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Is Olfactory Training Effective Treatment for Postinfectious Smell Loss?

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BACKGROUND

Olfactory dysfunction affects approximately 15% of people and influences quality of life, psychiatric wellbeing, and safety.[1,2] One of the most common causes of smell loss is persistent olfactory dysfunction after an upper respiratory illness.[1] Over half of the patients who present with postinfectious smell loss (PISL) do not spontaneously improve, presumably due to virally mediated neuroepithelial damage.[1,3] Although current therapies for smell loss are limited, olfactory training (OT) has shown promise with improvement of olfactory function in select patients who undergo repeated exposures to various odors in a structured paradigm. This review summarizes pertinent studies assessing the effectiveness of OT in PISL.

LITERATURE REVIEW

In 2009, Hummel et al.[1] first reported the utility of OT in smell loss. In this prospective controlled study, 24 patients with PISL underwent twice-daily (BID) training with 10-second exposures to four odors (i.e., rose, eucalyptus, clove, and lemon) for 3 months, whereas 11 controls awaited spontaneous recovery without OT. Olfactory function was measured with Sniffin' Sticks (Burghart, Wedel, Germany), which are felt-tip pens impregnated with odorants, such that a threshold, discrimination, identification (TDI) score was generated before and after the study period. Of the patients with PISL, 21% who completed OT experienced an improvement in TDI of ≥6 points. This degree of change (≥6 points) is relevant, as it represents the threshold at which olfactory function improvement is perceived by a majority (60%) of patients.[4] This threshold was also reached in 6% of the control group at 3 months, demonstrating the potential for spontaneous improvement. This landmark study was the first to demonstrate the efficacy of OT compared to spontaneous recovery.

In 2013, Damm et al.[2] conducted a randomized, investigator-blinded, controlled, multicenter cross-over trial that evaluated OT in patients with PISL. Participants underwent BID training with four odors using a similar technique to that described above, but with 15-second exposures to each odor twice per session. Because a true placebo arm would be difficult, odors were provided as either subthreshold concentrations (10th percentile threshold for healthy volunteers, n = 74) or therapeutic concentrations (undiluted, n = 70). After 4 months, an improvement in TDI of ≥6 points was reached in 26% of the therapeutic concentration group versus 15% of the subthreshold concentration group. These findings suggest that 15% of patients improved either spontaneously or from the act of sniffing (without detectable odors present), whereas an additional 11% of patients beyond that benefited from OT. Following cross-over, an additional 20% of the group that underwent subthreshold concentration OT from 4 to 8 months reached an improvement in TDI of ≥6 points, whereas only an additional 16% of the group that underwent therapeutic concentration OT during that subsequent timeframe achieved this threshold. This finding suggests that earlier initiation of therapeutic concentration OT may be more beneficial than delayed. Patients with <12 months of smell loss were more likely to achieve an improvement in TDI of ≥6 points than those with >12 months of smell loss at enrollment (63% vs. 19%, P = .03). Patient age was not significantly associated with olfactory improvement. The study found an 8% rate of minor adverse events during OT (e.g., epistaxis, nasal burning, and hay fever).

Altundag et al.[3] prospectively studied age- and gender-matched patients with PISL using either a classical (n = 33) or modified (n = 37) OT regimen compared to a control group without training (n = 15) over a duration of 8 months. In their classical training group, patients were trained BID on the standard four odors. In their modified

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training group, different sets of four new odors were introduced at 3 and 6 months of training (i.e., menthol/thyme/tangerine/jasmine and bergamot/rosemary/gardenia/green tea). In olfactory testing at both 6 and 8 months, an improvement in TDI of ≥6 points was reached in 46% of the classical training group versus 56% of the modified training group, whereas no control patients reached this threshold spontaneously. Of note, the rates of improvement in TDI of ≥6 points did not increase after 6 months of training in either paradigm. Both OT groups demonstrated greater olfactory improvement compared to the control group ($P < .05$), and the modified training group demonstrated greater improvement in TDI score compared to the classical training group ($P = .034$). The authors also found greater benefit from OT in patients who had a shorter duration of smell loss ($P < .01$). Overall, this study showed that introducing new odors during training may provide additional benefit; however, no additional benefit was observed after 6 months of training.

Konstantinidis et al.[5] performed a prospective study of patients with PISL, comparing OT durations of either 13 months (n = 34, longer term) or 4 months (n = 36, shorter term) versus controls without training (n = 41). Participants underwent BID training with the standard four odors, but with a 10-second exposure, followed by a 10-second break, rotating through all odors for a total of 5 minutes per session. Both training groups showed rapid improvement in the first 4 months of training, and the shorter-term training group sustained its improvement in TDI score over the subsequent 9 months after halting training. The longer-term training group showed slower improvement over the subsequent 9 months, such that 71% of the total TDI improvement occurred during the initial 4 months. At 13 months, an improvement in TDI of ≥6 points was reached by 58% of the shorter-term training group and by 71% of the longer-term training group ($P = .07$). In comparison, the control group showed a more linear improvement over the 13 months, with only 37% reaching this threshold, presumably due to spontaneous improvement. Similar to prior studies, olfactory improvement was not associated with patient age ($P > .05$) but was inversely associated with duration of smell loss ($P < .05$). This study demonstrated that the majority of benefit from OT is achieved within the first 4 months and sustained long term (9 months beyond training).

BEST PRACTICE

Existing evidence suggests that OT is a low-risk intervention that provides clinically relevant and sustained benefit in some PISL patients beyond the observed rates of spontaneous recovery. The majority of improvement is observed within the first few months of OT and is not dependent upon patient age. Earlier initiation of OT appears to offer greater benefit, and modifications to the training paradigm, including adding new odors or extending the duration of training, may offer some additional modest gains. Further research is required to determine the optimal OT parameters, to clarify the adjunctive potential of OT when paired with other proposed treatments for PISL (e.g., corticosteroids, vitamin B, and acupuncture), and to identify the additive benefit of OT compared to spontaneous recovery over the long term.

LEVEL OF EVIDENCE

This best practice recommendation is based on level 1b (one randomized controlled trial) and level 2b (three prospective cohort studies) evidence.

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