Smell Changes & Efficacy of Nasal Theophylline (SCENT)

NCT03990766

Principal Investigator: Jake J. Lee, MD

Institution: Washington University School of Medicine in St. Louis

Document Date: April 18, 2019

Intranasal Theophylline Irrigation for Treatment of Post-Viral Olfactory Dysfunction

Principal Investigator: Jake J. Lee, MD

Short Title: Intranasal Theophylline Irrigation

Research Team Members: Jay Piccirillo, MD; Pawina Jiramongkolchai, BA; Daniel Lander, BS; Dorina Kallogjeri, MD, MPH; John Schneider, MA, MD; Cristine N. Klatt-Cromwell, MD, Sara Kukuljan, BS, CCRC, RN

Project to be registered on ClinicalTrials.gov

ABSTRACT
Olfactory dysfunction affects approximately 15% of the adult population and significantly impacts quality of life. Current available treatments include systemic corticosteroids, intranasal corticosteroids, and olfactory training, with limited evidence of efficacy. *In vitro* and *in vivo* studies have demonstrated the crucial role of elevated cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) levels in olfactory signaling and sensory axonal regeneration. Theophylline, a medication commonly used to treat asthma, inhibits phosphodiesterase, thereby increasing cAMP and cGMP levels. This effect on key messengers provides a possible mechanistic explanation for theophylline's role in the treatment of olfactory dysfunction. Therefore, we propose a single-site, double-blinded, placebo-controlled randomized clinical trial to evaluate the efficacy of intranasal theophylline irrigation on subjective and objective olfaction outcomes in 32 adults with post-viral olfactory dysfunction. The study statistician, Dr. Dorina Kallogjeri, will use a randomized block design for study drug assignment will use a randomized block design for study drug assignment. The randomization scheme will be a 1:1 ratio. The addition of theophylline in a large-volume, low-pressure nasal saline irrigation will enhance drug penetration to the olfactory cleft compared to nasal spray. We hypothesize that intranasal theophylline irrigation will be more effective in improving olfactory recovery than placebo nasal saline irrigation and that there will be minimal systemic absorption and adverse effects. If the results of this phase II study suggest that theophylline added to nasal saline lavage improves olfactory dysfunction, then a larger phase III randomized controlled trial based on the results from this study can be designed.

1.4 Research Question & Study Aims
AIM 1: Evaluate the efficacy of intranasal theophylline delivered via high-volume, low-pressure nasal saline irrigation on olfactory recovery in patients with post-viral olfactory dysfunction.
Participants will be randomized to 6 weeks of either theophylline and nasal saline irrigation or nasal saline irrigation alone. The primary outcome will be within- and between-subject changes in subjective rating of smell. The secondary outcome will be within- and between-subject changes in University of Pennsylvania Smell Identification Test (UPSIT) scores. Compared to nasal saline irrigation alone, we hypothesize that intranasal theophylline irrigation will be more effective in improving olfactory recovery.

AIM 2: Describe adverse effects related to theophylline nasal saline irrigation.
All participants will be monitored for adverse effects throughout the study. A subset of participants will undergo serum theophylline measurements to assess the level of systemic absorption, if any. Based on prior studies which failed to demonstrate detectable serum theophylline levels after intranasal spray, we hypothesize that intranasal theophylline irrigation will have minimal systemic absorption and adverse effects.

Background & Significance
Olfactory dysfunction is a very prevalent condition affecting **15%** of all American adults and **25%** of adults older than 53 years of age.[1,2] Commonly, afflicted individuals describe impairments in food preparation and diet, weight changes, concerns over environmental safety, poor personal hygiene, impaired interpersonal relationships, and social withdrawal, even comparing it to "living a life without color" or "living in a plastic bag".[3] As a result, those affected have **reduced quality of life and increased 5-year mortality**.[4,5] Most causes of olfactory dysfunction are acquired, and etiologies include post-viral, inflammatory such as in chronic rhinosinusitis (CRS), traumatic, neurodegenerative such as in Parkinson's disease, and idiopathic.[6]

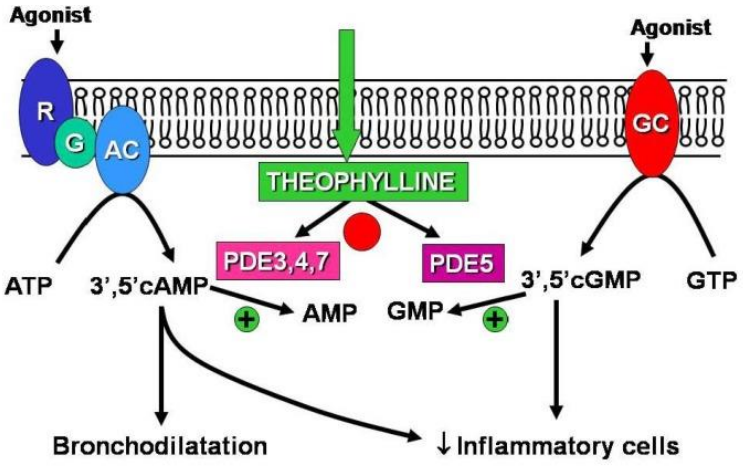
Post-viral olfactory dysfunction is characterized by sudden loss of smell following an upper respiratory infection and is the underlying etiology in up to **40%** of patients with olfactory dysfunction, making it one of the most common causes of impaired olfaction.[7] Up to one-third of patients with post-viral olfactory dysfunction have some degree of spontaneous olfactory recovery, but recovery is often incomplete.[8,9] Other studies revealed lower spontaneous olfactory improvement rates of 18% in this patient population after 7-9 months, indicating that the natural time course is not clearly defined.[10,11] Furthermore, the pathophysiology of post-viral olfactory dysfunction is not well understood, thereby frustrating both clinicians and patients.

To add to the frustration, **there is no universally effective treatment**, leaving many patients with olfactory dysfunction feeling hopeless.[3] Historically, corticosteroids have been used as an initial treatment modality. While multiple studies have demonstrated improvement in olfaction outcomes after systemic corticosteroid therapy, most of these studies have low quality of evidence and lack an appropriate control group.[12-15] The one randomized controlled trial (RCT) of patients with post-traumatic anosmia that compared a group treated with oral prednisolone versus a control group receiving no treatment demonstrated no significant differences in recovery rates of olfactory function.[12]

In addition, two studies, including an RCT (level 1B evidence), on topical corticosteroid treatment with nasal spray have demonstrated no significant differences in olfaction outcomes pre- and post-intervention.[16,17] A systematic review examining the efficacy of systemic and topical corticosteroid therapy on non-CRS olfactory dysfunction concluded that corticosteroid nasal sprays have no effect on olfaction (level 1B evidence) while systemic corticosteroids may improve olfactory loss (level 4 evidence).[18] Recently, an RCT comparing combined olfactory training and budesonide irrigation to olfactory training alone demonstrated a significantly higher improvement rate in objective smell scores via the UPSIT in the combined arm.[19]

Olfactory training, without corticosteroid use, is a promising treatment modality based on **olfactory neuroplasticity.** Olfactory training involves repeated exposure to four different odors in an attempt to regenerate olfactory receptor cells and recreate the signaling pathway to the olfactory cortex.[20] Two meta-analyses of patients with olfactory dysfunction who completed olfactory training revealed significant improvements in odor discrimination and identification scores compared to controls.[20,21]

On a molecular level, prior *in vitro* and *in vivo* studies have investigated the **importance of cAMP and cGMP as secondary messengers in olfactory responses**. Olfactory neuronal dendrites are highly enriched with adenylate cyclase and guanylate cyclase, which convert adenosine triphosphate (ATP) to cAMP and guanosine triphosphate (GTP) to cGMP, respectively (Figure 1).[22-24] Once odorants attach to olfactory receptors, these olfactory neuronal dendrites have rapid potent increases in adenylate cyclase and guanylate cyclase activity, resulting in elevated cAMP and cGMP levels.[25] Increased levels of these secondary messengers result in the opening of sodium and calcium ion channels leading to depolarization and action potentials for olfaction.[26]



Key: R = receptor, Gs = stimulatory G-protein, AC = adenylyl cyclase, GC = guanylyl cyclase, PDE = phosphodiesterase, cAMP = cyclic adenosine monophosphate, ATP = adenosine triphosphate, cGMP = cyclic guanosine monophosphate, GTP = guanosine triphosphate.

Fig. 1. The mechanism of action of theophylline, non-selective phosphodesterase inhibitor, on cAMP and cGMP signaling, adapted from Barnes PJ.[24]

In addition to impacting olfactory signaling, **cAMP appears to affect sensory axonal regeneration**. Unlike neonatal axons, adult axons do not regenerate after injury due to the inhibitory effect of myelin and myelin-associated glycoprotein (MAG) likely related to the precipitous drop in cAMP levels in dorsal root ganglion neurons shortly after birth, which never recovers.[27] Elevated cAMP levels appear to increase the regenerative capacity of injured sensory axons *in vitro* and *in vivo* by blocking the inhibition of axonal regeneration by myelin and MAG.[28] While the above literature studied spinal cord neurons, cAMP levels may also have similar effects in other sensory neurons, such as those involved in olfaction. Henkin and Velicu discovered that cAMP and cGMP levels in nasal mucus were significantly lower in hyposmic patients compared to normosmic controls.[29] Furthermore, a **stepwise increase in olfactory dysfunction was**

associated with a stepwise decrease in nasal mucus cAMP and cGMP levels, thereby underscoring the potential significance of cAMP and cGMP in the olfactory response.[30]

Since phosphodiesterases (PDE) break down cAMP and cGMP into adenosine monophosphate (AMP) and guanosine monophosphate (GMP), respectively, investigators have studied the use of PDE inhibitors to improve olfaction. **Theophylline**, an inexpensive and widely available treatment for asthma and chronic obstructive pulmonary disease (COPD), is a **non-selective PDE inhibitor**, thereby increasing intracellular levels of cAMP and cGMP which then result in bronchodilation, smooth muscle relaxation, and decreased inflammation downstream (Figure 1).[24] Its **anti-inflammatory properties** may also be mediated by its ability to prevent the translocation of nuclear factor-κB (NF-κB), a pro-inflammatory transcription factor, into the nucleus.[31] Due to its dual ability to increase cyclic nucleotide levels and decrease inflammation, theophylline offers promise as a newer adjunct to treat olfactory dysfunction.

In fact in a single-arm longitudinal study of **oral theophylline** treatment on hyposmic patients, **50% (157/312)** reported subjective improvement in smell with 11% (34/312) reporting return of normal smell function.[32] In addition, on objective olfactometry of 4 different odors, there were significant improvements in **mean odor detection and recognition thresholds**. Similar improvements in smell in responders to oral theophylline treatment have also been associated with significant increases in brain activation signal in response to odors on functional magnetic resonance imaging (fMRI).[33] Some patients only responded to theophylline in a dose-dependent manner, requiring further escalation of dosing and prolonged treatment duration, thereby exposing them to adverse events including headache, nausea, vomiting, lightheadedness, tachycardia, abdominal discomfort, and restlessness.[24,32]

Due to systemic theophylline's relatively narrow therapeutic index and desire for improved therapeutic efficacy, topical administration of theophylline has also been studied. The same investigators from the single-arm oral theophylline study conducted a small pilot study on **intranasal theophylline spray** in 10 patients who had submaximal responses to prior oral theophylline treatment.[34] Eight of these ten patients reported subjective improvement in smell function after intranasal theophylline, and there was a mean **28% increase in quantitative subjective scores** compared to 14% after oral theophylline, which was a statistically significant difference. Objective testing via olfactometry revealed significant improvements in **detection and recognition thresholds** for 4 different odorants. Lastly, **serum theophylline levels were undetectable** in all patients. A more recent abstract detailed a study of 8 patients with chronic anosmia and hyposmia also treated with intranasal theophylline spray, of whom **4 of 8** had improvement on subjective and/or objective testing via the Monell-Jefferson Taste and Smell Questionnaire and UPSIT, respectively.[35] Interestingly, these participants' response to prednisone did not predict response to intranasal theophylline, offering a promising treatment modality to patients with olfactory loss refractory to corticosteroid treatment.

Despite the novelty of the two published studies investigating nasal theophylline spray, it is difficult interpreting the clinical significance of intranasal theophylline from the data due to the heterogeneity of the study populations, non-standard measurement modalities of olfaction, and lack of a control group.[34,35] Both studies included patients with olfactory dysfunction of multiple etiologies. Henkin et al.'s study population may also represent a relatively refractory group since all participants previously either had suboptimal responses to oral theophylline or could not tolerate its course, thereby limiting generalizability. Additionally in Henkin et al.'s studies on oral and intranasal theophylline, an increase of 5 points on the 100-point scale for quantitative subjective smell change was considered clinically significant without sufficient explanation of that determination.[32,34] Furthermore, Goldstein et al.'s study was limited to an abstract, which categorized people as complete responders if they improved on both subjective and objective testing and partial responders if they only improved on one without detailing effect sizes or measures of clinically significant change.[35] A discussion between the PI (Lee) and Dr. Greg Davis, a rhinologist at the University of Washington who was a panelist at the New & Improved Treatment Options for Olfactory Loss session at the AAO-HNS 2018 Meeting (Atlanta, GA), confirmed the above concerns, thereby putting the published 50% response rate into question.

While topical delivery of theophylline via nasal spray has been studied, there is no literature utilizing delivery via nasal saline **irrigation**. Various additives, including corticosteroids and antibiotics, to irrigation devices are gaining popularity as a result of improved distribution of the medication throughout the nasal cavity and paranasal sinuses.[36] We believe the large-volume, low-pressure nasal saline irrigation delivery system will result in **better penetration of the middle meatus and olfactory cleft** than nasal spray.

Participant Population Description

Participants will be recruited from our institution's Otolaryngology-Head and Neck Surgery based on the following eligibility criteria.

Inclusion criteria include:

1) males and females ages 18 to 70 years

2) subjective or clinically diagnosed olfactory dysfunction of 6 months to 36 months duration after a presumed viral upper respiratory infection

3) ability to read, write, and understand English.

Exclusion criteria include:

1) dependence on theophylline for comorbid conditions such as asthma and COPD

2) history of an allergic reaction to theophylline or other methylxanthines

3) prior sinonasal or anterior skull base surgery

4) nasal polyposis

5) history of neurodegenerative disease (ie. Alzheimer's dementia, Parkinson's disease, Lewy body dementia, frontotemporal dementia)

6) pregnant or breastfeeding mothers.

7) current use of medications with significant (≥40%) interactions with theophylline, which include cimetidine, ciprofloxacin, disulfiram, enoxacin, fluvoxamine, interferon-alpha, lithium, mexiletine, phenytoin, propafenone, propranolol, tacrine, thiabendazole, ticlopidine, and troleandomycin.

Individual Data Elements

To determine potential eligibility for the study, we will query the medical record based on the following inclusion/exclusion criteria:

- Age (18 to 70 years of age)
- Medication history to assess for dependence on theophylline (exclusion)
- Allergy history to theophylline or other methylxanthines (exclusion)
- Past surgical history for prior sinonasal surgery (exclusion)
- Past medical history for nasal polyposis (exclusion)

Existing diagnoses of neurodegenerative disease (ie. Alzheimer's dementia, Parkinson's disease, Lewy body dementia, frontotemporal dementia) (exclusion)

For those meeting the criteria, we will access name, telephone number, age, sex, and date/time of any clinic visits related to olfactory dysfunction.

Recruitment and Consent Process

Adult patients with reported smell loss after an upper respiratory infection (URI) with duration between 6 to 36 months will be recruited from the clinics of the Washington University School of Medicine. Attending physicians from both the Departments of Otolaryngology – Head & Neck Surgery and other departments such as Internal Medicine will be informed of the study.

Eligible patients who present to clinic will be approached by a research team member to review the informed consent process and thoroughly discuss the research protocol, potential benefits, and risks of the study with the patient and any available family members in person. Any subsequent questions or concerns from the potential participant and any family members will also be addressed at that time. After discussion, the patient will be asked to re-summarize the steps involved in the study to ensure understanding. If interested, written consent may be obtained during that visit. Patients will be reminded that study participation is voluntary and will in no way affect their current or future care.

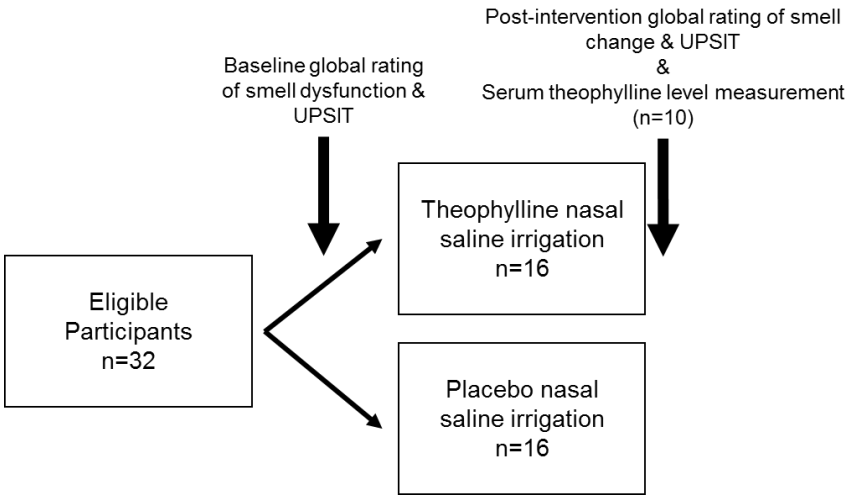
Study Procedures

This study will be a single-site, double-blinded, placebo-controlled randomized clinical trial performed at a tertiary academic medical center. The proposed study flow diagram is shown in Figure 2.

<u>Aim 1</u>: Evaluate the impact of intranasal theophylline delivered via high-volume, low-pressure nasal saline irrigation on olfactory recovery in patients with post-viral olfactory dysfunction.

We hypothesize that intranasal theophylline irrigation will be more effective in improving olfactory recovery compared to nasal saline irrigation alone. After enrollment, all patients will undergo anterior rhinoscopy at the initial visit to rule out polyps. Enrolled subjects will then undergo baseline olfactory testing using:

Fig. 2. Proposed study flow.



1) Global Rating of Smell Dysfunction. This **baseline global rating** is adapted from the Clinical Global Impressions-Severity scale to address smell.[37] It measures the severity of baseline smell loss by asking: "Overall, please rate your current sense of smell. Response options: *Excellent, Very good, Good, Fair*, *Poor*, or *Absent.*"

2) Modified Questionnaire of Olfactory Disorders. A 42-item questionnaire, which includes negative statements, positive statements, sincerity statements, and parosmia statements to evaluate quality of life (QOL) related to olfactory dysfunction.

3) Veterans RAND 12 (VR-12) Emotional Health Survey. The VR-12 is a widely established 12-item questionnaire that evaluates physical and emotional health status. The seven questions pertaining to emotional health will be utilized.

4) University of Pennsylvania Smell Identification Test (UPSIT, Sensonics, New Jersey**).** The **UPSIT** is a validated 40-question forced-choice odor identification test where microencapsulated odorants on a strip are released by scratching.[38,39] Out of a total of 40 points, normosmia is defined as ≥34 for males and ≥35 for females, and an increase in ≥4 points is considered a clinically significant improvement.[38]

All enrolled participants will then undergo simple randomization to receive 6 weeks of either **theophylline 12 mg capsules** or identical-appearing **placebo lactose capsules**. We determined the theophylline dose to be 12 mg based on the literature by calculating a ratio using the same concentration of 20 mcg/0.4 mL that was utilized in the nasal spray.[34,35] Using equivalent ratios, 20 mcg / 0.4 mL = X / 240 mL, so X = 12,000 mcg = 12 mg dissolved in 240 mL of nasal saline.

The use of theophylline in a nasal saline rinse is a change in the approved route of administration. An exemption from IND requirements is requested as the proposed use of theophylline in this study fulfills all of the criteria for exemption:

1. Theophylline is lawfully marketed in the United States.
2. This study is not intended to be reported to the FDA in support of a new indication or significant change in labeling.
3. This study is not intended to support a significant change in the advertising for the drug.
4. The study does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of theophylline.
5. The study will be conducted in compliance with the requirements for review by an IRB (21 CF R part 56) and with the requirements for informed consent (21 CFR part 50).
6. The study is not intended to promote or commercialize theophylline.

The placebo product will contain lactose monohydrate and will be supplied in clear plastic capsules, which are identical to the theophylline capsules. The lactose capsule will only contain lactose as there are no other ingredients.

Participants will dissolve the contents of either the theophylline or lactose capsules into the sinus rinse bottle containing nasal saline. All participants will receive an 8-ounce sinus rinse bottle and a 6-week supply of USP Grade Sodium Chloride & Sodium Bicarbonate Mixture (pH balanced, Isotonic & Preservative & Iodine Free) commercially prepared packets. Participants will either need to purchase distilled water or boil tap water for five minutes for use with the saline irrigation. A member of the research team will instruct participants on how to irrigate each nasal cavity with one-half of the contents of the sinus rinse bottle. Written instructions and a video demonstration will also be provided to ensure proper technique. Because the half-life of theophylline in healthy adults (16-60 years) is 8.7 hours and 9.8 hours in the elderly (> 60 year), irrigations will be performed **twice daily** – once in the morning and once at night for all subjects.[40]

The **primary outcome** will be the self-reported **Global Rating of Smell Change** on a 7-point Likert scale, which asks, "Overall, how would you rate your change in smell after your 6 weeks of irrigations?

Response options: *Much better, Somewhat better, Slightly better, Neither better nor worse, Slightly worse, Somewhat worse*, or *Much worse*." Subjects that report a change of slightly better or more will be defined as responders to treatment. Efficacy will be determined by the difference in the rate of responders in the two intervention arms. **Secondary outcomes** will be within- and between-subject changes in **UPSIT** scores from baseline to post-intervention.

Aim #2: Describe any adverse effects related to theophylline nasal saline irrigation.

We hypothesize that systemic absorption of theophylline delivered via nasal saline irrigation will be minimal, and thus, there will be minimal adverse effects. One study on intranasal theophylline spray measured serum theophylline levels in 10 patients, all of which were immeasurable.[34] Following intranasal administration, a drug may enter systemic circulation through direct local absorption in the nasal mucosa or oral absorption of any swallowed medication.[41] If a drug enters the systemic circulation through the nasal mucosa, the medication is subject to plasma protein binding, which renders it bio-inactive, reducing the potential for adverse effects. Approximately 40% of theophylline is bound to plasma proteins after entering systemic circulation.[42]

A portion of the drug may also be cleared into the throat and swallowed, making it available for gastrointestinal absorption. Medications absorbed through the gastrointestinal tract are subject to first-pass hepatic metabolism, which largely determines the amount of medication that reaches systemic circulation. Following oral administration, theophylline does not undergo any measurable first-pass elimination, therefore approaching 100% of the available drug.[43]

Another factor to account for is the volume of nasal irrigation that will remain in the sinus cavity. In patients with chronic rhinosinusitis who undergo nasal saline irrigation with a 240 mL sinus rinse bottle, up to 5% of the solution remains in the sinuses.[44] Therefore, the maximum amount of fluid left in the sinuses after a 240 mL nasal irrigation is estimated to be 12 mL. Applying this data, the maximum absorption of 12 mg of theophylline added to a 240 mL saline filled rinse bottle for irrigation may be estimated by calculating 12 mg / 240 mL = 0.05 mg/mL or 50 mcg/mL. Since the maximum volume that is estimated to be retained in the sinuses is 12 mL, 12 mL x 50 mcg/mL = 600 mcg per dose. For twice daily dosing, the **total daily dose is 1200 mcg or 1.2 mg.**

On average 1 mg/kg of theophylline results in blood levels rising 2 mcg/mL.[45] Therapeutic effects of theophylline occur at a serum concentration of 5-20 mcg/mL.[46] Unwanted side effects, such as headache, nausea, vomiting, restlessness, and tachycardia, occur when plasma levels exceed 20 mcg/mL.[24] Given the available information, a total daily dose of 1.2 mg administered by nasal irrigation should be well tolerated.

In our study, the **first 10 participants** will undergo **serum theophylline level measurements** at the **end of Week 1**. To maintain the blind, 5 participants will be selected from each intervention arm. Assuming the time to peak absorption of topical theophylline is similar to oral theophylline, which is 2 hours, we will draw serum theophylline levels approximately 2 hours after administration of the nasal sinus rinse with assigned capsule. If we identify a measurable amount of theophylline in the serum, we will repeat the test in the same subject. If presence of theophylline is detected in the second sample, we will continue to measure in another 10 subjects to better define the generalizability of the risk of systemic absorption.

In addition to the serum theophylline level test, all participants will be regularly queried throughout the study regarding any adverse effects experienced with the intervention. If theophylline-related adverse effects are suspected, the participant will be instructed to stop the medication and present to either the nearest emergency department, his/her primary care provider, or the Otolaryngology-Head & Neck Surgery clinic, depending on severity of the adverse effect.

Potential Benefits

The potential benefit to the participant is improvement of their smell and taste using this novel therapy. The potential benefit to the society is the use of the results to initiate a large phase III study to definitively determine efficacy of intranasal theophylline use for treatment of post-viral olfactory dysfunction so that intranasal theophylline may become a mainstay treatment of this disease which currently has no effective treatment.

Analysis Methods

An intention-to-treat analysis will be used where all participants will be examined in the groups to which they were initially assigned regardless of the treatment actually received. Standard descriptive statistics will be used to assess the demographics, clinical characteristics, and olfactory test results of the study population. The **difference in rate of responders between the two groups** will estimate the effect size of the primary

outcome measure, and the 95% CI around that point estimate will measure precision. In each group, the frequency and relative frequency of the participants' response to the global rating of smell change will be reported for each Likert category. Fisher's exact test will be used for comparing the responders' rates between the 2 groups. Histograms and Shapiro-Wilks test will be used to test the normal distribution assumption of the continuously measured **UPSIT** scores and the differences pre-post treatment in each of the groups. Independent samples *t*-test or its nonparametric equivalent Mann-Whitney U test will be used to compare the pre-post change in scores between the two groups. Effect sizes with 95% CIs will be reported for each analysis. All statistical analyses will be conducted in SPSS 25 (IBM Corp., Armonk, NY).

Rationale or Power Analysis

To date, there is no study that explores the effect of theophylline in post-viral olfactory dysfunction alone, and among the 2 published pilot studies, none utilizes a control group. This phase II study will provide us with the needed observed effect size for future phase III RCTs. While pilot data from previous studies suggest a 50% response rate after 4 weeks of intranasal theophylline treatment,[32,34,35] we believe that 50% is overly optimistic from our discussion with Dr. Greg Davis, who prescribes nasal theophylline spray in his clinical practice and estimates a more realistic response rate of 25%.

Thus, unlike a traditional sample size and power calculation, we will instead utilize a fixed sample size based on feasibility. At our institution, an annual average of **172 patients** presented with ICD-10 code R43 (Disturbances of smell & taste), and our two full-time rhinologists report seeing a total of 2-5 patients with post-viral olfactory dysfunction per week, providing a conservative estimate of **100 patients per year**. Based on these numbers and Dr. Jiramongkolchai's recruitment rate for CORE grant #575133 (see Preliminary Studies), a realistic estimate for enrollment within a 12-month period is **40 participants**. With an anticipated 20% drop-out and withdrawal rate, we estimate **32 participants** – 16 in each arm – will complete the study. Based on the sample size of 32, we calculated a range of possible effect sizes defined as the difference in rate of responders between the two groups and 95% confidence intervals (CI). We assumed two placebo response rates of 6.25% (1/16) and 12.5% (2/16) and a reasonable range of intranasal theophylline response rates from 18.75% (4/16) to 50.0% (8/16) (Table 1).

Table 1. Effect size and 95% confidence interval (CI) estimates given various combinations of intranasal theophylline and placebo saline irrigation response rates for a sample of 32 patients with 16 in each group.

Hypothetical Study Result	Placebo Response Rate, %	Intranasal Theophylline Response Rate, %	Effect Size, %	Lower Bound of 95% CI, %	Upper Bound of 95% CI, %
1	6.25	50	43.8	16.5	71.0
2	6.25	37.5	31.3	4.7	57.8
3	6.25	25	18.8	-5.6	43.1
4	6.25	18.75	12.5	-10.0	35.0
5	12.5	50	37.5	8.1	66.9
6	12.5	37.5	25.0	-3.7	53.7
7	12.5	25	12.5	-14.2	39.2

Given the sample size of 32 patients and reasonable rates of response, the upper bound of the 95% CIs for all 7 hypothetical studies displayed in the Table shows that a clinically meaningful result is plausible in the study population and warrants pursuit with future phase III studies using sample sizes based on our study's effect size and precision estimates in order to conclusively test the efficacy of intranasal theophylline irrigation.

Assessment of Treatment Safety

In our study, the first 10 participants will undergo serum theophylline level measurements at the end of week 1. To maintain the blind, 5 participants will be selected from each intervention arm. Assuming the time to peak absorption of topical theophylline is similar to oral theophylline, which is 2 hours, we will draw serum theophylline levels approximately 2 hours after administration of the last nasal sinus rinse with assigned capsule. If we identify a measurable amount of theophylline in the serum, we will repeat the test in the same subject. If presence of theophylline is detected in the second sample, we will continue to measure in another 10 participants to better define the generalizability of the risk of systemic absorption. Treatment safety will also be assessed by patient interview and will include collection of adverse events experienced by the patient during the six-week participation.

Data and Safety Monitoring

The specific monitoring plan for this study is based on the potential risk of participation and size and complexity of the planned investigation. Based on these considerations, this study will have a monitoring board comprised of Dr. Piccirillo and Ms. Kukuljan, and Dr. Kallogjeri, the study biostatistician. The monitoring board will meet to review data at least every 6 months. All reports of a Serious Adverse Event (SAE) or an Unexpected Adverse Event will be investigated by the monitoring team and reported to Washington University HRPO according to the reporting requirements.

Participant Remuneration

Every participant will receive $40 after the initial visit and $40 at the completion of the 6-week study for a total of $80. The first ten patients that undergo phlebotomy for serum theophylline measurement at the end of the study period will receive an additional $40 for a total of $120. Parking vouchers will also be provided at each visit.

Provisions to Protect the Privacy Interests of Participants, Confidentiality and Data Management

Procedures that are in place to curb risks of breaches in confidentiality and patient privacy are 1) formal training protocols centered on the maintenance of confidentiality for all study team members; 2) de-identified databases using only the study ID numbers assigned by the research coordinator; 3) a password-protected computer file of a master list that contains the identity of subjects, corresponding ID numbers, and contact information but no clinical information; and 4) a locked cabinet to store identified data forms such as completed questionnaires and UPSIT exams.

Only members of the study team will have access to the computer file and password for the master list. All research data files will be stored on secure Washington University servers with computer, network, and database-level passwords that will only be accessible to study team members. A key to the locked cabinet containing identified data forms will also only be available to study team members. Accordingly, these mechanisms intend to limit access to information that can link clinical data to individual subjects. No subject identifying information will be revealed in any publications or presentations.

A member of the study team will be available by phone or pager 24 hours a day for 7 days a week to respond to any concerns or address any adverse events experienced by any study participant.

Calendar of Events

Study Activity	Baseline (Time 0)	Week 1	Weeks 2, 4	Week 6
Consent	X			
Randomization	X			
Theophylline blood draw		X		X
Global Rating of Smell Dysfunction Questionnaire	X			
Modified Questionnaire of Olfactory Dysfunction	X			
VR-12 Questionnaire	X			
UPSIT	X			X
Written instructions for administration of intervention	X			

Intervention - theophylline or placebo		X	X	X
Telephone Visit (adverse event)			X	X
Participant Remuneration	X			X

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