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Cluster analysis of upper airway stimulation adherence patterns and implications on clinical care

Ryan J. Soose[1,*], Matheus Araujo[2], Kevin Faber[3], Asim Roy[4], Kent Lee[5], Quan Ni[5], Jaideep Srivastava[2] and Patrick J. Strollo[6]

[1]UPMC Department of Otolaryngology, University of Pittsburgh, Pittsburgh, PA, USA, [2]Department of Computer Science and Engineering, University of Minnesota, Minneapolis, MN, USA, [3]Sanford Health, Sleep Medicine, Fargo, ND, USA, [4]Ohio Sleep Medicine Institute, Columbus, OH, USA, [5]Inspire Medical Systems, Golden Valley, MN, USA and [6]UPMC Division of Pulmonary Allergy and Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA, USA

*Corresponding author. Ryan J. Soose, Department of Otolaryngology, University of Pittsburgh, UPMC Mercy, Suite 2100, 1400 Locust Street, Pittsburgh, PA 15219, USA. Email: sooserj@upmc.edu.

Abstract

Study Objectives: Upper airway stimulation (UAS) therapy is effective for a subset of obstructive sleep apnea (OSA) patients with continuous positive airway pressure (CPAP) intolerance. While overall adherence is high, some patients have suboptimal adherence, which limits efficacy. Our goal was to identify therapy usage patterns during the first 3 months of therapy to enable targeted strategies for improved adherence.

Methods: Therapy data was retrieved from 2098 patients for three months after device activation. Data included mean and standard deviation (SD) of hours of use, therapy pauses, hours from midnight the therapy was turned ON and OFF, percentage of missing days, and stimulation amplitude. Cluster analysis was performed using Gaussian mixture models that categorized patients into six main groups.

Results: The six groups and their prevalence can be summarized as Cluster 1A: Excellent Use (34%); Cluster 1B: Excellent Use with variable timing (23%); Cluster 2A: Good Use with missing days and late therapy ON (16%), Cluster 2B: Good Use with missing days, late therapy ON, and early therapy OFF (12%); Cluster 3A: Variable Use with frequent missing days (8%); Cluster 3B: Variable Use with frequent pauses (7%). Most patients (85%) are excellent or good users with mean therapy use >6 hours per night.

Conclusions: Cluster analysis of early UAS usage patterns identified six distinct groups that may enable personalized interventions for improved long-term management. Differentiation of the patient clusters may have clinical implications with regard to sleep hygiene education, therapy discomfort, comorbid insomnia, and other conditions that impact adherence.

Statement of Significance

Outcomes with medical device therapy for OSA, including upper airway stimulation (UAS), are intimately tied to therapy adherence. Identification of specific usage patterns enables clinicians to implement targeted interventions to improve adherence and optimize long-term outcomes. In this study, we performed cluster analysis on objective adherence data from over 2000 UAS patients during the first three months after therapy initiation.

The cluster analysis identified six distinct groups of UAS therapy usage with potential implications on therapy adjustments, management of comorbid sleep conditions, sleep hygiene education, and other clinical interventions. Determining the specific patterns of adherence and mechanisms underlying these patterns, rather than simple hours of use, may better tailor targeted troubleshooting efforts and optimize adherence and long-term OSA control.

Key words: cluster analysis; obstructive sleep apnea; upper airway stimulation; hypoglossal nerve stimulation

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Introduction

Upper airway stimulation (UAS) therapy is an alternative treatment for a subset of moderate-to-severe OSA patients, who fail continuous positive airway pressure (CPAP), with improvements in patient-reported and polysomnographic outcomes as well as favorable adherence [1,2]. The system consists of an implantable pulse generator that stimulates the hypoglossal nerve to improve airflow, is programmed and titrated by a physician, and has a handheld patient remote for at-home use. The patient remote records data on therapy usage patterns and stimulation settings, which are uploaded to a cloud-based monitoring platform, providing clinicians with information on long-term therapy adherence. This platform provides graphic visualization of objective adherence parameters and can identify patterns of suboptimal usage, such as a higher number of missing days, erratic timing of use, frequent pauses, and short therapy duration [3].

In both UAS and CPAP therapies, regular nightly use is crucial for effective long-term OSA management. In UAS, the first 60–90 days are used for therapy accommodation and self-adjustment at home, often followed by a confirmatory home portable study or in-lab titration study. UAS objective therapy usage has been reported at 6.4 hours/night at 6 months, and 5.6 hours/night at 12 months [4]. In a large-scale study of CPAP manufacturer remote data from over 4 million CPAP users in the United States, mean daily usage was 5.1 hours/night in the first 90 days with 74% of patients meeting minimum adherence criteria (more than 4 hours/night on at least 70% of nights in a consecutive 30-day period) [5]. In another real-world patient population outside of a clinical trial setting, minimum CPAP adherence rates were 54-65% depending on the CPAP delivery method [6]. Since both therapies show a decline in the amount of therapy usage during the first year of therapy, understanding the reasons for this decline has the potential to guide more personalized and effective interventions.

CPAP adherence has been widely studied and a multitude of factors have been associated with CPAP usage patterns. These factors include mask- or pressure-related side effects, heated humidification, patient education, early usage trends, symptomatic response, and socioeconomic and psychosocial factors [6-8]. Identification of the specific issues impacting adherence enables clinicians to implement targeted interventions to improve CPAP adherence. Moreover, clustering analysis has been a popular approach to identify patient cohorts with similar characteristics, to better tailor intervention strategies appropriately. For example, the longitudinal clustering of mean, standard deviation, and slope of therapy usage during the early treatment with CPAP was used to find four patient subgroups: great users, good users, lower users, and slow decliners after six months of therapy [7]. Another study described five distinctive clusters based on demographic and baseline medical conditions [8]. The authors used gender, insomnia complaints, OSA metrics, and depression symptoms to trace cluster boundaries. Similar analysis in oral appliance therapy patients identified three distinct groups of usage patterns: consistent users, inconsistent users, nonusers [9]. To the best of our knowledge, clustering methods have not been used to identify patterns and reasons for variable adherence among UAS patients.

As with CPAP adherence studies, we hypothesized that mathematical cluster analysis of UAS data downloads would identify distinct clusters of usage patterns with direct implications on clinical care. In this study, we examine patient cohorts based on retrospective UAS therapy data usage. After highlighting the main differences among cohorts, we also discuss how different types of interventions can be effective in managing patient adherence.

Methods

Data sources

Anonymized patient-specific UAS adherence data was queried from the cloud-based monitoring system (Inspire Cloud, Inspire Medical Systems, Golden Valley, MN). In total, 2098 patients from 127 centers were included in the analysis. The inclusion criteria were all patients who had at least 90 days of data from October 2016 to March 2021. The first day of therapy is defined by the first recording of therapy usage by the patient remote. In the first 90 days after activation, UAS patients enter an accommodation phase where they are instructed to start at a lower and potentially subtherapeutic amplitude, and gradually increase amplitude over the subsequent weeks based on comfort and symptomatic response. The system contains detailed nightly therapy use patterns, including the time the device was turned on, turned off, paused and the stimulation settings used. Demographic data were not recorded in the system. The data are anonymized and available for internal research purposes.

For each patient, and each night of therapy since the first day of therapy use, we collected the six variables listed in Table 1.

IRB review

The study protocol was reviewed by the WCG Institutional Review Board, and was deemed exempt from review based on Federal regulation 45 CFR 46, as the study used retrospectively-collected, de-identified, patient usage information, and the identity of the subject could not be determined or ascertained from the data.

Statistical methods

The period of data aggregation was from the 1st to the 90th day of therapy usage. Cluster analysis was performed using the mean and standard deviation of the following nightly recorded variables from the patient remote: missing days, therapy duration, the number of pauses, hours from midnight the therapy was turned on, and hours from midnight the therapy was turned off. For all variables except missing days, only days of therapy use were considered. Days of therapy use was utilized to avoid inadvertent bias from missing days, and the daily use pattern would be more representative of daily patient behavior. To capture if patients followed the recommendation to increase amplitude during the titration period, we aggregated the therapy amplitude by computing the difference between the last day of the analyzed period and the first day of therapy usage. An eleven-dimension data point represents each patient's therapy amplitude trajectory.

We applied the Gaussian Mixture Model implementation from the scientific library scikit-learn [10] version 0.23.1 for the programming language Python 3.7 to identify the number

Table 1. Therapy usage variables derived from the UAS patient remote

Description of UAS variables	
Nightly variable	Description
Missing days	A 0 or 1 value—1 if the therapy was not turned on at least once.
Therapy duration (hours)	The number of hours the therapy was active on any given night. If therapy was not turned on, duration was 0 hours.
Number of pauses	The number of times the therapy was paused on any given night.
Hours from midnight when therapy was turned ON	The first time of day when therapy was turned on. Negative values indicate therapy was turned on before midnight.
Hours from midnight when therapy was turned OFF	The last time of day when the therapy was turned off. This occurs after the first time the therapy was turned on.
Therapy amplitude (V)	Average normalized stimulation amplitude during the night of sleep.

of clusters to be found by the model. This clustering strategy uses the Expectation-Maximization algorithm to find a mixture of multidimensional Gaussian probability distributions that best cluster the input data. Patient representation was normalized using a standard scaler (z-score transformation) that converts values to zero mean and unit variance before use as input to the clustering model. We used the "elbow method" to find the best K, representing the number of clusters, by looking at the Bayesian Information Criterion (BIC) generated by the fitted model for every K from 1 to 20.

After identifying the best number of clusters to be used in the clustering analysis, we refitted the Gaussian-Mixture models with our patients' data. Since Gaussian-Mixture models predict stochastically which cluster a patient belongs to, we assigned each patient to the cluster with the highest probability according to the model output. Each cluster can be interpreted by analyzing its centroid. We computed each centroid by the mean value of each variable across every patient that belongs to the cluster.

A Kruskal–Wallis H statistic test was performed to ensure that the use of an eleven-dimensions data point is meaningful for the clustering performance. If the occurrence of a value for each dimension is predominant in a certain cluster (e.g. the cluster is distinguishable at the dimension), we expect a high statistical value and a low *p*-value. A similar feature significance test was used to define pediatric CPAP users clusters [11].

Results

We analyzed 2098 patients with at least 90 days of usage data from October 2016 to March 2021. Each patient is represented by eleven dimensions. Table 2 shows the mean and standard deviation of these dimensions over the 2098 patients on days of therapy use. This serves as a reference when comparing each cluster individually. Across the entire cohort for the first 90 days, the average patient uses the therapy 6.78 hours per night, pauses therapy just under once per night, missed activating their therapy 8% of the days, turns therapy on at 11:39 pm, turns off the therapy at 6:39 am, and increases the therapy amplitude by 0.48 V. The mean therapy usage standard deviation of 1.72 hours and the mean missing days standard deviation of 19% suggest relative variability in therapy use by some patients.

In Figure 1, using the Bayesian Information Criterion (BIC), we find its plateau after $K = 6$, which indicated that including more clusters does not justify the extra complexity. Therefore, we chose $K = 6$ as the number of clusters in this work. The

Table 2. Summary of the first 90 days of UAS therapy use for each variable.

Summary first 90 days of UAS therapy (n = 2098)		
Variable	Mean	std
Therapy Usage, hours (mean)	6.78	1.54
Therapy Usage, hours (std)	1.72	0.65
Count Pauses (mean)	0.98	1.59
Count Pauses (std)	1.14	1.03
% Missing Days (mean)	8%	14%
Missing Days (std)	0.19	0.14
ON time relative to midnight, hours (mean)	-0.36	1.71
ON time relative to midnight (std)	1.83	1.07
OFF time relative to midnight(mean)	6.65	1.71
OFF time relative to midnight, hours (std)	1.89	0.91
Amplitude increase from day 1 of use (V)	0.48	0.46

Kruskal–Wallis H statistic is the value that compares patients of each assigned cluster according to a specific dimension (see Supplementary Material). Every dimension presents a $p < .001$ demonstrating strong significance. The mean and standard deviation of missing days has the highest Kruskal–Wallis *H* statistic value, which can be interpreted as the feature that gives more contrast between the clusters. The mean ON time and the mean OFF time have the lowest segregation influence among the clusters but are still significant.

After assigning each patient to one of six clusters, we present the cluster centroids in Table 3. Each value is the mean among all patients in that cluster for each dimension. They are sorted by the mean therapy use within each cluster, from higher usage (left) to lower usage (right). We used a color map from green to red to better differentiate desired to undesired values between clusters, respectfully. A lower value is desired for the mean of missing days, mean pause duration, mean ON time, and all standard deviation dimensions. A higher value is desired for amplitude difference, therapy usage, and mean OFF time. The population prevalence in absolute and relative numbers are also shown.

Cluster 1A is characterized by "**Excellent Use**", representing 34% of the population, with mean therapy use of 7.23 hours/night. Patients in this group have the highest therapy usage with the lowest standard deviation of usage and therapy time. The mean pauses per night is close to 1 and they also present with a low 1% of missing days of usage.

Cluster 1B is also characterized by "**Excellent Use**" but with "**variable timing**", representing 23% of the population, and a mean therapy use of 7.14 hours/night. Patients in Cluster 1B are distinguished from 1A by increased night-to-night variability with a higher standard deviation of therapy usage and missing days.

Cluster 2A is defined by "**Good Use**" with "**missing days and late therapy ON**" and comprises 16% of the population, with mean therapy use of 6.63 hours/night. Patients start the therapy later (approximately midnight) and do not use therapy for 8% of days.

Cluster 2B is also defined by "**Good Use**" with "**missing days and late therapy ON**"—similar to 2A—but with the addition of "**early therapy OFF**". Cluster 2B represents 12% of the population and has a mean therapy use of 6.21 hours/night. Patients in this group miss treatment on 23% of the days. On nights used, they also have the shortest nights of any cluster, turning the therapy ON the latest (after midnight) and OFF the earliest (approximately 6:20 am).

Cluster 3A is marked by "**Variable Use**" with "**frequent missing days**" with mean therapy use of 6.16 hours/night and representing 8% of the population. Patients in this cluster have a high standard deviation of therapy usage at 2.23 hours, a high number of missing days (34%), and the highest standard deviation of therapy ON and OFF times.

Cluster 3B is also marked by "**Variable Use**" but is most differentiated by "**frequent therapy pauses**". Patients in this cluster have a mean therapy use of 5.50 hours/night—the lowest among all clusters. They represent 7% of the population and they did not use the therapy on 8% of days. They average more than four pauses per night of use. Furthermore, they have the lowest increase of therapy amplitude during the first 90-day period.

Overall, most patients (85%) were excellent or good users with mean therapy use >6 hours per night. To provide parallels with CPAP therapy reports and additional insight into overall mean disease alleviation, Table 4 compares mean and median therapy use on *nights used* with mean therapy use across *all nights* (taking into account missing days). Finally, we observed that the majority of patients complied with the recommendation to gradually increase therapy amplitude during the first 90 days, although Cluster 3B had the lowest increase in voltage of any group.

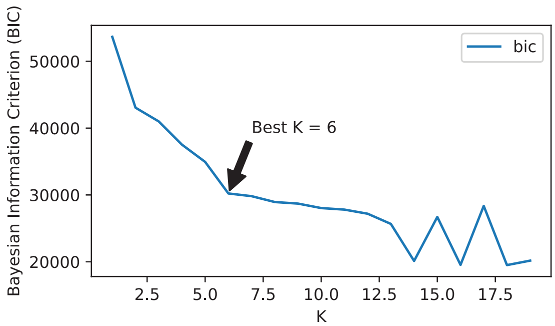

Figure 1. BIC scores for $K = 1$ to $K = 20$. Using the elbow method, we identified $K = 6$ as the optimal number of clusters.

Discussion

For the first time, we demonstrate unique clusters of UAS patient adherence patterns. Timely identification of the specific behavior pattern, and a better understanding of the reasons underlying such usage patterns provide an opportunity to optimize long-term treatment outcomes. To a database of over 2000 UAS patients, we applied Gaussian mixture models to perform a cluster analysis of therapy use patterns in the first 90 days after device activation. The cluster analysis identified six unique groups of UAS therapy usage with potential direct implications on clinical care.

OSA is a chronic long-term condition that changes across the lifespan. Likewise, OSA treatments specifically and sleep in general are modified by physical and/or mental health conditions,

Table 3. Cluster centroids with original units ordered from left to right by mean therapy usage. Green represents more desired behavior, yellow intermediate, and red more undesired usage characteristics.

Cluster centroids results

Data type	Dimensions	Excellent use	Excellent use with variability	Good use with missing days and late ON	Good use with missing days, late ON, early OFF	Variable use with frequent missing days	Variable use with frequent pauses
Cluster ID	-	1A	1B	2A	2B	3A	3B
Population	# of patients in cluster	722	478	331	249	174	144
	% of total	34%	23%	16%	12%	8%	7%
Usage hours	Therapy Hours (mean)	7.23	7.14	6.63	6.21	6.16	5.50
	Therapy Hours (SD)	1.40	1.62	1.85	2.12	2.23	2.01
	# Pause Clicks (Mean)	0.97	0.60	0.57	0.49	0.92	4.11
	# Pause Clicks (SD)	1.11	0.88	0.90	0.85	1.25	3.14
	Missing days (mean)	1%	3%	8%	23%	34%	8%
	Missing Days (SD)	0.05	0.17	0.27	0.41	0.31	0.23
Therapy timing	Hours to midnight, on (mean)	-0.54	-0.35	0.04	0.22	-1.04	-0.59
	Hours to midnight, on (std)	1.46	1.71	1.96	2.29	3.17	2.16
	Hours to midnight, off (mean)	6.80	6.71	6.55	6.36	6.70	6.40
	Hours to midnight, off (std)	1.58	1.57	1.73	1.96	3.27	2.26
Amplitude	Amplitude Increase (V)	0.56	0.51	0.41	0.41	0.42	0.36

Table 4. Mean and median therapy usage for each cluster: days used vs all days during the first 90-day period

Mean ± SD, Median and interquartile range of UAS therapy adherence over 90 days (n = 2098)							
Cluster ID	1A	1B	2A	2B	3A	3B	All patients
All days (h)	7.19 ± 1.18	6.92 ± 1.24	6.08 ± 1.27	4.77 ± 1.37	4.3 ± 2.95	5.08 ± 1.67	6.28 ± 1.81
Median	7.29	6.93	6.12	4.68	3.79	4.98	6.54
Interquartile range	6.48 to 7.99	6.11 to 7.77	5.38 to 6.98	3.83 to 5.68	1.89 to 6.62	4.01 to 6.19	5.28 to 7.53
Days used (h)	7.23 ± 1.19	7.14 ± 1.28	6.63 ± 1.37	6.21 ± 1.61	6.16 ± 2.34	5.5 ± 1.65	6.79 ± 1.54
Median	7.31	7.17	6.68	6.25	6.29	5.28	6.93
Interquartile range	6.51 to 8.03	6.3 to 8.05	5.82 to 7.64	5.07 to 7.37	4.65 to 7.6	4.37 to 6.64	5.89 to 7.85

Table 5. Summary of clinically applicable interventions for each cluster of patients

Hypothesized interventions per group of patients	
Group ID	Hypothesized interventions
1A	No intervention needed
1B	Minor sleep behavior modifications
2A	Sleep/OSA education; reminders to turn therapy ON
2B	Sleep/OSA education; reminders to turn therapy ON; increased total sleep time
3A	Multimodality management including Sleep/OSA/Therapy education, adjunctive OSA treatments, therapy reprogramming, management of comorbid sleep and medical conditions, close clinical follow-up
3B	Multimodality management including Sleep/OSA/Therapy education, adjunctive OSA treatments, therapy reprogramming, hypnotic medication, management of comorbid sleep and medical conditions, close clinical follow-up

weight change, pain, life stressors, allergies, alcohol use, family and occupational obligations, and many other environmental factors. Favorable, consistent adherence is crucial to successful outcomes with CPAP, UAS, and any other medical device therapy for OSA. Longitudinal objective monitoring of therapy usage and targeted interventions to optimize adherence are key components of successful OSA management over time.

Although surgically implanted, UAS inherently consists of an adjustable medical device with a 10–12-year generator battery life on average, and thus parallels may be drawn with CPAP therapy and other OSA medical devices. Similar to CPAP data download reports, the UAS device provides the clinician with cloud-based adherence data to monitor usage and promptly identify areas of concern. Identifying and describing more granular usage patterns can provide the clinician with a focused framework to more efficiently implement changes.

Our analysis also suggests that the majority of patients (85%) are excellent or good users with favorable nightly usage. However, our data suggests that defining the specific patterns of adherence and mechanisms underlying these patterns, rather than simple hours of use, may be essential to tailor individual patient troubleshooting efforts accordingly. Targeted troubleshooting in the form of therapy adjustments, management of comorbid sleep conditions, and patient education efforts, has the potential to restore optimal adherence and therefore long-term OSA control. In Table 5, we provide a summary of hypothesized interventions for each identified group, though their application and effectiveness must be investigated in future prospective studies.

Patients in Cluster 1 (57%) average over 7 hours per night of use with relatively low number of missing days. Cluster 1B is primarily distinguished from 1A by a higher standard deviation of use and more night-to-night variability. This study was not able to determine the specific factors associated with the increased variability of 1B patients but we hypothesize this may represent common night-to-night changes in sleep behaviors. Family commitments, work schedules, screen time, and other psychosocial and environmental factors may explain isolated variability in the timing of therapy use. There was no indication based on the pauses or amplitude changes that the variability in Cluster 1 was directly related to the therapy itself.

Patients in Cluster 2 (28%) also had overall usage that compared favorably to historic CPAP adherence data, with an average nightly usage of >6 hours on nights used. Patients in Cluster 2 were distinguished by a higher percentage of missing days and a later therapy ON time. This pattern may represent more complex behavioral issues or simply falling asleep before activating the device. Either way, the missing days suggest a potential opportunity for an education program that emphasizes the sleep and health benefits of more consistent nightly OSA treatment. Furthermore, leveraging the UAS smartphone application or other electronic alarms to provide reminders to turn the therapy on each night may improve adherence.

The later therapy ON time for Clusters 2A and 2B may also signify a delayed sleep phase pattern in this group. They were the only groups with an average therapy ON time after midnight. Cluster 2B was further distinguished by the earliest OFF time which resulted in the shortest time between therapy ON and OFF of all the groups. Identifying this pattern of a short period of therapy use may provide clinicians with the opportunity to intervene with sleep hygiene education and recommendations for optimal total sleep time.

The patterns observed in Cluster 3 (15%) may be the most challenging group for clinicians to troubleshoot. On nights used, patients still averaged >5 hours per night, but the usage in Clusters 3A and 3B was marked by the highest standard deviation in therapy use and timing as well as a high percentage of missing days. The patterns in Cluster 3 likely represent, at least in part, a complex interplay of residual OSA, stimulation-related discomfort, and comorbid insomnia or other sleep comorbidities such as shift work. Such a complex pattern likely has implications for a multimodality troubleshooting approach.

In Cluster 3A, the combination of substantial night-to-night variability and one-third of the nights without use may represent multifactorial problems that include poor sleep hygiene, suboptimal OSA health literacy, insomnia, therapy discomfort, and/ or comorbid mental or physical health conditions. In Cluster 3B, the addition of frequent therapy pauses (average >4 pauses per night) strongly suggests stimulation-related discomfort with the electrical stimulation causing awakenings and/or difficulty returning to sleep. Adjusting the therapy start delay time and the therapy pause duration may benefit patients in this group. This group also may have a "low arousal threshold" endotype. Pharmacological interventions to modify arousal threshold could be an effective adjunctive therapy option in this cluster [12].

It should also be noted however that Cluster 3B also had the lowest increase in therapy amplitude during the first 90-day period. Although this feature may represent therapy discomfort or a need for more education on use of the sleep remote, the frequent pauses in conjunction with low amplitude could also represent subtherapeutic stimulation with arousals/awakenings due to persistent respiratory events and inadequately treated OSA.

In summary, as with CPAP adherence optimization strategies, cluster identification and targeted intervention strategies may improve UAS outcomes as well. In particular, Cluster 3 patients may benefit from closer clinical follow-up with the sleep medicine physician to identify barriers and facilitators of use. Such regular assessments could be used to implement adjunctive treatment strategies including hypnotic medication or cognitive behavioral therapy for insomnia (CBT-I) and to make targeted adjustments in the stimulation settings. When changes in the amplitude, patient control range, pulse width, stimulation frequency, and/or electrode configuration are made, scheduled follow-up is recommended to reassess patient-reported and objective outcome measures, and to correlate with a new data download report.

Limitations

Although we identified distinct clusters of patients along with corresponding hypothesized interventions, there are limitations with this type of analysis and classification. We acknowledge that some degree of overlap exists between clusters. Because the analysis was performed in the initial accommodation and self-titration phase, periods of subtherapeutic amplitude may affect the cluster usage pattern differently as compared to analyses performed later during long-term stable therapy use. Additionally, the cluster designation for a given patient likely changes over time and the reasons for change are likely complex and multifactorial. Demographics and OSA severity, such as AHI and ESS, were not in the database, and were not considered while forming the clusters. The implant volume and level of expertise of each of the 127 centers were not available in this dataset but might also factor into patient adherence patterns.

Patient factors, such as age [13], or socioeconomic factors such as health literacy [14], may also influence adherence. Similarly, the therapy effectiveness is likely closely intertwined with usage patterns. Varying improvements in snoring, subjective sleep quality, AHI, or ESS [15] could positively or negatively reinforce ongoing therapy use. Also, we observed that patients' behaviors could change within the three-month period—a finding also observed in CPAP patients [16] and representative of patient cluster transitions over time. Analysis of such clinical, demographic, and socioeconomic factors, as well as analysis of patient cluster transitions represent opportunities for future research.

Conclusion

Using cluster analysis of UAS data downloads in the first 90 days, we identified six distinct groups of UAS usage patterns and timing. Differentiation of the six groups may have clinical implications with regard to sleep hygiene education, therapy discomfort, comorbid insomnia, and other conditions that impact adherence. Cluster analysis may enable personalized interventions for improved long-term management.

Supplementary Material

Supplementary material is available at *SLEEP* online.

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