EFFICACY OF GABAPENTIN FOR POST-COVID-19 OLFACTORY DYSFUNCTION

Principal Investigator:
Jay Piccirillo, MD, Department of Otolaryngology-Head and Neck Surgery

Version Date/Number:

06/20/22,V11

TABLE OF CONTENTS

A Introduction

A1 Study Abstract

COVID-19 has now infected over 33 million people in the United States and approximately 185 million worldwide.[1,2] Of those, an estimated 85% have reported either a new clinical diagnosis or subjective onset of olfactory dysfunction.[3] While most patients will recover their sense of smell within 7-14 days, others may not return to their baseline function for months or at all.[4] Viral infections that target the upper respiratory system, such as COVID-19, often leave patients with diminished olfaction. This new-onset anosmia, hyposmia, and parosmia is theorized to be caused by damage to sensory neurons following viral insult. Unfortunately, there is no treatment for post-COVID olfactory dysfunction. Most patients are recommended to perform olfactory training with essential oils,[5]but the evidence base to support this recommendation is not firm.[6] Thus, there is a very big need for effective treatments for patients suffering from post-COVID olfactory dysfunction.

One potential therapy is gabapentin. Used as an antiepileptic and now first-line medication for the treatment of diabetic neuropathy, gabapentin is known for reducing pain secondary to diabetic neuropathy and post-herpetic neuralgia. Gabapentin works mainly on voltage-gated calcium channels (VGCC) with an ability to cross the basement membrane, a trait important for an antiepileptic. The α2δ2 subunit of VGCCs, with increased expression in corticospinal neurons, has been associated with loss of regrowth after spinal injuries. The α2δ2 blockage by gabapentin can allow increased nerve regeneration and return of function.[7] Inhibition of the α2δ2 subunit on VGCCs may allow nerves to regenerate more rapidly than physiologically normal. This study will evaluate the efficacy of gabapentin for olfactory dysfunction (anosmia, hyposmia, parosmia) in post-COVID-19 patients.

A2 Primary Hypothesis

We hypothesize that oral gabapentin will be more effective than placebo for COVID-19-related olfactory dysfunction (OD) improvement.

A3 Purpose of the Study Protocol

This study will evaluate the efficacy of gabapentin for olfactory dysfunction (anosmia, hyposmia, parosmia) in post-COVID-19 patients.

B Background

B1 Prior Literature and Studies

The SARS-CoV-2 virus, has infected an estimated 78 million in the United States with ~85% of patients reporting some form of olfactory dysfunction.[1,3] More recent studies have shown an increased prevalence of olfactory change reported in women over men and in Western countries when compared to Eastern countries.[8,9] Moreover, the percentage of patients with post-COVID-19 olfactory dysfunction is thought to be underreported as patients need to individually report the symptom to their physician for it to be recorded.[9]

Evidence has emerged to explain the pathophysiology of COVID-19 and its mechanism of action on neurosensory pathways. Research suggests that COVID-19 affects two genes commonly found in the human respiratory system, ACE2 and TMPRSS2.[10]. ACE2, commonly associated with the renin-angiotensin-aldosterone system, has another role as a receptor protein on cell surfaces – a receptor proven vital for SARS-CoV-2 to enter respiratory cells.[11] Similarly, TMPRSS2 also plays a role in SARS-CoV-2 entry into cells and both genes are expressed in neuronal support cells.[7] ACE2 and TMPRSS2 are found only in support cells and not neurons. The support cells, such as sustentacular cells, degenerate and are unable to sustain neurons. This lack of neuronal stability is what likely causes the temporary neurosensory loss seen in post-COVID-19 patients. However, evidence is now also supporting the theory that COVID-19-related olfactory dysfunction may be due to direct damage to olfactory receptor neurons (ORNs) as well, which would increase recovery time as neurons regenerate more slowly. Previous strains of human coronavirus have also been proven to target ORNs causing olfactory dysfunction but whether this direct damage to neurons is related to ACE2 and TMPRSS2 has yet to be determined.[10]

Patients who do recover their sense of smell after infection tend to notice improvement in just weeks, paralleling the rapid recovery rate of support cells. Those with lingering olfactory dysfunction either return to new normalcy in months instead of weeks or have yet to return to baseline. Some patients report a return of smell followed shortly by new smell distortion. This observation of differing recovery rates supports the theory that SARS-CoV-2 also damages olfactory receptor neurons directly leading to longer recovery times. Research has demonstrated the possible utility in olfactory training, a therapy thought to encourage neuroplasticity via repeat exposure to odors.[6,12] However, the evidence to support this treatment is not universally accepted and pharmacotherapy options for post-COVID-19 olfactory dysfunction are still being explored; one potential therapy is gabapentin.

Gabapentin is an antiepileptic medication now used as first-line therapy for diabetic neuropathy and herpetic neuralgia. Gabapentin works by binding to VGCCs, which play an important role in neuronal synaptic transmission. More specifically, gabapentin binds to $\alpha_2\delta$ isoforms which have been associated with neuropathic pain. The postsynaptic $\alpha_2\delta1$ subunit promotes spinogenesis, the development of neuronal dendritic spines, while the $\alpha_2\delta2$ works as a suppressor of axonal regeneration.[13] Gabapentin functions as an inhibitor of the $\alpha_2\delta2$ subunit and therefore blocks the suppression of axonal regeneration leading to increased neuronal regeneration and function. The medication is effective in the treatment

of chronic pain and burning mouth syndrome (BMS). The mode of action is thought to be primarily due to the fact that gabapentin is highly lipophilic and can enter the central nervous system (CNS) and iad in neuron regeneration.[14] For these reasons, gabapentin is thought to have the potential to improve post-COVID-19 olfactory dysfunction caused by neuronal damage. Our study will investigate the efficacy of gabapentin to increase recovery of olfactory dysfunction secondary to post-COVID-19 infection.

B2 Rationale for this Study

Olfactory dysfunction is a major symptom of SARS-CoV-2 affecting up to 80% of infected individuals. While most have a return to normal olfactory function in weeks, some may not see full improvement for months and a small percentage may not recover function and suffer long-term physical limitation and functional impairment. This placebo-controlled, double-blinded pilot RCT will evaluate the efficacy of oral gabapentin to improve chronic (>3 months) olfactory dysfunction secondary to COVID-19 infection. This study will provide data on the efficacy of gabapentin for the treatment of OD.

C Study Objectives

C1 Primary Aim

To evaluate the efficacy of oral gabapentin on improvement of olfactory dysfunction in patients with post-COVID-19 anosmia, hyposmia, or parosmia. Participants will receive a maximum of 14weeks of either gabapentin or placebo with the first four weeks serving as a titration phase and the last two weeks serving as a taper-down period.

C2 Secondary Aim

Describe the adverse effects of gabapentin. All participants will be monitored for adverse effects throughout the study.

C3 Rationale for the Selection of Outcome Measures

Primary Outcome:

***Clinical Global Impression of Improvement Scale* (*CGI-I*).** The response rate is defined as the number of participants self-reporting minimal change or larger on the *Clinical Global Impression of Improvement Scale* (*CGI-I*) scale, divided by the number of participants in each group. The CGI-Improvement *is a self-reported scale of improvement ranging from 1* to 7 (1 is Very Much Improved, 7 is Very Much Worsened) and will be measured after completing 8 weeks of the fixed, highest-tolerable dose. Each rating is well defined to maximize accuracy. Participants reporting 3 as *Minimally Improved*, 2 as *Much Improved*, or 1 as *Very Much Improved* in the CGI-I will be deemed responders to treatment, and the number of responders to non-responders will be compared between the two arms - CGI-Severity (CGI-S) and CGI-Improvement (CGI-I).

Secondary Outcomes:

1. **CGI-Severity.** The *CGI-Severity* scale ranges from 1 to 7, where 1 is normal function and 7 is complete anosmia. This assessment will provide subjective data on patients' baseline olfactory function prior to beginning the trial, after 8-week Fixed-Dose period, and 4 weeks after completion of Taper-Down phase.
2. **CGI-Improvement**. The CGI Improvement will also be administered 4 weeks after completion of Taper-Down phase which same analysis as described above.
3. ***University of Pennsylvania Smell Identification Test* (*UPSIT*).**[15] The *UPSIT* is composed of 40 strips of microencapsulated odorants, which are present on the bottom of each page, just below a four-alternative multiple-choice question. For a given item, the patient releases an odor by scratching the microencapsulated pad with a pencil tip, smells the pad, and indicates the odor quality from four alternatives. Even if no smell is perceived, a response is required (i.e., the test is forced-choice). The subject's total correct score out of the 40 items is determined.[16]

   The total UPSIT score can range from 0 to 40 and scores are interpreted as the level of absolute smell function (i.e., normosmia, mild hyposmia, moderate hyposmia, severe hyposmia, and anosmia), using the age- and sex-related normative classification system described in the UPSIT manual (Table 1) The minimal clinically important difference in UPSIT score is 4.

Disease Classification Based on UPSIT		Women	Men
Normosmia		>34	>33
Hyposmia			
	Mild	31-34	30-33
	Moderate	26-30	26-29
	Severe	19-25	
Anosmia		6-18	
Malingering		≤ 5	

4. ***Olfactory Dysfunction Outcomes Rating* (*ODOR*).** The *ODOR* questionnaire is a 28-item disease-specific health status survey to assess the physical problems, functional impairments, and emotional consequences secondary to olfactory dysfunction. *ODOR* was developed and validated by Dr. Jake Lee and colleagues in the Clinical Outcomes Research Office at Washington University.
5. ***NASAL-7***. *NASAL-7* is a simple diagnostic tool for olfactory dysfunction that is based on commonly found household items and can be used by adults who suspect olfactory dysfunction. The *NASAL-7* was developed by Dr. Piccirillo and colleagues in the Clinical Outcomes Research Office. The *NASAL-7*, contains 7 household items with each item scored as 0 for '*Cannot Smell'*, 1 for '*Smells Less Strong/Different Than Normal*', and 2 for '*Smells Normal'*, for a total possible score ranging from 0-14. The following four categories of olfactory function were defined based on *NASAL-7* score: *anosmia* (score 0-4), *severe dysfunction* (score 5-7), *mild dysfunction* (score 8-10), and *normosmia* (score 11-14).
6. ***Clinical Global Impression-Severity Scale for Parosmics (CGI-P)***. The *CGI-P* Scale is a global rating of parosmia and the single global rating ranges from 1-5, where 1 is *No Distortion*, 2 is *Mild Distortion*, 3 is *Moderate Distortion*, 4 is *Mostly Distorted*, and 5 is *Complete Distortion*. The response on the *CGI-P* will

provide information on the patient's perceived severity of the distortion of their smell.

D Investigational Agent

D1 Preclinical Data

Gabapentin is an antiepileptic medication now used as first-line therapy for diabetic neuropathy and herpetic neuralgia. Gabapentin works by binding to voltage-gated calcium channels (VGCCs), which play an important role in neuronal synaptic transmission. More specifically, gabapentin binds to $\alpha_2\delta$ isoforms which have been associated with neuropathic pain.

The α2δ2 subunit of VGCCs, with increased expression in corticospinal neurons, has been associated with loss of regrowth after spinal injuries. The postsynaptic $\alpha_2\delta1$ subunit promotes spinogenesis, the development of neuronal dendritic spines, while the $\alpha_2\delta2$ works as a suppressor of axonal regeneration.[13] The α2δ2 blockage by gabapentin can allow increased nerve regeneration and return of function.[7] Inhibition of the α2δ2 subunit on VGCCs may allow nerves to regenerate more rapidly than physiologically normal.

D2 Clinical Data to Date

Gabapentin is an antiepileptic medication now used as first-line therapy for diabetic neuropathy and herpetic neuralgia. Gabapentin works by binding to voltage-gated calcium channels (VGCCs), which play an important role in neuronal synaptic transmission. More specifically, gabapentin binds to $\alpha_2\delta$ isoforms which have been associated with neuropathic pain.

The medication has also proven effective in treated chronic pain from Burning Mouth Syndrome (BMS) since gabapentin is highly lipophilic and can enter the central nervous system (CNS).[14] For these reasons, gabapentin is thought to have the potential to improve post-COVID-19 olfactory dysfunction caused by neuronal damage. Gabapentin can penetrate the blood-brain barrier and enter the CNS where it can aid in neuron regeneration.

D3 Dose Rationale and Risk/Benefits

Gabapentin dosing for this study mirrors dosing for the prior study "Relief of Idiopathic Subjective Tinnitus" (IRB #02-0717)
Following randomization, participants in the gabapentin arm will take gradually titrated dosages in order to achieve a dose of 3600mg/d or highest tolerable dose. The titration schedule will span a maximum 4 weeks to reach 3600mg/d.

Week 1, 900 mg/d
Week 2, 1800 mg/d
Week 3, 2700 mg/d
Week 4, 3600 mg/d

Gabapentin (300 mg per capsule) and placebo will be supplied to patients in identical opaque capsules in blinded fashion. The medications will be distributed in 4 separate vials representing each of the four weeks of the Titration Period. All participants will be provided an equal number of capsules and instructed to follow a TID (i.e., 3 times per day) dosing schedule. All participants' dosages will be titrated to a maximum dose of 3600 mg/d, regardless of any possible beneficial effect achieved at lower dosages. If intolerable adverse reactions occur, the dosage will be decreased to previous tolerable dose (e.g. if 2700mg/d is intolerable, dosage will be decreased to 1800 mg/d). If, during the first week, 900 mg/d is intolerable, dosing will be decreased by 300 mg/d per day until tolerable (i.e., 600 mg/d, 300mg/d) or until they are no longer taking the medication. The dose established during the Titration Period will be maintained throughout the Fixed-Dose period. Participants receiving the matching placebo capsules will be provided similar instructions for titration and de-escalation, should side effects develop.

The potential benefit to the participant is improvement of their olfactory dysfunction using this therapy. The potential benefit to the society is the use of the pilot study results to initiate a larger trial to further evaluate the efficacy of gabapentin in the treatment of post-COVID-19 olfactory dysfunction.

The potential risk to participants during the study is an adverse event associated with the medication use. Abrupt cessation of gabapentin may alter the seizure threshold; for this reason, participants will be provided with a taper schedule specific to the gabapentin dose at time of completion of the Fixed Dose period. Gabapentin has a slight risk of dependence in patients with previous history of alcohol, cocaine, or opioid abuse so these individuals will be excluded from the study. [17]

E Study Design

E1 Overview or Design Summary

This study will be a double-blinded, placebo-controlled, randomized pilot clinical trial to evaluate the efficacy of gabapentin to improve post-COVID-19 olfactory dysfunction. This study will also describe adverse effects related to oral gabapentin use.

This study will be conducted via virtual research guidelines and procedures. We will not require in-person patient participation or evaluation. Following initial evaluation to ensure potential participants meet all inclusion criteria and none of the exclusion criteria, the research study will be explained in full via Zoom call, phone call if necessary. Participants will then be randomized in a 1:1 allocation via permuted-block sequencing into the oral gabapentin group or the placebo group. All assessments will be conducted through a HIPAA-compliant online survey form. Baseline assessments will help us determine subjective and objective rates of olfactory dysfunction. Assessments will be conducted again after the 8-week Fixed-Dose period and 4 weeks after completing taper.

The primary objective of this study is to assess the efficacy of oral gabapentin in improving olfactory dysfunction secondary to COVID-19.

E2 Subject Selection and Withdrawal

2.a Inclusion Criteria

Participants will be recruited based on the following inclusion criteria:

- Men and women between the ages of 18 and 65 years
- Residing within the states of Missouri or Illinois
- Clinically diagnosed or subjective olfactory dysfunction (anosmia, hyposmia, or parosmia) of at least 3 months duration associated with COVID-19 infection
- initial UPSIT score consistent with diminished olfactory function (score ≥ 6 and ≤ 33 in men and score ≥ 6 and ≤ 34 in women).
- Willing to respond daily to study surveys, preferably through smartphone with unlimited texting plan.
- In possession of all 7 household items associated with *NASAL-7*: soap, burnt candle, peanut butter, herb, garlic, lemon, and coffee

2.a Exclusion Criteria

Individuals will not be allowed to participate in this study if they meet one or more of the following exclusion criteria:

- Clinically diagnosed olfactory dysfunction secondary to non-COVID-19 viral infection, genetic abnormalities or congenital dysfunction, trauma, nasal polyps, neurodegenerative disorders
- Current use of: azelastine, bromperidol, orophenadrine, oxomemazine, kratom, paraldehyde, or thalidomide
- History of addiction to alcohol, cocaine, or opioids
- Impaired renal function, myasthenia gravis, or myoclonus
- Severe allergy to peanuts
- Pregnancy or attempting pregnancy during study participation
- Inability to participate in virtual trial due to lack of access to the; inability to comprehend or use English language
- Availability less than 18 weeks from time of enrollment
- Residency in states other than Missouri or Illinois.

2.b Ethical Considerations

This study relies on participation of human subjects. Informed consent will be obtained from each participant to ensure their safety, minimize risk, and ensure full confidentiality. All assessments will be conducted virtually via HIPAA-compliant online surveys at baseline and then throughout the study course. Selection of participants for the study will consider the variability in response to COVID-19 as well as response to gabapentin by ensuring the two groups are matched 1:1 by permuted block randomization. Gabapentin has a slight risk of dependence in individuals with previous

history of alcohol, cocaine, or opioid abuse so these patients will be excluded from the study.[17]The study team will be available at all times for participants during the full course of the trial.

2.c Subject Recruitment Plans and Consent Process

Recruitment will be done at the Washington University Department of Otolaryngology-Head and Neck Surgery outpatient clinics. Advertisements will also be sent to all members of the St. Louis ENT Club, and otolaryngologists whose practices are within 150 miles of Washington University Medical Center (WUMC). Direct recruitment of potential participants will also be achieved through use of the Washington University Volunteers for Health Research Participant Registry, and the Otolaryngology Research Participant Registry. This recruitment strategy has been successful for two current trials of treatment for COVID-associated anosmia VOLT (IRB ID# 202011046) and SCENT2 (IRB ID# 202101190). We may also attempt to recruit potential participants from past studies in our lab, such as the CODS trial (IRB ID# 202004146). Additionally, due to the focus on virtual research at this time, we may also use website postings and work with anosmia support groups such as AbScent and FifthSense to share the trial.

2.d Randomization Method and Blinding

Participants who remain eligible at the end of the screening period will be randomized in a double-blind fashion, according to a computer-generated random code, to receive either placebo or gabapentin. Dr. Kallogjeri will provide the randomization table to the BJH Research Pharmacist, who will prepare both gabapentin and placebo for the entire study. The research assistants will collect the gabapentin and placebo in a blinded fashion from the research pharmacist for distribution to the participants via FedEx.

2.e Risks and Benefits

The potential benefit to the participant is improvement of their olfactory dysfunction using this therapy. The potential benefit to the society is the use of the pilot study results to initiate a larger trial to further evaluate the efficacy of gabapentin in the treatment of post-COVID-19 olfactory dysfunction.

The potential risk to participants during the study is an adverse event associated with the medication use. Abrupt cessation of gabapentin may alter the seizure threshold; for this reason, participants will be provided with a taper schedule specific to the gabapentin dose at time of cessation. Gabapentin has a slight risk of dependence in individuals with previous history of alcohol, cocaine, or opioid abuse so these individuals will be excluded from the study. [17]

The consent process informs a volunteer about the study, indicates that participation is voluntary, and that he/she has the right to stop at any time. Risks are listed in the informed consent form and described orally during the consent process.

2.f Early Withdrawal of Subjects

If a subject decides to withdraw from all components of the research study, the investigator will discontinue all of the current and scheduled research activities in the study. Participants taking an intervention medication at the time of withdrawal will be provided with a taper-down schedule based on maximum intervention dose achieved.

2.g When and How to Withdraw Subjects

A participant can withdraw consent for the study at any time. Participants will be allowed to end participation in the study at any point should they desire. If a participant must be withdrawn due to a drug-related serious adverse event, then blind will be broken and, if on gabapentin, drug withdrawal will be tapered or completely stopped based on the clinical judgement of the PI. All participants will have an exit interview to ascertain any adverse effects and discuss the reason for ending participation. The study team will follow them for safety reasons up to 30 days after stopping use of the study drug.

2.h Data Collection and Follow-up for Withdrawn Subjects

If a participant has ended participation, the only data that will be collected are the data from the exit interview and the data collected prior to withdrawal. There will not be any other follow-up or data collected from these subjects.

Data collected up to this point will not be used in the analysis, and further data will not be collected from these participants.

E3 Study Drug

3.a Description

Gabapentin is an antiepileptic medication now used as first-line therapy for diabetic neuropathy and herpetic neuralgia. Gabapentin works by binding to voltage-gated calcium channels (VGCCs), which play an important role in neuronal synaptic transmission. More specifically, gabapentin binds to $\alpha_2\delta$ isoforms which have been associated with neuropathic pain.

3.b Treatment Regimen

During the titration period of maximum 4 weeks, participants randomized to the gabapentin arm will take gradually titrated dosages of gabapentin as follows:

Week 1, 900 mg/d (300 mg TID)
Week 2, 1800 mg/d (600 mg TID)
Week 3, 2700 mg/d (900 mg TID)
Week 4, 3600 mg/d (1200 mg TID)

If intolerable effects occur, dosage will be decreased by 1 dose (300 mg) step (e.g. if 2700 mg/d is intolerable, dosage will be decreased to 2400 mg/d). Further de-escalation

will be determined by PI clinical judgement to prior tolerable dose. The highest tolerable dose established during the Titration Period will be maintained throughout the 8-week Fixed-Dose period.

3.c Method for Assigning Subjects to Treatment Groups

The participants will be divided using permuted block randomization in a 1:1 allocation between two arms: the oral gabapentin group and the oral lactose placebo group with 20 persons in each group.

3.d Preparation and Administration of Study Drug

Gabapentin (300 mg per capsule) and placebo will be supplied to patients in identical opaque capsules in blinded fashion. The medications will be distributed in 4 separate vials representing each of the four weeks of the Titration Period and distributed in 8 separate vials prior to the Fixed-Dose period.

3.e Subject Compliance Monitoring

There will be check-ins with the study participants every two weeks conducted virtually through the participant's preferred communication method (i.e. phone call or video call) to answer questions and ensure participants are adhering to medication schedule. Subjects will be asked to keep a paper calendar for daily notes of pill count, side/adverse effects, and study barriers. The paper calendar will be mailed back to the RA after study completion.

3.f Prior and Concomitant Therapy

Patients receiving concomitant therapy specifically for the treatment of olfactory dysfunction will not be eligible for the trial unless they are able to stop taking those therapies during the conduct of the study. Participants who have tried previous therapies for their olfactory dysfunction, including over-the-counter treatments such as vitamin A or omega-3 fatty acids will be eligible for the trial. Information will be gathered on their use of prior or current therapies, and if needed, a sensitivity or subgroup analysis may be considered.

3.g Packaging

The Research Pharmacist will deliver the gabapentin and placebo in a blinded fashion to the research assistant for distribution to the participants via FedEx.

3.h Blinding of Study Drug

Participants will be divided into two groups; one group will be given oral gabapentin while the other group will be given oral placebo. The research pharmacist will receive the randomization assignment code from the biostatistician. The RA will pick up the study drug in blinded fashion from research pharmacist and distribute it to the participant via FedEx delivery. In this way, only the Research Pharmacist will know participant assignment. Adequate taper of gabapentin will be provided for those on gabapentin while the placebo group will receive additional placebo for taper in order to maintain the blind.

3.i Receiving, Storage, Dispensing and Return

The services of the Investigational Pharmacy at Barnes-Jewish Hospital will be used for this trial. The product used in this trial will be managed by the pharmacist according to the pharmacy SOP.

F Study Procedures

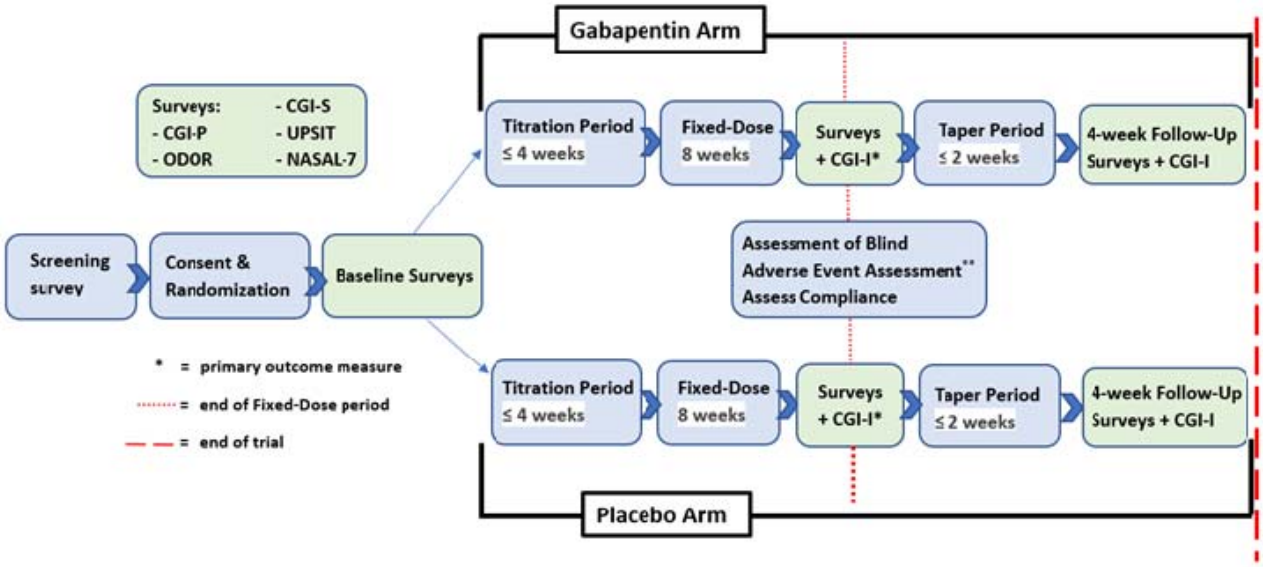
F1 Screening for Eligibility

Individuals who reach out with interest in the study after seeing the approved study flyer or who have contacted RA for participation in similar studies for which recruitment has ended will asked to complete an online screening questionnaire (survey titled: "ScreeningSurvey") to ensure he or she meets all the inclusion criteria and does not meet any exclusion criteria. Following eligibility confirmation, the RA will collect information required to mail screening smell identification test (UPSIT). Once received, the participant will complete the UPSIT and provide their response virtually through the REDCap survey. Once eligibility is confirmed based on UPSIT score, participants will be provided through REDCap an online consent form to review and complete. The RA will offer each participant the option to review the consent form independently or with the RA via zoom or phone call (zoom as the preferred option). Once the participant electronically signs the consent form, the RA will review it and sign. The REDCap software will automatically email the participant a copy of their completed form.

F2 Schedule of Measurements

Following the recruitment period and successful enrollment, baseline survey completion (survey titled Week0BaselineSurvey) and randomization of participants will occur. The timeline for measurements can be seen below.

Gabapentin Study Flow Chart



a. *Federal guidelines require timely reporting (within 15 calendar days) of an unanticipated or life-threatening event or death occurring within 30 days of active study participation.*

Titration Period: maximum duration 4 weeks

Placebo. In this study, we plan to use an inert placebo and not an active drug or non-active drug with side effects similar to gabapentin. Participants randomized to the Placebo arm will participate in a 4-week Titration Period. Placebo will be supplied to patients in opaque capsules in blinded fashion. The medications will be distributed in 4 separate vials representing each of the four weeks of the Titration Period. If intolerable adverse reactions occur, the dosage will be decreased to prior tolerable dose.

Gabapentin. Participants randomized to the gabapentin arm will take gradually titrated dosages of gabapentin as follows:

Week 1, 900 mg/d (300 mg TID)
Week 2, 1800 mg/d (600 mg TID)
Week 3, 2700 mg/d (900 mg TID)
Week 4, 3600 mg/d (1200 mg TID)

Gabapentin (300 mg per capsule) will be supplied to participants in opaque capsules in blinded fashion identical to the supply of Placebo. The medications will be distributed in 4 separate vials representing each of the four weeks of the Titration Period. All participants' dosages will be titrated to a maximum dose of 3600 mg/d, regardless of any effect achieved at lower dosages. If intolerable effects occur, dosage will be decreased by 1 dose (300 mg) step (e. g. if 2700 mg/d is intolerable, dosage will be decreased to 2400 mg/d). Further de-escalation will be determined by PI clinical judgement to prior tolerable dose. Participants with intolerable effects may have a lower maximum dose than 3600mg/d and may complete the Titration Period in less than 4 weeks. The dose established during the Titration Period will be maintained throughout the Fixed-Dose period.

WEEK 1	WEEK 2	WEEK 3	WEEK 4
900 MG	1800 MG	2700 MG	3600 MG
1 MORNING 1 NOON 1 NIGHT (21 PILLS)	2 MORNING 2 NOON 2 NIGHT (42 PILLS)	3 MORNING 3 NOON 3 NIGHT (63 PILLS)	4 MORNING 4 NOON 4 NIGHT (84 PILLS)

Gabapentin (300 mg pill) Titration Schedule

If at any point during the Titration Period, the participant wishes to discontinue the medication for any reason, they will be instructed to follow the taper down schedule (see below) in order to safely stop the medication. The participant will be informed that any abrupt stoppage of gabapentin could cause serious adverse effects.

Participants will be contacted by telephone or video call by the Research Assistant (RA) at the end of Titration period. The purpose of this call will be to query the participants about adverse effects. Participants will be provided with a paper calendar and asked to maintain diaries of olfactory and taste symptoms and adverse effects possibly related to the intervention.

Participants will not complete any forms at the completion of Titration period. Instead, they will proceed directly to Fixed-Dose Period.

Fixed-Dose Period: duration 8 weeks

During the Fixed-Dose period, participant's dose will remain at their maximum tolerated dosage established during the Titration phase. The study drug will be distributed in eight separate vials representing the eight weeks of the Fixed-Dose period. The RA will contact the participants at the end of Week 4 to administer the blind assessment using REDCap (survey titled: "Blind Assessment"). Participants will complete the following forms after completing the Fixed-Dose Period (survey titled: "FixedDoseSurvey"):

1.) *Clinical Global Impression of Severity Scale* (*CGI-S*).
2.) *Clinical Global Impression of Improvement Scale (CGI-I)*
3.) *University of Pennsylvania Smell Identification Test* (*UPSIT*)
4.) *Olfactory Dysfunction Outcomes Rating* (*ODOR*)
5.) *NASAL-7*
6.) *Clinical Global Impression-Severity Scale for Parosmics (CGI-P)*
7.) Adverse Event assessment
8.) Compliance

Adverse events. Any unintentional or unfavorable clinical sign or symptom, any new illness or disease or the deterioration of existing disease or illness, or any clinically significant deterioration in any laboratory assessments or clinical tests while participating in this study will be captured. The study coordinator will contact participants virtually to answer questions and assess adverse effects after Titration period, Fixed-Dose period, and 4 weeks after Taper.

Taper Down: maximum duration 2 weeks

Upon completion of the Fixed-Dose period, all participants in the study will be titrated off study drug through a taper down period of maximum 2 weeks. Taper schedule will directly relate to maximum gabapentin dose achieved during trial and is described in the Table below. The study drug will be distributed in 2 separate vials representing each of the two weeks of the Taper-Down Period. It should be noted, participants randomized to placebo will also receive sufficient capsules to complete a taper down. In this way, the blind will be maintained.

AT 3600 MG	AT 2700 MG	AT 1800 MG	AT 900 MG
FOR 3 DAYS 3 MORNING 3 NOON 3 NIGHT	FOR 3 DAYS 2 MORNING 2 NOON 2 NIGHT	FOR 3 DAYS 1 MORNING 1 NOON 1 NIGHT THEN STOP	NO TAPER REQUIRED
NEXT 3 DAYS 2 MORNING 2 NOON 2 NIGHT	NEXT 3 DAYS 1 MORNING 1 NOON 1 NIGHT THEN STOP		
FINAL 3 DAYS 1 MORNING 1 NOON 1 NIGHT THEN STOP			

Gabapentin Taper Down Schedule

End of Study Intervention: Exit Interview/ Data Collection: 4 weeks after completing Taper Down

The RA will contact the participants to query participants about compliance with taper-down schedule and maintenance of diaries. Participants will complete the following forms (survey titled: "FinalSurvey"):

1. *Clinical Global Impression of Severity Scale* (*CGI-S*).
2. *Clinical Global Impression of Improvement Scale (CGI-I)*
3. *University of Pennsylvania Smell Identification Test* (*UPSIT*)
4. *Olfactory Dysfunction Outcomes Rating* (*ODOR*)
5. *NASAL-7*
6. *Clinical Global Impression-Severity Scale for Parosmics (CGI-P)*

F3 Safety and Adverse Events

3.a Safety and Compliance 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 committee comprised of Dr. Piccirillo, Ms. Kukuljan, and Dr. Kallogjeri, the study biostatistician. All reports of a Serious Adverse Event (SAE) or

an Unexpected Adverse Event (UAE) will be investigated by the monitoring team and reported to Washington University HRPO according to the reporting requirements.

Participants who experience serious adverse effects with gabapentin therapy will be removed from the study. Participants with serious adverse effects will be instructed to call 911, seek immediate medical care and discontinue all further gabapentin treatment. If tolerated, all participants will complete the Titration period (≤ 4 weeks), Fixed-Dose period (8 weeks), and Taper-Down period (2 weeks) for maximum 14 weeks of active participation. In addition, there will be a 4-week, post-Taper completion follow-up for maximum total of 18-week trial duration.

3.a Medical Monitoring

i Investigator only

The PI and the study team will be monitoring patients for any safety concerns, such as SAE or UAE, in real time for the duration of the 18-week study. In addition, participants will be specifically asked about any adverse events after the Fixed-Dose period via REDCap. Participants will be able to get in touch with a member of the study team 24/7 via phone or pager for the duration of the 18-week clinical trial. The study biostatistician will hold the randomization codes and remain blinded to the intervention assignment. In the event of an SAE or UAE in which the blind needs to be broken, the Research Pharmacist will be contacted by the PI or a member of the study team. The participant will receive appropriate care and will be removed from the trial. A description of the event will be included in the report of adverse events for the clinical study.

3.b Definitions of Adverse Events

Adverse event (AE) means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related (21 CFR 312.32(a)).

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a drug, without any judgment about causality or relationship to the drug.

An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

Serious adverse events (SAEs) are special cases of an adverse event where adverse outcomes are severe. SAEs include the following events:

- Death of any of the participants associated with a clinical trial.
- An event which can lead to life-threatening complications or put the life of participants at risk as a result of participation in a clinical trial.

- Events that result in such a condition where the participants may require immediate hospitalization or increase the duration of hospitalization.
- Any events that lead to a permanent or temporary physical disability in the body of the participants. Any sort of incapacity is also regarded as SAE.
- Any events that lead to any type of congenital abnormalities. It also includes any cases of birth defects resulting from the clinical trials.
- Any events where an investigator or team of investigators finds feel that it can lead to significant hazards.

Classification of Events

i Relationship

An AE or SAE may or may not be causally related to the study intervention. A causal relationship means that the intervention caused (or is reasonably likely to have caused) the AE. This usually implies a relationship in time between the intervention and the AE (e.g., the AE occurred shortly after the participant received the intervention). For all AEs, it is the responsibility of the Principal Investigator who examines and evaluates the patient to determine the relatedness of the event to the study intervention.

ii Severity

Severity refers to the intensity of a specific event and is a matter of individual clinical judgment.

- Grade 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; no intervention indicated
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
- Grade 3: Severe; or medically significant but not immediately life- threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
- Grade 4: Life-threatening; urgent intervention indicated.
- Grade 5: Death related to an AE

iii Expectedness

An adverse event or suspected adverse reaction is considered "unexpected" if it is not consistent with the risk information described in this protocol or on the informed consent or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

3.c Data Collection Procedures for Adverse Events

All adverse events and suspected adverse reactions are collected from ‘source documentation’ and the research coordinator will abstract the events. Documentation can

be within Washington University EPIC medical records, but at times the research coordinator will also need to have the subject or family send outside source documentation.

3.d Reporting Procedures

The Principal Investigator (PI) will be responsible for ensuring participants' safety on a daily basis and for reporting Serious Adverse Events and Unanticipated Problems to the Institutional Review Board (IRB) as required.

All SAEs will be reported immediately to the Principal Investigator upon identification.

3.e Adverse Event Reporting Period

All AEs and unanticipated problems will be reported to the IRB in a prompt and timely manner to protect other subjects from avoidable harm. The appropriate time frame for satisfying the requirement for prompt reporting will vary depending on the specific nature of the unanticipated problem. For this study, unanticipated problems that are serious adverse events will be reported to the IRB within 1 week of the investigator becoming aware of the event. Any other unanticipated problem will be reported to the IRB within 2 weeks of the investigator becoming aware of the problem.

Determining the appropriate time frame for reporting a particular unanticipated problem requires careful judgment by the Research Coordinator and the Principal Investigator knowledgeable about human subject protections. The primary consideration in making these judgments is the need to take timely action to prevent avoidable harms to other subjects.

F4 Study Outcome Measurements and Ascertainment

Participants will complete an assessment of blind after completion of 4 weeks of the 8-week Fixed-Dose period using REDCap (survey titled: "Blind Assessment")

Participants will also complete the following forms using REDCap (survey titled "FixedDoseSurvey") after completing the 8-week Fixed-Dose Period:

1.) *Clinical Global Impression of Severity Scale* (*CGI-S*).
2.) *Clinical Global Impression of Improvement Scale (CGI-I)*
3.) *University of Pennsylvania Smell Identification Test* (*UPSIT*)
4.) *Olfactory Dysfunction Outcomes Rating* (*ODOR*)
5.) *NASAL-7*
6.) *Clinical Global Impression-Severity Scale for Parosmics (CGI-P)*
7.) Adverse Event assessment
8.) Compliance

Participants will also complete the following forms using REDCap (survey titled FinalSurvey) 4 weeks after completing the Taper Period.

1) *Clinical Global Impression of Severity Scale* (*CGI-S*).
2) *Clinical Global Impression of Improvement Scale (CGI-I)*
3) *University of Pennsylvania Smell Identification Test* (*UPSIT*)
4) *Olfactory Dysfunction Outcomes Rating* (*ODOR*)
5) *NASAL-7*
6) *Clinical Global Impression-Severity Scale for Parosmics (CGI-P)*

G Statistical Plan

G1 Sample Size Determination and Power

To date there have been no studies investigating efficacy of gabapentin in COVID-19 related olfactory dysfunction. Due to the lack of preliminary data and effect size, estimates of the sample size for this study will be determined based on feasibility. For this pilot study, we plan to enroll 60 subjects. The sample size of 60 subjects is feasible given the incidence of COVID-19 cases in Missouri and considering a conservative estimate of a 10% rate of permanent olfactory dysfunction among those (~50%) who experience olfactory dysfunction as one of the presenting symptoms. Using a 33% drop out rate, we estimate that the sample size of 60 subjects randomized in a balanced way between the two treatment groups will provide us with 40 evaluable cases. A previous study exploring a different treatment for COVID-19 related anosmia in our lab showed that 30% of the participants randomized to placebo reported improvement at the end of the trial as compared to baseline. We aim to observe a 25% difference in the response rate between gabapentin and placebo groups. Assuming that this will be the response rate in the placebo group of our trial, the sample size of 20 subjects per group will provide us with a 95% Confidence Interval -5% to 55% around the desired proportion difference of 25% between gabapentin and placebo groups.

G2 Interim Monitoring and Early Stopping

There will not be a planned interim monitoring, nor will there be early stopping rules.

G3 Statistical Methods

An intention-to-treat analysis will be used for the primary analysis of the data. All participants will be examined in the groups to which they were initially assigned. 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 after Fixed-Dose period 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 change in UPSIT scores between the two groups. Mixed effects model will be used to test whether the change in UPSIT score from baseline to end of treatment is significantly different between 2 groups. Subjects will be treated as random factors, and group and time will be used as fixed factors in the model. Interaction of group by time will be explored. Effect sizes with 95% CIs will be reported for each analysis. All statistical analyses will be conducted in SPSS 28 (IBM Corp., Armonk, NY).

G4 Missing Outcome Data

All attempts will be made using Good Clinical Practice and through the reduction of the complexity and number of assessments to minimize the occurrence of missing outcome data. It will be assumed that all missing data will be at random. As this is a small pilot study, no computational techniques will be employed to adjust analyses for missing data.

G5 Unblinding Procedures

The blind will be broken for individual participants for safety concerns. Knowledge of the treatment received is necessary for interpreting the event, may be essential for the medical management of the subject, and may provide critical safety information about gabapentin that could have implications for the ongoing conduct of the trial (e.g., monitoring, informed consent). For unblinding, the research coordinator will contact the research pharmacist and provide the study ID number for the participant to be unblinded. The research pharmacist will contact the PI directly and reveal the intervention assignment. The research coordinator will remain blinded.

H Data Handling and Record Keeping

H1 Confidentiality and Security

Procedures that are in place to curb risks of breaches in confidentiality and privacy are 1) formal training protocols centered on the maintenance of confidentiality for all study team members and secure storage for identified data such as completed questionnaires and UPSIT exams; and communication with study team via secure email, phone line, or televideo call.

Only members of the study team will have access to the electronic research files. 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. Accordingly, these mechanisms intend to limit access to information that can link clinical data to individual participants. No participant identifying information will be revealed in any publications or presentations.

Case report forms will be created as electronic documents and stored within each study participants electronic file. Original hard-copy source documents will be electronically scanned and stored in the participants electronic file and stored in a locked file cabinet.

H2 Records Retention

All records will be retained for a minimum of six years after completion of the study and closure with the WU IRB.

I Study Administration

I1 Subject Stipends or Payments

Participants will be provided a Forte/Advarra debit card. They will receive $60 for completing all study requirements. If participants do not complete all requirements, they will be paid proportionally for the work they have completed.

I2 Study Timetable

January 2022: IRB approval process and acquisition of resources
February 2022 - March 2022: Rolling recruitment
February 2022 - August 2022: 18-week clinical trial
September 2022: Statistical analysis and publication of results

J Publication Plan

We plan to analyze accumulated data throughout the month of September 2022 and publish the results by the end of September 2022. This data includes the analysis of the CGI-I, UPSIT, ODOR, NASAL-7, and CGI-P as well as a discussion of the potential adverse effects associated with oral gabapentin therapy for treatment of post-COVID-19 olfactory dysfunction.

K Attachments

K1 Questionnaires or surveys

- Screening Survey
- Screening UPSIT
- Week0BaselineSurvey
- Blind Assessment
- FixedDoseSurvey
- FinalSurvey

L References

1. Prevention CfDCa. COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#datatracker-home. Published 2021. Accessed.
2. Organization WH. WHO Coronavirus (COVID-19) Dashboard. https://covid19.who.int/. Published 2021. Accessed.
3. Lechien JR, Chiesa-Estomba CM, De Siati DR, 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.
4. Boscolo-Rizzo P, Borsetto D, Fabbris C, et al. Evolution of Altered Sense of Smell or Taste in Patients With Mildly Symptomatic COVID-19. *JAMA Otolaryngol Head Neck Surg.* 2020.
5. Hummel T, Rissom K, Reden J, Hahner A, Weidenbecher M, Huttenbrink KB. Effects of olfactory training in patients with olfactory loss. *Laryngoscope.* 2009;119(3):496-499.
6. Turner JH. Olfactory training: what is the evidence? *Int Forum Allergy Rhinol.* 2020;10(11):1199-1200.
7. Biole C, Bianco M, Nunez-Gil IJ, et al. Gender Differences in the Presentation and Outcomes of Hospitalized Patients With COVID-19. *J Hosp Med.* 2021;16(6):349-352.
8. Butowt R, von Bartheld CS. Anosmia in COVID-19: Underlying Mechanisms and Assessment of an Olfactory Route to Brain Infection. *Neuroscientist.* 2020:1073858420956905.
9. Bilinska K, Butowt R. Anosmia in COVID-19: A Bumpy Road to Establishing a Cellular Mechanism. *ACS Chem Neurosci.* 2020;11(15):2152-2155.
10. Kuba K, Imai Y, Penninger JM. Multiple functions of angiotensin-converting enzyme 2 and its relevance in cardiovascular diseases. *Circ J.* 2013;77(2):301-308.
11. Mollica V, Rizzo A, Massari F. The pivotal role of TMPRSS2 in coronavirus disease 2019 and prostate cancer. *Future Oncol.* 2020;16(27):2029-2033.
12. Damm M, Pikart LK, Reimann H, et al. Olfactory training is helpful in postinfectious olfactory loss: a randomized, controlled, multicenter study. *Laryngoscope.* 2014;124(4):826-831.
13. Schopf CL, Ablinger C, Geisler SM, et al. Presynaptic alpha2delta subunits are key organizers of glutamatergic synapses. *Proc Natl Acad Sci U S A.* 2021;118(14).
14. Lopez-D'alessandro E, Escovich L. Combination of alpha lipoic acid and gabapentin, its efficacy in the treatment of Burning Mouth Syndrome: a randomized, double-blind, placebo controlled trial. *Med Oral Patol Oral Cir Bucal.* 2011;16(5):e635-640.
15. Doty RL, Shaman P, Dann M. Development of the University of Pennsylvania Smell Identification Test: A standardized microencapsulated test of olfactory function. *Physiol Behav.* 1984;32(3):489-502.

16. Doty RL. Olfactory dysfunction and its measurement in the clinic. *World J Otorhinolaryngol Head Neck Surg.* 2015;1(1):28-33.
17. Mersfelder TL, Nichols WH. Gabapentin: Abuse, Dependence, and Withdrawal. *Ann Pharmacother.* 2016;50(3):229-233.