident in the present analysis in more than half of the patients with narcolepsy. Autoimmune-related pathology has been suggested for both narcolepsy and schizophrenia,[37,42–45] and potentially overlapping autoimmune mechanisms remain a possibility.[33]

Previous smaller studies have examined psychiatric comorbidities associated with narcolepsy, but with conflicting conclusions. The study by Ohayon[46] included 320 patients with narcolepsy and 1,464 age-, gender-, and body mass index–matched subjects from the general population. The results indicated that most mood and anxiety disorders were more common in patients with narcolepsy than in the control population. In fact, major depressive disorder (odds ratio [OR] = 2.67) and social anxiety disorder (OR = 2.43) were the most common psychiatric disorders identified. Jennum et al,[47] in a study of 757 patients with narcolepsy and 3,013 control subjects selected from the Danish National Patient Registry, found that "mental and psychiatric" diagnoses were more than 2-fold higher among patients with narcolepsy, although the difference (OR = 1.46; 95% CI, 0.89–2.40) was not statistically significant, due to a small sample size. That study[47] evaluated only the broad category of "mental and psychiatric disorders" and did not examine specific psychiatric conditions. Mayer et al[48] found an increased rate of depression in 106 patients with narcolepsy in a retrospective analysis study.

There is clearly a complex relationship between narcolepsy and psychiatric symptomatology. Patients with narcolepsy may report nonspecific complaints such as fatigue and mood/anxiety problems that can be easily misdiagnosed as psychiatric illness, especially when the narcolepsy is not accompanied by cataplexy. Auditory and visual hallucinations can occur in narcolepsy patients while transitioning between periods of wakefulness and sleep (hypnagogic hallucinations) and between sleep and wake (hypnopompic hallucinations), which can lead to incorrect diagnoses of schizophrenia or other psychoses.[32,35,49] As a result, delayed recognition of narcolepsy is a common and unfortunate reality, as the symptoms of narcolepsy are commonly misattributed to depression, thought disturbance, or even epilepsy or medication side effects (eg, sleepiness/hypersomnia or insomnia from selective serotonin reuptake inhibitors).

The average duration from time of narcolepsy symptom onset to correct diagnosis is typically 10 years or longer.[8,9] Unfortunately, a common scenario for patients with unrecognized narcolepsy is to be treated for concomitant psychiatric diagnoses for years, typically with poor outcomes, without the coexisting narcolepsy being recognized and addressed. In addition, when comorbid with a psychiatric condition, untreated narcolepsy can contribute to inadequate

response to psychiatric treatment. In fact, effective treatment of an underlying sleep disorder is often a prerequisite before substantial improvement in a patient's psychiatric symptoms can be achieved.[50] It may be helpful to seek information from family members or others who are close to the patient regarding behaviors and sleep patterns. Narcolepsy can be readily screened for by a noninvasive evaluation including an overnight sleep study followed by a multiple sleep latency test.

Psychiatric drugs used in the treatment of narcolepsy include modafinil, armodafinil, methylphenidate, and amphetamines (for excessive daytime sleepiness) and most types of antidepressants for cataplexy.[5,51,52] Our data reflect the increased usage of these drugs, as well as a wide range of additional drugs used in psychiatric care, among patients with narcolepsy. High use of psychiatric medication in patients with narcolepsy is an additional factor that can complicate diagnostic work-up and delay appropriate therapy. Medications commonly used to treat depression can also be useful for the treatment of cataplexy, and their use in apparently depressed patients may thus inhibit the accurate diagnosis of cataplexy in patients with narcolepsy.[5,51,52] Another particular consequence of antidepressant use in patients with narcolepsy is a potential rebound in cataplexy manifestation following withdrawal of treatment.[53]

The medical claims–based nature of our research imparts certain limitations. Of note, this analysis deliberately implemented a 5-year cross-sectional approach without regard to the timing of the narcolepsy diagnosis code(s) relative to the comorbidity diagnosis codes. Because narcolepsy can be a lifelong chronic illness and diagnosis is often delayed by up to a decade, it is difficult in claims data to reliably identify whether codes for comorbid conditions are occurring before, after, or concurrent with a narcolepsy diagnosis. Therefore, in the current analysis, we have taken the approach of looking at all of the psychiatric conditions that appear within the same time period even though the patients with narcolepsy most likely include both incident and prevalent cases. We acknowledge that some of the psychiatric comorbidities captured in our data may actually represent misdiagnoses secondary to unrecognized narcolepsy symptomatology. Kryger et al[10] retrospectively evaluated the diagnoses reported in a cohort of 77 patients with narcolepsy within the year prior to a diagnosis of narcolepsy, compared with a cohort of 1,155 matched controls. In that analysis,[10] patients with a subsequent narcolepsy diagnosis were more likely to have been recently diagnosed with neurotic disorders, depression, personality disorders, or adjustment reaction. Unfortunately, that study[10] did not investigate whether these psychiatric diagnoses disappeared or persisted after the narcolepsy diagnosis. More research of a longitudinal nature is needed to understand the extent to which the psychiatric conditions identified in the current analysis may be overestimated in our data because of misdiagnosis prior to a narcolepsy diagnosis.

As with all claims analyses, our study population is not representative of persons who could not or did not maintain continuous insurance coverage during the study period for any reason (including mortality) or who were insured by Medicaid. In our analysis, this is particularly relevant for both the youngest and oldest age categories studied, since the pool of persons with 5-year continuous insurance in plans contributing data to MarketScan is substantially lower at the insurance transition periods of young adulthood and retirement. Thus, persons aged 19 to 24 years and 60 to 64 years are quite likely underrepresented in the study population.

Our data confirm a marked association between narcolepsy and psychiatric illness, suggesting a high likelihood that psychiatric health care providers may interface with diagnosed and undiagnosed narcolepsy patients. These findings underscore the importance of awareness and suspicion of narcolepsy among psychiatry professionals as a potential comorbid condition in their patients, particularly in patients reporting fatigue or daytime sleepiness and in those who do not respond well to treatment. Greater awareness and more thorough evaluations of appropriate cases, combined with collaboration with a sleep specialist as necessary, are expected to shorten time to narcolepsy diagnosis, improve patient care and outcomes for both narcolepsy and psychiatric conditions, and avoid unnecessary or ineffective therapy. Likewise, sleep specialists need to be vigilant for evidence of treatable psychiatric illness in patients with an existing narcolepsy diagnosis.

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Drug names: armodafinil (Nuvigil and others), methylphenidate (Ritalin and others), modafinil (Provigil and others).

Potential conflicts of interest: **Dr Black** is a part-time employee of and holds stock options in Jazz Pharmaceuticals. **Mss Reaven** and **Funk** and **Dr McGaughey** are consultants to Jazz Pharmaceuticals. **Dr Ohayon** has received research grants from Jazz Pharmaceuticals. **Dr Ruoff** has served as an advisory board member and unpaid consultant for Jazz Pharmaceuticals. **Dr Guilleminault** has no conflicts of interest to report.

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