PROTOCOL TITLE: Proof of Concept Study of an Oral Orthotic in Reducing Tic Severity in Chronic Tic Disorder and Tourette Syndrome

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BACKGROUND

In the process of developing treatments for temporomandibular joint dysfunction (TMD), Drs. Anthony Sims and Brendan Stack observed improvement in tic severity in patients with co-occurring TMD and tic disorders. Sims and Stack's observation has been reported in the medical literature (Sims & Stack, 2009), and multiple positive video testimonials of Tourette Syndrome patients successfully treated with an oral orthotic can be viewed on the internet (please see the URLs in the attachments). Sims and Stack posit that the mechanism by which the oral orthotic reduces TS symptoms is not within the striatal-thalamo-cortical-circuits commonly thought to be related to TS. Rather Sims and Stack believe that the tics of TS are reflexive muscle contractions (tics) related to irritation of peripheral nerves. The reflex occurs at the spinal cord level within the spinal trigeminal nucleus, specifically the subnucleus caudalis. They posit that, for some individuals, asynchronous development of the bone structure of the face during childhood leads to misalignment of the temporomandibular joint (TMJ). The misalignment results in irritation of the sensory afferent fibers of the trigeminal nerve leading to crosstalk (i.e. ephaptic transmission) at the level of the spinal cord within the subnucleus caudalis between the trigeminal nerve sensory fibers and motor efferent fibers in other cranial nerves and in the spinal motor tract more generally. Perhaps the simplest common example of the stimulation of a sensory nerve and a reflexive muscle contraction is when the corneal of the eye is irritated and a blink reflex occurs. The oral orthotic is thought to relieve the irritation of the trigeminal nerve, and thus alleviate tics. If oral orthotics are effective in reducing tic severity it will be a paradigm shift in the treatment of TS and in understanding the pathophysiology of TS. The first logical step to evaluate whether an oral orthotic can reduce tic severity is to conduct a pilot trial to establish whether a larger, definitive randomized controlled trial is feasible. The goal of this proposal is to conduct a 2 week randomized, blinded, controlled clinical feasibility trial to establish methods for a larger definitive clinical trial and for treatment responders to assess durability of treatment over an additional 10 week follow-up period (12 weeks total treatment). Perhaps the most critical aspect of the study's design is to fully establish procedures for the blinding of the treating clinician, patient and evaluator (blinding procedures detailed in the attachments). Without well established and effective blinding procedures there is a substantial risk that utility of this novel and potential controversial approach will not be realized. Though hundreds of children have been treated with this orthotic for tic disorders, these children were not treated in a controlled research environment. The data on this device is therefore strictly anecdotal. Our objective is to obtain pilot data on the efficacy of this device through a double blind, randomized, placebo controlled study in order to validate the potential benefit of this treatment option. This study is a double blind, randomized, placebo controlled trial. This protocol is designed as a feasibility trial: to ensure that our methods are sound before proceeding to a larger scale study. Our mission in this trial is two-fold: 1. To evaluate the feasibility of a 2-week randomized controlled trial of an active vs. sham occlusal splint to reduce tic severity. 2. To assess the durability of the occlusal splint among orthotic treatment responders over an additional 10 weeks.

STUDY DESIGN

The study is a 2 group, 2 week randomized controlled feasibility trial of an active vs sham oral orthotic to reduce tic severity in children and young adults ages 7-25 years. Responders to acute phase treatment will be followed for 10 additional week (12 weeks total) to assess intervention durability, safety and acceptability. Non-responders to the sham orthotic will be provided active treatment at the end of the 2 week acute phase. We aim to assess and enroll 24 participants; twelve participants will receive an orthotic adjusted to the appropriate therapeutic height, and twelve participants will receive an identical sham orthotic, but not adjusted to the recommended height for the given participant. An additional 6

participants will be enrolled in ABAB design of this study to further hone in on a potential mechanism of action of the occlusal splint by assessing changes in autonomic arousal as a result of wearing the device (procedural information below). This pilot will not be powered to determine efficacy or generate effect sizes, but will determine the feasibility of study procedures including recruitment, assessment, randomization, blinding, sample maintenance and acceptability and adherence to the orthotic treatment. Subjects will be required to obtain medical clearance from their treating dentist prior to participation. Population: The study will be enrolling subjects with both Tourette's Syndrome (TS) and Chronic Tic Disorder (CTD), which are both defined below: -For a person to be diagnosed with TS, he or she must meet the following criteria: A. The person must have both motor tics (for example, blinking or shrugging the shoulders) and vocal tics (for example, humming, clearing the throat, or yelling out a word or phrase), although they might not always happen at the same time. B. The person must have had tics for at least a year. The tics can occur many times a day (usually in bouts) nearly every day, or off and on, but there must not be a single tic-free period of more than 3 months. C. The person's tics must begin before he or she is 18 years of age. D. The person's symptoms must not be due to taking medicine or other drugs or to having another medical condition (for example, seizures, Huntington disease, or postviral encephalitis). -For a person to be diagnosed with a chronic tic disorder, he or she must meet the following criteria: A. The person must have one or more motor tics (for example, blinking or shrugging the shoulders) or vocal tics (for example, humming, clearing the throat, or yelling out a word or phrase), but not both B. The person must have tics that occur many times a day nearly every day or on and off throughout a period of more than a year. During this period, there must not be a single tic-free period of more than 3 months. C. The person's tics must start before he or she is 18 years of age. D. The person's symptoms must not be due to taking medicine or other drugs or to having a another medical condition (for example, seizures, Huntington disease, or postviral encephalitis).

To evaluate the feasibility of a 2 week randomized controlled trial of an active vs sham oral orthotic to reduce tic severity.

To assess the durability of the oral orthotic among oral orthotic treatment responders over an additional 10 weeks.

We aim to assess and enroll 24 participants; twelve participants will receive an orthotic adjusted to the appropriate therapeutic height, and twelve participants will receive an identical sham orthotic, but not adjusted to the recommended height for the given participant. We aim to assess and enroll an additional 8 participants in an ABAB design to further hone in on a potential mechanism of action of the occlusal splint. This pilot will not be powered to determine efficacy or generate effect sizes, but will determine the feasibility of study procedures including recruitment, assessment, randomization, blinding, sample maintenance and acceptability and adherence to the orthotic treatment.

INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria are as follows: 1.Age 7-25 inclusive. 2. Presence of motor and/or vocal tics for at least 12 months. 3. Tics are of at least moderate clinical severity as evidenced by a Yale Global Tic Severity score of 14 or higher for motor or vocal tics only and 22 or higher for Tourette syndrome and present during the baseline assessment. 4. IQ estimate of 70 or higher 5. Comorbid disorder (e.g., ADHD, OCD, ODD) will be allowed provided that the tic symptoms are of primary concern to parents and comorbid

symptoms are not of sufficient severity to require immediate treatment other than that provided by the current study. 6. Pre-existing stable medication (see protocol for details), tic or otherwise, will also be allowed provided the family agrees to refrain from med changes over the course of the acute phase of the study 7. Sufficient command of the English language to participate in informed consent and assessment procedures. 8. Agree for videotaping of study procedures 9. Clearance by treating dentist: Certification of good dental health provided by the subject's current dentist prior to enrollment in the study

Exclusion Criteria as follows: 1. Major psychiatric disorder at screening that would preclude full participation in study procedures including psychosis, mania, depression, untreated combined type ADHD, autism and pervasive developmental disorders. 2. Medication changes are planned during the acute and follow-up phase of treatment. 3. Other dental health problems that might interfere with the assessment, installation, or wearing of orthotic device. 4. Does not consent to being videotaped

DATA AND SAFETY MONITORING PLAN

The research does involve administration of physical stimuli other than auditory and visual stimuli associated with normal classroom situations; The occlusal splint is a removable dental appliance that fully covers the occlusal surface of the lower teeth. Distinct from a simple bruxism device (mouthguard), the splint for this study will have extra material built up vertically along the lower pre-molars and the molars. The height of this vertical build up is specific to each patient, as determined in an initial orthotic fitting session. Subjects will be fit for and given this oral orthotic to help with their tics. Subjects may find the fitting and/or the use of the orthotic to be uncomfortable, or otherwise foreign. Subjects will be told that they can take out the orthotic should it ever prove too uncomfortable.

The research does not involve any deprivation of physiological requirements such as nutrition or sleep, manipulation of psychological and/or social variables (i.e. sensory deprivation, social isolation, psychological stress, etc.).

The research does not involve any use of deceptive techniques without the knowledge of the subject.

The research does involve probing of information which might be considered personal or sensitive, including the examination of the medical record; The interviews during the course of the study involve no specific risk or discomfort beyond those of a standard clinical interview. However, parents and children will be asked to disclose personal information and to discuss potentially emotional topics related to the subject's symptoms, and the impact of these symptoms on the subject and his/her family It is possible that some children and parents may become uncomfortable discussing such information during the assessments. All of our investigators are highly experienced clinicians that have been trained in administering such assessments, and monitoring distress in patients and subjects. Subjects will also not have to answer any questions that they do not feel comfortable answering.

The research does not involve any presentation to the subject of any materials which they might find to be offensive, threatening or degrading.