Olfactory training: what is the evidence?

Olfactory dysfunction affects between 3% and 25% of the general population and has severe impacts on quality of life.[1] Given the prevalence of olfactory disorders and increased risk of hazardous events and mortality among those affected, one could argue that olfactory dysfunction should be considered a major public health issue. Unfortunately, there are a lack of proven interventions that can recover olfactory ability in affected individuals, despite the unique neural plasticity of the olfactory epithelium and olfactory tract that would suggest potential for regeneration and/or recovery. In an approach that exploits this regenerative capacity, olfactory training has recently been introduced as a potential treatment for olfactory dysfunction due to multiple etiologies. This intervention has been rapidly incorporated as a foundational treatment for olfactory disorders both within specialized smell and taste clinics and in general otolaryngology practices. So exactly what is the evidence for olfactory training and should this be considered standard of care in the patient with olfactory dysfunction?

Odor detection is not static, but rather a developing sense that emerges from childhood to adulthood. Although olfactory sensitivity is generally equivalent among age groups, "odor learning" requires repeated experiences with different smells to develop discriminatory ability, and this is a process that takes years.[2] This learning process has been confirmed in multiple psychosocial studies[3,4] and has served as a foundational tenet for clinical olfactory training as we know it today. In 2009, Hummel et al.[5] reported a prospective, controlled, nonblinded study to investigate the potential efficacy of olfactory training in patients with olfactory loss of multiple etiologies[5]. Training was performed over a period of 12 weeks and involved patients exposing themselves twice daily to 4 different odors for 10 seconds each. Patients undergoing olfactory training experienced a mean improvement of 10.3 points on the threshold, discrimination, and identification (TDI) score. The TDI score is a widely used semi-objective global measure of olfaction administered using standardized odor dispensing devices. There is no published minimal clinically important difference (MCID) in TDI score; however, the correlation between a patient's self-reported noticeable improvement in olfaction and objective changes in the total TDI score after repeat testing has been reported as between 5.5 and 6 points.[6] Significant (>6 points) improvement occurred in 28% of patients in the training group vs 6% in the no training group, suggesting potential promise as an effective intervention for a subset of individuals. Multiple additional studies have been performed over the last 10 years, with a comprehensive systematic review showing a statistically significant improvement in TDI score in patients undergoing training vs a control population.[7] However, it should be noted that the mean difference in posttreatment TDI between groups was <4 points, suggesting that intervention may be effective in some patients but that there may be either substantial variability in response among individuals or improvements in many patients that may not be clinically significant.

Despite increasing acceptance as an appropriate intervention, questions with respect to both efficacy and mechanism of action have persisted. It is well established that many patients with olfactory loss will have some level of spontaneous recovery, and deconvoluting this spontaneous recovery from improvement due to olfactory training itself has proved difficult. Appropriate selection of a true placebo has been logistically challenging, and most studies have been of low quality and heterogeneous with respect to patient populations, protocols, and outcome measures.[7] Fornazieri et al. evaluated olfactory training in a prospective observational study[8] and found that the effectiveness of olfactory training in their population approximated or was worse than that expected from spontaneous recovery alone[9,10]. In addition, adherence was relatively low when patients did not experience noticeable improvements within the first 3 months.[8]

Olfactory training has also been rapidly and directly introduced into patient care despite a lack of any clearly established mechanism of action, and it remains unknown whether any potential improvements are due to effects on central or peripheral components of the olfactory system. Negoias et al.[11] found that olfactory training increased olfactory bulb volumes in healthy participants, however, the study (which employed single nostril training) did not include a control group and similar increases in bulb volume were noted between the side of training and the untrained side.[11] Furthermore, olfactory thresholds actually worsened after treatment. A functional magnetic resonance imaging (MRI) study in humans undergoing olfactory training identified modifications in functional connections between different signaling networks, though no control group was included.[12] Notwithstanding what could be interpreted as marginal mechanistic evidence in human

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studies, the efficacy of olfactory training is supported by a small number of animal experiments. Kim et al.[13] evaluated olfactory recovery in olfactory-lesioned mice via a food-finding test and simulated olfactory training using common odorants over a period of 3 weeks.[13] Olfactory training improved olfactory recovery time and was accompanied by changes in gene transcriptional pathways associated with neurogenesis. Kim et al.[14] subsequently showed that olfactory ensheathing cells may play an integral role in recovery.[14] Another study showed that simulated olfactory training in lesioned mice prevented olfactory dysfunction, caused increased neurogenesis in the olfactory bulb, and resulted in an increase in dopaminergic interneurons.[15]

So what should clinicians and investigators conclude from this assorted evidence? There appears to be substantial experimental data to suggest that olfactory training may modulate the olfactory system and potentially improve olfactory function. However, the degree of improvement may be marginal, and current evidence suggests that the real-world results of olfactory training as a stand-alone intervention could prove disappointing. There may also be subgroup effects, with differences in improvement among populations based on duration of smell loss and/or etiology of olfactory dysfunction.[16-20] Ultimately, a combination of interventions may prove superior, as suggested by a small number of studies that combined olfactory training with systemic or topical corticosteroids.[21,22] As evidenced by this review, many questions remain with respect to both the efficacy and mechanism of olfactory training, and high-quality investigations are needed in order to optimize management and identify the populations who will derive the most benefit.

Justin H. Turner, MD, PhD
Department of Otolaryngology–Head and Neck Surgery, Vanderbilt University Medical Center, Nashville, TN
Guest Editor

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