ORIGINAL ARTICLES

ORal Appliance Network on Global Effectiveness (ORANGE): Start-Up and Design Description

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Summary: Oral appliance (OA) therapy is the main non-surgical alternative to CPAP treatment in patients with obstructive sleep apnea (OSA). There are clear benefits from OA when compared to placebo, but a larger variability compared to CPAP has been documented for the reduction of OSA. These results are based on less than 30 randomized controlled trials. In addition, an important variability regarding study design and methodology has been observed in these studies published over the past 15 years. Therefore, a need for more knowledge in larger studies with standardized data collection is required to better understand the role and effectiveness of OA in patients with OSA.

Study Objectives: Fifteen academic researchers from nine countries have founded a network focused on OA long-term outcomes. The primary aim of this network called ORANGE (ORal Appliance Network on Global Effectiveness) is to evaluate the long-term effectiveness of OA therapy in OSA patients and assess long-term health outcomes of OA therapy related to cardiovascular disease. Exploratory aims include: assessment of objective adherence and tolerance; incidence of cardiovascular events and related cardiovascular and cerebrovascular mortality; exploration of health care costs associated with this type of therapy across different countries; assessment of the cost-effectiveness of treatment; evaluation of side effects; examination of the impact of OA on quality of life; comparison of differences between OA types and titration methods; evaluation of the incidence of OA contraindications.

Methods: In March 2012, researchers attended the first strategic meeting, funded by the American Academy of Dental Sleep Medicine (AADSM) in Chicago. During the meeting, objectives and feasibility of the cohort were discussed. Subcommittees were created to decide on data collection priorities and standardization, which were divided into anthropometrics, medical history, sleep test data, questionnaires, dental variables, side effects, adherence, and titration factors. Consecutive patients who consent to participate will be included, and the data will be entered in web-based software called REDCap (Research Electronic Data Capture). The finalized data to be included in the cohort were discussed and determined in June 2012 in Boston. The network met again in April 2013 in Paris to finalize patient data entry needs, charts, and ethics board requirements.

Conclusion: ORANGE is a multinational observational cohort study, creating a unique opportunity to explore effectiveness and cardiovascular outcomes of OA therapy in OSA patients.

Keywords: oral appliance, sleep apnea, ORANGE, cohort study, network

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Breathing problems during sleep have an internationally reported prevalence of from 3% to 27% for primary snoring, 4% to 20% for sleep disordered breathing, and 1% to 10% for obstructive sleep apnea (OSA).[1] In the adult population, despite increasing knowledge and facilities, the majority of patients remain undiagnosed. The epidemic of obesity is a major contributor to the rise in the incidence of OSA in all developing countries. OSA prevalence is even higher in subpopulations with cardiovascular and metabolic comorbidities such as stroke, arterial hypertension, heart insufficiency, diabetes mellitus, or metabolic syndrome.[2]

One of the two main treatments for adult OSA is provided by dentists. The knowledge in dental sleep medicine is not fully disseminated. There is a lack of programs in the field to educate dentists and few centers worldwide have developed research in this field. As a consequence, there are many dentists unaware of or not trained to provide oral appliance (OA) therapy, and as a consequence, a small number of studies have been conducted in the dental sleep medicine and oral appliance field.[3]

Oral appliances provide a simple, reversible, quiet, and cost-effective therapy for selected patients with OSA.[4] The American Academy of Sleep Medicine (AASM) reviewed the available literature in 2006 and recommended that OAs may be used as first line therapy in adult patients with primary snoring, mild and moderate OSA and in patients with severe OSA who are intolerant of or refuse treatment with nasal CPAP.[5,6] However, oral appliance therapy for OSA remains underutilized.

There are a variety of adjectives or synonyms for oral appliances—intraoral, dental, mandibular, device, splint, or prosthesis. OAs can be divided into two major types: (1) those that

reposition the mandible and the attached tongue, the mandibular advancement splints (MAS) or mandibular advancement devices (MAD); and (2) those that hold the tongue forward, the tongue retaining devices (TRD). OAs decrease OSA severity because of an increase in upper airway patency, the provision of a stable anterior position of the mandible and advancement of the tongue and its attached structures.[7-9] OA therapy for OSA is a long-term commitment, so the appliance must be comfortable for the patient.[10,11] MAS, like CPAP, require titration to achieve optimum efficacy.[12,13] Previous studies have demonstrated also that if the titration is based on symptomatic improvement only, about 30% of patients who could ideally be treatment responders are missed.[14,15]

There are clear OA treatment effects when compared to placebo.[16] While oral appliances have lesser efficacy in controlling OSA compared to CPAP, many studies suggest similar outcomes of these treatments in relation to improvements in blood pressure, endothelial function, sleepiness and quality of life.[17-22] This discrepancy is generally hypothesized to be related to the greater acceptance and adherence to OA.[17,23] Also, these studies are grounded on fewer than 30 randomized controlled trials published over the past 15 years, with a large variability regarding study design, methodology, type of appliance, and patient selection (mostly in mild-to-moderate OSA). There is only one study[4] to our knowledge on cost-effectiveness, which is based on assumptions and not on prospective data analysis.

OSA is a chronic disease where long-term observational studies have suggested a beneficial impact of CPAP on cardiovascular outcomes by demonstrating a reduced incidence of cardiovascular (CV) events in patients successfully treated compared to untreated or poorly adherent patients. Buchner and collaborators[24] have also confirmed the decrease in CV morbidity and mortality in successfully treated mild-to-moderate OSA, and interestingly they have not distinguished CPAP from OA. Despite the study being focused on CPAP, there were 20 patients among the 209 treated patients who actually used OA and not CPAP. There are several other studies compiling evidence linking OSA and CV disease and that treatment of OSA may reduce these risks. However, as shown in other areas of medicine (hormone replacement), tests of whether treatment of OSA reduces cardiovascular morbidity and mortality require long-term, large-scale trials focused on "hard" cardiovascular outcomes. El-Sohl and collaborators[25] recently found an equivalent reduction in fatal cardiovascular events under CPAP and OA compared to untreated severe OSA patients, but their sample size was relatively small and the study design retrospective analysis.

It is clear that the effectiveness of a treatment, especially for chronic diseases, is determined by a combination of efficacy and adherence. A major limitation of studies comparing OA and CPAP has been the lack of objective adherence monitoring for OA therapy. It was not until recently that Vanderveken and colleagues showed a reliable and now commercially available monitor.[21] With the advances in technology, the ability to measure objective adherence to OA is possible.

We believe this is the right time to start a large prospective cohort study focusing on OA effectiveness (being the product of the treatment's efficacy and its adherence) and long-term CV outcomes. A secondary and important initiative of the project will be to share the protocol used in this trial with interested institutions to further standardize, stimulate, and enhance new protocols in a wider number of research and clinical centers.

COHORT PLANNING

The ORANGE (Oral Appliance Network for Global Effectiveness) cohort started with the willingness of the American Academy of Dental Sleep Medicine (AADSM) to support a first strategic meeting to assess the viability of such an endeavor. In March 2012, the network's first meeting comprised 15 academic related centers from 9 countries across the globe. The partnership presented a variety of specialists, involving physicians from University of Sydney (Australia), Stanford University (USA), University of Pennsylvania (USA), Kaiser Permanente (USA), Cambridge University (UK), Paris Hospital (France), Angers University Hospital (France), and University of Antwerp (Belgium), and dentists from Japan Somnology Center (Japan), Kyushu University (Japan), University of British Columbia (Canada), University of Montreal (Canada), Laval University (Canada), University of Groningen (Netherlands), and Umea University (Sweden). These centers have been involved with research in the field of OSA and also on OA therapy for many years. They have the necessary expertise to design and conduct the proposed trial. At this point, the only institution interested in helping fund this initiative is the AADSM. Different subgroups are searching and submitting grants in their own regions (Canada, Europe, and Japan) to fund the parts of the trials conducted at their centers.

As decided during the first meeting, the primary aim is to evaluate the long-term effectiveness of OA therapy in OSA patients and the impact of OA therapy on CV morbidity and mortality. Secondary/exploratory aims include objective adherence and tolerance, cost-effectiveness of treatment, side effects, the impact of OA on quality of life and mood indices, health care costs of this type of therapy in different countries, indications for combination of OA and CPAP, and comparison of different OA types and titration methods.

STUDY DESIGN

Once the group was developed and the main objectives were agreed upon, subcommittees were created to decide on data collection priorities and standardization, which were divided into anthropometrics, medical history, sleep test data, questionnaires, dental variables, side effects, adherence, and titration. It was decided that 1,000 consecutive patients who consent to participate will be included and the data will be entered in web-based software called REDCap (Research Electronic Data Capture). To overcome the challenges of a multicenter/multinational trial, we have taken various steps to minimize the differences between centers. We have decided not to change each institution's main clinical protocol, such as polysomnography versus portable monitoring, titration modality or OA design, but record those variables to enable us to use the data for future data analysis. Therefore all types of oral appliances will be accepted. However, since most centers tend to work mostly with custom-made, titratable appliances, they may represent the majority.

The effectiveness of the treatment will be measured as a combination of efficacy and adherence. Efficacy will be quantified by the changes concerning the severity of sleep disordered breathing in terms of AHI and/or ODI during treatment[26] as compared to baseline, improvement of symptoms, and improved health outcomes[27] (e.g., FOSQ, SF-36) and adherence will be encouraged to be measured by a recently developed adherence monitoring system.[21] Predictors of treatment outcome will be analyzed in relation to background data and living habits.[28] In a parallel assessment, the cost-effectiveness of treatment will be analyzed, including variables such as the cost of treatment in each country as well as the generation of quality of life adjusted years based on the calculations from the changes before and after treatment on quality of life questionnaire, Short-Form 36.

The long term follow-up period will include a systematic assessment of the patients in years one, three, and five. For years two and four, a systematic phone interview will be utilized. A standard questionnaire will be used to follow noncompliant patients, and they will be followed within the same time intervals.

TIMELINES DURING THE START-UP PHASE

As summarized in Figure 1, timelines were collectively generated by members of the network. During the second strategic meeting held in April 2013 funded by the AADSM, data collection and forms were further discussed. All data collection points have been reviewed and will be transferred into the REDCap database. In early 2014, participating centers will start the ethics approval process and all centers will start entering mock patients into the database. Once the centers have entered a few cases, the network will meet and determine the absolutely necessary versus desirable but not essential data fields.

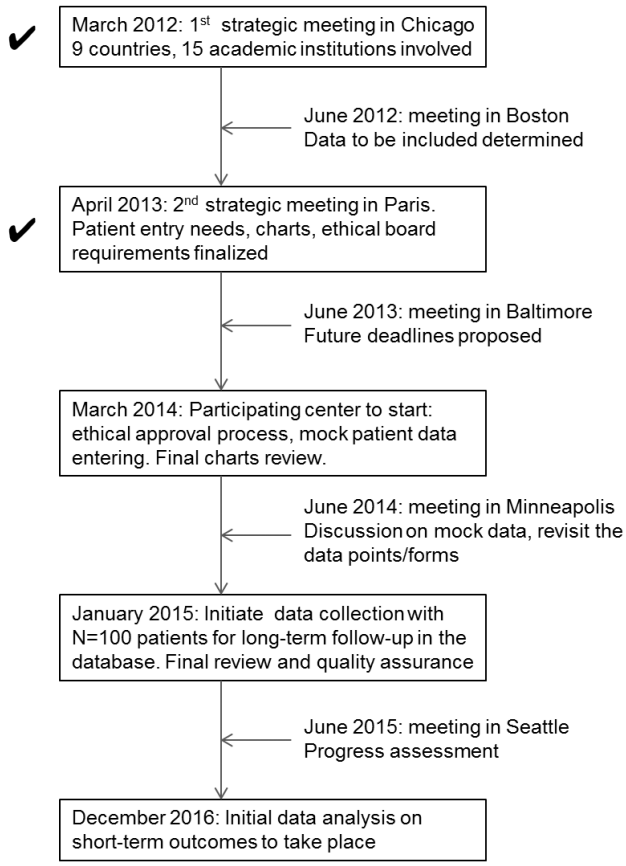
Once ethical approval is granted, the centers will start collecting prospective data. By the end of 2014, the network will revisit the data points/forms to evaluate the burden of the study to the patient and clinician, the accuracy and completeness of questions and potential areas of missing data. Changes required will be implemented into REDCap with the respective final forms. It is expected that by the beginning of 2015 the first 100 patients will be entered in the database for long-term follow-up.

A quality assurance protocol will be implemented to assure completeness and accuracy of data. The network will be open to include a larger number of interested research centers. The protocol, questions, and structure of the network will be presented to the AADSM, and a possible clinical database may be then developed. A standardized protocol may facilitate the integration of dental and medical charts, develop a patient-centered approach, improve medical and dental communication, and ensure long-term follow-up of patients.

Funding will constitute a barrier for the sustainability of the cohort. All centers have current funds to start collecting data; once pilot data are generated, this will facilitate funding opportunities to enlarge the cohort and continue data collection.

In conclusion, the proposed cohort plans to generate data to fulfill the needs and identify the elements for integrated care that are central to providing patient-centered medicine, longitudinal evaluation of patients, and accessible, comprehensive, and coordinated treatment. As a multicenter group spread through four continents, the elements of care will be sensitive to cultural differences, able to provide ongoing care for patients with chronic conditions with optimal coordination of care with the patient's physician/dentist team. It is anticipated that by the year 2016, initial data analysis will take place.

Figure 1—Timelines and future phase schedule.



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