E xcessive daytime sleepiness occurring at least 3 times weekly affects nearly 20% of the population and severe excessive daytime sleepiness affects approximately 5% of the population, with men and women equally affected. Excessive sleepiness, defined as the ongoing inability to maintain alertness during the waking episodes, imposes a significant clinical, quality-of-life, safety, and economic burden on society. In 2007, the National Highway Traffic Safety Administration estimated that sleep problems contributed to more than 100,000 motor vehicle crashes in the United States, resulting in an estimated 1550 deaths, 71,000 injuries, and $12.5 billion in monetary losses annually. Excessive daytime sleepiness is associated with many medical conditions, including shift work disorder (SWD), obstructive sleep apnea (OSA), and narcolepsy. The prevalence of excessive sleepiness among night shift workers and among rotating shift workers is 14.1% and 8.1%, respectively; the corresponding prevalence of SWD is 10% among shift workers aged 18 to 65 years. An estimated 9% of women and 24% of men aged 30 to 60 years have at least mild OSA. Excessive daytime sleepiness is the most common symptom of OSA.
sidual excessive sleepiness is present in 6% to 12% of patients with OSA even after treatment with continuous positive airway pressure.8

The prevalence of narcolepsy is estimated to be between 25 and 50 persons per 100,000 people.9 Almost all patients with narcolepsy experience periods of extreme daytime sleepiness and sudden bouts of sleep that can strike at any time.10 Because of the high prevalence and significant economic impact of excessive sleepiness, attention is warranted for the selection of the most appropriate and cost-effective, wake-promoting treatment.

Armodafinil and modafinil improve wakefulness in patients with excessive sleepiness associated with SWD, treated OSA, and narcolepsy.11-18 Armodafinil is the longer-lasting, R-isomer of racemic modafinil. A comparison of armodafinil and modafinil on a milligram-to-milligram basis showed that armodafinil sustained higher plasma concentrations than modafinil, as indicated by a 37% higher maximum plasma concentration, and a 69% greater area under the curve.19

This present study was conducted to explore any potential differences in all-cause healthcare costs and the individual cost components (ie, inpatient visits, emergency department visits, physician office visits, outpatient visits, and other visits) between patients prescribed initial armodafinil therapy and patients prescribed initial modafinil therapy for the treatment of excessive sleepiness associated with OSA, SWD, or narcolepsy.

Methods

Data Source

This retrospective cohort study was based on data from the IMS LifeLink Health Plan Claims Database, a nationally representative database containing data from more than 79 health plans in the United States. This is the largest, most comprehensive database of integrated medical and pharmacy claims for approximately 87 million de-identified individuals as of March 2012, with the majority of them (82%) commercially insured.

Patients in the database are tracked longitudinally using 3 component files: medical claims, pharmacy claims, and eligibility for insurance coverage. The medical claims file contains data on the diagnostic and therapeutic services rendered in the inpatient and outpatient settings. The pharmacy claims file contains data on the prescription drugs dispensed in the retail and mail-order settings. The eligibility file contains demographic characteristics and periods of eligibility for enrollment in the plan for each patient.

Patient Selection

The study included patients with a pharmacy claim for armodafinil or for modafinil between June 1, 2009, and February 28, 2012. The fill date of the patients’ first armodafinil or modafinil prescription within this time frame was designated as the index date. Patients were included in this study if they were aged at least 18 years at the index date, and were continuously eligible for insurance coverage for 6 months before the index (ie, preindex) date and at least 1 month after the index (ie, postindex) date.

In addition, patients were required to have an International Classification of Diseases, Ninth Revision (ICD-9) diagnosis code for at least 1 of the US Food and Drug Administration–approved indications for armodafinil or for modafinil—OSA (327.23), SWD (327.36), or narcolepsy (347.0x)—in the 6-month preindex period or on the index date. Patients were not required to be treatment naive to all therapies for OSA, SWD, or narcolepsy, but patients with an index prescription fill date for armodafinil or for modafinil before June 1, 2009, or after February 28, 2012, were excluded from this study.

The cohort assignment was based on an intent-to-treat approach, and patients meeting the selection criteria were placed into 1 of 2 treatment cohorts according to their index prescription; patients remained in that cohort throughout the study period. The patients were

KEY POINTS

➤ Excessive daytime sleepiness is associated with medical conditions, such as shift work disorder, obstructive sleep apnea, and narcolepsy, and carries a significant clinical and economic burden.

➤ This is the first large, real-world economic analysis comparing the differences in healthcare costs associated with armodafinil and modafinil for the treatment of excessive sleepiness.

➤ This study was conducted between June 2009 and February 2012, before the generic form of modafinil became available.

➤ The results show that armodafinil had a lower daily average consumption (DACON) compared with modafinil (1.04 vs 1.47, respectively).

➤ The postindex mean annualized medical costs were significantly lower with armodafinil ($11,363) compared with modafinil ($13,775).

➤ Total annualized healthcare costs were also lower with armodafinil ($18,309) compared with modafinil ($23,530).

➤ Based on this analysis, armodafinil provides real-world DACON advantages and may be associated with lower overall healthcare utilization and costs compared with modafinil.
followed until the earlier of either their health plan enrollment end date, or the end of the analysis period on March 31, 2012 (Figure 1). This allowed for patients to be followed for a minimum of 1 month and a maximum of 34 months after their index date. The 6-month period before the index date was used to assess baseline characteristics, healthcare costs, and resource utilization.

Outcomes
The all-cause healthcare costs were calculated from all claims regardless of the diagnosis codes. The costs were defined as the allowed amount on claims; the allowed amount typically reflects the amount paid by the health plan plus any member liability (ie, copay, deductible, or coinsurance) for the service. The allowed amount was chosen as the cost measure, because it best represents the actual cost amount received from all payers.

The total medical costs and the component costs for inpatient hospitalizations, emergency department visits, physician office visits, outpatient visits, and other visits (ie, laboratory and diagnostic claims that were not part of a hospitalization, emergency department visits, physician office visits, or outpatient visits) were evaluated.

The pharmacy costs included all medications for which claims were filed (ie, not restricted to armodafinil and to modafinil). The drug-specific costs were restricted to pharmacy costs for armodafinil or for modafinil. The total healthcare costs included the sum of all medical and pharmacy costs. Because patients had varying lengths of follow-up, annualized costs were calculated by multiplying by 12 the average monthly cost for each patient.

The costs in the analysis were adjusted to March 2012 US dollars using the Medical Consumer Price Index. The daily average consumption (DACON) for armodafinil and for modafinil was calculated by dividing the total tablets dispensed for each drug by the prescription days supplied.

Statistical Methods
Baseline characteristics were compared between the 2 cohorts using the chi-square tests for categorical variables (eg, sex, region, index payer, conditions of interest) and independent samples t-tests for continuous variables (eg, age, Charlson Comorbidity Index [CCI] score). The CCI score was used to represent the patients’ overall health status. It contains 19 categories of comorbidity and reflects the cumulative burden of comorbidity with higher scores indicating a more severe burden. (The categories of the CCI include myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, diabetes, hemiplegia, moderate-to-severe renal disease, diabetes with end-organ damage, any tumor, leukemia, lymphoma, moderate-to-severe liver disease, metastatic solid tumor, and AIDS.)

The CCI scores were derived by evaluating the presence of various ICD-9 codes in the 6-month preindex period for each patient. To account for baseline differences between the 2 treatment cohorts, multivariate generalized linear models based on gamma distribution and log link function were used to compare postindex costs between the 2 cohorts; age, sex, CCI scores, region, index payer, and log-transformed preindex costs were used as covariates in the models. Paired t-tests were used to compare differences between the preindex and the postindex costs within each drug cohort. All analyses were conducted with SAS version 9.2 (SAS Institute; Cary, NC). A P value ≤.05 was considered significant.

Results
Patient Characteristics
A total of 5693 patients receiving armodafinil and 9212 patients receiving modafinil met all of the inclusion criteria. The patients in the modafinil cohort were followed for an average of 19.35 months, and the patients in the armodafinil cohort were followed for an average of 13.95 months. At baseline, patients in the modafinil cohort were older (50.3 years vs 47.3 years; P <.001) and had higher percentages of patients with a diagnosis of OSA (84% vs 81.4%; P <.001) and SWD (7.7% vs 4.2%; P <.001), and a lower percentage of patients.

Daily Average Consumption
During the study period, 27,555 armodafinil prescriptions were filled by 5693 unique patients for an average of 4.8 armodafinil fills per patient. For modafinil, 57,196 prescriptions were filled by 9212 unique patients for an
average of 6.2 modafinil fills per patient. A lower DACON was observed for armodafinil (1.04; Figure 2). The mean monthly drug-specific pharmacy costs were $166 for armodafinil and $326 for modafinil (P < .001).

**Healthcare Costs**

The postindex mean medical costs were significantly lower for the armodafinil cohort compared with the modafinil cohort after adjusting for baseline differences ($11,363 vs $13,775, respectively; P = .005 (Figure 3). Within each cohort, decreased medical costs were observed in the postindex period compared with the preindex period ($13,155 vs $11,363, respectively, for armodafinil; $15,323 vs $13,775, respectively, for modafinil; P < .001 for both). Of the postindex component medical costs, inpatient hospitalization costs ($3099 vs $4308, respectively; P = .014) and other costs ($643 vs $1035, respectively; P < .001) were significantly lower for the armodafinil cohort compared with the modafinil cohort.

**This is the first large, real-world, retrospective, economic study to evaluate the cost differences between armodafinil and modafinil.**

The physician and outpatient costs were also lower for the armodafinil cohort; however, these differences did not reach significance. All-cause emergency department visits was the only cost category that was higher among patients receiving armodafinil than among patients receiving modafinil (P < .001).

The postindex mean total healthcare costs were lower for the armodafinil cohort compared with the modafinil cohort after controlling for baseline differences ($18,309 vs $23,530, respectively; P < .001; Figure 4).

**Discussion**

This is the first large, real-world, retrospective, economic study to evaluate the cost differences between armodafinil and modafinil. The results of this analysis indicate that after therapy initiation, the armodafinil cohort had lower total all-cause medical costs compared with the modafinil cohort. In addition, the armodafinil cohort had lower pharmacy costs than the modafinil cohort after therapy initiation. The differences in the pharmacy costs between the armodafinil and the modafinil cohorts were partly driven by the differences in the pharmacy cost between the 2 medications, with armodafinil having a lower price than modafinil on a per-tablet basis (approximately $10.44 vs $16.56, respectively, per tablet).

Furthermore, this analysis was conducted before the approval of generic modafinil in June 2012. When the armodafinil and modafinil pharmacy costs were subtracted from the total pharmacy costs, the remaining pharmacy costs were still lower for the armodafinil cohort compared with the modafinil cohort, suggesting that lower total pharmacy costs may be seen with armodafinil compared with generic modafinil.

DACON is a technique used by managed care organizations to assess drug utilization and the associated eco-

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Armodafinil (N = 5693)</th>
<th>Modafinil (N = 9212)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex, %</td>
<td>49.5</td>
<td>51.5</td>
<td>.056</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>50.5</td>
<td>49.5</td>
<td>.056</td>
</tr>
<tr>
<td>Mean age on index date (SD)</td>
<td>47.3 (13.4)</td>
<td>50.3 (13.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean Charlson Comorbidity Index score in the 6-month preindex period and on index date (SD)</td>
<td>0.64 (1.11)</td>
<td>0.81 (1.31)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean follow-up time, mo</td>
<td>13.95</td>
<td>19.35</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diagnoses for indications in the 6-month preindex period and on index date*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstructive sleep apnea, %</td>
<td>84.0</td>
<td>81.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Shift work disorder, %</td>
<td>7.7</td>
<td>4.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Narcolepsy, %</td>
<td>20.3</td>
<td>22.8</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Conditions are not mutually exclusive, and the total can sum to greater than 100%.

SD indicates standard deviation.
Economic implications between medications with similar therapeutic indications. Although armodafinil and modafinil are available for once-daily dosing in multiple tablet strengths, differences in the real-world utilization of these medications can be underscored in a DACON analysis. Armodafinil has a DACON of 1.04 compared with a DACON of 1.47 for modafinil. These results support true once-daily dosing for armodafinil and provide real-world support for the pharmacokinetic data showing that on a milligram-to-milligram basis, armodafinil sustains higher plasma concentrations versus modafinil during a 24-hour period. These pharmacokinetic advantages may have translated into DACON differences seen in this real-world analysis.

Limitations

The findings of this study should be interpreted with the study limitations in mind. First, the results of this analysis are based on observational claims data and therefore cannot be interpreted as implying any difference in efficacy or other clinical outcome, such as disease progression or quality of life. As with all claims analyses, the data elements may be subject to coding irregularities and inaccuracies. For example, SWD is known to be undercoded in medical claims, and physicians may also classify patients presenting with excessive sleepiness associated with OSA or narcolepsy to a broader or different diagnosis. Because study eligibility required a coded indication, relevant patients might have been excluded from the analysis. Hence, the generalizability of the results is restricted to a population that is similar to the current study group.

Second, the costs reported in this analysis are all-cause pharmacy and medical costs and are not specific to OSA, SWD, and/or narcolepsy. Excessive sleepiness is a risk factor for comorbidities and can exacerbate several comorbidities, making all-cause medical resource utilization the most relevant costs for this analysis. Because patients in this analysis had multiple comorbidities, it was difficult to separate disease-specific costs. In addition, total costs, regardless of their origin, are the most relevant costs to a health plan. It is likely that an excessive sleepiness–specific cost analysis would underestimate the true costs associated with this condition because OSA, SWD, and narcolepsy—the underlying causes of excessive sleepiness—are often undercoded.

Third, this analysis did not capture the time since diagnosis and did not correct for the potential increased cost of the initial diagnosis and treatment. This analysis included a 6-month preindex period to ensure a diagnosis for OSA, SWD, or narcolepsy, but patients were not required to be newly diagnosed. Previous research has shown that men and women with OSA have higher costs in the period immediately before disease diagnosis.

Fourth, the study design and the analytic techniques contain some inherent limitations. Because of the intent-to-treat design, patients who switched therapies during follow-up were still considered members of the cohort to which they were originally assigned, and their

**Figure 3** Mean Annualized Medical Costs: Armodafinil versus Modafinil

![Figure 3](image-url)

\[ P = .005 \text{ for mean medical costs.}^a \]

*P values adjusted using a generalized linear model for preperiod differences between armodafinil and modafinil cohorts in age, sex, Charlson Comorbidity Index, region, index payer, and preindex costs.

**Figure 4** Postindex Mean Annualized Total Costs: Armodafinil versus Modafinil

![Figure 4](image-url)

\[ P < .001 \text{ for mean total costs.}^a \]

*P values adjusted using a generalized linear model for preperiod differences between armodafinil and modafinil cohorts in age, sex, Charlson Comorbidity Index, region, index payer, and preindex costs.
costs were attributed to their index drug. Administrative claims do not provide information regarding reasons for treatment discontinuation or switching. Furthermore, the IMS database is fully de-identified and therefore does not contain information on the benefit design of payers.

Finally, an observational retrospective cohort study design restricts the ability to draw direct causal inferences between treatments and outcomes. Although background characteristics, such as age, sex, CCI score, index payer, and preindex costs were controlled for in this analysis, residual confounding cannot be ruled out.

**Conclusions**

Based on this analysis, armodafinil provides real-world DACON advantages and may be associated with lower overall healthcare resource utilization and costs compared with modafinil. In light of these new comparative economic data, healthcare decision makers may have to consider DACON and real-world total cost differences in their formulary decision-making. Future studies are needed to explain the drivers of healthcare resource utilization and cost differences between patients receiving armodafinil and those receiving modafinil.

**Funding Source**

This study was funded by Teva Pharmaceuticals.

**Author Disclosure Statement**

Dr Carlton, Dr Lunacek, and Mr Regan are employees of Xcenda, which received funding from and provided consulting services to Teva Pharmaceuticals to conduct this analysis. Dr Carroll is a former employee of and had stocks in Teva Pharmaceuticals.

**References**


**STAKEHOLDER PERSPECTIVE**

**Out-of-Pocket Cost of Therapy Can Affect Patients’ Excessive Sleepiness and Daytime Functioning**

By Teresa M. DeLuca, MD, MBA
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The article by Carlton and colleagues in this issue of American Health & Drug Benefits is the first large, real-world, retrospective, economic analysis comparing the differences in healthcare costs associated with armodafinil and modafinil for the treatment of excessive daytime sleepiness. The results indicate that ar-
modafinil has a lower daily average consumption compared with modafinil, as well as significantly lower medical costs, and lower total healthcare costs. These findings have obvious implications for provider prescribing and treatment planning, as well as for health plan formulary decision-making. They also provide useful consumer price information for patients to discuss with their physicians to arrive at a cost-effective treatment choice.

PATIENTS: Excessive daytime sleepiness, the inability to maintain alertness while awake, is associated with medical conditions, including shift work disorder (SWD), obstructive sleep apnea (OSA), and narcolepsy. It is also associated with insufficient quality or quantity of sleep, either is a contributing factor likely to increase exponentially, based on studies showing that 65% of us sleep with our cell phones within reach.1 It is also well established in the scientific literature that people exposed to mobile radiation take longer to fall asleep and spend less time in deep sleep.2

Healthcare costs are not the only costs associated with excessive sleepiness. Lowered employee productivity affects not only the employer’s bottom line but also leads to workers’ frustration, as they struggle to stay awake and complete their tasks. Excessive daytime sleepiness also has consequences for society. Carlton and colleagues cite a National Highway Traffic Safety Administration estimate that in 2007, sleep problems contributed to more than 100,000 motor vehicle crashes in the United States, resulting in 1550 deaths; 71,000 injuries; and $12.5 billion in annual monetary loss.3 Those numbers alone should jolt us awake.

Patient out-of-pocket spending is an increasingly important factor as health plan members are asked to take on a greater share of the cost of their care. The present study findings are particularly instructive here. The daily average consumption was lower for armodafinil (1.04) than for modafinil (1.47). This translated into mean monthly drug-specific pharmacy costs of $166 per patient for armodafinil and $326 per patient for modafinil.

For health plan members responsible for coinsurance, the rates per prescription range from 32% to 36% (based on prescription drug coinsurance amounts for the metal plans available under the Affordable Care Act). This amount could result in out-of-pocket consumer savings of $60 to $117 monthly. As we know, out-of-pocket costs correlate with patient adherence to prescribed medications; therefore, armodafinil could potentially be associated with a higher patient adherence rate than modafinil, leading to better-controlled daytime sleepiness.

PAYERS: Total healthcare costs are the metric of most interest to payers, whether they are self-funded employers or fully insured health plans. Carlton and colleagues rightly note that patients in this analysis had multiple comorbidities, making it difficult to separate out disease-specific costs. The likelihood of undercoding OSA, SWD, and narcolepsy also make total costs, regardless of the origin, the most helpful metric for payers to weigh when evaluating these medications.

Of note, all-cause emergency department visits were the only cost category that was higher among patients receiving armodafinil than among patients receiving modafinil. I would suspect this is because of the differences in a patient’s presenting symptoms or in the main complaint; however, without further research, this is a mere assumption.

PROVIDERS: The majority of providers do not check the patient’s formulary before writing a prescription. Instead, they base prescribing decisions on their experience and on their comfort level with each drug. As a result, providers are not aware of the patient’s out-of-pocket cost. Cost information from this study could arm providers with a resource to help them factor in the cost to the patient when writing a prescription, potentially increasing the likelihood that their patient will fill the prescription and will continue to use the prescribed treatment.

Sleep is a natural process that enhances confidence, creativity, and cognitive function. The irony is that patients with excessive daytime sleepiness do not benefit from this sleep. Both armodafinil and modafinil have the potential to help patients achieve normal daily function in a safe environment. Based on this study’s analysis, armodafinil offers advantages over modafinil in lower overall healthcare resource utilization and cost. Such clear comparative economic data can, and should, be factored into decision-making by patients, providers, and payers.