A descriptive analysis of objectively-monitored real-world adherence to eXcite$^{OSA®}$

Real-world patients use eXcite^{OSA} therapy for an average of 680 minutes (11:20 hh:mm) within the first six weeks, representing over 80% of the total duration prescribed.

Patients use eXcite^{OSA} on 81% of days, on average.

These analyses are based on all US-based patients who began eXcite^{OSA} on or before June 30th, 2022 (n=3,561). The dataset represents the entire population of patients established on eXcite^{OSA} in the US since the product was launched, with no additional behavioral support beyond usual clinical care.

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INTRODUCTION

Recent estimates indicate that 55 million adults in the United States suffer from obstructive sleep apnea (OSA), with more than half falling into the mild range (apnea hypopnea index [AHI] ≥5 and <15 events/hour).[1] Although there is some debate around the optimal treatment pathway for those with less severe disease,[2,3] population-based cohort studies have consistently demonstrated that mild OSA can be symptomatic and associated with adverse health outcomes. For example, the Sleep Heart Health Study found that patients with mild OSA were more likely to report poor quality of life compared to controls, after adjusting for confounders including age, gender, ethnicity, marital status, smoking, education, and co-morbidities.[4] Epidemiological analyses have found that compared with controls, patients with mild OSA have a 224% increased risk of developing hypertension,[5] are 83% more likely to be diagnosed with diabetes,[6] and 59% more likely to have abnormal fasting glucose.[7] Although efficacious therapies exist, OSA remains vastly underdiagnosed and

therefore undertreated.[8] Even amongst individuals who do progress to treatment, adherence to traditional therapies requiring night-time use is a major challenge,[9] particularly amongst those at the milder end of the OSA spectrum.[10]

Building on prior studies from several locations demonstrating significantly reduced endurance[11,12] and increased fatiguability[13] of the genioglossus amongst individuals with OSA, Signifier Medical Technologies developed and commercialised eXcite^{OSA}, a neuromuscular electrical stimulation (NMES) device designed to apply gentle, low-frequency electrical stimulation intraorally to the tongue muscle. Low-frequency NMES is commonly used in other fields to promote endurance of skeletal muscles,[14] and a recent mechanistic study reported significantly increased genioglossus endurance associated with one month of eXcite^{OSA} therapy.[15] As a result, studies have shown that eXcite^{OSA} is associated with reductions in both objectively-measured and bed-partner reported snoring, along with significant improvements in disease severity, the Epworth Sleepiness Scale, and Pittsburgh Sleep Quality Index.[16-18] Clinical trial participants experienced an average 33% reduction in the AHI overall, with a 52% reduction evident in the responder subset.[18] Following a successful FDA submission through the de novo pathway, eXcite^{OSA} was launched in the United States in early 2021 as the first daytime therapy product indicated for treatment of primary snoring and mild OSA.

The eXcite^{OSA} regimen involves application of NMES during a single 20-minute therapy session per day, controlled through the accompanying smartphone app. Although there is no requirement for adherence during sleep, consistent completion of eXcite^{OSA} sessions during the day is still critical to achieving success with NMES therapy. As a connected product with cloud-based remote monitoring, Signifier Medical Technologies has been able to collect eXcite^{OSA} usage patterns dating back to the very first session completed by any patient worldwide, which occurred in April 2021. The purpose of this analysis was to describe various metrics of eXcite^{OSA} adherence in the complete population of real-world patients in the United States (US).

METHODS

When registering an eXcite^{OSA} account, all users agree to allow Signifier Medical Technologies to monitor and analyze all data collected through the HIPAA-compliant eXcite^{OSA} platform including descriptive information and therapy data such as adherence. Internet connectivity is required in order to begin an eXcite^{OSA} therapy session, ensuring data completeness.

A de-identified dataset was extracted from the eXcite^{OSA} portal on August 12th 2022, including all US-based patients who began therapy on or before June 30th, 2022. Self-reported age, sex, height, weight, and the first six weeks of therapy usage data (date and duration of each session) were extracted from each record. No minimum usage threshold was applied when extracting the data. Body mass index (BMI) values <16 and >60 kg/m2 were removed as presumed data entry errors. Other than date constraints, no additional filters or exclusions were applied when generating the dataset.

The following metrics of adherence were then calculated for each patient over a six week period:

- Total usage (hh:mm);
- Average usage (hh:mm per week);
- Total number of sessions;
- Percentage of days with any usage;
- Percentage of days with maximum usage (20 minutes);
- Average days per week with usage.

Although the eXcite^{OSA} app will prevent initiation of a therapy session following completion of a session earlier in the same day, if a session is terminated early (<20 minutes) it is possible to complete a subsequent session within the same day. By reporting the percentage of days containing at least one session, we have taken a conservative approach and not allowed days with multiple sessions to inflate the adherence metrics. All sessions contributed to the duration-based metrics (total usage and average usage) regardless of whether more than one was started within a single day, as these metrics reflect total exposure to therapy. Data were analyzed using descriptive statistics.

RESULTS

We identified 3,561 patient records in total. Descriptive information is presented in Table 1, and adherence metrics are presented in Table 2. Figure 1 depicts the percentage of days used after grouping patients according to the month that they began therapy. Total duration of usage, as a proportion of the prescribed target, is shown in Figure 2.

Table 1: Demographics and descriptive characteristics

Variable	Median (Quartile 1; Quartile 3) or *n* (%)
Age (years)	51 (40, 60)
Body mass index (kg/m^2)	28 (25, 32)
Sex	
• Male	2,422 (68%)
• Female	1,007 (28%)
• Not reported	132 (4%)

Total sample size n=*3,561. Age, sex, and BMI values were available for n=3,429, n=3,312, and n=3,206, respectively.*

Table 2: Average adherence to eXcite^{OSA} over the first 42 days of therapy (n= 3,561)

Adherence metric	Median (Quartile 1; Quartile 3)
Total usage (hh:mm) [target in 42 days: 14:00 hh:mm]	11:20 hh:mm (7:20, 13:00)
Average usage (hh:mm per week) [target in 7 days: 02:20 hh:mm]	1:53 hh:mm (1:13, 2:10)
Total number of sessions	34 sessions (22, 39)
% of days with any usage	81% (52, 93)
% of days with maximum usage	79% (50, 93)
Average days per week with usage	5.7 days (3.7, 6.5)

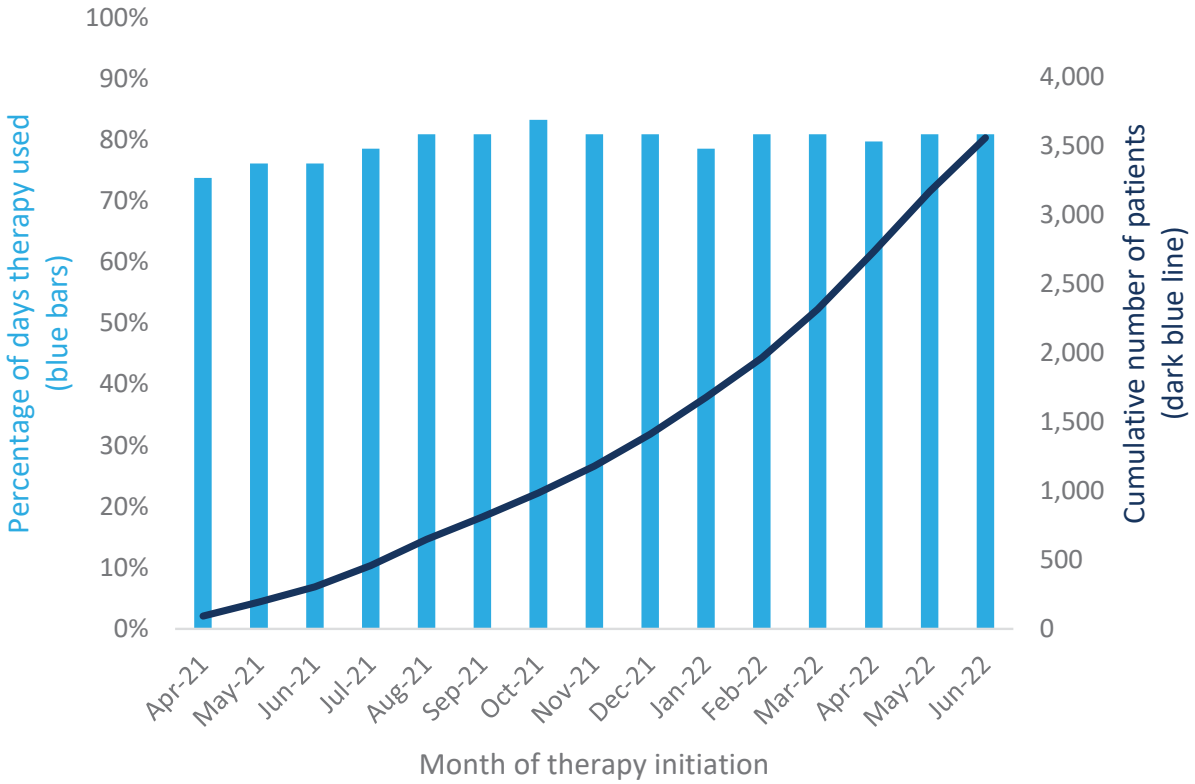

Figure 1: Percentage of day eXcite[OSA] used based on month of initiation

Bars represent the percentage of days therapy was used within the first six weeks, broken down by the month of therapy initiation dating back to product launch in April 2021. The line represents the cumulative number of patients, reaching the total sample size of n=3,561.

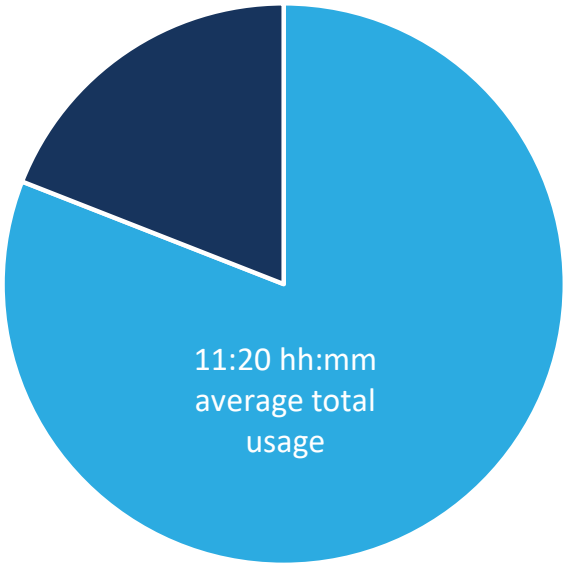

Figure 2: Proportion of prescribed therapy minutes completed

Data are summarized over the first six weeks of usage for each patient, during which all patients were instructed to complete sessions seven days per week (giving a prescribed target of 14:00 hh:mm over six weeks). Total sample size n=3,561.

DISCUSSION

In this descriptive analysis of real-world data from 3,561 individuals, we have demonstrated that patients established on eXcite^{OSA} up until June 2022 have used therapy on 81% of days over their first six weeks. These data are comparable to adherence reported in the largest clinical trial of eXcite^{OSA} conducted to date, in which patients used therapy on 83% of days,[16] with similar adherence found amongst those with primary snoring versus mild OSA.[16,18] As such, although sleep study data are not available for this cohort, given the similar adherence rates we anticipate that real-world eXciteOSA users with OSA experience similar treatment efficacy as clinical trial participants.[15,16,18] The analyses presented here are based on the entire population of patients established on eXcite^{OSA} in the US since the product was launched, with no additional behavioral support beyond usual clinical care.

The clinical trial data[15,16,18] were collected prior to the commercial launch of eXcite^{OSA}, and at that time, objective usage was recorded as the number of sessions completed without the ability to capture the duration of each session. For the first time, we have reported that real-world patients use therapy for an average of 680 minutes (11:20 hh:mm) within the first six weeks, representing over 80% of the total duration prescribed (840 minutes). In addition, the average percentage of days with maximum usage was 79%, compared to 81% of days with usage of any duration, indicating that the vast majority of therapy sessions were completed as prescribed rather than terminated early. These analyses therefore represent the first analyses of duration-based adherence to eXcite^{OSA}, and the first analyses based on real-world data.

Alongside the aforementioned strengths of this analysis, there are some important limitations to consider. Firstly, medical records data including pre- and post-therapy sleep studies were not available to analyze, and therefore it is not possible to determine the proportions of patients treated for primary snoring vs. mild OSA, or the impact of eXcite^{OSA} on indices related to sleep-disordered breathing. Although it is reasonable to hypothesize that given the similarities in average adherence, patients contributing to these real-world analyses would experience similar treatment efficacy as reported in prior clinical trials of eXcite^{OSA}, this is an assumption and there may be important differences in aspects such as patient selection. We limited our analyses to the first 42 days (six weeks) of therapy, because during this 'training phase' patients are instructed to complete one session per day. If a patient completes this phase successfully, they are automatically moved to the 'maintenance phase' and instructed to complete therapy twice per week; if not, they return to the beginning of the training phase. The eXcite^{OSA} smartphone app will also move patients from the maintenance phase back to the training phase if they do not use therapy for a consecutive 14-day period. Clinical trials of eXcite^{OSA} completed to date have also been limited to six weeks, and therefore it is not yet possible to determine the clinical relevance of usage patterns within the maintenance phase.

As a new-to-world therapy, there is much to learn about eXcite^{OSA}, including the characteristics of patients most likely to respond, and the optimal dose required to achieve clinically-relevant improvements in snoring, OSA severity, patient-reported outcomes, and downstream health-related outcomes. In addition to the number and duration of sessions, the dose of NMES applied to the genioglossus depends on aspects such as the stimulation level (adjustable on a scale of 1-15 within the app), the stimulation frequency which ranges between 3 and 20Hz across the course of a therapy session, and potentially the time of day relative to the main sleep period. It is not yet clear whether there is a dose-response relationship based on any of these factors, beyond the impact of adherence. It should also be noted that adherence is simply a mediator of a therapy's ability to improve disease severity and health-related quality of life. The eXcite^{OSA} ecosystem has recently expanded to include the ability for patients to track improvements in validated patient-reported outcomes in domains such as sleepiness and functional status, with additional objective metrics currently under development. Future analyses will focus on changes in these outcomes, with respect to adherence.

Signifier Medical Technologies is dedicated to engaging with the sleep research community to produce high-quality evidence from rigorous clinical trials. Randomized trials are currently recruiting in order to understand the potential placebo effect (ClinicalTrials.Gov NCT04974515), the impact of therapy relative to usual care without treatment (NCT05183009; NCT05252156), and the impact of therapy amongst those with moderate OSA (NCT05252156). Finally, comparative-effectiveness trials are yet to be conducted; these will be important to compare the various treatment pathways currently available, and the extent to which therapy effectiveness is impacted by adherence. With existing data, for example, it is not straightforward to compare adherence to eXcite^{OSA} against adherence to night-time therapies such as positive airway pressure, oral appliances, or implantable neurostimulators. Night-time therapies must be used during 100% of total sleep time in order to achieve optimal benefits, and any periods of non-use result in a rapid return to baseline (or near-baseline) OSA severity. As a daytime therapy, eXcite^{OSA} is more akin to medications for chronic conditions, in that a missed dose results in diminished effectiveness over much longer time periods. Further studies and real-world evidence protocols are under development, to address these important questions and ensure broad access to this new therapy for suitable patients seeking a different approach to treating their sleep-disordered breathing.

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