Novel Protocol Using a Comprehensive Training 'N' Treatment (TNT) Approach Rapidly Reverses Olfactory and Gustatory Dysfunction in Patients with Acute Loss of Taste and Smell Induced by SARS-CoV-2 Infection

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Research Article

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Abstract

Infection with SARS-CoV-2 causes COVID-19 and has a well-established set of clinical symptoms. Olfactory and gustatory dysfunction are among the non-life threatening sequalae observed with both acute and chronic SARS-CoV-2 infection. This can lead to the loss of taste and smell and has been observed in large subsets of COVID-19 patients. Although non-life threatening, loss of taste and smell can contribute to decreased quality of life and prevent sufficient nutrient intake, which may negatively affect prognosis and recovery. Despite progress in the treatment of other symptoms caused by COVID-19, there are currently no standardized treatment protocols to mitigate loss of taste and smell caused by SARS-CoV-2 infection and most approaches thus far have evaluated sensory training and regimen-based treatment strategies independently. In this retrospective case series, we demonstrate the effectiveness of a comprehensive, combined treatment protocol for COVID-19-induced taste and smell dysfunction using olfactory and gustatory training in combination with vitamins and supplements, nasal irrigations, nerve stimulation exercises, and anti-inflammatory prophylaxis. Acutely infected patients with COVID-19-related loss of taste and smell were given a daily regimen of zinc, vitamin A, B-complex, vitamin D, and alpha lipoic acid in addition to saline nasal irrigation, fluticasone spray, nerve stimulation exercises, and repeated olfactory-gustatory training. Triamcinalone paste, theophylline, and prednisone were included daily with the observation of partial recovery. At two timepoints over approximately 20–37 days of treatment, taste and smell scores were quantified based on detection of agents included on each sensory training panel. Following this novel and comprehensive “Training ‘N’ Treatment” (TNT) protocol, every patient exhibited a complete recovery of taste and smell. Given the potential to provide relief to the many people with olfactory and gustatory dysfunction following SARS-CoV-2 infection, the effectiveness of this protocol warrants validation in a larger study.

Introduction

The novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified in 2019 and results in a characteristic infectious disease (COVID-19). SARS-CoV-2 has since spread across the globe and was classified as a pandemic by the World Health Organization on March 11, 2020. In addition to deadly sequela, COVID-19 also has a well-characterized set of less severe symptoms that can affect clinical recovery and quality of life. Ageusia (loss of taste) and anosmia (loss of smell) are symptoms associated with COVID-19 and can have acute and chronic onset with variable lengths of duration. Although not life threatening, these symptoms decrease drive for nutritional intake, which can significantly impact recovery time with both acute infection and chronic disease [1–3]. Recent studies have shown that up to 98% of those infected with COVID-19 had reported ageusia or anosmia [4–6], and the Centers for Disease Control and Prevention (CDC) includes sense of taste or smell loss as a disability that can occur in the acute phase following SARS-CoV-2 infection (2–14 days after exposure) [7, 8]. As this disability may become more prevalent and recognized, standardized treatment and monitoring is necessary to support patient recovery and improve outcomes. Consequently, a treatment protocol leading

to complete taste and smell recovery in acutely and previously infected COVID-19 patients could have a significant impact on immediate clinical status and overall quality of life for patients.

SARS-CoV-2 invades and infects host cells through membrane fusion of viral spike glycoprotein to human angiotensin-converting enzyme 2 (ACE2) receptor. The ACE2 receptor is widely prevalent in the gastrointestinal tract, nasal and bronchial epithelium, type II alveolar epithelial cells in the lung parenchyma, and glial cells and neurons [9]. Although oral and mucosal cavities are susceptible to SARS-CoV-2 infection and are vulnerable initial viral entry points [10], research has shown that as little as 13% of individuals with SARS-CoV-2-induced olfactory dysfunction have rhinitis (nasal blockage) [11]. This suggests that the clinical manifestation of taste and smell loss may have pathogenic influence outside of mucosal membrane or nasal inflammation specifically [12]. Accordingly, evidence suggests that SARS-CoV-2 infection can cause damage to the mucosal epithelium to facilitate CNS invasion through the olfactory nerve [13]. Furthermore, SARS-CoV-2 infection of cells via ACE2 receptors in the taste buds can lead to cellular apoptosis and receptor degradation, which can lead to decreased sensitivity of the neurons [14]. Olfactory and gustatory training using repeated exposure to a standardized panel of agents may enhance regeneration of damaged sensory neurons and has been proposed to treat loss of smell caused by viruses, including SARS-CoV-2 [15–17]. Additionally, manual stimulation of the chorda tympani and the trigeminal nerve can also assist in recovering and regenerating olfactory and gustatory functionality [18–20].

In addition to olfactory-gustatory training, other intranasal and/or systemic treatment strategies (both monotherapeutic and combinational approaches) have been trialed with promising results [14]. Zinc is an essential trace element that is involved broadly in enzymatic activity and is associated with gustatory dysfunction. To this accord, taste disorders have been treated with orally administered zinc to directly promote food intake via stimulation of appetite-stimulating hypothalamic neuropeptide Y [21]. Furthermore, vitamin A increases the regeneration of olfactory neurons and can result in an increase of taste and smell in patients who experience hyposmia and hypogeusia [22, 23]. Vitamin A can also stimulate regeneration and repair of the olfactory system to help restore the sense of smell in cases of post-viral smell loss [23, 24]. In addition, B-complex vitamins containing B6 and B12 have been associated with gustatory treatment recovery and the addition of these minerals appears to impact the resolution of hyposmia along with other interventions [25]. Vitamin D has anti-inflammatory effects [26] and has been shown to protect against increased infection and mortalities observed with COVID-19 [27, 28]. Alpha lipoic acid decreases ACE2 receptor activity after SAS-CoV-2 infection and has antioxidative effects that could reduce NADPH oxidase activity [29]. Moreover, considering that high levels of the pro-inflammatory cytokine TNFα are observed in the olfactory epithelium of patients with COVID-19, alpha lipoic acid-mediated inhibition of TNFα can reduce inflammation and enhance sensatory recovery [30]. Triamcinolone paste is added to the tongue to stimulate the sodium-potassium adenosine triphosphatase (Na/K-ATPase) present locally on salivary glands, which is required for the secretion of saliva in the glandular acini and may be dysregulated during the anosmia and ageusia caused by COVID-19 [31]. Theophylline has been shown in animal studies to improve sense of smell and taste by stimulating gustatory and olfactory stem cells to secrete nasal mucus and saliva growth factors such as cAMP and

cGMP, which can promote neuronal excitability and synaptic transmission [32, 33]. Since each of these treatment strategies has shown promise individually and/or has a mechanistic rationale for restoring gustatory and olfactory dysfunction caused by COVID-19, we designed a comprehensive protocol that would incorporate them all into a daily regimen (Table 1).

Table 1
Treatments Included in the 'TNT' Protocol.

Treatments	Dose	Function	Rationale/Purpose	Reference
Zinc	50 mg	Required for enzymatic reactions, gene expression, immune function, DNA and protein synthesis, wound healing, and growth and development	Taste disorders have been treated with orally administered zinc to directly promote food intake via stimulation of appetite-stimulating hypothalamic neuropeptide Y	[21]
Vitamin A	10,000 IU	Supports cell growth, immune function, and vision	Promotes regeneration and repair of olfactory neurons and cells of the olfactory system	[22, 24]
Vitamin D3	10,000 IU	Critical for building bone, controlling infections, reducing inflammation, and supporting the immune system	Regulates the immune system response from infection to reduce inflammation in the olfactory and gustatory systems	[26, 27]
Alpha Lipoic Acid	300–600 mg x2 per day	Reduces inflammation, has antioxidant properties, and promotes both nerve function and cellular growth	Decreases ACE2 receptor activity after SAS-CoV-2 infection and has antioxidative effects that could reduce NADPH oxidase activity; inhibition of TNFα in the olfactory epithelium to reduce inflammation and enhance sensatory recovery	[29, 30]
B-Complex (B6 and B12)	100 mg (B6), 100 mcg (B12)	Helps prevent infections and supports and promotes cell health, stimulates red blood cell growth, promotes brain function, helps digestion and appetite, stimulates nerve function, and promotes production of hormones and cholesterol	Associated with treatment-mediated gustatory recovery and the addition of B6 and B12 can impact the resolution of hyposmia along with other interventions	[48]

Treatments	Dose	Function	Rationale/Purpose	Reference
Triamcinolone paste	0.01%	Used for temporary relief of symptoms such as swelling, itching, and pain in the mouth resulting from mouth sores	To stimulate the sodium-potassium adenosine triphosphatase (Na/K-ATPase) present locally on salivary glands, which is required for the secretion of saliva in the glandular acini and may be dysregulated during the anosmia and ageusia caused by COVID-19	[31]
Fluticasone Spray	1 spray per nostril x2 per day	A localized corticosteroid that relieves symptoms such as sneezing and runny, stuffy, or itchy nose	Associated with reducing viral load and helps with olfactory and taste functions of patients with COVID-19 by reducing localized inflammation	[49]
Sodium Citrate Spray	1 spray per nostril x2 per day	Reduces calcium in nasal mucosa	Reducing free mucosal calcium with reduced negative feedback and increased sensitivity to odorants; reduction in free calcium ions (Ca^{2+}) is likely to increase the excitability of olfactory neurons, thereby improving the sense of smell	[14]
Theophylline Spray	3–4 sprays per nostril 1x per day	Asthma medication promoting cAMP and cGMP	Growth factors such as cAMP and cGMP can improve sense of smell and taste by stimulating gustatory and olfactory stem cells to secrete nasal mucus and saliva to stimulate neuronal excitability, olfactory receptor cells, and synaptic transmission	[32, 33]
Prednisone	60 mg per day	A systemic corticosteroid that lowers immune system activity and suppresses inflammation	Mitigating the COVID-19-induced systemic inflammatory response manifesting in the olfactory and gustatory system	[15]

Treatments	Dose	Function	Rationale/Purpose	Reference
Chorda Tympani Stimulation	Protracted Smiling for 3–5 seconds 20x (3x per day)	The chorda tympani carries taste sensation from the anterior portion of the tongue; physical stimulation of this nerve via smiling helps improve reactivity; this nerve is part of the facial nerve (CN VII), and meets the lingual nerve of the mandibular branch of the trigeminal nerve (CN V_3), which is responsible for sensory information from the mandibular region of the face	Chemoreceptors for individual tastes trigger cellular depolarization and run through the chorda tympani; stimulation of this nerve may promote regeneration and lead to taste recovery	[18–20]
Trigeminal Nerve Stimulation	Cotton ball application to mandible 1–2 minutes (4x per day)	The third branch of the trigeminal nerve (CN V_3) is the mandibular branch, which travels alongside the chorda tympani to the anterior portion of the tongue; manual stimulation of these nerves with a cotton ball in the mandibular region can improve sensory response	The nerves for taste sensation run alongside nerves for touch sensation innervating the anterior portion of the tongue; sensory stimulation of this region using the mandibular branch of the trigeminal nerve as a landmark can help improve nerve response in attempts to restore taste	[18–20]
Nasal Irrigation	Neti pot rinsing with saline 2x per day	Washes out virus, mucus, and other proinflammatory allergens/antigens	Odors activate intranasal chemosensory system; irrigation of the nasal passages ensures open airflow, and should allow for optimal activation	[50]
Sensory training	3x daily taste training; 4x daily smell training	Olfactory and gustatory training can restore damaged sensory neurons	SARS-CoV-2 infection can lead to CNS invasion, olfactory nerve damage, and decreased sensitivity of taste buds	[17, 51]

Despite some encouraging results, there currently are no accepted uniform guidelines to treat COVID-19-induced olfactory and gustatory dysfunction. Here, we evaluated a comprehensive protocol comprising treatment with vitamins and supplements, repeated olfactory-gustatory training, nasal irrigation, anti-inflammatory treatments, and nerve stimulation exercises and incorporated them into a structured regimen designed to improve the sense of taste and smell in acutely infected patients with COVID-19: the

Training ‘N’ Treatment (TNT) approach (Fig. 1). All patients exhibited 100% recovery of taste and smell within 20–37 days of starting the TNT protocol.

Methods

Study Participants: During scheduled appointments, patients were treated from clinic locations in Kalamazoo, MI (Simon Medical Services) and Los Angeles, CA (Private Health Management Medical Group, Inc.) and verbally agreed to participate in this treatment approach (N = 5). Clinical and treatment protocol data were collected during each patient visit, including smell and taste evaluations and cranial nerve assessments. Participants were between the ages of 31 and 71 with a diagnosis of ageusia and anosmia subsequent to confirmed SARS-COV-2 infection by reverse transcription polymerase chain reaction (RT-PCR)-based testing; exclusion criteria included inability to both read and speak English, significant mental impairment, psychiatric disorder that would limit ability to participate or that might cause additional risks, non-stable autoimmune disease(s), or if current medications included steroids or other anti-inflammatory drugs. This retrospective case series includes patients seen from July 2, 2021 through December 1, 2021. Retrospective chart review and analysis was conducted according to an approved Institutional Review Board (IRB) protocol: PHM-2023-01; “Evaluation of a Treatment Protocol to Mitigate Olfactory and Gustatory Dysfunction in Patients with Acute Loss of Taste and Smell Induced by SARS-CoV-2 Infection – Retrospective Cohort Analysis”.

Training ‘N’ Treatment (TNT) Protocol: Upon initial clinic visit, each patient had both their smell and taste evaluated qualitatively (yes/no) to establish their deficits. Sense of smell was assessed by panel of six agents (gently wafted within six inches of the nose): essential oils (sweet orange, lemongrass, peppermint, eucalyptus, lavender), cinnamon, cloves, crushed garlic, crushed onions, and cocoa. Sense of taste was evaluated by a panel of four agents (added to the tongue): sugar, salt, lemon juice, and orange bitters. The first phase of the protocol included instructing each patient to conduct: daily smell and taste training, nerve stimulation exercises, neti pot nasal irrigation, fluticasone spray, and vitamin supplements. Taste stimulation training was performed three times daily by adding each agent to the tongue. After the qualitative taste response was recorded, water was used to rinse before addition of the subsequent agent. Smell stimulation was performed in each nostril separately four times daily by gently wafting each agent independently within six inches of the nose and inhaling for 3–5 seconds. Qualitative results were recorded after exposure of each agent to both nostrils. Patients were started on a daily supplement regimen: zinc 50 mg, vitamin A 10,000 IU, vitamin D3 10,000 IU, alpha lipoic acid 300–600 mg twice daily, and a B-complex containing B6 100 mg and B12 100 mcg. All vitamins used were certified Good Manufacturing Practices (GMP); not all commercially available vitamins uphold this stringent requirement through the U.S. Food and Drug Administration. Nerve stimulation exercises were performed to stimulate the chorda tympani (3 sets daily) and trigeminal nerve (4 times daily). Each set of chorda tympani stimulation exercises consisted of protracted smiling 20 times held for 3–5 seconds. In order to stimulate the third division of the trigeminal nerve, a cotton ball was firmly stroked in the mandibular region (both sides) for 1–2 minutes. Also, patients were instructed to use a neti pot with saline packets per manufacturer’s protocol twice daily to irrigate each nostril. After irrigation, patients would blow their

nose and spray Fluticasone twice in each nostril per manufacturer recommendations. Smell and taste detection was reevaluated in the clinic approximately 10 days after beginning the initial phase of treatment. If there was not complete resolution, a second phase was implemented, which included modifications specific to partial recovery of either taste or smell. If only partial taste recovery was measured, triamcinolone dental paste (0.1%) was applied to the tongue two times daily for one hour. Additionally, increasing amounts of the unreturned tastes were titrated for daily training along with one patient-identified taste that returned (if applicable). If only partial recovery of smell was achieved, the daily neti pot irrigations were suspended. Alternatively, intranasal sodium citrate spray was used two times per nostril daily along with theophylline nasal spray 3–4 times per nostril daily (240 mg/400 cc normal saline). Also, a 10-day course of prednisone (60 mg/day) was initiated. Approximately one week later, patients were reevaluated again with all agents on the taste and smell panel. While all study participants had reported complete resolution of olfactory and gustatory function in our case series at this timepoint, we have extrapolated our treatment protocol recommendations for future, larger-scale efforts. In the event of partial taste recovery at this timepoint of evaluation, triamcinolone dental paste would be continued along with daily gustatory training consisting of further increased titrations of the unreturned tastes along with one patient-identified taste that has returned (if applicable). If continued olfactory dysfunction is observed at this timepoint, prednisone treatment would be suspended, but daily intranasal treatment with sodium citrate and theophylline would continue indefinitely. A schematic of this treatment protocol is shown in Fig. 2.

Smell/Taste Score Evaluations and Statistical Analysis: For each olfactory and gustatory function evaluation in the clinic, patients were exposed to all smell and taste panel agents as described above. Qualitative (yes/no) detection was recorded for each individual agent and overall smell and taste scores were reported as a percentage. Timepoints for evaluation included baseline (initial clinic visit), timepoint 1 (approximately 10-days post-treatment), and timepoint 2 (approximately 17-days post-treatment). Statistical analysis for all three groups collectively was performed by one-way ANOVA followed by Tukey's post hoc test using Graph Pad Prism software (v8.3.0). All numerical datasets were expressed as mean values with standard error of the mean indicated (SEM). Data was considered statistically significant if $p \leq 0.05$.

Results

Study Cohort of Patients with Acute SARS-CoV-2-induced Loss of Taste and Smell

In this retrospective case series, the cohort of patients included for evaluation consisted of two males and three females with an average age of 53.6 years (ranging from 31–71 years of age). Current medications did not include steroids, targeted anti-inflammatories, or any other medication with influence over gustatory and olfactory function. No relevant co-morbidities were identified aside from hypothyroidism (N = 1), hypertension (N = 1), and obesity (N = 1); the participant with hypothyroidism has been stable for

many years on a regular treatment consisting of conventional TSH/T3/T4 monitoring and Synthroid medication. All study volunteers were unvaccinated for SARS-CoV-2, apart from one who completed the initial BNT162b2 mRNA SARS-CoV-2 vaccine series (Pfizer/BioNTech). All patients were diagnosed with acute SARS-CoV-2 infection that was confirmed with a commercially available, laboratory-conducted RT-PCR test. Positive genomic viral detection was measured at an average of 4.2 days post-symptom onset with a range of 0–8 days. The TNT protocol was initiated at the clinic visit immediately after (within 48 hours) symptom onset and positive RT-PCR test result. Two patients received a seven-day course of ivermectin that was implemented within 48 hours of symptom onset. COVID-19 manifestation was considered mild for one study volunteer and was characterized by upper respiratory infection (URI) and gastrointestinal (GI) symptoms, but no detectable fever or hospitalization requirements. The remaining four COVID-19 cases were moderate, characterized by URI or GI symptoms with the presence of sustained fever (maximum recorded temperature greater than 100.4°F). While all patients experienced olfactory and gustatory dysfunction, other COVID-19 symptoms varied; nasal congestion and fever were observed in four patients, cough and mucous production in three, sore throat in two, and shortness of breath in one. Four patients never smoked, and one was a moderate smoker previously. A summary of patient demographics for this pilot cohort is included in Table 2.

Table 2
Baseline Characteristics of Study Participants.

Demographic Information	Number
Total Participants	5
Age (yrs), median, [range]	53.6 [31–71]
Sex	
Male	2
Female	3
Vaccinated	1 (Pfizer)
Unvaccinated	4
RT-PCR Confirmed SARS-CoV-2 Infection	5
Time from COVID-19 Symptoms until TNT Protocol Initiated	
Average (days), median, [range]	4.2 [0–8]
Relevant COVID-19-Associated Interventions	
Ivermectin x 7 days	2
Severity of Disease*	
Mild	1
Moderate	4
Severe	0
COVID-19 Symptoms Observed	
Olfactory Dysfunction	5
Gustatory Dysfunction	5
Nasal Congestion	4
Mucus production	3
Fever	4
Cough	3
Sore Throat	2
Shortness of Breath	1

*Classification of disease: mild = not requiring hospitalization, no fever present, URI or GI symptoms present; moderate = mild + presence of fever (T_{max} > 100.4 F); severe = moderate + hospitalization

Comorbidities	
Hypothyroidism	1
Hypertension	1
Obesity	1
Smoking History	
Never	4
Former	1
Current	0
*Classification of disease: mild = not requiring hospitalization, no fever present, URI or GI symptoms present; moderate = mild + presence of fever (T_{max} > 100.4 F); severe = moderate + hospitalization	

Relevant to adherence of Consensus-based Clinical CAse REporting (CARE) Guidelines [34] and not reported above or listed in Table 2, additional information was also collected from study participants. Average sleep was approximately 7 hr/night with one participant reporting as little as 4 hrs and one claiming 8–10 hrs. Regular exercise was reported by 4/5 participants and included daily cycling for 40 min, elliptical twice a week, elliptical and weights 1.5 hrs/day for 5 days/week, and treadmill 3 times/week for 50 min. Family histories of illness included, diabetes, metabolic syndrome, cardiac disease, high lipids, and asthma. Minimal to mild psychological stress was self-reported (no participants with severe stress). No adverse events were reported during treatment with the TNT protocol.

Complete Recovery of Gustatory Function with TNT Protocol

To recover the loss of taste following acute SARS-CoV-2 infection, the TNT protocol was implemented as described in the materials and methods and summarized in Fig. 2. At the initial clinic visit, the baseline results of the taste panel assessment showed that three participants had no detectable tastes and two could only identify one agent. These measurements calculated to an average taste score of 10% across all volunteers. At the first timepoint (approximately 10 days post-TNT), all study participants showed a partial recovery of gustatory function and the average taste score had significantly increased to 58% relative to baseline ($p = 0.0002$). Approximately one week later, all study participants achieved a full recovery, as reflected by successful detection of all agents on the assessment panel. The results from this final timepoint demonstrated a statistically significant increase in taste relative to the first timepoint ($p = 0.0004$) and baseline scores ($p < 0.0001$). By day 37 post-TNT, all patients had achieved complete recovery of gustatory function. Evaluation of taste scores are shown as line graphs for each individual patient and expressed collectively at each timepoint for statistical analysis (Fig. 3A-B).

Complete Recovery of Olfactory Function with TNT Protocol

Patients presenting with a putative olfactory dysfunction were treated with the TNT protocol as outlined in the materials and methods section and summarized in Fig. 2. Baseline olfactory function was measured by determining smell scores following qualitative assessment of each patient using the agents included on the panel. The results of initial testing indicated an average smell score of 6%, with three study volunteers reporting no detection of any agent on the panel. After approximately 10-days of the TNT protocol, olfactory function had improved in all patients and yielded a significantly increased average score that was 44% higher than baseline measurements ($p = 0.0031$). Similar to the results evaluating gustatory function above, a complete recovery of smell was observed at the second timepoint in all participants. Specifically, the improvement of olfactory dysfunction with the TNT protocol was statistically significant relative to both the previous timepoint ($p = 0.0012$) and baseline levels ($p < 0.0001$). Evaluation of smell scores are shown as line graphs for each individual patient and expressed collectively at each timepoint for statistical analysis (Fig. 3C-D).

Discussion

Considering the immediate and life-threatening concerns associated with COVID-19, olfactory or gustatory dysfunction resulting from SARS-CoV-2 infection is often overlooked. However, focus has turned more recently towards understanding the underlying pathophysiology of COVID-19-associated ageusia and anosmia, allowing for putative prophylactic protocols to be evaluated clinically. Since olfactory and gustatory dysfunction have been observed with other upper respiratory infections of viral etiology, including influenza, the common cold viruses, and other coronaviruses, pathogenesis and treatment interventions can be comparatively considered [1, 35, 36]. While there have been interventional strategies proposed and studies performed to help COVID-19 patients recover their sense of taste and smell, they typically include either sensory stimulation training or treatment-based approaches (combinational or monotherapy); a more comprehensive strategy combining both modalities has not been evaluated previously. Since larger epidemiological analyses have shown that residual olfactory and gustatory dysfunction occurs in approximately 25% of COVID-19 patients more than 60 days post-recovery [37], a standardized treatment protocol that can provide rapid recovery from ageusia and anosmia could have significant clinical impact and contribute to enhanced quality of life. Furthermore, this protocol can be referenced and implemented in the event of a future viral pandemic that also causes chronic olfactory and gustatory dysfunction in patients. In this study, we outline a novel and comprehensive protocol consisting of both sensory training exercises and a treatment regimen that resulted in a rapid and complete recovery of taste and smell in a pilot cohort of patients with acute COVID-19.

Chemosensory dysfunction during acute and chronic COVID-19 has been linked to several complex mechanisms. Our multitiered approach, using both sensory stimulation and treatment considers multiple pathophysiological contributions to olfactory and gustatory dysfunction. The prevalence of ACE2 receptors on olfactory and gustatory cells leads to significant cell damage during SARS-CoV-2 infection. The loss of taste has been associated with damage to the salivary glands and sialic acid receptors [38, 39], while damage to olfactory sensory and receptor neurons, olfactory epithelium, and supporting cells

contribute to the loss of smell [40–42]. In addition, immune responses to SARS-CoV-2 generate inflammation, which exacerbates damage to the cellular microenvironment [43, 44]. The TNT protocol combines stimulation to increase regeneration of olfactory and gustatory cells with treatments to modulate immune responses, reduce inflammation, and promote cell growth. Using the TNT protocol, we demonstrate 100% recovery in all patients in under 40 days. Four patients fully recovered by day 20 with one patient demonstrating a more delayed response. The complexity of chemosensory dysfunction and the multifactorial cause resulting from SARS-CoV-2 infection requires persistent and continual training to recover senses over time, particularly in initially refractory cases.

Although these data are encouraging and demonstrate a rapid, complete recovery of olfactory and gustatory function, the conclusions are limited by the scope of this retrospective case series. The number of visits to the clinic was not consistent for each patient and the measurements of sensory recovery are qualitative and subjective assessments. Additionally, the limited number of patients and the lack of an untreated control group for comparison prevent definitive conclusions despite meeting statistical significance by ANOVA analysis. In order to validate these observations in a larger study, a multicenter, randomized, double-blinded, and controlled design would be recommended. Moreover, since natural history studies have demonstrated 72% recovery of olfactory function and 84% recovery of gustatory function approximately one month after SARS-CoV2 infection [45], distinguishing the direct impact of the TNT protocol in acutely infected patients is not clear. Despite these limitations, it is reasonable to presume that a qualitative assessment of sensory detection and confirmation of full recovery is indeed the most informative datapoint, as the goal is to rapidly restore quality of life to those affected.

Although the number of individuals collectively described in this series is limited, the TNT protocol was also evaluated in our clinics in numerous additional scenarios of SARS-CoV-2-induced ageusia and anosmia with full recoveries observed. While previous studies have found it difficult to completely recover olfactory and gustatory function after a prolonged period, a 51-year-old male patient reporting loss of taste and smell for 13 months experienced smell recovery in 7 weeks and taste recovery after 3 months with the TNT protocol. This is the longest case of sensory loss that was seen in our clinics before any intervention was made. Continued multilayered training and stimulation allowed for slow and step-wise recovery of both taste and smell over time with individual tastes and smells returning at different time points. Additionally, individuals with severe disease and co-morbidities have prolonged recoveries and often continue to experience clinical complications beyond the acute infection phase [46]. In this scenario, COVID-19-induced ageusia and anosmia could impact the sufficient nutritional intake required for improved prognosis. In a 71-year-old patient who experienced moderate to severe COVID-19 with interstitial eosinophilic bronchitis, secondary asthma, and high blood pressure, the TNT protocol successfully restored taste and smell in 37 days. Furthermore, studies have reported some level of olfactory and gustatory dysfunction in 62% and 54% of patients after receiving a vaccination for SARS-CoV-2, respectively [47]. In our clinic, the TNT protocol was also able to completely correct chemosensory dysfunction following the 2nd dose of the Pfizer BioNTech COVID-19 mRNA vaccine. The patient experienced metallic taste suddenly and simultaneously when receiving the injection with continued deteriorating loss of taste and smell over the subsequent 5.5 months before starting mitigative treatment.

She had no known exposure or detectable symptoms related to SARS-CoV-2. After 3 months of treatment, the TNT protocol stimulated the complete return of both taste and smell in this patient. This collection of COVID-19-associated clinical scenarios with chemosensory dysfunction emphasizes the imperative to establish a standardized and effective treatment strategy to restore senses. The TNT protocol outlined here provides a consistently effective regimen for treating a multitude of different clinical scenarios of gustatory and olfactory dysfunction resulting from COVID-19 and should be evaluated in larger cohorts of future prospective studies.

The complexity and multisystemic damage leading to olfactory and gustatory dysfunction requires a temporal and comprehensive approach to both repair and restore sensory loss caused by SARS-CoV-2. The TNT protocol is a dynamic, multifaceted approach that addresses diverse pathoetiology and allows training over time for continued restoration of senses. Studies have demonstrated the difficulty of recovering 100% of taste and smell after prolonged periods and/or in more problematic cases. Thus, this case series underscores the need for future work to assess the durability and totality of sensory recovery following interventional treatment. As SARS-CoV-2 infections persist worldwide, more individuals continue to experience lingering symptoms from COVID-19, including many experiencing post-acute COVID syndrome (i.e., long COVID). As our understanding of persistent symptoms, such as ageusia and anosmia, resulting from post-acute COVID syndrome develops, larger clinical studies investigating efficacy of interventional strategies will continue to be evaluated. Accordingly, we are proposing future work assessing the effectiveness of the TNT protocol to mitigate SARS-CoV-2-associated loss of taste and smell in acute infections, chronic infections, long COVID, and vaccine-mediated reactions. These large-scale, multicenter, double-blinded, and controlled trials should also monitor and characterize other endpoints, including inflammation-associated biomarkers, immune response biomarkers, and histology of the nasal epithelium and tongue. Measuring targeted restoration of specific tastes and smells and stratifying recovery longitudinally more quantitatively would allow for greater understanding of pathologic mechanisms. Collectively, there is great potential for the application of this work as olfactory and gustatory dysfunction resulting from COVID-19 persists.

Declarations

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COMPETITING INTERESTS

None declared.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA SHARING STATEMENT

All of the data collected during this study, the data analysis plan, and the treatment protocol are on-file for sharing immediately following publication to anyone who wishes to access the data for any purpose with no end date. Proposals should be directed to nyoung@privatehealth.com. To gain access, requestors will need to sign a data access agreement.

PATIENT CONSENT AND INSTITUTIONAL REVIEW BOARD APPROVAL

All study activities were conducted according to an approved Institutional Review Board (IRB) protocol: WCG Protocol Number: 20230376, Study Number: 1348687; Sponsor Protocol Number: PHM-2023-01; “Evaluation of a Treatment Protocol to Mitigate Olfactory and Gustatory Dysfunction in Patients with Acute Loss of Taste and Smell Induced by SARS-CoV-2 Infection – Retrospective Cohort Analysis”. Prior to compiling, analyzing, and reporting the data included in this case series, written consent for publication was also obtained from all participants.

AUTHOR CONTRIBUTIONS

Conceived and designed the experiments of the study: IB, NO, RS. Data collection and analysis: NY, SM, NO, IB, RS. Performed experiments: RS. Edited manuscript: NY, CS, FT, SM, ML, TW, TP, KR, NO, IB, GB, JP, EG, RS. Statistical assessments: NY, SM. Wrote manuscript: NY, CS, FT, TP, KR, EG, RS. Contributed reagents/materials/analysis tools: NO, IB, RS. Made substantial, direct, and intellectual contributions to the work, and approved it for publication: NY, CS, FT, SM, ML, TW, TP, KR, NO, IB, GB, JP, EG, RS.

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References

1. Othman, B.A., et al., *Olfactory dysfunction as a post-infectious symptom of SARS-CoV-2 infection.* Ann Med Surg (Lond), 2022. **75**: p. 103352.

2. De Groot, L. and A. Vivanti, The frequency of nutrition impact symptoms and reduced oral intake among consecutive COVID-19 patients from an Australian health service. Br J Community Nurs, 2022. **27**(3): p. 136-142.
3. Laviano, A., A. Koverech, and M. Zanetti, *Nutrition support in the time of SARS-CoV-2 (COVID-19).* Nutrition, 2020. **74**: p. 110834.
4. Borsetto, D., et al., Self-reported alteration of sense of smell or taste in patients with COVID-19: a systematic review and meta-analysis on 3563 patients. Rhinology, 2020. **58**(5): p. 430-436.
5. Speth, M.M., et al., Olfactory Dysfunction and Sinonasal Symptomatology in COVID-19: Prevalence, Severity, Timing, and Associated Characteristics. Otolaryngol Head Neck Surg, 2020. **163**(1): p. 114-120.
6. Mullol, J., et al., The Loss of Smell and Taste in the COVID-19 Outbreak: a Tale of Many Countries. Curr Allergy Asthma Rep, 2020. **20**(10): p. 61.
7. Mehraeen, E., et al., Olfactory and gustatory dysfunctions due to the coronavirus disease (COVID-19): a review of current evidence. Eur Arch Otorhinolaryngol, 2021. **278**(2): p. 307-312.
8. Tenforde, M.W., et al., Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network - United States, March-June 2020. MMWR Morb Mortal Wkly Rep, 2020. **69**(30): p. 993-998.
9. Eslami, N., et al., *SARS-CoV-2: Receptor and Co-receptor Tropism Probability.* Curr Microbiol, 2022. **79**(5): p. 133.
10. Xu, H., et al., High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci, 2020. **12**(1): p. 8.
11. Li, H., Q. Xue, and X. Xu, *Involvement of the Nervous System in SARS-CoV-2 Infection.* Neurotox Res, 2020. **38**(1): p. 1-7.
12. Najjar, S., et al., Central nervous system complications associated with SARS-CoV-2 infection: integrative concepts of pathophysiology and case reports. J Neuroinflammation, 2020. **17**(1): p. 231.
13. Meinhardt, J., et al., Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19. Nat Neurosci, 2021. **24**(2): p. 168-175.
14. Neta, F.I., et al., Pathophysiology and possible treatments for olfactory-gustatory disorders in patients affected by COVID-19. Curr Res Pharmacol Drug Discov, 2021. **2**: p. 100035.
15. Hura, N., et al., Treatment of post-viral olfactory dysfunction: an evidence-based review with recommendations. Int Forum Allergy Rhinol, 2020. **10**(9): p. 1065-1086.
16. Seo, M.Y. and S.H. Lee, Treatment and Prognosis of COVID-19 Associated Olfactory and Gustatory Dysfunctions. J Pers Med, 2021. **11**(10).
17. Doty, R.L., Treatments for smell and taste disorders: A critical review. Handb Clin Neurol, 2019. **164**: p. 455-479.
18. Payne, T., M. Kronenbuerger, and G. Wong, *Gustatory Testing*, in *StatPearls*. 2022: Treasure Island (FL).

19. Ganjaei, K.G., et al., Variability in Retronasal Odor Identification Among Patients With Chronic Rhinosinusitis. Am J Rhinol Allergy, 2018. **32**(5): p. 424-431.
20. Finger, T.E., et al., ATP signaling is crucial for communication from taste buds to gustatory nerves. Science, 2005. **310**(5753): p. 1495-9.
21. Yagi, T., et al., *The role of zinc in the treatment of taste disorders.* Recent Pat Food Nutr Agric, 2013. **5**(1): p. 44-51.
22. Hummel, T., et al., *Intranasal vitamin A is beneficial in post-infectious olfactory loss.* Eur Arch Otorhinolaryngol, 2017. **274**(7): p. 2819-2825.
23. Rawson, N.E. and A.S. LaMantia, A speculative essay on retinoic acid regulation of neural stem cells in the developing and aging olfactory system. Exp Gerontol, 2007. **42**(1-2): p. 46-53.
24. Reden, J., et al., Olfactory function in patients with postinfectious and posttraumatic smell disorders before and after treatment with vitamin A: a double-blind, placebo-controlled, randomized clinical trial. Laryngoscope, 2012. **122**(9): p. 1906-9.
25. Shakoor, H., et al., *Be well: A potential role for vitamin B in COVID-19.* Maturitas, 2021. **144**: p. 108-111.
26. Leaf, D.E. and A.A. Ginde, *Vitamin D3 to Treat COVID-19: Different Disease, Same Answer.* JAMA, 2021. **325**(11): p. 1047-1048.
27. Santaolalla, A., et al., Association Between Vitamin D and Novel SARS-CoV-2 Respiratory Dysfunction - A Scoping Review of Current Evidence and Its Implication for COVID-19 Pandemic. Front Physiol, 2020. **11**: p. 564387.
28. Bae, M. and H. Kim, Mini-Review on the Roles of Vitamin C, Vitamin D, and Selenium in the Immune System against COVID-19. Molecules, 2020. **25**(22).
29. Dragomanova, S., et al., Therapeutic Potential of Alpha-Lipoic Acid in Viral Infections, including COVID-19. Antioxidants (Basel), 2021. **10**(8).
30. Kanjanaumporn, J., et al., Smell and taste dysfunction in patients with SARS-CoV-2 infection: A review of epidemiology, pathogenesis, prognosis, and treatment options. Asian Pac J Allergy Immunol, 2020. **38**(2): p. 69-77.
31. Khani, E., et al., Potential pharmacologic treatments for COVID-19 smell and taste loss: A comprehensive review. Eur J Pharmacol, 2021. **912**: p. 174582.
32. Nikodijevic, O. and D.C. Klein, Adenosine stimulates adenosine 3',5'-monophosphate and guanosine 3',5'-monophosphate accumulation in rat pinealocytes: evidence for a role for adenosine in pineal neurotransmission. Endocrinology, 1989. **125**(4): p. 2150-7.
33. Gustafsson, L., B.B. Fredholm, and P. Hedqvist, Theophylline interferes with the modulatory role of endogenous adenosine on cholinergic neurotransmission in guinea pig ileum. Acta Physiol Scand, 1981. **111**(3): p. 269-80.
34. Gagnier, J.J., et al., The CARE guidelines: consensus-based clinical case reporting guideline development. BMJ Case Rep, 2013. **2013**.

35. Parma, V., et al., More Than Smell-COVID-19 Is Associated With Severe Impairment of Smell, Taste, and Chemesthesis. Chem Senses, 2020. **45**(7): p. 609-622.
36. Huttenbrink, K.B., *[Disorders of the sense of smell and taste].* Ther Umsch, 1995. **52**(11): p. 732-7.
37. Lechien, J.R., et al., Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur Arch Otorhinolaryngol, 2020. **277**(8): p. 2251-2261.
38. Kuchipudi, S.V., et al., Sialic Acid Receptors: The Key to Solving the Enigma of Zoonotic Virus Spillover. Viruses, 2021. **13**(2).
39. Doyle, M.E., et al., Human Type II Taste Cells Express Angiotensin-Converting Enzyme 2 and Are Infected by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Am J Pathol, 2021. **191**(9): p. 1511-1519.
40. Vaira, L.A., et al., Olfactory epithelium histopathological findings in long-term coronavirus disease 2019 related anosmia. J Laryngol Otol, 2020. **134**(12): p. 1123-1127.
41. Butowt, R. and C.S. von Bartheld, Anosmia in COVID-19: Underlying Mechanisms and Assessment of an Olfactory Route to Brain Infection. Neuroscientist, 2021. **27**(6): p. 582-603.
42. Brann, D.H., et al., Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. Sci Adv, 2020. **6**(31).
43. de Melo, G.D., et al., COVID-19-related anosmia is associated with viral persistence and inflammation in human olfactory epithelium and brain infection in hamsters. Sci Transl Med, 2021. **13**(596).
44. Wang, H., et al., *Inflammation and taste disorders: mechanisms in taste buds.* Ann N Y Acad Sci, 2009. **1170**: p. 596-603.
45. Reiter, E.R., et al., Subjective smell and taste changes during the COVID-19 pandemic: Short term recovery. Am J Otolaryngol, 2020. **41**(6): p. 102639.
46. Karthaka, C., S.S. Baliga, and P.R. Walvekar, *Clinical profile and outcomes of COVID-19 positive patients -A cross sectional study.* J Family Med Prim Care, 2021. **10**(11): p. 4036-4040.
47. Caponio, V.C.A., et al., *Symptomatic SARS-CoV-2 Infection with Ageusia after Two mRNA Vaccine Doses.* Int J Environ Res Public Health, 2022. **19**(2).
48. Stankevice, D., A.W. Fjaeldstad, and T. Ovesen, Isolated taste disorders in patients referred to a flavor clinic with taste and smell loss. Brain Behav, 2021. **11**(4): p. e02071.
49. Singh, C.V., S. Jain, and S. Parveen, The outcome of fluticasone nasal spray on anosmia and triamcinolone oral paste in dysgeusia in COVID-19 patients. Am J Otolaryngol, 2021. **42**(3): p. 102892.
50. O'Byrne, L., et al., Interventions for the treatment of persistent post-COVID-19 olfactory dysfunction. Cochrane Database Syst Rev, 2021. **7**: p. CD013876.
51. Huart, C., et al., Systemic corticosteroids in coronavirus disease 2019 (COVID-19)-related smell dysfunction: an international view. Int Forum Allergy Rhinol, 2021. **11**(7): p. 1041-1046.

Figures

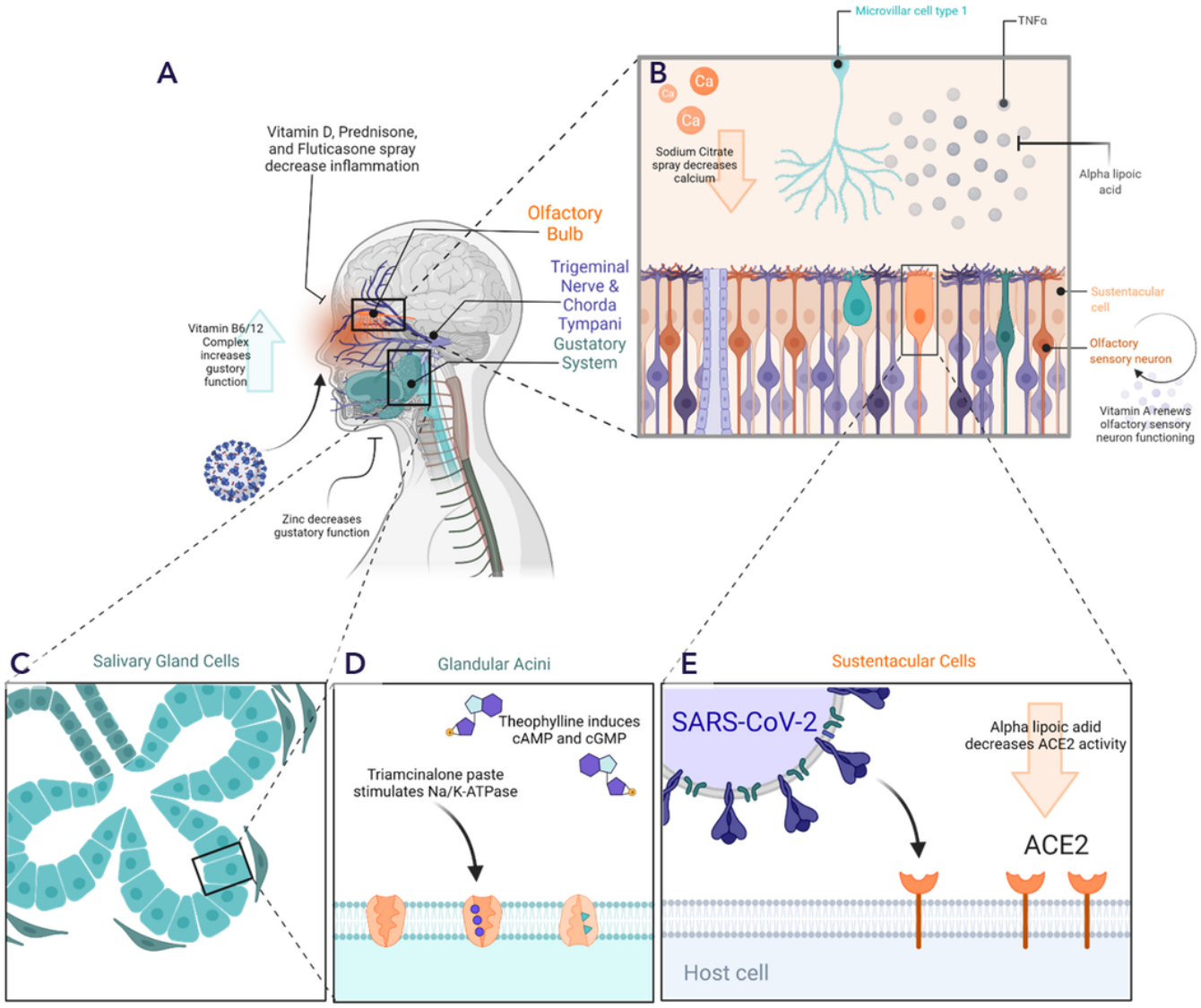

Figure 1

Intranasal and systemic treatment effects of the Training 'N' Treatment (TNT) protocol on olfactory and gustatory systems. (A) SARS-CoV-2 enters the body via inhalation, impacting the olfactory bulb (orange), trigeminal nerve (purple), and gustatory system (teal) by inducing localized inflammation and intracellular responses. TNT components vitamin D, vitamin B6/B12 complex, zinc, nasal irrigation, and fluticasone play a broad role in counteracting the effects of SARS-CoV-2 on these systems, as indicated. **(B)** Within the olfactory bulb epithelium, TNT components work to inhibit inflammatory signals and renew functioning of the olfactory sensory neuron. **(C)** The salivary glands of the gustatory system are comprised of several cell types that regulate saliva production and can be damaged by SARS-CoV-2 infection. **(D)** The glandular acini of the salivary gland are stimulated by triamcinolone paste and theophylline, which increase energy production within these cells. **(E)** Inside the sustentacular cells of the olfactory bulb, alpha lipoic acid reduces the impact of SARS-CoV-2 by decreasing ACE2 expression levels.

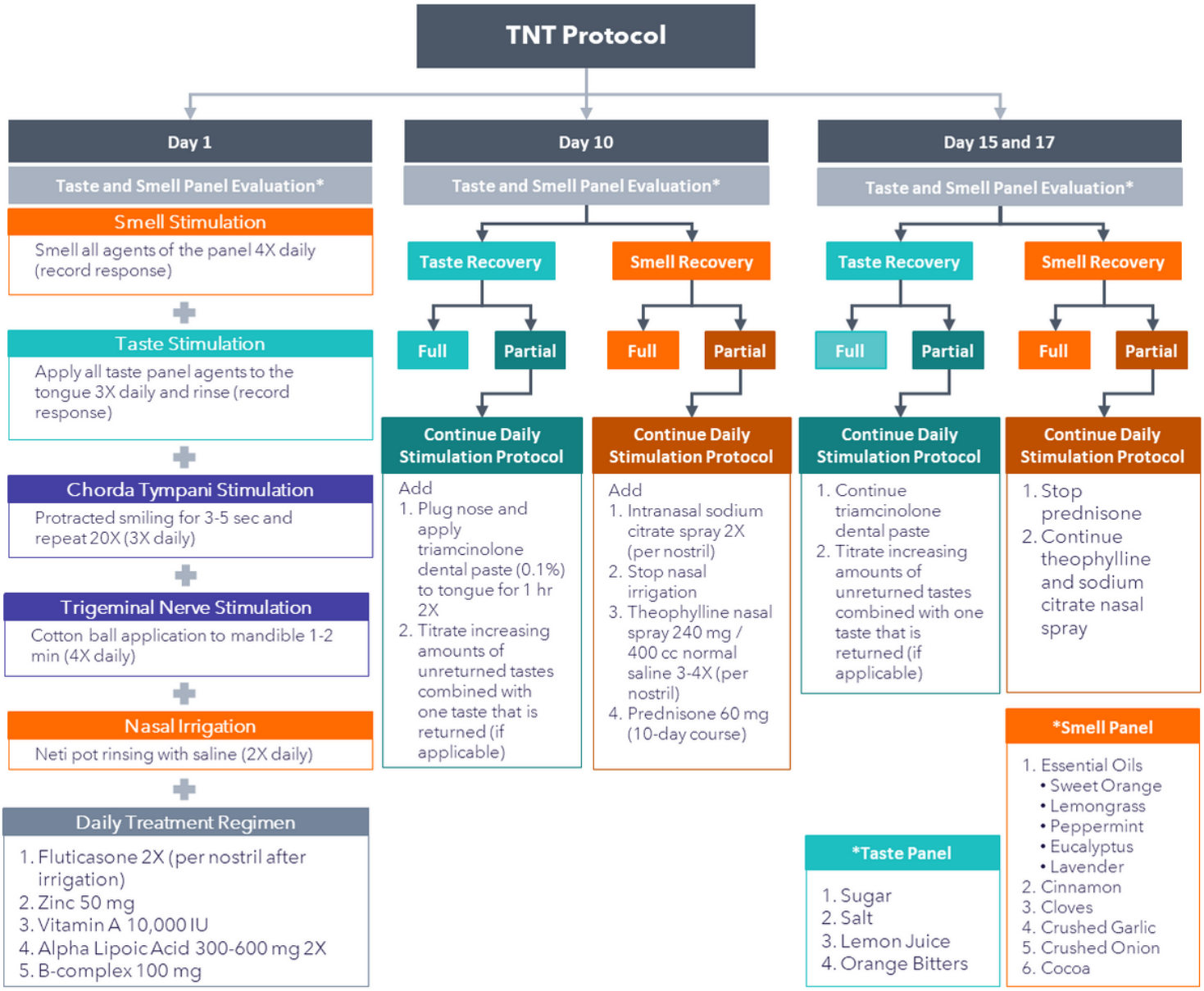

Figure 2

Schematic of Training 'N' Treatment (TNT) protocol to restore lost taste and smell resulting from acute COVID-19.

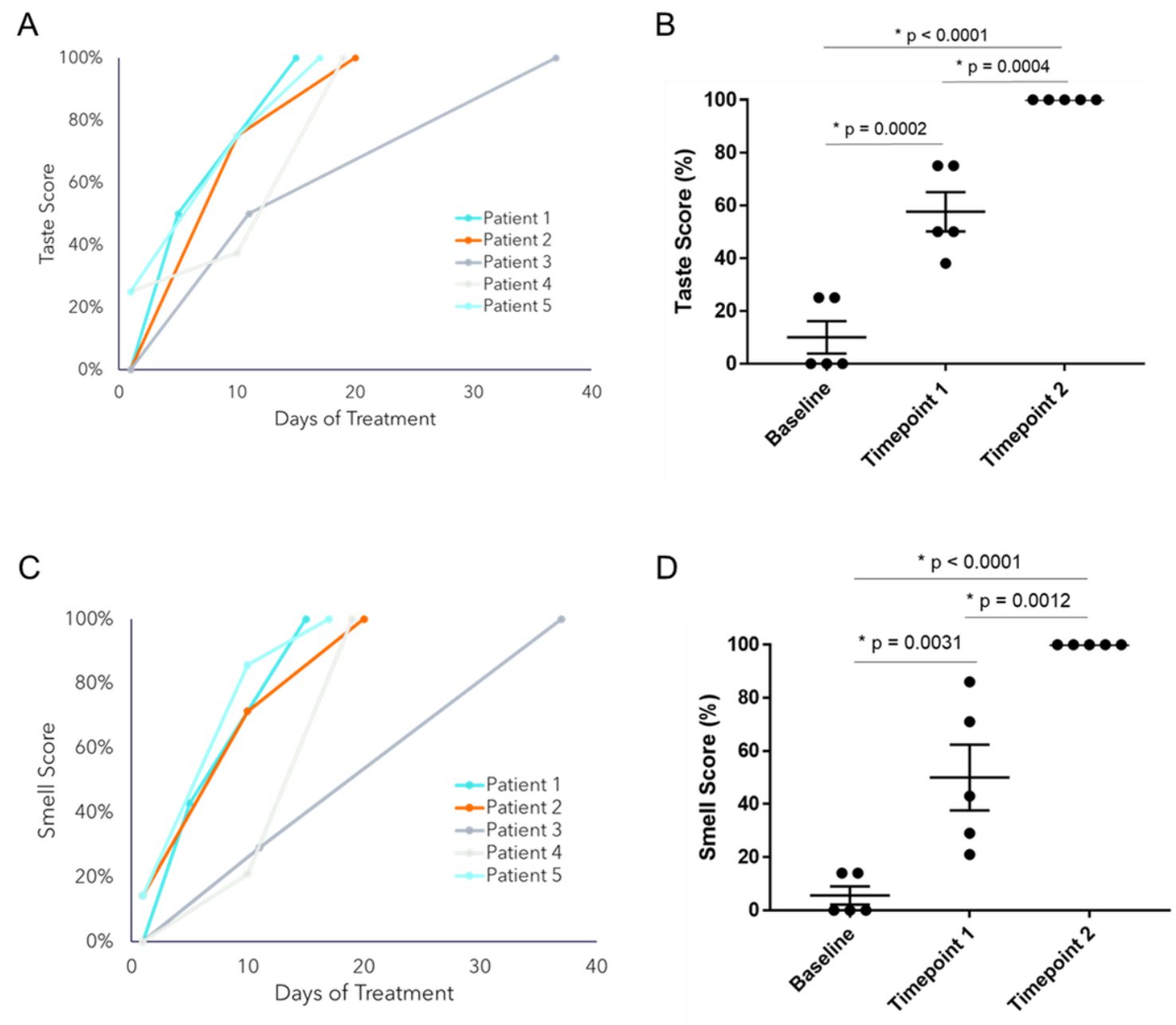

Figure 3

Recovery of taste and smell from acute SARS-CoV-2 infection-mediated gustatory and olfactory dysfunction. Patients (N = 5) with loss of taste and/or smell resulting from acute SARS-CoV-2 infection were treated with the TNT protocol as described in the materials and methods. At three timepoints, patients recorded qualitative responses to all agents included on the taste or smell panels. Results are represented as a percentage of agents on the respective panels that were successfully detected. (**A, C**) Longitudinal taste or smell scores for each patient. (**B, D**) Analysis by one-way ANOVA for each timepoint followed by Tukey's post hoc test. Averaged values shown are the mean ± SEM. *All values of $p \leq 0.05$ considered statistically significant.