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Clinical Trials in Obstructive Sleep Apnea: Recognizing Trends and Future Opportunities

Sameer K. Singh, BA; David Gu, BA; Robson Capasso, MD; Stanley Liu, MD; Christopher J. Gouveia, MD

Objectives/Hypothesis: Examine US and international clinical trials in obstructive sleep apnea (OSA) to characterize researchers involved, interventions being studied, and opportunities for future investigation.

Study Design: Retrospective database review.

Methods: The information from ClinicalTrials.gov was used to assess OSA clinical trials between 1999 and 2017. Information was gathered on principle investigator (PI) demographics, interventions studied, study funding source, and regional distribution of research institutions.

Results: There were 813 clinical trials studied. The majority of trials examined continuous positive airway pressure interventions (43.7%), with pharmacotherapies being the second most commonly investigated treatment (19.2%). Surgical interventions made up 10.7% (n = 87) of clinical trials for OSA. Most studies were based internationally (59.9%). PIs were predominantly male (72.0%); 72.7% had an MD and 28.6% had a PhD. There were no significant differences in funding source (National Institutes of Health vs. industry, P = .14) or institutional geography (international vs. US, P = .73) between surgical and nonsurgical studies. Surgical trials were significantly more likely to have a male PI and involve pediatric patients compared to nonsurgical trials (P < .001). Otolaryngologists represented 9.2% of all PIs and had similar rates of NIH funding compared to other medical specialists (P = .22).

Conclusions: This study provides a broad overview of past, current, and future treatment paradigms for OSA. Sleep surgery, specifically otolaryngology, is a small voice in the overall landscape of clinical trials for OSA. This information can help guide future research efforts and direct our specialty when setting priorities regarding research funding while encouraging a broad and interdisciplinary pursuit.

Key Words: Clinical trials, ClinicalTrials.gov, obstructive sleep apnea.

Level of Evidence: NA

INTRODUCTION

Obstructive sleep apnea (OSA) is a significant public health burden, affecting nearly 20% of the US adult population.1 OSA is associated with an increased risk of cardiovascular disease,2 decreased productivity,3 and diminished quality of life.4 As a result, significant research efforts have been focused on better understanding and managing this chronic disease.

Clinical trials, studies that prospectively assign human participants to one or more health-related interventions and evaluate the effects on outcomes, are essential in research efforts for OSA. Two recent landmark studies, one showing the promise of hypoglossal nerve stimulators5 and another questioning the efficacy of continuous positive airway pressure (CPAP) in at-risk patients,6 were both clinical trials. In an effort to increase transparency, ClinicalTrials.gov was opened in 2000; originally as a repository for National Institutes of Health (NIH)-funded research, it now includes protocols and results for thousands of studies conducted in all 50 states and in more than 200 countries. Prior examinations of this database focusing on head and neck cancer,7 skull base tumors,8 and otolaryngology at large have shown underrepresented areas that can help guide researchers and policy. There are no such studies examining clinical trials in OSA.

The primary goal of this study is to describe the trends and overall landscape of clinical trials in OSA. Recognizing which specialties are actively involved in clinical trials and which treatment modalities are being studied provides worthwhile insight to scientists and physicians. Additionally, given that recent literature has shown that females are underrepresented in high-level otolaryngology research,9,10 we reviewed the status of female principal investigators (PIs) in sleep apnea clinical trials in an effort to identify any disparities across gender within this field. Our primary hypothesis was that medical treatments would be the focus of the majority of clinical trials in OSA. Our secondary hypothesis was that there would be an increase in the number of trials led by sleep surgeons, and a corresponding increase in the...
number of trials examining surgical treatment modalities over time.

**MATERIALS AND METHODS**

This study was determined to be exempt by the Northwestern University Institutional Review Board.

**ClinicalTrials.gov Database Search**

The authors used the ClinicalTrials.gov database for this project. This website, maintained by the National Library of Medicine within the NIH, represents the largest and most comprehensive listing of clinical trials in the world. All submitted studies contain a brief overview regarding the PI or industry sponsor, the primary disease being studied, along with a range of descriptive details regarding the planned observation or intervention.

The term “obstructive sleep apnea” was placed in the search query for all available years (1999–2017). A separate search was done for “observational studies” and for “interventional studies” on September 1, 2017. Interventional studies are defined as those in which participants are assigned by an investigator to receive one or more intervention (including no intervention) with the goal of evaluating effects on health-related outcomes. The trial sponsor or PI submits this delineation. Projects with obstructive sleep apnea or OSA in their titles were automatically included in the study. Examinations of sleep-disordered breathing, snoring, and upper airway resistance syndrome were included, as these are on the OSA spectrum and important to its understanding. Studies focusing on other sleep disorders and studies for which OSA was not the primary focus of the study design or outcomes, as judged by the reviewing authors (C.J.G. and S.K.S.) upon reading the detailed description, were not included. For example, many studies examining interventions for CPAP in different patient populations mentioned shared lessons for OSA treatment. These were included only if they met the above-stated criteria or there was specific mention of how the study pertained to the management of OSA. Similarly, studies examining adjuvant therapies (e.g., hemostatic agents, acupuncture) in pediatric tonsillectomy to improve morbidity outcomes were not included unless the goal was to examine their role on the treatment of OSA.

**Variables Measured**

After reviewing search results for study inclusion, the study title, start date, funding support, PI name, and institution was exported from ClinicalTrials.gov into a Microsoft Excel (Microsoft, Redmond, WA) spreadsheet. The authors conducted an Internet search on each PI to find online faculty profiles or department pages to establish gender, degree, and academic department/specialty. If more than one PI was listed, the first PI was used for analysis. If PI medical specialty was not listed, this was recorded as unlisted.

All studies were recorded for pediatric, adult, or both focus. Although the pathophysiology and treatment for OSA is very different between adults and pediatrics, we chose to examine clinical trials in both fields to widen the scope of our study and to compare trial characteristics across patient populations. For interventional studies, focus on CPAP, surgical treatment, mandibular devices, medications, or other interventions was tabulated. A study was only counted as one of these categories if they specified utilized the treatment modality as an intervention; for example, a study focusing on telemedicine interventions to increase CPAP adherence was scored as “other” and not for CPAP. If a study examined more than one therapy, it was scored for each intervention being utilized.

Funding source of individual clinical trials was also recorded. ClinicalTrials.gov categorizes funding sources as NIH, US federal government (US fed) (e.g., Veteran’s Administration), and industry. International studies were classified as such. US studies were classified as NIH, US fed, industry, or unlisted.

**Statistical Analysis**

SPSS version 21 (IBM, Armonk, NY) was used for summary data and statistical analysis. $\chi^2$ analysis was used to assess differences in number of clinical trials between intervention categories, medical specialties, funding sources, and PI demographics, with threshold for significance set at $P < .05$. A nonparametric Mann-Kendall test was used to assess for the existence of significant trends in the number of clinical trials over time. The Mann-Kendall test was performed using XLSTAT 2017 (Addinsoft, Brooklyn, NY).

**RESULTS**

Our initial search yielded 1,171 clinical trials. Of these, studies not primarily related to OSA as outlined above were excluded (n = 54). Next, purely observational studies (n = 304) were excluded, leaving a total of 813 interventional OSA clinical trials ranging from 1999 to 2017 (Fig. 1). The majority of study interventions assessed adult versus pediatric patient populations (90.7% vs. 9.3%, respectively) and the majority of trials were internationally based (59.9%). The majority of PIs were male (72.0%), and PI education consisted largely of MD (52.4%) and MD/PhD (20.3%) degrees. Of US clinical trials with listed funding sources, 51% were funded by industry, 28% by the NIH, and 20% by the US fed (Table I).

The most common specialty was pulmonology (34.7%), followed by otolaryngology (9.2%). Internal medicine and anesthesiology were also commonly represented (7.4% and 5.5%, respectively) (Table II). CPAP interventions made up the largest proportion of interventional clinical trials (43.7%). Pharmacological interventions

![Flowsheet for study selection. OSA = obstructive sleep apnea. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.](https://www.laryngoscope.com/)](https://www.laryngoscope.com/)
(19.2%), and surgical interventions (10.7%) were the next most common studies. Mandibular devices were investigated in 6.4% (n = 52) of studies (Table III).

Several differences were identified between surgical and nonsurgical trials. Surgical interventions were significantly associated with male PIs (P = .002), whereas female PIs were significantly more associated with studies of CPAP (P = .017) and mandibular devices (P = .011). Surgical treatments were significantly associated with pediatric patients (P < .001). Adult studies most often focused on CPAP interventions (P < .001). There was a similar distribution of funding sources (NIH vs. industry, P = .14) and similar institutional geography (international vs. US, P = .73) when examining medical versus surgical studies. Of studies conducted by otolaryngologists, the majority explored surgical interventions (60%); a smaller percentage explored pharmacological interventions (16%) and CPAP (11%). Otolaryngologists had similar proportions of NIH funding compared to other medical specialists (P = .22) for their clinical trials.

Overall, from 2004 to 2016 there was a significant increase in the total number of OSA clinical trials over time (P < .001). The total number of surgical trials, however, has not increased significantly over the same period (P = .13) (Fig. 2). The total number of trials led by otolaryngologists did show a significant positive trend over the same time period (P = .029).

**DISCUSSION**

OSA represents a significant public health burden.1 Otolaryngologists have begun treating this population in record numbers nationwide,13 providing both surgical and medical management. As a whole, the academic community continues to refine existing and develop new treatment modalities through research efforts to address this troublesome chronic disease. However, it is unclear what the clinical landscape of OSA research is at present. A recent publication by Araslanova et al.14 demonstrated that adult OSA research publications are significantly underrepresented when compared to other chronic medical conditions such as coronary artery disease, diabetes mellitus, and osteoarthritis. OSA had significantly fewer randomized controlled trials and meta-analyses when compared to these other conditions. Furthermore, surgical OSA literature has not significantly increased over time when compared to other medical specialties.15 Collectively, these results are concerning for OSA research, but especially for the role of otolaryngology within it.

The goal of this study was to assess the trends and overall landscape of clinical trials in OSA, in particular to identify shortcomings and specific areas for improvement. Our results show a variety of interesting findings. Overall, the number of OSA clinical trials has significantly increased over time. Several medical specialties contribute to research efforts, with pulmonology being the most common, representing 35% of study PIs worldwide. Otolaryngology as a specialty, however, remains a small voice in the overall landscape of OSA clinical trials (12%). Furthermore, although OSA trials are increasing collectively, the rate of surgical trials remains stagnant (Fig. 2). These results must be viewed in light of the fact that sleep surgery has only recently become a prominent

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**TABLE I. Clinical Trial Characteristics.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (%)</th>
<th>n = 1,117</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study type</td>
<td>813 (73)</td>
<td></td>
</tr>
<tr>
<td>Interventional</td>
<td>304 (27)</td>
<td></td>
</tr>
<tr>
<td>Observational</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study population</td>
<td>737 (91)</td>
<td></td>
</tr>
<tr>
<td>Adult</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediatrics</td>
<td>76 (9)</td>
<td></td>
</tr>
<tr>
<td>Geography</td>
<td>461 (60)</td>
<td></td>
</tr>
<tr>
<td>International</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Domestic</td>
<td>309 (40)</td>
<td></td>
</tr>
<tr>
<td>Funding source</td>
<td>84 (27)</td>
<td></td>
</tr>
<tr>
<td>Industry</td>
<td>45 (15)</td>
<td></td>
</tr>
<tr>
<td>NIH</td>
<td>33 (11)</td>
<td></td>
</tr>
<tr>
<td>US fed</td>
<td>147 (47)</td>
<td></td>
</tr>
<tr>
<td>Unlisted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI gender</td>
<td>504 (72)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>200 (28)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI education</td>
<td>426 (52)</td>
<td></td>
</tr>
<tr>
<td>MD</td>
<td>89 (11)</td>
<td></td>
</tr>
<tr>
<td>PhD</td>
<td>165 (20)</td>
<td></td>
</tr>
<tr>
<td>MD, PhD</td>
<td>34 (4)</td>
<td></td>
</tr>
<tr>
<td>Unlisted/unknown</td>
<td>170 (21%)</td>
<td></td>
</tr>
</tbody>
</table>

| NIH = National Institutes of Health; PI = principle investigator; US fed = US federal government. |

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**TABLE II. PI Specialty.**

<table>
<thead>
<tr>
<th>Specialty</th>
<th>Total, n = 813</th>
<th>% Surgical intervention</th>
<th>% Medical intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonology</td>
<td>282 (35%)</td>
<td>4%</td>
<td>96%</td>
</tr>
<tr>
<td>Otolaryngology</td>
<td>75 (9%)</td>
<td>60%</td>
<td>40%</td>
</tr>
<tr>
<td>Internal medicine</td>
<td>60 (7%)</td>
<td>0%</td>
<td>100%</td>
</tr>
<tr>
<td>Anesthesiology</td>
<td>45 (6%)</td>
<td>7%</td>
<td>93%</td>
</tr>
<tr>
<td>Neurology</td>
<td>33 (4%)</td>
<td>3%</td>
<td>97%</td>
</tr>
<tr>
<td>Other</td>
<td>132 (16%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI not listed/unknown</td>
<td>170 (21%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| PI = principle investigator. |
part of the field of otolaryngology. Sleep medicine became an official certification within otolaryngology in 2008 and an accredited fellowship in 2012, which may partially explain why the number of surgical trials has been slow to grow substantially. Interestingly, the flatline in surgical studies does not seem to have changed since the formal recognition of sleep medicine certification or accredited sleep fellowships (Fig. 2).

CPAP remains the most widely used treatment strategy for OSA, and studies to increase tolerance, adherence, and efficacy are worthwhile. However, the majority of patients prescribed CPAP do not tolerate it, making surgery an important alternative to consider. In this study, only 10% of OSA clinical trials explored surgical treatment options. A large proportion of these were investigations of different modalities and treatment arms for pediatric tonsillectomy (pediatric studies made up 32.2% of all surgical studies). This relative lack of clinical trials exploring surgical treatments of adult OSA is concerning, especially with increasing literature demonstrating the benefit of surgical therapy for OSA. In the future, it is important that surgical options remain an available and investigated part of OSA management. This finding of a minor role for ear, nose, and throat specialists in sleep apnea research is consistent with several prior recent studies expressing concern about the diminishing role of our specialty in OSA care. It remains important for otolaryngologists to be active in the treatment and research of OSA, to promote or at least keep surgical options available as part of its management.

There remain some signs of optimism for otolaryngology’s involvement in OSA. Only pulmonologists conducted more clinical trials for OSA than otolaryngologists. Furthermore, although pulmonologists focused mainly on CPAP, otolaryngologist-led trials were more diverse: 60% exploring surgical options, 16% pharmacological intervention, 11% CPAP, and 7% mandibular devices. This suggests sleep surgeons as comprehensive managers of OSA, with expertise in a variety of medical and surgical treatment options. This is particularly important in a clinical environment where one-third of OSA patients initially present to otolaryngologists for their care. We also found that the majority of PIs conducting OSA clinical trials were male (72%). Recent literature has shown that men represent about 81% of all academic otolaryngology faculty positions in the United States. This indicates that although a gender disparity does exist within sleep surgery research, it is comparable, if not less disparate, than that of otolaryngology as a whole.

This study has several limitations. First, ClinicalTrials.gov does not contain information about all clinical studies conducted worldwide. In addition, it contains information on unpublished as well as published trials. However, ClinicalTrials.gov is a condition of publication for peer-reviewed journals, has been utilized by multiple prior publications examining the landscape of ongoing investigation, and stands as the most widely used database for clinical trials. We believed that this source is the most comprehensive and valid resource available for characterizing interventional studies for OSA. Although some trials may not go on to publication, they still represent active areas of exploration within this field. The authors chose to not include several studies in the initial search that we believed were outside of the scope of this study. These included studies examining the prevalence of a multitude of sleep disorders (i.e., narcolepsy, rapid eye movement disorders, and central sleep apnea), different modalities of noninvasive ventilation/positive airway pressure masks, and postoperative complications in different surgical populations with concurrent OSA as a risk factor. Several studies, particularly international ones, listed their funding source as “other.” Because of this, our study most likely undervalues contributions from specific foundations, such as the American Sleep Medicine Foundation. However, our study focused on NIH, US federal (Veteran’s Administration), and industry funding grants that we were able to gather from the provided data and have the most immediate translational importance domestically. Additionally, there was no way to capture multidisciplinary collaborations between various medical providers and specialties. Finally, examining PI race disparities would be a worthwhile investigation, but unfortunately we were limited by the lack of this information on faculty profiles. Although these factors do limit extrapolation from our results, we feel that the overall findings and trends of this study are valid and meaningful. This study stands as the only investigation of clinical trials in OSA.

CONCLUSION

Overall, the number of OSA clinical trials has increased dramatically over the past 2 decades. However, otolaryngology remains a small voice in the overall landscape of this dynamic environment. Although, the number of surgical trials has not significantly increased with time, otolaryngologists continue to display diverse interests in both the surgical and medical management of this disease in clinical trials. Future studies may explain the underserved role for otolaryngology in OSA research, as well as ways to improve it. We hope this study will encourage otolaryngologists to conduct and encourage OSA clinical research.

Fig. 2. Number of obstructive sleep apnea clinical trials over time. ENT = ear, nose, and throat. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]
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