Original Research

Solriamfetol Titration & AdministRaTion (START) in Patients With Narcolepsy

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ABSTRACT

Purpose: Solriamfetol, a dopamine/norepinephrine reuptake inhibitor, is approved (in the United States and European Union) to treat excessive daytime sleepiness (EDS) in adults with narcolepsy (75–150 mg/d) or obstructive sleep apnea (OSA) (37.5–150 mg/d). This study characterized real-world titration strategies for patients with narcolepsy (with or without comorbid OSA) initiating solriamfetol therapy.

Methods: This virtual, descriptive study included a retrospective medical record review and qualitative survey. US-based physicians prescribing solriamfetol for EDS associated with narcolepsy or OSA participated. Data are reported for patients with narcolepsy with or without comorbid OSA (OSA alone reported separately). On the basis of medical record review, titration strategies were classified de novo (EDS medication naive), transition (switched or switching from existing EDS medication[s] to solriamfetol), or add-on (adding solriamfetol to current EDS medication[s]). The survey included open-ended questions regarding a hypothetical patient—a 32-year-old woman with narcolepsy (Epworth Sleepiness Scale score of 8) treated with 35 mg/d of amphetamine and 6 g per night of sodium oxybate who experiences non–use-limiting adverse events from amphetamine.

Findings: Twenty-six physicians participated: 23 provided data from 70 patients with narcolepsy (type 1, n = 24; type 2, n = 46; mean [SD] age, 40 [11] years; 57% female; 6 with comorbid OSA), and 26 responded to the hypothetical patient scenario. From the medical record review, solriamfetol therapy initiation was de novo for 19 of 70 patients (27%), transition for 31 of 70 patients (44%), and add-on for 20 of 70 patients (29%). Efficacy profile of solriamfetol was the primary reason for de novo (12 of 19 [63%]), transition (18 of 31 [58%]), and add-on (19 of 20 [95%]) initiation. Most (86%) initiated use of solriamfetol at 75 mg/d and were stable at 150 mg/d (76%). Most (67%) had 1 dose adjustment, reaching a stable dose over a median (range) of 14 (1–60) days. Physicians most often considered EDS severity (44%) when titrating. Among transitioning patients, 14 of 22 (64%) using wake-promoting agents discontinued their use abruptly, and 5 of 9 (56%) using stimulants were tapered off. At data collection, 90% continued to take solriamfetol. Regarding the hypothetical patient scenario, most physicians (81%) thought solriamfetol was appropriate, highlighting tolerability issues with current treatment and lack of symptom control as drivers for switching; however, 3 physicians (12%) did not think solriamfetol was appropriate, noting current symptoms were not severe enough and/or symptoms could be managed by increasing sodium oxybate dose; 2 (8%) thought it would depend on other factors. Physicians emphasized managing withdrawal symptoms while maintaining EDS symptom control

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when titrating off a stimulant and starting solriamfetol therapy.

Implications: In a real-world study, physicians initiated solriamfetol therapy at 75 mg/d for most patients with narcolepsy, adjusted dosages once, tapered stimulants, and abruptly discontinued therapy with wake-promoting agents. (*Clin Ther.* 2022;44:1356–1369.)

Keywords: excessive daytime sleepiness, JZP-110, narcolepsy, pharmacotherapy, real-world evidence, Sunosi.

INTRODUCTION

Narcolepsy is a hypersomnolence disorder with an estimated US prevalence of 30.6 to 56.3 per 100,000 population.[1,2] Excessive daytime sleepiness (EDS), a core symptom of both narcolepsy phenotypes (types 1 and 2), can be treated with sodium oxybate, wake-promoting agents (WPAs; modafinil and armodafinil), stimulants (methylphenidate and amphetamine), or the histamine 3 receptor antagonist/inverse agonist pitolisant.[3,4] Because physicians' dosing and titration strategies for managing narcolepsy symptoms are based on specific patient needs, these strategies may require optimization of the individual treatment regimens; for some patients, transitioning from one EDS medication to another can lead to difficulties.[5,6]

Solriamfetol,* a dopamine and norepinephrine reuptake inhibitor, demonstrated efficacy and safety in treating EDS associated with narcolepsy in a 12-week Phase III clinical trial[7] and a subsequent long-term follow-up study.[8] Solriamfetol was approved in 2019 in the United States[9] and 2020 in the European Union[10] to improve wakefulness in adult patients with EDS associated with narcolepsy (75–150 mg/d) or obstructive sleep apnea (OSA; 37.5–150 mg/d). The recommended titration strategy for patients with narcolepsy is to initiate treatment at 75 mg/d, after which the dose may be doubled at intervals of at least 3 days up to a maximum dose of 150 mg/d.[9] For patients with moderate and severe renal impairment, the recommended titration strategy is to initiate treatment at 37.5 mg/d. The dose may be increased to a maximum dose of 75 mg/d after at least 7 days for patients with moderate renal impairment; for patients with severe renal impairment, the maximum dose is 37.5 mg/d.[9] For patients with hepatic impairment, no dose adjustments are required; modafinil and armodafinil require the dose to be reduced by half for patients with severe hepatic impairment.[9,11,12]

*Trademark: Sunosi™ (Axsome Therapeutics, New York, New York).

The efficacy of solriamfetol has been demonstrated in Phase III clinical trials. In these trials, both patients with narcolepsy and patients with OSA had significant improvements in ability to maintain wakefulness and self-reported EDS, as evidenced by increases of 3 to 11 minutes in mean sleep latency on the Maintenance of Wakefulness Test and reductions of 2 to 5 points on the Epworth Sleepiness Scale (ESS) relative to placebo, respectively.[7,13] In addition, 31% to 49% of patients with narcolepsy and 52% to 73% of patients with OSA reduced their EDS to the normal sleepiness range (ESS scores $\leq$10), further evidencing the efficacy of solriamfetol.[14] The most common treatment-emergent adverse events associated with solriamfetol treatment were headache, nausea, decreased appetite, nasopharyngitis, dry mouth, insomnia, and anxiety.[7,8,13] Recent American Academy of Sleep Medicine clinical practice guidelines strongly recommend that clinicians use solriamfetol for the treatment of narcolepsy in adults based on associated improvements in EDS, disease severity, and quality of life.[15]

During clinical trials, patients used solriamfetol alone for EDS after washing out prior EDS (and, for patients with narcolepsy, cataplexy) medications.[7] In clinical practice, however, patients may start solriamfetol therapy while taking multiple EDS medications[3] or tapering other EDS treatment. Titration to solriamfetol in the clinic also may be complicated by known effects of other drugs, such as rebound hypersomnolence with stimulants.[16] In light of potential pharmacodynamic effects (eg, cardiovascular effects associated with WPAs) and/or drug-drug interactions (eg, reduced effectiveness of hormonal contraceptives with modafinil, armodafinil, and pitolisant; contraindication of solriamfetol with monoamine oxidase inhibitors) associated with EDS medications,[9,11,12,17] treatment decisions can also be affected by the presence of common comorbidities, including diabetes, obesity, cardiovascular disease, psychiatric disorders, and OSA.[18–20] Factors that affect patient access to prescription medications (eg, cost and

insurance coverage) may also play a role in the selection of EDS treatments. Given the recent clinical availability of solriamfetol, data that describe real-world physician dosing and titration strategies could help optimize patient care.

Therefore, this study was designed to provide physicians with real-world evidence regarding solriamfetol dosing and titration strategies. Study objectives were to describe dosing and titration strategies used when initiating solriamfetol therapy; to assess whether physicians' titration strategies differed by patient type, current treatment, comorbidities, and patient lifestyle; and to understand the factors physicians considered when titrating patients to solriamfetol and how these factors affected their titration strategy based on a hypothetical patient scenario.

PARTICIPANTS AND METHODS

Study Design

This virtual, descriptive study included a quantitative retrospective patient medical record review and a cross-sectional qualitative survey of US-based physicians prescribing solriamfetol to patients with EDS associated with narcolepsy or OSA (data from patients with OSA alone are reported separately[21]). Study fielding occurred from June 3 to 19, 2020. The study was approved by a centralized independent review board (New England Institutional Review Board, no. 20201061).

Data Source and Participants

Eligible physicians included those who had previously prescribed solriamfetol to ≥3 patients with narcolepsy or OSA (to ensure the physicians had experience prescribing solriamfetol) and had ≥3 medical records (narcolepsy or OSA) that met the patient medical record inclusion criteria (to ensure that a sufficient number of patient medical records were collected). Physician exclusion criteria included lack of access to a mobile device that could send and receive text messages (or lack of access to a computer) and being an employee or immediate family member of an employee of Jazz Pharmaceuticals. Patient medical record inclusion criteria included patients ≥18 years of age at screening, diagnosis of narcolepsy and/or OSA, previously prescribed solriamfetol and had reached a stable dose, and 1 of the following: not receiving any pharmacologic treatment for EDS when prescribed solriamfetol, switched or was in the process of switching to solriamfetol from other EDS medication(s), or adding solriamfetol to existing EDS medication(s) and intending to continue to take both or all medications. Note that switching could involve any of several different strategies, including abrupt discontinuation of use of the previous medication before starting use of solriamfetol, tapering and discontinuation of use of the previous medication before starting use of solriamfetol, or cross-tapering (decreasing the dose of the previous medication while starting use of and titrating the dose of solriamfetol before full discontinuation of use of the previous medication). In addition, among patients who were switching to solriamfetol, there could be a range of different scenarios, given that patients may be taking 1 or multiple medications for EDS (eg, a patient may be switched from a WPA only to solriamfetol only or a patient who was taking a stimulant and WPA may be switched off the WPA to solriamfetol but continue to take the stimulant). Patient medical record exclusion criteria included those who were given solriamfetol as part of a clinical trial or early access program. Target enrollment was 25 physicians reporting information from 3 to 5 patient medical medical records, for a total of 75 to 125 patient medical records. Formal sample size calculations were not performed, given the descriptive nature of the study.

Procedures

Recruitment occurred in a stepwise manner. Physicians were invited to participate. Physician eligibility was assessed through an electronic screener via text message or e-mail, and consent was provided via an electronic informed consent form. Consenting physicians provided information related to their specialty, board certification, practice setting, years in practice, years treating patients with narcolepsy, and the total number of patients they had treated or managed during the past 12 months who had been prescribed and reached a stable dose of solriamfetol. Participating physicians were provided detailed instructions on identifying patient medical records that met the eligibility criteria. If physicians treated patients with both narcolepsy and OSA, they were asked to select medical records for both conditions in an effort to achieve a balance of information from patients with narcolepsy and OSA. Participating physicians identified the most recent 3 to 5 eligible patient medical records and entered all relevant information using a patient

data collection form they accessed through their mobile device or computer.

After completion of the patient data collection form, physicians were asked to complete a qualitative survey by calling into an automated voice response system. Physicians had the option to grant or not grant permission to the study team to use their audio voice recordings for presentations, publications, and internal or external meetings. The automated voice response system asked open-ended questions pertaining to 2 scenarios, a hypothetical patient with narcolepsy (Box 1) and a hypothetical patient with OSA (reported separately). All answers were recorded and transcribed.

Box 1. Hypothetical patient scenario.

> Imagine your physician colleague came to you for advice for a patient, Susan. Susan is a 32-year-old female diagnosed with narcolepsy who is currently being treated with an amphetamine stimulant as well as sodium oxybate to control her excessive daytime sleepiness (EDS) symptoms. Her current amphetamine dose is 35 mg/d, which she has been taking for 6 months. Her current total nightly sodium oxybate dose is 6 g, which she has also been taking for 6 months. Her most recent Epworth Sleepiness Scale rating was an 8. While Susan's amphetamine stimulant and sodium oxybate have helped her EDS symptoms, she occasionally experiences non-use-limiting adverse events from the amphetamine stimulant, which are bothersome to her. Susan has approached your colleague about trying solriamfetol for her EDS symptoms. Your colleague would like to get your advice on starting Susan on solriamfetol.

End Points and Key Measurements

For the medical record review, the following quantitative end points were assessed: (1) physician and patient characteristics, (2) treatment initiation strategies, (3) reasons for prescribing solriamfetol, (4) dosing strategies for solriamfetol and other EDS medications when titrating to solriamfetol, (5) factors physicians considered when titrating, (6) use of other medications for EDS, (7) physician confidence in titration strategy, and (8) number of patients still taking solriamfetol and reasons for discontinuation.

For the survey regarding the hypothetical patient scenario, the following qualitative end points were assessed: (1) description of whether physician agrees or disagrees patient is appropriate for solriamfetol, (2) description of whether physician would add solriamfetol to patient's current EDS treatment regimen or switch patient to solriamfetol (as well as titration approach physician would suggest and factors physician would consider in choosing the approach), and (3) description of how the initial solriamfetol titration approach would change based on different patient factors (eg, comorbidities, concomitant medications, and lifestyle factors).

Statistical Analysis

Physician characteristics were summarized for all enrolled physicians (ie, those who recorded data on $\geq$1 patient medical record) and for the subset of physicians who recorded data from $\geq$1 medical record of a patient with narcolepsy. Analysis of patient characteristics was based on all recorded medical records from patients with narcolepsy who met the inclusion and exclusion criteria. Demographic and baseline characteristics were summarized descriptively. For continuous variables, the number, mean (SD), and median (range) were described. For categorical variables, numbers (percentages) of physicians and patients within each category were described. Missing or partially missing data were not imputed.

For the quantitative analysis from the medical record review, data related to solriamfetol treatment were summarized overall and by solriamfetol therapy initiation strategy. Solriamfetol therapy initiation strategies were divided into 3 categories: de novo (patient not receiving any pharmacologic treatment for EDS when solriamfetol treatment was initiated), transition (patient switched or was switching to solriamfetol from $\geq$1 medications for EDS), and add-on (patient added solriamfetol to $\geq$1 EDS medications already being taken and intended to continue taking both or all medications). All quantitative data for this study were analyzed using SAS software, version 9.4 (SAS Institute Inc, Cary, North Carolina).

For the qualitative analysis from the hypothetical patient scenario, content analysis of the recordings identified themes in the responses, and a trained linguist captured language choice patterns based on discourse analysis techniques used in health care research.[22] Data for each end point were summarized descriptively.

Table I. Physician characteristics.

Characteristic	All Physicians (N = 26)	Physicians Reporting Data on Initiating Solriamfetol Therapy for Patients With Narcolepsy (n = 23)
Specialty, No. (%)		
Internal medicine	7 (27)	5 (22)
Neurology	7 (27)	7 (30)
Pulmonology	6 (23)	5 (22)
Psychiatry	5 (19)	5 (22)
Otolaryngology	1 (3.8)	1 (4.3)
Practice setting, No. (%)		
Private practice	21 (81)	19 (83)
Regional, local, or community hospital or clinic	4 (15)	3 (13)
Academic hospital	1 (3.8)	1 (4.3)
Practice duration, y		
Mean (SD)	16.9 (6.8)	16.6 (6.7)
Median (range)	15.5 (5-29)	15.0 (5-29)
Duration treating patients with narcolepsy, y		
Mean (SD)	15.7 (6.6)	15.4 (6.7)
Median (range)	15.5 (2-26)	15.0 (2-26)
Board-certified in sleep medicine, No. (%)		
Yes	19 (73)	17 (74)
No	7 (27)	6 (26)
Physicians who entered data from *x* number of total patient medical records,* No. (%)		
3 Records	4 (15)	3 (13)
4 Records	2 (8)	2 (9)
5 Records	20 (77)	18 (78)
Physicians who entered data from *x* number of narcolepsy medical records, No. (%)		
1 Records	NA	0
2 Records	NA	6 (26)
3 Records	NA	11 (48)
4 Records	NA	5 (22)
5 Records	NA	1 (4)

NA = not applicable.
* Includes narcolepsy or obstructive sleep apnea medical records.

RESULTS

Physician Recruitment and Characteristics

Of 87 physicians recruited, 82 completed the screener, 29 met the eligibility criteria, and 26 completed the study. A total of 23 physicians entered data from ≥1 medical record of a patient with narcolepsy (Table I). All 26 physicians responded to the hypothetical patient scenario. Physician specialties included internal medicine, neurology, pulmonology, psychiatry, and otolaryngology. Most physicians (73%) were board certified in sleep medicine and had been practicing for a mean (SD) of 16.9 (6.8) years,

with 15.7 (6.6) years treating narcolepsy. Physicians reported that, across the prior 12 months, they treated or managed a combined 409 patients with narcolepsy who had been prescribed solriamfetol, with a mean (SD) of 15.7 (17.8) patients per physician.

Patient Characteristics

Information was collected on 70 patients with narcolepsy (type 1, 34%; type 2, 66%); no patient medical records were excluded. Of these 70 patients, 6 (8.6%) also had OSA; all 6 were adherent to positive airway pressure therapy (continuous positive airway pressure, bilevel positive airway pressure, or automatic positive airway pressure) at the time of solriamfetol therapy initiation, according to physician report. Mean (SD) age was 40.0 (11.0) years, 57% of patients were female, and the mean (SD) body mass index was 28.2 (7.9) kg/m^2, with most patients being overweight or obese (Table II). Physicians characterized most patients as having moderate or severe EDS at the time solriamfetol was first prescribed (using a 0–3 scale, where 0 indicated no EDS and 3 indicated severe EDS). Most were employed full or part time. Forty-five patients (64%) had comorbidities, the most common being obesity, psychiatric disorders (most frequently depression), migraines, and cardiovascular disorders (most frequently hypertension).

Treatment Initiation Strategies and Rationale for Prescribing Solriamfetol

Of the 70 patients, 31 (44%) were transitioning to solriamfetol therapy from other medications for EDS (ie, transition patients); 20 of the 70 patients (29%) were adding solriamfetol to existing medications (ie, add-on patients), and 19 of 70 (27%) were initiating solriamfetol therapy de novo (ie, de novo patients). Conversations about starting solriamfetol therapy were primarily physician initiated (67 of 70 [96%]); 2 of 70 conversations (2.9%) were patient initiated, and 1 of 70 (1.4%) was undetermined. The most commonly cited primary reason prompting the discussion to prescribe solriamfetol de novo (63%) was its efficacy profile; a need for improved efficacy or augmenting the effects of other medications was the most common reason for patients transitioning to (58%) or adding on (95%) solriamfetol (Figure 1).

Dosing Strategies When Titrating to Solriamfetol

Most patients started therapy with solriamfetol at 75 mg, regardless of whether initiation was de novo, transition, or add-on. Overall, 60 patients (86%), 8 patients (11%), and 2 patients (2.9%) started solriamfetol therapy at 75 mg, 37.5 mg, and 150 mg, respectively. Across all patients, 150 mg was the most common stable dose (in 53 of 70 patients [76%]), followed by 75 mg (in 17 of 70 patients [24%]); the stable dose of 150 mg was reached by a higher percentage of transitioning patients than de novo or add-on patients (Figure 2A). A total of 47 patients (67%) had 1 dose adjustment to reach their stable dose; 3 (4.3%) had 2 adjustments, 3 (4.3%) had 3 adjustments, and 17 (24%) had none. Patients starting solriamfetol therapy de novo were the most likely to stabilize on their first dose (Figure 2B). For those 53 patients requiring dose adjustments, median (range) time to reach a stable dose was 14 (1–60) days overall, 14 (3–30) days for de novo (n = 11), 10.5 (1–60) days for transition (n = 28), and 8.5 (3–30) days for add-on (n = 14). The majority of patients (63 [90%]) were still taking a stable dose of solriamfetol at data collection. The most common reasons for discontinuing solriamfetol therapy were lack of efficacy (n = 3) and adverse effects (n = 3), including feeling full without eating (n = 1), hypertension (n = 1), and feeling jittery or anxious (n = 1).

Factors Physicians Considered When Initiating and Titrating Solriamfetol

When deciding to initiate solriamfetol therapy, physicians considered comorbidities for 13 of the 45 patients (29%) with comorbidities. Comorbidities considered were depression (n = 4), migraines and obesity (n = 3 each), anxiety and type 2 diabetes mellitus (n = 2 each), and attention-deficit/hyperactivity disorder, congestive heart failure, coronary artery disease, and hypertension (n = 1 each).

When deciding how to titrate solriamfetol, physicians most commonly considered EDS severity (overall, 44% of patients); however, for 36% of patients, physicians reported that they did not consider any specific patient factors. Factors considered for patients in each solriamfetol initiation strategy group are presented in Figure 3. For 10 patients, physicians also considered comorbidities when making titration decisions. Comorbidities considered were depression (n = 3); migraines, obesity, type 2 diabetes mellitus, and

Table II. Characteristics of study patients with narcolepsy.

Characteristic	Patients (N = 70)
Narcolepsy type, No. (%)	
Type 1	24 (34)
Type 2	46 (66)
Age, mean (SD), y	40.0 (11.0)
Sex, No. (%)	
Male	30 (43)
Female	40 (57)
EDS severity, No. (%)	
Mild	4 (5.7)
Moderate	41 (59)
Severe	25 (36)
Current employment status, No. (%)	
Employed full time (including self-employed)	43 (61)
Employed part time (including self-employed)	12 (17)
Unemployed	2 (2.9)
Student	6 (8.6)
Homemaker	1 (1.4)
Retired	2 (2.9)
Unknown	4 (5.7)
BMI, mean (SD), kg/m^2	28.2 (7.9)
BMI category, No. (%)	
Underweight (<18.5 kg/m^2)	1 (1.4)
Normal (18.5-24.9 kg/m^2)	25 (36)
Overweight (25.0-29.9 kg/m^2)	22 (31)
Obese (≥30.0 kg/m^2)	22 (31)
Comorbidities,* No. (%)	
Obesity	22 (31)
Psychiatric disorders†	20 (29)
Migraine headaches	12 (17)
Cardiovascular disorders‡	10 (14)
Type 2 diabetes mellitus	9 (13)
Obstructive sleep apnea	6 (8.6)
Fibromyalgia or chronic fatigue syndrome	2 (2.9)
Other neurologic disorder	1 (1.4)
Other	1 (1.4)
None	25 (36)

BMI = body mass index; EDS = excessive daytime sleepiness.

* Patients could be reported as having >1 comorbidity.

† Psychiatric disorders included depression (n = 10), anxiety (n = 6), attention-deficit/hyperactivity disorder (n = 3), and other psychiatric disorders (n = 1).

‡ Cardiovascular disorders included hypertension (n = 4), hyperlipidemia (n = 3), arrhythmia (n = 1), congestive heart failure (n = 1), and coronary artery disease (n = 1).

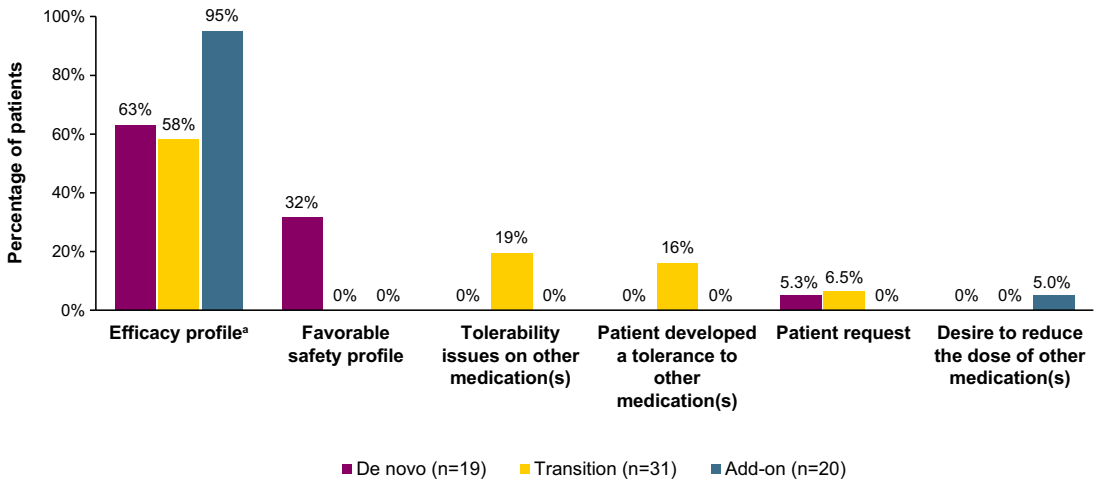

Figure 1. Primary reason for starting solriamfetol therapy.
[a]Includes efficacy profile (for de novo patients) and desire for improved efficacy or to augment the efficacy of other medications (for transition and add-on patients).

hypertension (n = 2 each); and congestive heart failure and coronary artery disease (n = 1 each).

Prior EDS Medications

In total, 51 patients (31 transition and 20 add-on) were taking medication(s) for EDS before starting solriamfetol therapy. Among those 20 patients adding solriamfetol, 16 (80%) were taking 1 medication, 3 (15%) were taking 2 medications, and 1 (5.0%) was taking 3 medications. Regarding the type of EDS medication add-on patients were taking, 11 (55%) were taking sodium oxybate, 90 (45%) were taking stimulants, and 5 (25%) were taking WPAs.

Among the 31 patients transitioning to solriamfetol, 29 (94%) were taking 1 EDS medication and 2 (6.5%) were taking 2 medications. A total of 22 (71%) had been taking WPAs, 9 (29%) had been taking stimulants, and 2 (6.5%) had been taking sodium oxybate (one of whom continued to take sodium oxybate and transitioned off their other medication). Of the 22 patients transitioning from a WPA, 14 (64%) discontinued treatment abruptly, and 8 (36%) tapered off. Of the 9 patients transitioning from a stimulant, 5 (56%) tapered off, and 4 (44%) discontinued treatment abruptly. The patient who transitioned from sodium oxybate was tapered off (Figure 4). Most of the patients transitioning to solriamfetol and tapering off their previous EDS medication(s) had 0 to 2 dose adjustments for the other medication(s) before starting solriamfetol therapy and/or 1 or 2 dose adjustments after starting solriamfetol therapy and before discontinuing use of the other medication completely.

Physician Confidence in Their Titration Strategy

For each medical record, physicians were asked to rate how likely they were to recommend their approach to a colleague with a similar patient. Physicians were likely or very likely to recommend the approach used for 74% of de novo patients, 97% of transitioning patients, and 95% of add-on patients; they were neutral about recommending it for the remaining patients (there were no patients for whom physicians indicated they would be unlikely or very unlikely to recommend their approach for a similar patient).

Qualitative Analysis (Hypothetical Patient Scenario)

Of the 26 physicians, 21 (81%) thought solriamfetol was appropriate for the hypothetical patient (Box 1), 3 (12%) thought it was not appropriate, and 2 (7.7%) thought the answer depended on other (unspecified) factors. Physicians focused on the patient's tolerability issues and the current treatment's lack of efficacy as reasons to switch; some thought the symptoms were not severe enough to warrant switching or would be better managed by increasing the sodium oxybate

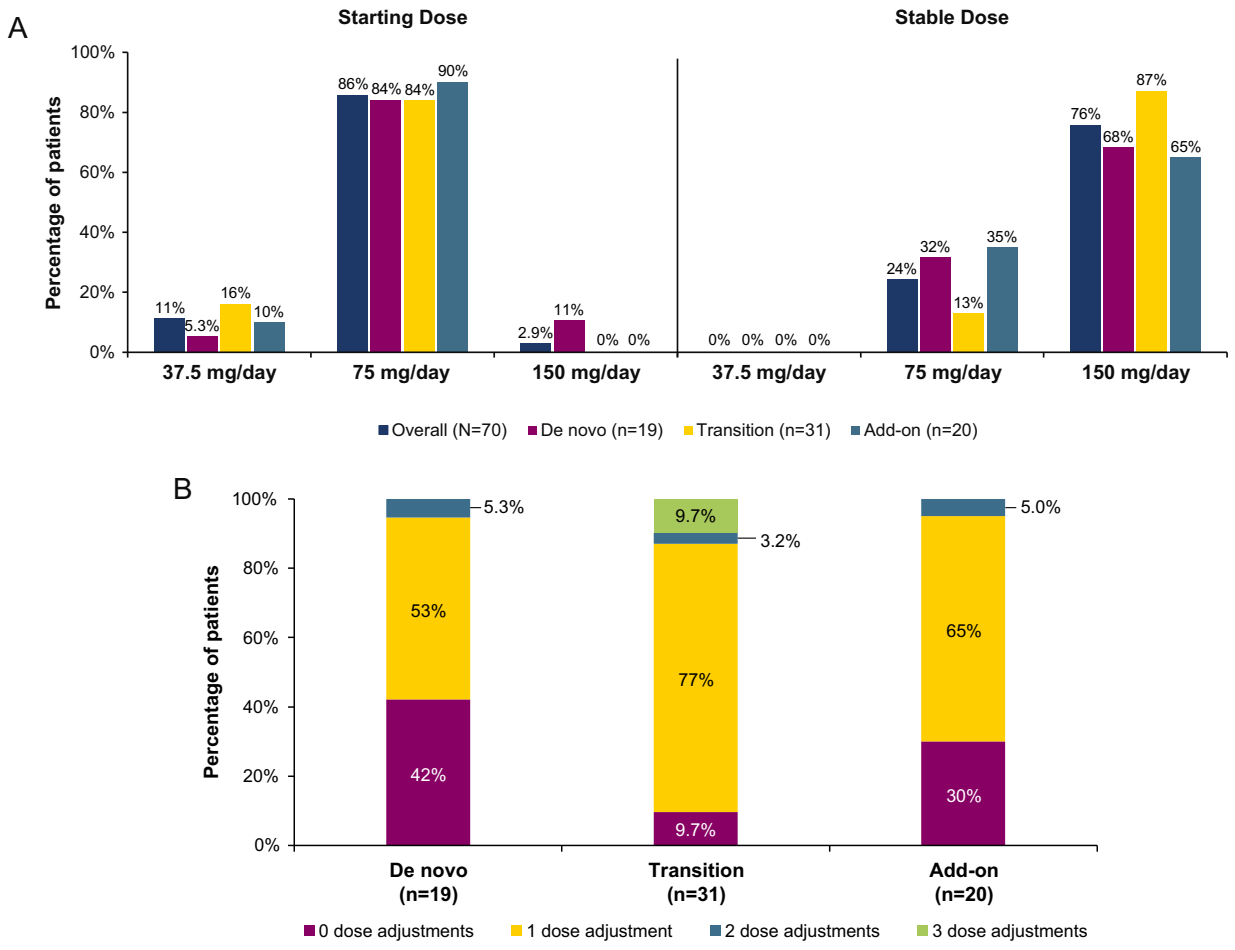

Figure 2. Dosing strategies.
(A) Starting and stable solriamfetol doses; (B) Number of dose adjustments to reach a stable dose of solriamfetol.

dose rather than switching. Regarding strategies for adjusting the current treatment regimen, 16 physicians (62%) suggested adjusting the stimulant, 3 (12%) suggested adjusting both the stimulant and sodium oxybate, and 1 (3.8%) suggested adjusting neither; the question was not answered by 4 physicians and was not applicable for 2.

Physicians were asked what their titration approach would be for prescribing the patient solriamfetol and, if they recommended discontinuing use of the stimulant, what their approach would be for titrating off it. To titrate solriamfetol, 19 physicians (73%) said they would follow the label, starting at 75 mg/d; of the 7 (27%) who would take a different approach, 4 recommended starting at 37.5 mg/d, and 3 did not specify. Most physicians did not specify a final dose of solriamfetol, but 13 (50%) would aim for 75 mg/d and reassess for efficacy, 8 (31%) would aim for 150 mg/d, and 1 indicated the final dose of solriamfetol would depend on the dose of stimulant taken before discontinuation of stimulant use. Regarding how physicians would discontinue use of the stimulant, most of the 26 recommended tapering: 10 (38%) would taper and discontinue *before* starting solriamfetol therapy, 7 (27%) would taper *while* starting solriamfetol therapy, and 1 (4%) would taper while starting solriamfetol therapy with the goal of eventually switching off the stimulant. Eight physicians (31%) would discontinue the stimulant abruptly. Although some physicians indicated that stopping use of the stimulant before starting solriamfetol would allow them to better assess treatment tolerability and efficacy,

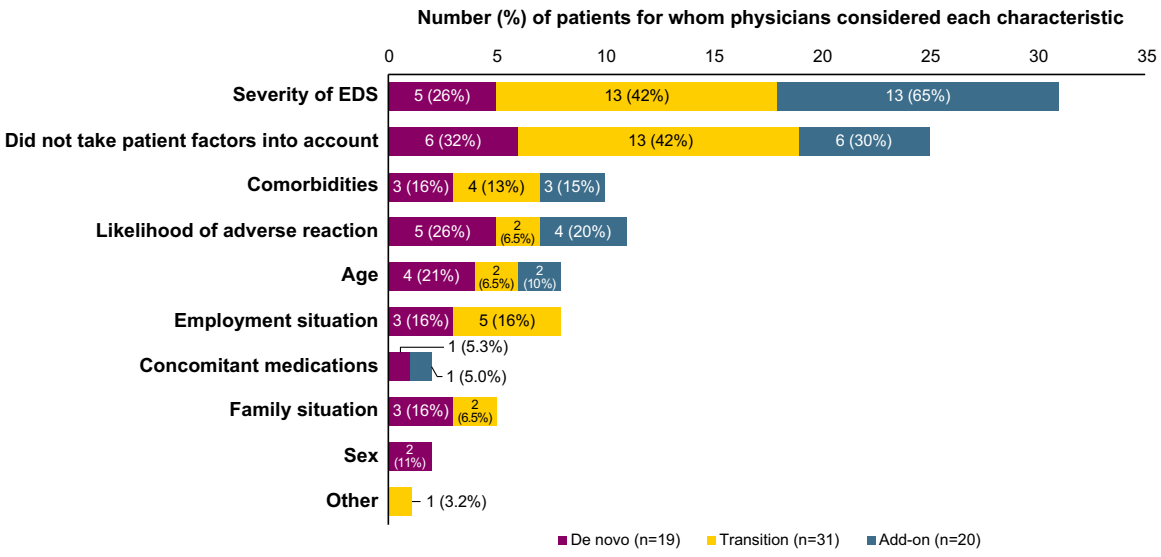

Figure 3. Factors physicians considered when titrating to solriamfetol. EDS = excessive daytime sleepiness.

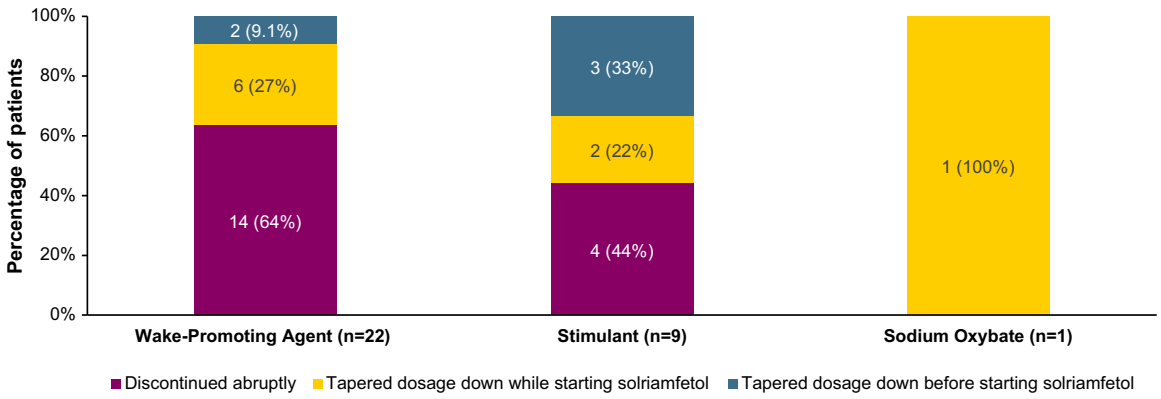

Figure 4. Discontinuation approach for other excessive daytime sleepiness medications among patients who transitioned to solriamfetol.
EDS, excessive daytime sleepiness.

those who suggested tapering the stimulant while starting solriamfetol therapy cited concerns about withdrawal symptoms and maintaining symptom control.

When asked if they would change their approach if the stimulant dose were 60 mg/d instead of 35 mg/d, 6 of 26 physicians (23%) answered yes and 19 of 26 (73%) answered no; 1 (3.8%) indicated their decision would depend on other factors. Physicians who reported they would change their approach cited the need for a longer taper and a concern about withdrawal symptoms when titrating off the higher dose.

DISCUSSION

This study reported real-world dosing and titration strategies from 26 experienced physicians across 5 specialties. Analysis was based on 70 patient medical records, which was in line with the target enrollment and deemed to provide meaningful information. Initiating solriamfetol therapy was driven mainly by efficacy considerations (ie, the efficacy profile of

solriamfetol and desire for better efficacy or to augment effects of other EDS medications). Mirroring this, the factor physicians most often considered when titrating was EDS severity. Most patients were initially prescribed 75 mg of solriamfetol, reached a stable dose of 150 mg within 2 to 3 weeks, and maintained that dose until data collection. Median time to reach a stable dose was 14 days for patients starting solriamfetol therapy de novo compared with 10.5 days for those transitioning from previous EDS medication(s) and 8.5 days for those adding solriamfetol to previous EDS medication(s). Physicians were overall confident in their treatment approach and reported that they would recommend their approach for similar patients. Regarding the hypothetical patient scenario, physicians emphasized managing withdrawal symptoms while maintaining EDS symptom control when titrating off a stimulant and starting solriamfetol therapy.

Although physicians generally followed prescribing recommendations when initiating solriamfetol therapy, there were some exceptions. For example, although prescribers initiated treatment with solriamfetol at 75 mg for most patients, a starting dose of 37.5 or 150 mg was used for a small number of patients. As reflected in the median time to reach a stable dose of 2 weeks, physicians titrated at intervals longer than the 3 days the label suggests.[9] Slow titration has been noted to reduce the incidence of some adverse effects associated with modafinil and sodium oxybate,[23] which may have contributed to physicians' more cautious approach to titrating solriamfetol.

Most of this study's patients with narcolepsy had at least 1 comorbidity, reflecting the comorbidity burden seen among larger cohorts of patients with narcolepsy.[18,24] In the present study, however, physicians did not frequently consider comorbidities when deciding whether to initiate solriamfetol therapy or as part of their titration or dosing strategy. Whether this finding is unique to solriamfetol or reflects a broader attitude toward pharmacologic treatment of narcolepsy is unclear.

Medications approved by the US Food and Drug Administration for the treatment of narcolepsy at the time of data collection included stimulants (methylphenidate and amphetamine) and WPAs (modafinil and armodafinil), as well as solriamfetol, sodium oxybate, and pitolisant.[9,17,25,26] This study found that, for WPAs, abrupt discontinuation of treatment was more common than tapering, whereas for stimulants tapering was the more common approach. Known issues of rebound hypersomnolence and other withdrawal symptoms associated with discontinuation of stimulant use may account for a stimulant-tapering strategy.[16] Consideration of these issues is consistent with responses to this study's hypothetical patient scenario. Physicians indicated a preference for tapering off stimulants and using longer tapers for higher stimulant doses, citing concerns about withdrawal symptoms and the need to maintain EDS symptom control.

The efficacy profile of solriamfetol was the most common primary reason prompting the discussion to prescribe solriamfetol across all 3 patient groups. In particular, for 95% of add-on patients, solriamfetol use was initiated because of a desire for improved efficacy or to augment the efficacy of their EDS treatment regimen before receiving solriamfetol. Some of these patients were already taking 2 or more medications to treat EDS. This finding highlights the need for improved treatments that may benefit patients without adequate symptom relief from their current treatment.

A particular strength of this study was the extent of the physicians' experience in treating patients with narcolepsy, as well as the wide range of physician specialties represented and the real-world nature of the study. This diversity of physician background broadens the applicability of the results obtained and provides insight on the range of specialties treating patients with narcolepsy. However, study limitations must be noted. First, this study is based on feedback from a US physician population. The clinician experience outside the United States may vary because of differences in available treatments or other aspects of clinical practice. Second, no analysis was performed on how titration differed among physician specialties, although because of the number of physicians in each group this would unlikely yield meaningful results. Third, the study did not collect data on how strategies for tapering off other EDS medication(s) or titrating to solriamfetol could have changed adverse effects, clinical responses, or physicians' satisfaction with their approaches. Outreach to physicians who had difficulty titrating solriamfetol could help in identifying common problems and potentially improve clinical care for patients with narcolepsy. Fourth, the nature of the survey questions made it difficult to understand the rationale for specific dosing approaches (eg, why some patients started treatment with solriamfetol on a lower

dose than recommended by the label [because of renal impairment, age, or physician caution]). Fifth, EDS was not assessed using a standardized scale, such as the ESS; instead, EDS was characterized by the physicians using a Likert scale.

CONCLUSIONS

This study identified efficacy and the need for improved efficacy over that of existing medication(s) as key considerations for physicians prescribing solriamfetol treatment to patients with narcolepsy in clinical practice. Patients previously taking sodium oxybate were more likely to be prescribed solriamfetol as an add-on treatment, whereas patients previously taking WPAs were more likely to be transitioned to solriamfetol. Most physicians initially prescribed patients solriamfetol at 75 mg/d, tapered stimulants but abruptly discontinued use of WPAs, made 1 dose adjustment, and had their patients reach a stable dose (most commonly 150 mg/d) over a median of 14 days. Most patients were still taking a stable dose of solriamfetol at data collection, and physicians were confident in recommending the treatment approach they used with most patients described.

DECLARATIONS OF INTEREST

Michael J. Thorpy is a consultant/advisory board member for Axsome, Balance Therapeutics, Flamel/Avadel, Harmony Biosciences LLC, Jazz Pharmaceuticals, Suven Life Sciences Ltd, Takeda Pharmaceutical Co Ltd, and Eisai Pharmaceuticals. Danielle Hyman is a former full-time employee of Jazz Pharmaceuticals, who, in the course of this employment, received stock options exercisable for, and other stock awards of, ordinary shares of Jazz Pharmaceuticals, plc. Gregory S. Parks is a full-time employee of Axsome Therapeutics, Inc. Catherine Foley was employed by Stratevi, a consulting firm that received research funding from Jazz Pharmaceuticals to conduct this study, at the time of the study and during development of the manuscript. She is now a former employee of Stratevi and currently employed by AbbVie, who had no involvement in this study or manuscript. Diane Ito is an employee of Stratevi, a consulting firm that received research funding from Jazz Pharmaceuticals to conduct this study. Beth Baldys is an employee of inVibe Labs, who received professional fees from Jazz Pharmaceuticals to conduct this research. Haramandeep Singh is a speakers' bureau member, consultant, principal investigator, and advisory board participant for Harmony Biosciences LLC, Jazz Pharmaceuticals, Balance Therapeutics, and Flamel/Avadel. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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