The evidence for olfactory training in treating patients with olfactory loss

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Purpose of review
The purpose of this review is to go over the only therapy for olfactory loss supported by level 1a evidence that is currently available, which is olfactory training. This therapy is widely underutilized and has the potential to help many patients with olfactory dysfunction who are otherwise offered no management options.

Recent findings
We will review the rationale, clinical studies, and quality of the evidence regarding olfactory training, specifically the olfactory system's inherent ability to regenerate, the plasticity of the system, and the multiple protocols and modifications of protocols present in the literature.

Summary
Olfactory training is an effective therapy for some patients suffering from olfactory loss, and, while we do not yet know the optimal duration or number of odorants or exact patient population it may be most beneficial for, as an extremely easy, self-driven therapy with no significant side-effects, it should be consistently offered to this patient population.

Keywords
anosmia, hyposmia, olfaction, olfactory dysfunction, olfactory loss, olfactory training

INTRODUCTION

Olfactory dysfunction occurs at much higher rates than most expect, with the frequency of decreased olfactory ability as high as 15% and estimates of almost 5% of the general population being functionally anosmic [1]. The urgency to find a solution to this problem has taken a backseat to sensory losses with more dramatic and immediately perceived deficits, such as deafness and blindness, but the slow, cumulative effect of loss of smell and taste has been shown to have a large effect on quality of life and psychiatric wellness as well as a significant effect on mortality [2▪,3,4].

One of the most frustrating situations for a physician is to see a patient and not be able to help them with their problem. Unfortunately, until very recently, we did not have much to offer our patients with olfactory loss. Often they are offered a course of steroids if seen early enough after their initial loss, but all too often they wait 6 months, a year, even longer before presenting to a doctor and are then often told there is nothing we can do. All one has to do is search the internet for solutions for smell loss and hundreds of different pills and sprays are offered up as a panacea – a tell-tale sign that no one solution really works. The scientific literature is full of pilot studies and reports on possible effects of sprays or medications, which all either show no benefit or have not been powered well enough to show a convincing benefit. Although basic science research looking into the neuronal signaling pathways and function of the separate parts of the olfactory system has been accelerating, clinical research in this area had stagnated, until recently.

RATIONALE

The olfactory nerve is unique when compared with all the other cranial nerves, in that it has the inherent ability to regenerate and likely regenerates throughout our lifetime [5]. Knowing that there are

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KEY POINTS

- Olfactory training has level 1a evidence supporting its use in patients with olfactory loss from multiple causes, but has never been trialed in patients with olfactory loss because of chronic rhinosinusitis.
- Olfactory training improved a patient's ability to smell in about 30–50% of patients studied.
- Olfactory training is well tolerated and easy for patients to perform on their own and can be offered to any patient who complains of olfactory loss, regardless of cause.

basal cell progenitors within the olfactory epithelium allows us to reason that if the olfactory receptor neurons are damaged but these other cells remain intact, we have a chance at inciting regeneration [6]. Additionally, there is evidence that repeated exposure to odors promotes this neuroregenerative capacity [7,8].

OLFACTORY TRAINING – WHAT IS IT?

Although the exact duration and quantity of odorants varies in the literature, as outlined below, the basic idea is to have patients perform a repetitive and structured smelling of different odorants over a long period of time. It appears to be important to choose odors from different odorant categories, such as floral, fruity, aromatic, and resinous, and the patients are instructed to focus on what they are smelling during this protocol. Most protocols have patients smelling these scents at least twice a day and the duration may vary from 12 to 56 weeks.

A GROWING BODY OF EVIDENCE

Seven years ago, Hummel *et al.* [9] published a manuscript entitled 'Effects of Olfactory Training in Patients with Olfactory Loss.' They concluded that structured short-term (12 weeks) exposure to four particular odors (rose, eucalyptus, clove, and lemon) could increase olfactory sensitivity in patients with olfactory dysfunction. The causes of smell loss varied in this original population from postinfectious to traumatic to idiopathic, and the average duration of loss was just over 4 years. The world of neurology and otolaryngology took little notice at that time and physicians instead continued to try supplements such as zinc and α-lipoic acid without great effect. Slowly however, in Europe in particular, researchers began investigating this idea further.

In 2012, Fleiner *et al.* [10] tried the technique, again in a group of patients with disparate causes and this time included those whose olfactory loss came from sinonasal disease. They found that when they added a topical steroid they could replicate the significant improvement with olfactory training over 12 weeks in patients from all causes [10]. In 2013, Haehner *et al.* [11] looked specifically at patients with Parkinson's disease with olfactory loss and showed improvement in that population using olfactory training, and later that year Konstaninidis *et al.* [12] found improvement using olfactory training in patients with olfactory loss from postinfectious and posttraumatic sources. In 2014, several interesting studies were published, with Geissler *et al.* [13] showing improving efficacy of olfactory training with a longer duration of training after postinfectious olfactory loss, using 32 weeks instead of the previously used 12 weeks.

The finding of an increased interval of olfactory training having greater efficacy was carried over in the only published randomized controlled trial (RCT) evaluating olfactory training in postinfectious olfactory loss, carried out across multiple centers. The duration for olfactory training in this trial was 18 weeks and included a cross-over study design. Establishing a control arm for olfactory training is difficult, considering the long time period of training and likely exposure of the odorants to friends and family who would be able to easily distinguish the scented from unscented samples. In this RCT, Damm *et al.* [14▪▪] used low-dose (sub-threshold) and high-dose olfactory training arms to compare and establish a control. Patients who had duration of loss less than 1 year and received the high-dose olfactory training had a statistically significant improvement, compared with the control arm [14▪▪].

The protocol of olfactory training was further modified in 2015 by Altundag *et al.* [15] who demonstrated improved efficacy by adding more odors to the previously used four, changing to different odors at both the 12 and 24-week time points. Konstantinidis *et al.* [16] took the earlier results that showed increasing duration of olfactory training improved efficacy a step further, and compared a 16-week trial of olfactory training with a 56-week trial. This showed a nonstatistically significant difference between the two groups, where improvement was seen in both arms. Also, this study showed that the short-term gains made after 16 weeks of olfactory training were sustained at 56 weeks even without continuing the training [16].

All of the above studies used Sniffin' Sticks as the olfactory test of choice, to examine threshold,

identification and discrimination ability, and delineated very standardized concentrations of odorants for the patients to use. To modify this protocol to a cost-effective and convenient methodology for patients in the United States, Patel *et al.* recently performed a randomized trial evaluating the efficacy of substituting random concentrations of odorants in essential oil formulation over 6 months and testing patients using the University of Pennsylvania Smell Identification Test (UPSIT). Results mirrored those from the prior RCT. (This study was presented at the Combined Otolaryngology Sections Meeting in 2016, currently submitted for publication and undergoing peer review.)

EVIDENCE OF PLASTICITY WITHIN THE OLFACTORY SYSTEM

Striking evidence exists of olfactory training-induced plasticity in the neural circuitry of both patients with olfactory dysfunction and in healthy controls.

Kollndorfer *et al.* [17] took a small group of patients with olfactory dysfunction and performed both olfactory testing as well as functional MRI. This study showed that before olfactory training, patients had a chaotic and disorganized connectivity from the pyriform cortex to multiple nonolfactory regions of the brain, but after 12 weeks of training these nonolfactory connections disappeared [17].

Also, just this year, Negoias *et al.* [18] demonstrated that lateralized olfactory training increases olfactory bulb size on both the trained and untrained nostril, suggesting for the first time in humans that olfactory training may involve a top-down process.

Interestingly, 5 years before the first clinical study assessing olfactory training as an interventional protocol, Wang *et al.* [19] showed that repeated odor exposure improves olfactory sensitivity at the level of the olfactory epithelium as demonstrated on the electro-olfactogram.

These different objective indicators of neural plasticity at differing levels of the olfactory system underscore how little we currently know about the exact mechanism by which olfactory training is improving olfactory function, whether it is a peripheral or central process, or perhaps both.

QUALITY OF EVIDENCE

Pekala *et al.* [20▪▪] performed a systematic review and meta-analysis of the studies outlined above and were able to both assess the quality of the evidence as well as objectively evaluate and pool some of the results. They were able to include 10 studies in their qualitative review and three in the meta-analysis. They found the risk of bias to be low to intermediate for the studies included, but when study quality was assessed quantitatively using the modified Jadad test, the majority of the studies (with the exception of the RCT) were found to be of low quality (<3). In spite of this, when evaluating the three studies with pooled analysis, there did appear to be a statistically significant effect of olfactory training when compared with control patients.

CONCLUSION

Olfactory training is a simple protocol with no significant side-effects and proven efficacy in some patients with olfactory dysfunction. More research is needed to establish the optimal quantity of odorants, duration of training, and patient population most likely to improve using this technique.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
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