Strategies for Evaluating Anosmia Therapeutics in the COVID-19 Era—Coming to Our Senses

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Two studies in this issue of JAMA Otolaryngology–Head & Neck Surgery evaluate the use of nasal theophylline, a phosphodiesterase inhibitor that may promote neural olfactory signaling and recovery for postviral olfactory dysfunction (OD). The first, a dose-modification Research Letter by Lee et al1 was conducted in patients with non-COVID-19–related hyposmia or anosmia secondary to viral infection and confirmed by the objective University of Pennsylvania Smell Identification Test. This open-label, dose-escalation trial provides an educational description of how to evaluate the appropriate dose for an emerging pharmacologic intervention. Specifically, the authors identified 400 mg of theophylline twice daily as a tolerated dosage. This was calculated as an equivalent oral dose of 20 mg. A phase 2 pilot study by Gupta et al2 was designed using this valuable information. Patients with suspected COVID-19–related OD completed the University of Pennsylvania Smell Identification Test and were randomized to either theophylline or placebo nasal irrigations for 6 weeks. This study was inconclusive regarding the clinical benefit of theophylline nasal irrigations, although there was suggested improvement by subjective assessments. The authors acknowledge several limitations, including small sample size, the virtual nature of the study design and subsequent inability to conduct endoscopic nasal examinations, lack of information regarding participant COVID-19 vaccination status, lack of polymerase chain reaction–documented COVID-19 infection, and short-term participant follow-up. These acknowledgments are justified, and many can be overcome in subsequent studies with adequate funding and time. However, the heterogeneous nature of COVID-19 and associated research make this area of work particularly challenging. Herein, we propose several approaches to improve the rigor of OD research in the COVID-19 era.

One common strategy to improve study quality is to use a statewide or national registry to include a larger number of patients, thus increasing external validity, power, and the ability to discern smaller effect sizes. Findings from the phase 2 pilot study,2 such as effect size and variation, may be used to define an appropriate sample size a priori, a critical aspect of successful study design. Treatment effects may depend on other factors that can be collected through registries, such as the use of other nasal, anti-inflammatory, or neuromodulating medications. However, it is possible that theophylline is an effective and safe treatment for COVID-19 or other postviral OD, though it might not be effective for everyone. The risk of large trials with lenient inclusion criteria, while helpful for patient recruitment, is that findings are averaged among all participants. Important treatment effects may be lost in these analysis models. The alternative overarching strategy is to become more granular regarding patient inclusion and exclusion criteria. For example, to determine specific cohorts of patients in which theophylline or other medications may be effective, multi-institutional studies could incorporate strict inclusion and/or stratification criteria, including polymerase chain reaction–documented COVID-19 infection, stratification by variant, vaccination status, and endoscopic examinations. This methodology with multivariate modeling is similar to studies seeking to identify novel biomarkers and other factors associated with treatment outcome for chronic rhinosinusitis with nasal polyps.3 Considerable work is currently under way to determine appropriate algorithms for topical and biologic treatments for specific chronic rhinosinusitis with nasal polyps cohorts because the treatment effect is variable for different subtypes.4 Similarly, OD is a common diagnosis with multiple causes and variations, and all patients should not be treated identically, in clinical practice nor in research.

Other alternative research designs may be beneficial for the study of OD. For example, pragmatic trials are an alternative to traditional explanatory trials. Pragmatic trials attempt to determine real-world effectiveness, as patients are not blinded to treatment in actual practice. In pragmatic studies, patient-centered outcomes are the focus of study end points, and effort is put toward attempts to recruit a diverse study population.5 Response-adaptive randomization may be an appropriate strategy for recruitment. This method allows for the ratio of randomization to be altered during the study, if data suggests superiority of one arm. Overall, flexibility and adaptive study design could improve OD research. Patients often become frustrated by lack of improvement but are motivated to try new possible treatments. It may be beneficial to consider trials in which patients are offered alternative treatments or enrollment into other clinical trials if they do not show improvement following an initial predetermined time course of treatment. Patients randomized to the placebo group may also later be offered treatment free of charge to encourage participation and compliance.

The last consideration for OD, a disorder largely responsible for quality-of-life concerns, is the use of objective vs subjective testing. Several recent studies have relied on subjective questionnaires regarding olfactory improvement post–COVID-19 infection.6 Other research has relied heavily on objective measures for confirmation of OD and subsequent improvement.7 While there may be some safety concerns for complete anosmics, we do need to ask ourselves, if patients have subjective improvement in smell and taste, and quality of life is improved, what is the additional benefit of objective testing? And how do we interpret results in which subjective and objective outcomes are conflicting, an all-too-common finding in rhinology research?

Overall, OD research is challenging, particularly during the ongoing COVID-19 pandemic. COVID-19 variants differ in ad-
verse effect profiles on smell and taste distortion, and patients have variable immunization status records and COVID-19 reinfection rates. Patients may have trialed various treatments prior to presenting for study enrollment. Ultimately, patient quality of life is the most important outcome. While objective measures are beneficial for research purposes and documentation, subjective measures are most useful for characterizing the patient experience. We believe that the future of OD research is a balance of pragmatic study design and a focus on endotyping or stratification of OD. If the COVID-19 pandemic has taught us anything, it is that things are always in flux. As we experience new variations and new knowledge, we must remember that patients are unique and are changing as well.

REFERENCES