The COVID-19 pandemic affected millions of people and has become a dominant etiology of olfactory dysfunction (OD). No interventions with definitive clinical utility exist. Gabapentin represents a potential therapy for COVID-19–induced OD.

**OBJECTIVE** To evaluate the efficacy of oral gabapentin on olfactory function and olfaction-related quality of life in patients with COVID-19–induced OD.

**DESIGN, SETTING, AND PARTICIPANTS** This pilot double-blinded, placebo-controlled randomized clinical trial (RCT) was conducted at Washington University School of Medicine in St Louis from January 7, 2022, to February 3, 2023. Adults with at least 3 months of OD after COVID-19 infection were eligible for inclusion. Participants with a history of other causes of OD or contraindications to gabapentin were excluded.

**INTERVENTION** Patients were randomized 1:1 to oral gabapentin or placebo. All patients underwent titration to a maximum tolerable dose, which was maintained during an 8-week fixed-dose (FD) phase then tapered off. Participants were monitored for 4 weeks following cessation of study medication.

**MAIN OUTCOMES AND MEASURES** Outcomes were assessed following the 8-week FD phase and 4 weeks after taper completion. The primary outcome measure was the response rate determined by subjective improvement in OD on the Clinical Global Impression of Improvement (CGI-I) after the FD phase. Other subjective and objective measures of olfactory function were also assessed as secondary outcome measures.

**RESULTS** Sixty-eight participants were enrolled (34 randomized to each arm), a total of 44 participants completed the FD period and 20 (45.4%) reported response to treatment with at least slight improvement in olfaction from baseline. Of those randomized, 51 (75%) were women and 56 were White (82%) with a mean (SD) age of 43 (13.5) years. Baseline demographic features including age, sex, and race and ethnicity were not significantly different between the groups. Of the 18 participants in the gabapentin group, 8 (44%) were responders and of the 26 participants in the placebo group, 12 (46%) reported response to treatment (percent difference, 1.7%; 95% CI, −31.6% to 28.2%). Mixed-model analysis of all secondary outcome measures demonstrated no clinically meaningful or statistically significant difference between the gabapentin and placebo groups throughout the trial. There were no serious adverse events.

**CONCLUSIONS AND RELEVANCE** In this randomized clinical trial, gabapentin was not associated with statistically significant or clinically meaningful benefit over placebo and likely is not an efficacious therapy for COVID-19–induced OD.

**TRIAL REGISTRATION** ClinicalTrials.gov Identifier: NCT05184192

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The SARS-CoV-2 virus has infected an estimated 100 million people in the US, with approximately 85% of patients reporting some degree of olfactory dysfunction (OD). Patients with OD frequently suffer impaired quality of life and may have greater rates of depressive symptoms. Currently, no interventions with definitive clinical utility exist. Thus, continued effort is needed to better define the etiology of COVID-19–induced OD and develop efficacious therapies for those suffering from it.

Evidence suggests that COVID-19–induced OD may be due to direct damage to olfactory receptor neurons (ORNs). Previous strains of human coronavirus have also been shown to target ORNs, resulting in OD. Following COVID-19 infection, most patients recover their sense of smell in just weeks. Those with persistent OD either regain their olfactory function in months or have not fully recovered.

Gabapentin is an antiepileptic medication used for diabetic neuropathy and postherpetic neuralgia, which has been reported to improve COVID-19–induced parosmia. Gabapentin works by binding voltage-gated calcium channels, which play an important role in neuronal synaptic transmission. More specifically, gabapentin acts as an inhibitor of the α2δ2 subunit leading to neuronal regeneration and function. Its lipophilic properties allow it to cross the blood-brain barrier and treat central nervous system disorders, such as chronic pain and burning mouth syndrome. Due to its neuroregenerative properties and ability to enter the central nervous system, gabapentin represents an effective treatment option for COVID-19–induced OD. This study investigated the efficacy of gabapentin to improve olfaction and olfactory-related quality of life in patients with COVID-19–induced OD.

Methods

Study Design

This was a double-blinded, placebo-controlled, pilot randomized clinical trial (RCT) investigating oral gabapentin for COVID-19–induced OD. Recruitment and follow-up took place from January 7, 2022, to February 1, 2023. This study was conducted virtually with all assessments completed online. The study duration was up to 18 weeks with outcomes assessed at baseline, after an 8-week fixed dose (FD) phase, and 4 weeks after cessation of the study medication. The trial protocol (Supplement 1) was reviewed and approved by the Washington University School of Medicine institutional review board (IRB #202110011) and all participants provided written informed consent.

Key Points

Question Does gabapentin represent a safe and efficacious treatment for COVID-19–induced olfactory dysfunction (OD)?

Findings In this double-blinded, placebo-controlled pilot randomized clinical trial (RCT), the rate of response as determined by the Clinical Global Rating of Improvement (CGI) after an 8-week fixed-dose phase was 44.4% and 46.2% for the gabapentin and placebo treatment groups, respectively. Changes in odor identification and olfaction-related quality of life were not significantly different between the 2 treatment groups.

Meaning The lack of a statistically significant or clinically important effect of oral gabapentin suggests that it should not be considered as a potential therapeutic agent for COVID-19–induced OD.

Participant Selection

Participants were recruited through the Washington University School of Medicine Volunteers for Health Research Participant Registry and the Otolaryngology Research Participant Registry. In addition, advertisements were posted in the Washington University School of Medicine Department of Otolaryngology–Head and Neck Surgery outpatient clinics.

Inclusion criteria included (1) age 18 to 65 years, (2) residence in Missouri or Illinois, (3) clinical diagnosis of subjective OD of at least 3 months duration associated with COVID-19 infection, (4) objective OD as determined by a University of Pennsylvania Smell Identification Test (UPSIT) score of between 6 and 33 for men or between 6 and 34 for women, (5) possession of all NASAL-7–associated household items. Exclusion criteria included (1) OD due to other etiologies, (2) current use of azelastine, bromperidol, orophenadrine, oxomemazine, kratom, paraldehyde, or thalidomide, (3) history of addiction to alcohol, cocaine, or opioids, (4) impaired kidney function, myasthenia gravis, or myoclonus, (5) severe peanut allergy, (6) pregnancy or attempting pregnancy during study participation, (7) lack of internet access.

Randomization and Blinding

Participants were randomized in a 1:1 allocation via permuted-block sequencing into the gabapentin group or the placebo group. Participants and all study team members were blinded to the treatment assignment. Study medication was prepared by an unblinded research pharmacist. The active treatment and placebo were identical in appearance. Assessment of the blind was conducted 4 weeks after the start of the FD phase by asking participants which treatment group they believed they were assigned to.

Study Intervention

The study followed a titration period, an 8-week FD phase, and a taper period. The titration period lasted up to 4 weeks with the following dosage schedule: week 1, 900 mg per day (mg/d) (300 mg 3 times per day [TID]); week 2, 1800 mg/d (600 mg TID); week 3, 2700 mg/d (900 mg TID); and week 4, 3600 mg/d (1200 mg TID). All participants were titrated to a maximum dose of 3600 mg/d, regardless of any benefit achieved at lower doses.
If intolerable effects occurred, the dose was decreased to the previously tolerated dose. Once the maximum tolerable dose was achieved, the participant maintained this dose for an 8-week FD phase. All participants then completed a taper period, which ranged from 0 to 9 days. Participants were followed for an additional 4 weeks following taper completion.

**Baseline Assessments and Outcomes**
Demographic information, including race, ethnicity, and sex, was collected at baseline through an online survey. In addition, participants completed the Olfactory Dysfunction Outcome Rating (ODOR), NASAL-7, Clinical Global Impression of Severity (CGI-S), Clinical Global Impression of Parosmia (CGI-P) at baseline. The UPSIT used for eligibility screening served as the baseline UPSIT for included participants. These assessments along with the Clinical Global Impression of Improvement (CGI-I) were completed following the 8-week FD phase and 4 weeks after taper.

The primary outcome measure was the treatment response rate following the 8-week FD phase as determined by the CGI-I. The CGI-I is a modified 7-point Likert scale of perceived change. Response options include (1) much better, (2) somewhat better, (3) slightly better, (4) neither better nor worse, (5) slightly worse, (6) somewhat worse, (7) much worse. The response rate was defined as the number of participants self-reporting least “slightly better” divided by the number of participants in each treatment group. The number of treatment responders was compared between the 2 treatment groups. A response rate difference of 25% was determined by the investigators to be the minimal clinically important difference (MCID).

The secondary outcome measures were changes in UPSIT, ODOR, NASAL-7, CGI-S, and CGI-P scores after the FD phase and 4 weeks after taper. In addition, CGI-I responses were recorded 4 weeks after taper.

The UPSIT is a 40-question multiple-choice odor identification test. Microencapsulated odorants are contained in the test and released by scratching. The UPSIT is scored out of 40 points. Score ranges are used to classify patients by degree of OD (ie, normosmia, mild hyposmia, moderate hyposmia, severe hyposmia, and anosmia). A change of 4 points or greater is considered the MCID.

The ODOR questionnaire is a validated 28-item patient-reported outcome measure which assesses the physical, functional, and emotional consequences of OD. Each of the 28 items is scored 0 to 4. The maximum total score is 112 with higher scores representing greater quality of life impairment. The MCID is 15.

The NASAL-7 is a self-administered diagnostic tool for OD that uses commonly found household items. The NASAL-7 assesses the ability to smell 7 household items with each item scored as (0) cannot smell, (1) smells less strong/different than normal, (2) smells normal. The total possible score ranges from 0 to 14 with higher scores indicating more severe OD. Four categories of olfactory function were defined based on the NASAL-7 score: anosmia (score 0–4), severe dysfunction (score 5–7), mild dysfunction (score 8–10), and normosmia (score 11–14).

The CGI-S scale is a global rating of self-perceived olfactory function. The scale ranges from 1 to 6, with the following response options: (1) excellent, (2) very good, (3) good, (4) fair, (5) poor, and (6) absent. The CGI-P scale is a global rating of parosmia severity. The scale ranges from 1 to 5, with the following response options: (1) no distortion, (2) mild distortion, (3) moderate distortion, (4) mostly distorted, and (5) complete distortion. Because this study did not exclude participants with phantosmia, the CGI-P was used to capture dysosmia, a distortion of smell.

**Compliance and Safety Monitoring**
Virtual check-ins were conducted every 2 weeks for the duration of the study. At each check-in, compliance and adverse events were assessed. In addition, each participant was instructed to complete a daily log to assist with compliance monitoring. A final pill count was also conducted to confirm compliance.

**Sample Size**
A sample size of 60 participants was determined based on feasibility given the COVID-19 incidence during study development and accounting for a 10% rate of permanent OD. It was estimated that this would provide 40 participants with complete data, allowing for a 30% drop out rate. Given an anticipated placebo response rate of 30%, a sample size of 20 participants in each treatment arm would allow a 95% confidence interval (CI) of -5% to 55% around the desired 25% difference between the gabapentin and placebo groups.

**Statistical Analysis**
Data were analyzed using an intention-to-treat protocol. Normally distributed continuous variables were described using means and standard deviations and medians and ranges were used to report nonnormally distributed continuous variables. Categorical variables were reported using frequencies and percentages. The treatment response rate, defined by CGI-I, was compared between the 2 groups using proportion difference with 95% CIs. Independent samples t test or Mann-Whitney U tests were used to compare changes in UPSIT, ODOR, and NASAL-7 scores between treatment groups. Cliff’s δ was used to express the effect of the intervention. The 95% confidence intervals around the effect size were used to describe the precision of the estimate. Suggested values for the interpretation of Cliff’s δ are small (≥0.11); medium (≥0.28); large (≥0.43). Linear mixed models with participants as random factors and group and time as fixed factors was used to compare outcomes across study assessments between the study groups. Least square marginal mean differences and 95% CIs around them were used as measures of the effect size and precision. All statistical analyses were conducted in IBM SPSS Statistics software (version 28, IBM Corp).

**Results**

**Study Population**
A total of 188 individuals were screened for eligibility, with 89 meeting all study criteria and 68 participants providing informed consent and randomized (Figure 1). Thirty-four participants were randomized to gabapentin and 34 were...
Figure 1. CONSORT Flow Diagram of the GRACE Trial

188 Patients screened for eligibility

123 Passed screening

2 Excluded (lost to follow-up)

121 Screening UPSITs sent

24 Excluded
20 Did not complete UPSIT
4 Declined participation

97 Screening UPSITs completed

8 Failed UPSIT

89 Met enrollment criteria

68 Randomized

21 Excluded
13 Did not provide informed consent
5 Lost to follow-up
3 Withdrew prior to randomization

34 Randomized to placebo

1 Withdraw due to adverse effects

33 Titration phase

1 Lost to follow-up

32 Fixed-dose phase

6 Excluded
3 Lost to follow-up
1 Adverse effects
1 Medication schedule
1 PI withdrawalb

26 Taper phase

26 Complete

34 Randomized to gabapentin

7 Excluded
4 Concern for adverse effects
2 Lost to follow-up
1 PI withdrawalb

27 Titration phase

7 Excluded
4 Adverse effects
3 Lost to follow-up

20 Fixed-dose phase

2 Excluded
1 Lost to follow-up
1 PI withdrawalb

18 Taper phase

17 Complete

1 Lost to follow-up

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a The participant noted the presence of a gastric ulcer prior to starting medication. The principal investigator elected to remove this participant due to safety concerns.
b The participant informed study team that she has been starting and stopping medication without titration or taper. Due to safety concerns of potential adverse effects, the principal investigator elected to withdraw this patient.
c The participant received laboratory results indicating low glomerular filtration rate. The principal investigator withdrew this participant due to increased risk of adverse effects.
randomized to placebo. Of those randomized, 51 (75%) were women and 56 were White (82%) with a mean (SD) age of 43 (13.5) years. Baseline demographic features including age, sex, and race and ethnicity were not significantly different between the groups (Table 1).

Primary Outcome
CGI-I
Distribution of CGI-I scores after the 8-week FD phase and 4 weeks after taper are displayed in Figure 2. A total of 44 participants completed the FD period and 20 (45.4%) reported response to treatment with at least slight improvement in olfaction from baseline. Of the 18 participants in the gabapentin group, 8 (44.4%) were responders and of the 26 participants in the placebo group, 12 (46.2%) reported response to treatment (percent difference, −1.7%; 95% CI, −31.6 to 28.2%). One (3.8%) participant in the placebo group noted a slight decline in olfaction after the FD phase, whereas no participant in the gabapentin group noted worsening. The CGI-I distribution after the FD phase showed a negligible difference between the groups (Cliff’s δ = 0.03; 95% CI, −0.23 to 0.34).

Secondary Outcomes
A summary of secondary outcome measure results is included in Table 2.

UPSIT
The median change in UPSIT scores from baseline to FD phase was 2.0 (95% CI, −3.0 to 6.0) in the gabapentin group and 1.5 (95% CI, −3.0 to 5.0) in the placebo group. Four of the 18 (22%) participants in the gabapentin group and 10 of the 26 (38%) participants in the placebo group had an increase of 4 or more points from baseline to FD phase (percent difference, −16%; 95% CI, −43 to 11%). Mixed-model analysis (Figure 3A) showed no significant difference in UPSIT scores between the groups through any of the assessment times.

Table 1. Baseline Demographic and Disease Characteristics of Randomized Participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo group (n = 34)</th>
<th>Gabapentin group (n = 34)*</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>44 (15.5)</td>
<td>42 (10.6)</td>
<td>2.3 (−4.7 to 9.3)</td>
</tr>
<tr>
<td>Race and ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>33 (97)</td>
<td>23 (86)</td>
<td>−0.12 (−0.26 to 0.03)</td>
</tr>
<tr>
<td>Black/African-American</td>
<td>0</td>
<td>2 (7)</td>
<td>0.07 (−0.25 to 0.17)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1 (3)</td>
<td>0</td>
<td>−0.03 (−0.09 to 0.03)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>2 (7)</td>
<td>0.07 (−0.25 to 0.17)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>25 (74)</td>
<td>26 (76)</td>
<td>0.03 (−0.18 to 0.24)</td>
</tr>
<tr>
<td>Male</td>
<td>9 (26)</td>
<td>8 (24)</td>
<td>−0.03 (−0.24 to 0.18)</td>
</tr>
<tr>
<td>UPSIT score, median (range)</td>
<td>25.5 (7 to 34)</td>
<td>24.5 (8 to 33)</td>
<td>0 (−3.0 to 3.0)</td>
</tr>
<tr>
<td>ODOR score, median (range)</td>
<td>54.5 (0 to 101)</td>
<td>56 (14 to 102)</td>
<td>2 (−9 to 12)</td>
</tr>
<tr>
<td>NASAL-7 categories</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anosmia (0-4)</td>
<td>11 (32)</td>
<td>9 (33)</td>
<td>−0.01 (−0.23 to 0.25)</td>
</tr>
<tr>
<td>Severe dysfunction (5-7)</td>
<td>16 (47)</td>
<td>12 (45)</td>
<td>−0.03 (−0.28 to 0.22)</td>
</tr>
<tr>
<td>Mild dysfunction (8-10)</td>
<td>5 (15)</td>
<td>4 (15)</td>
<td>0 (−0.18 to 0.18)</td>
</tr>
<tr>
<td>Normosmia (11-14)</td>
<td>2 (6)</td>
<td>2 (7)</td>
<td>0.02 (−0.11 to 0.14)</td>
</tr>
<tr>
<td>CGI-S of smell</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>5 (15)</td>
<td>6 (22)</td>
<td>0.08 (−0.12 to 0.27)</td>
</tr>
<tr>
<td>Poor</td>
<td>20 (59)</td>
<td>17 (63)</td>
<td>0.04 (−0.20 to 0.29)</td>
</tr>
<tr>
<td>Fair</td>
<td>7 (20)</td>
<td>3 (11)</td>
<td>−0.10 (−0.28 to 0.09)</td>
</tr>
<tr>
<td>Good</td>
<td>1 (3)</td>
<td>1 (4)</td>
<td>0.01 (−0.08 to 0.10)</td>
</tr>
<tr>
<td>Very good</td>
<td>1 (3)</td>
<td>0</td>
<td>−0.03 (−0.09 to 0.03)</td>
</tr>
<tr>
<td>Excellent</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CGI-S of parosmia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete distortion</td>
<td>9 (26)</td>
<td>9 (33)</td>
<td>0.07 (−0.16 to 0.30)</td>
</tr>
<tr>
<td>Mostly distorted</td>
<td>10 (30)</td>
<td>13 (48)</td>
<td>0.19 (−0.06 to 0.43)</td>
</tr>
<tr>
<td>Moderate distortion</td>
<td>9 (26)</td>
<td>5 (19)</td>
<td>−0.08 (−0.29 to 0.13)</td>
</tr>
<tr>
<td>Mild distortion</td>
<td>4 (12)</td>
<td>0</td>
<td>−0.12 (−0.23 to −0.01)</td>
</tr>
<tr>
<td>No distortion</td>
<td>2 (6)</td>
<td>0</td>
<td>−0.06 (−0.14 to 0.02)</td>
</tr>
</tbody>
</table>

Abbreviations: CGI-S, Clinical Global Impression of Severity; ODOR, Olfactory Dysfunction Outcome Rating; UPSIT, University of Pennsylvania Smell Identification Test.

*7 participants withdrew prior to baseline survey completion.

As a result, data on age, race and ethnicity, NASAL-7, ODOR, CGI-S Smell, and CGI-S parosmia results were unavailable.
The CGI-S and CGI-P scores are summarized in Table 2. There was no clinically meaningful difference in CGI-S and CGI-P scores at baseline, through end of FD phase, and 4 weeks after taper.

**Table 2. Secondary Outcome Measures of Study Groups**

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Placebo group (n = 26)</th>
<th>Gabapentin group (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CGI-S of smell, No. (%)</td>
<td>Baseline Fixed dose Post-taper*</td>
<td>Baseline Fixed dose Post-taper*</td>
</tr>
<tr>
<td>Absent</td>
<td>4 (15)</td>
<td>5 (19)</td>
</tr>
<tr>
<td>Poor</td>
<td>16 (62)</td>
<td>13 (50)</td>
</tr>
<tr>
<td>Fair</td>
<td>4 (15)</td>
<td>4 (15)</td>
</tr>
<tr>
<td>Good</td>
<td>1 (4)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Very good</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Excellent</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CGI-S of parosmia, No. (%)</td>
<td>Complete distortion</td>
<td>Mostly distorted</td>
</tr>
<tr>
<td>Complete distortion</td>
<td>6 (23)</td>
<td>6 (23)</td>
</tr>
<tr>
<td>Mostly distorted</td>
<td>8 (31)</td>
<td>21 (81)</td>
</tr>
<tr>
<td>Moderate distortion</td>
<td>7 (27)</td>
<td>9 (35)</td>
</tr>
<tr>
<td>Mild distortion</td>
<td>4 (15)</td>
<td>7 (27)</td>
</tr>
<tr>
<td>No distortion</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>UPSIT, median (range)</td>
<td>24 (7-34)</td>
<td>25 (15-34)</td>
</tr>
<tr>
<td>UPSIT responders, No. (%)</td>
<td>NA</td>
<td>10 (38)</td>
</tr>
<tr>
<td>ODOR, median (range)</td>
<td>54.5 (30-96)</td>
<td>49.5 (8-96)</td>
</tr>
<tr>
<td>ODOR responders, No. (%)</td>
<td>NA</td>
<td>8 (31)</td>
</tr>
<tr>
<td>NASAL-7, No. (%)</td>
<td>Anosmia (0-4)</td>
<td>10 (38)</td>
</tr>
<tr>
<td>Severe dysfunction (5-7)</td>
<td>12 (46)</td>
<td>9 (35)</td>
</tr>
<tr>
<td>Mild dysfunction (8-10)</td>
<td>3 (12)</td>
<td>6 (23)</td>
</tr>
<tr>
<td>Normosmia (11-14)</td>
<td>1 (4)</td>
<td>4 (15)</td>
</tr>
</tbody>
</table>

Abbreviations: CGI-S, Clinical Global Impression of Severity; NA, not applicable; ODOR, Olfactory Dysfunction Outcome Rating; UPSIT, University of Pennsylvania Smell Identification Test.

* 26 participants in placebo group completed treatment, but 25 participants completed the post-taper survey.

**NASAL-7**

The median NASAL-7 scores for the gabapentin group were 6 (0-12), 6 (0-12), and 7 (0-14) at baseline, after the FD phase, and 4 weeks after taper, respectively. The scores for the placebo group were 6 (0-11), 6 (0-11), and 7 (0-14) at baseline, after the FD phase, and 4 weeks after taper.
FD phase, and 4 weeks after taper, respectively. Mixed-model analysis (Figure 3B) showed no significant difference in NASAL-7 scores between the groups through baseline, end of FD phase, and after taper.

ODOR
Six of 18 (33%) participants in the gabapentin group and 8 of 26 (31%) participants in the placebo group had a decrease in their ODOR score by 15 points or greater from baseline to after the FD phase (percent difference, 2.6%; 95% CI, −25.5% to 30.7%). Mixed-model analysis (Figure 3C) showed no significant difference in ODOR scores between the groups through baseline, end of FD phase, and after taper.

Compliance
In the gabapentin group, 10 of 18 participants (56%) were receiving the maximum dose (3600 mg daily) at FD completion. Four of 18 (22%) were receiving 2700 mg, 3 of 18 (17%) were receiving 1800 mg, and 1 participant (5.6%) was receiving 900 mg daily.

In the placebo group, 19 of 26 participants (73%) were receiving the maximum dose of 4 pills (3600 mg equivalent) at FD completion. Five of 26 participants (19%) were receiving 3 pills TID (2700 mg equivalent) and 2 of 26 (7%) were receiving 2 pills TID (1800 mg equivalent).

In the gabapentin group, 11 participants (65%) missed 0 doses, 3 (18%) missed between 1 and 5 doses, 1 participant (6%) missed between 6 and 10 doses, and 2 participants (12%) missed more than 20 doses (27, 53). In the placebo group, 12 participants (46%) did not miss any doses during the study period, 8 participants (31%) missed between 1 and 5 doses, 4 (15%) missed between 6 and 10 doses, 2 participants (8%) missed more than 10 doses (11, 49).

Assessment of Blinding
Of the 48 participants who completed the assessment of blinding (18 in the gabapentin group and 30 in the placebo group), 11 (61%) participants in the gabapentin group and 17 (57%) in the placebo group correctly identified their study group.

Adverse Events
Adverse events are summarized in the eTable in Supplement 2. Fatigue, reported by 10 participants in the gabapentin group and 11 participants in the placebo group, was the most common adverse effect. Dizziness was reported by 6 participants in the gabapentin group and by no participants in the placebo group. Weight gain was reported by 5 participants in the gabapentin group and no participants in the placebo group. Brain fog was reported by 6 participants in the gabapentin group and 2 participants in the placebo group. These were expected adverse effects of the study medication. No serious adverse events were noted in either group.

Discussion
This double-blinded, placebo-controlled RCT found no benefit of gabapentin for COVID-induced OD. Although the upper bound of the 95% CIs for CGI-I responders (28.2%) barely exceeded the predefined MCID (25%), the width of the CI was quite wide (imprecise), and was centered around 0%. This pattern of difference did not change 4 weeks after taper. These results, while not definitive, suggest no benefit of gabapentin for COVID-19–induced OD. The wide CIs were likely due to small sample size and unbalanced group distribution because 7 participants randomized to the gabapentin group withdrew prior to starting the medication. The secondary outcomes also demonstrated no meaningful differences between the study groups at baseline, after the FD phase, and after taper.

Gabapentin was well tolerated overall, but 48% of participants were unable to tolerate the maximum dose of 3600 mg and had their dosage reduced during the trial. Furthermore, there were higher rates of dizziness, brain fog, and weight gain notes in the gabapentin group.

To our knowledge, no RCT that tests the effect of gabapentin on COVID-19–induced OD has been published. Although there is a growing body of literature that suggests promising treatments for OD include olfactory training,11 intranasal theophylline,16 and intranasal corticosteroids,21 none of these treatments have been definitively proven to be clinical effective. Gabapentin was assessed as a potential therapeutic target to mitigate viral-induced damage to the ORNs. However, the findings of this study showed that an 8-week course of gabapentin did not improve subjective or objective measures of smell.
A 2022 prospective cohort study by Garcia et al.\(^1\) reported subjective improvement in parosmia in 8 of 9 patients after 3 weeks of gabapentin. The limited sample size, lack of blinding, and absence of a placebo group are serious weaknesses of this prospective cohort study. In addition, participants were simultaneously undergoing alternative therapies for OD while receiving gabapentin, which reduced the internal validity. In this RCT, 11 of 17 (65%) participants taking gabapentin reported less severe dysosmia after the FD phase, mixed-model analysis demonstrated that this change was no different than that experienced by the placebo group. Thus, the results of this double-blind placebo-controlled RCT suggest that gabapentin is not an efficacious treatment for post-COVID OD, including dysosmia.

**Limitations**

Female predominance was noted in both the gabapentin and placebo groups. Other clinical trials related to OD have also demonstrated this sex difference. Though not possible in this study, future studies could consider overenrolling for male participants to allow for subanalysis by sex. Ethnicity was predominantly White for this single-center trial. Future studies could consider a multicenter trial to increase generalizability. All participants were screened virtually through an online survey. The absence of an in-person screening visit limited the ability to identify any potential causes of OD on physical examination. All participants had reported at least 3 months of OD, but the exact duration of OD was not measured. There could be differences in duration of OD between the 2 treatment groups, though this was likely mitigated through randomization. This study did not find gabapentin received at the maximum tolerable dose for 8 weeks to be an effective treatment, but this conclusion does not extend to a longer treatment period. There could be significant improvement in olfaction with gabapentin taken for longer than the 8 weeks studied.

**Conclusion**

This pilot placebo-controlled RTC demonstrated that gabapentin was not an efficacious treatment for COVID-19–induced OD. Changes in subjective olfactory function, objective odor identification, and olfactory-related quality of life were neither clinically meaningful nor statistically significant. Further research is warranted to identify effective treatments for COVID-19–induced OD and efforts should target novel therapeutic agents.

**REFERENCES**


