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RESEARCH PAPER

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Effect of drug therapies on self-reported chemosensory outcomes after COVID-19

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Abstract

Objective: The aim of this study was to assess the relative efficacy of medications used following severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection on self-reported alterations in taste and/or smell function.

Methods: Seven hundred and fourteen persons with self-reported postcoronavirus disease 2019 (post-COVID-19) chemosensory disorders were personally interviewed regarding specific medications they were administered following the acute phase of the disease. The dependent measure—self-reported total recovery of chemosensory symptoms—was subjected to stepwise logistic regression. Independent predictors included demographic and clinical variables, in addition to specific medications used to mitigate disease symptoms (i.e., systemic corticosteroids, oseltamivir, vitamin C, ibuprofen, hydroxychloroquine, azithromycin, ivermectin, nitazoxanide, anticoagulants, and zinc).

Results: The median time between COVID-19 symptom onset and the interviews was 81 days (interquartile range: 60–104). Of the 714 subjects, 249 (34.9%) reported total recovery of their chemosensory function; 437 (61.2%) had at least one treatment since the beginning of the disease. Women and those with more comorbidities had undergone more treatments. The recovery rates of the treated and nontreated groups did not differ significantly. Nonetheless, respondents who had used nitazoxanide tended to have a higher rate of self-reported taste or smell recovery. Those who took oral zinc were less likely to improve.

Conclusions: No medication employed during the first months after SARS-CoV-2 infection had a clear positive effect on returning self-reported smell or taste function to normal, although nitrazoxide trended in a positive direction. Oral zinc had a negative effect on the reported recovery of these senses.

KEYWORDS

chemosensory disorder, coronavirus infections, COVID-19, drug therapy, SARS-CoV-2, smell loss, taste loss

Abbreviations: COVID-19, coronavirus disease 2019; OT, olfactory training; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

Key points

- Various treatments, including azithromycin, ivermectin, vitamin C, systemic corticosteroids, and oral zinc, were administered for coronavirus disease 2019.
- Oral zinc intake was associated with a decreased likelihood of improvement in taste or smell recovery.
- While some treatments like systemic corticosteroids and azithromycin showed tentative associations with worse recovery rates, none reached statistical significance.

INTRODUCTION

During the acute phase of coronavirus disease 2019 (COVID-19), deficits in smell and taste function are among the most common symptoms. These disturbances affect the majority of patients, with studies using validated olfactory tests showing prevalence rates as high as 98%.[1] In a number of persons, some degree of smell deficit, which can be quite bothersome, remains after the acute phase, although the deficit declines markedly in the majority of persons within a few weeks. Nevertheless, in one study employing validated psychophysical testing, 40% of subjects continued to have some degree of decreased function 6–8 weeks after disease onset.[2] Several studies have shown that even after a year, the prevalence of self-reported COVID-19 chemosensory dysfunction can exceed 20%.[3–6]

The degree to which COVID-19 symptoms, most notably the olfactory deficits, are mitigated by medications given around and following the time of disease onset is not well established. To date, corticosteroids have been the primary therapy for smell loss, although studies comparing those who received corticosteroid therapy to untreated controls are lacking. Because a plethora of medications have been employed to mitigate COVID-19 symptoms, post hoc analyses can be made to establish whether some such medications may facilitate the return of function in some patients. Medications with high effectiveness for improving olfactory loss are needed.[7]

In this study, we compared the frequency of return of self-reported smell function between individuals who had received one or more medications to quell their COVID-19 symptoms to that of persons who received no such treatments. We also sought to establish the relative effectiveness of such drugs in aiding recovery from smell loss.

MATERIALS AND METHODS

The Strengthening of the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cross-sectional studies was followed in this study.

Study population

The subject selection procedure is shown in Figure 1. The sample consisted of 178 men and 536 women [respective mean (SD) ages = 36.8 (10.1) and 36.4 (10.8)] obtained from electronic contact in advertisements on social networks. Individuals with a history of COVID-19-like symptoms, including olfactory and/or taste disturbances, were invited to participate by electronic means such as social media and emails. By design, all had reported a smell and/or taste loss, with 93% reporting taste loss and 99.2% smell loss. The symptoms had to appear after February 26, 2020, the date of the first confirmed COVID-19 case in Brazil. All patients were interviewed by telephone or social network connections by most of the authors (M. A. F., J. L. B. S., S. P. N., L. K. A., B. M. C., A. F. N.). The median time between the interview and the appearance of the first COVID-19 symptoms was 81 days (interquartile range: 60–104).

The subjects were asked specifically about the type of diagnostic exams done to confirm the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. Those without a test confirmation, but with a highly suspicious diagnosis for COVID-19 by familial history or tomography findings, were also included. Individuals who had COVID-19, but did report

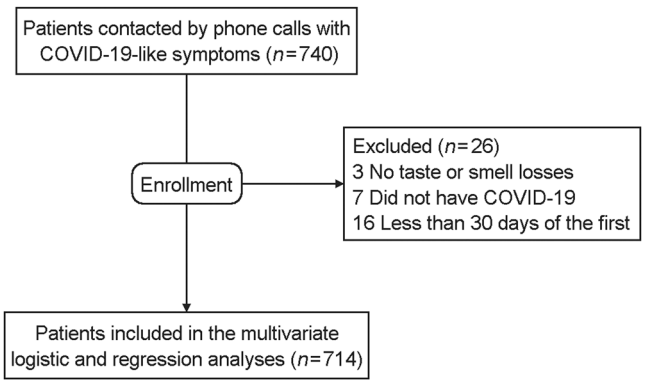

FIGURE 1 Summary of the patient enrollment scheme. COVID-19, coronavirus disease 2019.

experiencing chemosensory symptoms, were excluded from the sample, as were those with less than 30 days since their first symptom. This ensured sufficient time for olfactory recovery in the majority of our sample,[2,8] as well as a mitigation of acute complaints associated with the disease.

Questionnaire

During the interviews, the following information was collected from each patient: age, gender, ethnic group, years of education, city of current residence, profession, days since first symptom, numerous comorbidities, medications continuously used before and during the disease, and the apparent adverse effects of these medications. Previous diagnoses of rhinitis, diabetes, obesity, essential hypertension, asthma, stroke, hypothyroidism, and rheumatoid arthritis were noted. We asked about the use, during and after their COVID-19 symptoms, of systemic corticosteroids, oseltamivir, vitamin C, ibuprofen, hydroxychloroquine, azithromycin, ivermectin, nitazoxanide, anticoagulants, and zinc.

End points

The primary end point was the percentage of self-reported total smell and taste recovery. Secondary end points were self-reported chemosensory dysfunction severities on a scale from 0 to 10 (0 = *no function*; 10 = *complete normal function* or *as before deinfection*).

Statistical analyses

The sample size was based on a previous study that measured olfactory recovery using topical vitamin A, in which a 14 percentage-point difference in the percentage of patients for which smell improved between those who received vitamin A plus olfactory training (OT) and those who received only OT.[9] A sample size of at least 248 patients per group was estimated to provide 90% power to detect a 14 percentage-point difference between the total olfactory recovery group and the no or partial recovery group at a two-sided α level of 0.05. Percentages of total taste and smell recovery were statistically compared using Fisher's exact test. Continuous data, for example, the severity of olfactory deficit, are reported as means and standard deviations or as indicated. Logistic regression models were used to estimate the association between the variables and the smell and taste total recovery end points. The variables assessed by a stepwise procedure were demographic factors, the use of at least one therapy for COVID-19, the interval in days since the first symptom, the number of comorbidities, the different types of treatments used for the SARS-Cov-2 infection, and their interactions. The Akaike information criterion was employed to achieve the best model to predict recovery.[10] Similar logistic regression models were used to evaluate the severity of the olfactory and taste losses. p Values below 0.05 were considered significant. When multiple comparisons were made, the Bonferroni correction was employed. The statistical software used was STATA 17 (StataCorp LP).

RESULTS

The univariate comparisons of the data from the patients with total recovery of smell or taste function to those from patients with no or partial recovery are shown in Table 1. In these univariate analyses with Bonferroni-adjusted p values, total recovery was less common in women, non-whites, those with no comorbidities, those who used at least one medication for COVID-19, and those with a longer period between symptom onset and testing. Of the 437 patients who used treatments for the SARS-CoV-2 infection, 315 (65.2%) used azithromycin, 150 (31.1%) ivermectin, 149 (30.9%) vitamin C, 146 (30.2%) systemic corticosteroids, 108 (22.4%) oral zinc, 67 (13.9%) chloroquine or hydroxychloroquine, 56 (11.6%) oseltamivir, 27 (5.6%) nitazoxanide, 12 (2.5%) anticoagulants, and 107 (24%) other medications. Univariate comparisons of complete recovery rates among those who used or did not use each of these medications can be seen in Figure 2.

Study end points

Return to pre-COVID-19 levels of olfactory and taste function was reported by 249 (34.9%) patients. Considering only subjects between 30 and 60 days of the first symptom, 30.7% reported complete taste and smell recovery. This percentage was 44% for those between 61 and 90 days and 41.1% for those with more than 90 days since symptom onset.

In the stepwise logistic model controlling for covariates (Table 2), people who used at least one medication specifically for their COVID-19 infection were no more likely to report total improvement of their chemosensory symptoms than patients who did not use any medication. Individuals who used zinc had a 66% less chance to return to a normal olfaction or taste capacity (odds ratio: 0.24; 95% confidence interval: 0.1–0.5; $p < 0.001$; Table 3). Women and those with a longer time since the SARS-CoV-2 infection also had a lower chance of complete smell and taste recovery. Although the use of systemic corticosteroids and azithromycin was nominally associated with poorer recovery and nitazoxanide with

TABLE 1 Demographic and clinical characteristics of patients reporting total or no/partial recovery of chemosensory symptoms after SARS-CoV-2 infection.

Characteristics	Total (*n* = 714)	Total recovery of taste and smell (n = 249)	No or partial recovery of taste and smell (*n* = 465)	*p* Value
Age, mean (SD) (year)	36.7 (10.3)	36.4 (10.8)	36.8 (10)	0.55
Sex, *n* (%)				<0.001
Female	536 (75.1)	160 (29.8)	376 (70.2)	
Male	178 (24.9)	89 (50.0)	89 (50.0)	
Race, *n* (%)				0.030
White	546 (76.9)	203 (37.2)	343 (62.8)	
Non-White	164 (23.1)	46 (28.1)	118 (71.9)	
Years of schooling, mean (SD) (year)	13.9 (1.9)	13.8 (1.9)	14.1 (1.7)	0.010
Number of comorbidities, *n* (%)				0.020
0	414 (58.0)	165 (39.9)	249 (60.1)	
1	211 (29.6)	59 (28.0)	152 (72.0)	
2	64 (8.9)	20 (31.3)	44 (68.7)	
3	15 (2.1)	2 (13.3)	13 (86.7)	
4	8 (1.1)	2 (25.0)	6 (75.0)	
5	2 (0.3)	1 (50.0)	1 (50.0)	
Comorbidities, *n* (%)				0.002
Yes	307 (43)	162 (39.8)	245 (60.2)	
No	407 (57)	87 (28.3)	220 (71.7)	
Rhinitis, *n* (%)				0.620
Yes	207 (29)	75 (36.2)	132 (63.8)	
No	507 (71)	174 (34.3)	333 (65.7)	
Obesity, *n* (%)				0.140
Yes	77 (10.8)	21 (27.3)	56 (72.7)	
No	637 (89.2)	228 (35.8)	409 (64.2)	
Hypertension, *n* (%)				0.650
Yes	62 (8.7)	20 (32.3)	42 (67.7)	
No	652 (91.3)	229 (35.1)	423 (90.9)	
Diabetes, *n* (%)				0.310
Yes	10 (1.4)	5 (50)	5 (50)	
No	704 (98.6)	244 (34.7)	460 (65.3)	
Asthma, *n* (%)				0.770
Yes	56 (7.8)	18 (32.1)	38 (67.9)	
No	658 (96.2)	231 (35.1)	427 (64.9)	
Dyslipidemia, *n* (%)				0.840
Yes	28 (3.9)	9 (32.1)	19 (67.9)	
No	686 (96.1)	240 (34.9)	446 (65.1)	
Stroke, *n* (%)				0.280
Yes	3 (0.4)	2 (66.7)	1 (33.3)	
No	711 (99.6)	247 (34.7)	464 (65.3)	

(Continues)

TABLE 1 (Continued)

Characteristics	Total (n = 714)	Total recovery of taste and smell (n = 249)	No or partial recovery of taste and smell (n = 465)	p Value
Hypothyroidism, n (%)				0.020
Yes	39 (5.5)	7 (17.9)	32 (82.1)	
No	675 (94.5)	242 (35.9)	433 (64.2)	
Rheumatoid arthritis, n (%)				0.350
Yes	11 (1.5)	2 (18.2)	9 (81.8)	
No	703 (98.5)	247 (35.1)	456 (64.9)	
Others, n (%)				0.440
Yes	17 (2.4)	4 (23.5)	13 (76.5)	
No	697 (97.6)	245 (35.1)	452 (64.9)	
Confirmed COVID-19 case with RT-PCR or serology				0.020
Yes	628 (95.2)	225 (35.8)	403 (64.2)	
No	32 (4.8)	5 (15.6)	27 (84.3)	
Interval onset symptoms and interview [days (IQR)]	81 (60–104)	76 (63–95)	84 (60–115)	0.009
Medications for COVID-19				<0.001
Yes	437 (61.2)	122 (27.9)	315 (72.1)	
No	277 (38.8)	127 (45.8)	150 (54.2)	

Abbreviation: COVID-19, coronavirus disease 2019; RT-PCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

better recovery, these findings did not reach statistical significance after Bonferroni correction. The number and type of comorbidities did not interfere with the rate of total recovery of these symptoms.

Regarding the severity of the smell and taste losses (Tables 3 and 4), as measured by the self-reported rating scales, systemic corticosteroids were associated with a higher severity of a taste deficit. Similar to what happened with the complete chemosensory symptoms recovery rate, women and patients with more days after COVID-19 onset reported more severe symptoms.

Adverse effects

Fifty-five out of the 483 (11.4%) who used medications for COVID-19 complained of adverse events. The medication with a high percentage of side effects was chloroquine or hydroxychloroquine (22.4%), followed by azithromycin (14.3%) and oral zinc (13.9%). The most common reactions were upper abdominal pain in 14 patients (2.9%), upper abdominal pain in 13 patients (2.7%), and nausea in nine patients (1.86%). Four subjects (0.8%) had cardiac arrhythmia after taking the prescribed medications. No other severe adverse events were reported.

DISCUSSION

This study is one of the few to explore the effects of different interventions used in COVID-19 patients on smell and taste dysfunction. Few therapies are efficacious for treating persistent olfactory loss and, before COVID-19, it was rare to treat patients with chemosensory disturbances due to any cause proactively.

The present study is an early step in assessing the influences of diverse medications on smell and taste function. Perhaps, the most important finding of our study is that oral zinc was significantly related to a lower chance of total recovery. Thus, in the context of its apparent adverse effects on chemoreception, it would seem prudent to refrain from prescribing it for COVID-19. Many doctors prescribe zinc due to its potential anti-replication viral effect.[11] It is noteworthy that besides the known negative impact of zinc in nasal sprays for flu in olfactory function, other studies have observed that high doses of oral zinc sulfate appear to damage the smell function of some individuals.[12,13]

Another potentially important finding of our study is that patients who had used nitazoxanide to quell their COVID-19 symptoms tended to have a higher rate of total recovery in the statistical logistic model that controlled for other factors. It is known that this antiprotozoal agent is a broad-spectrum antiviral drug and has been repurposed for the treatment of upper

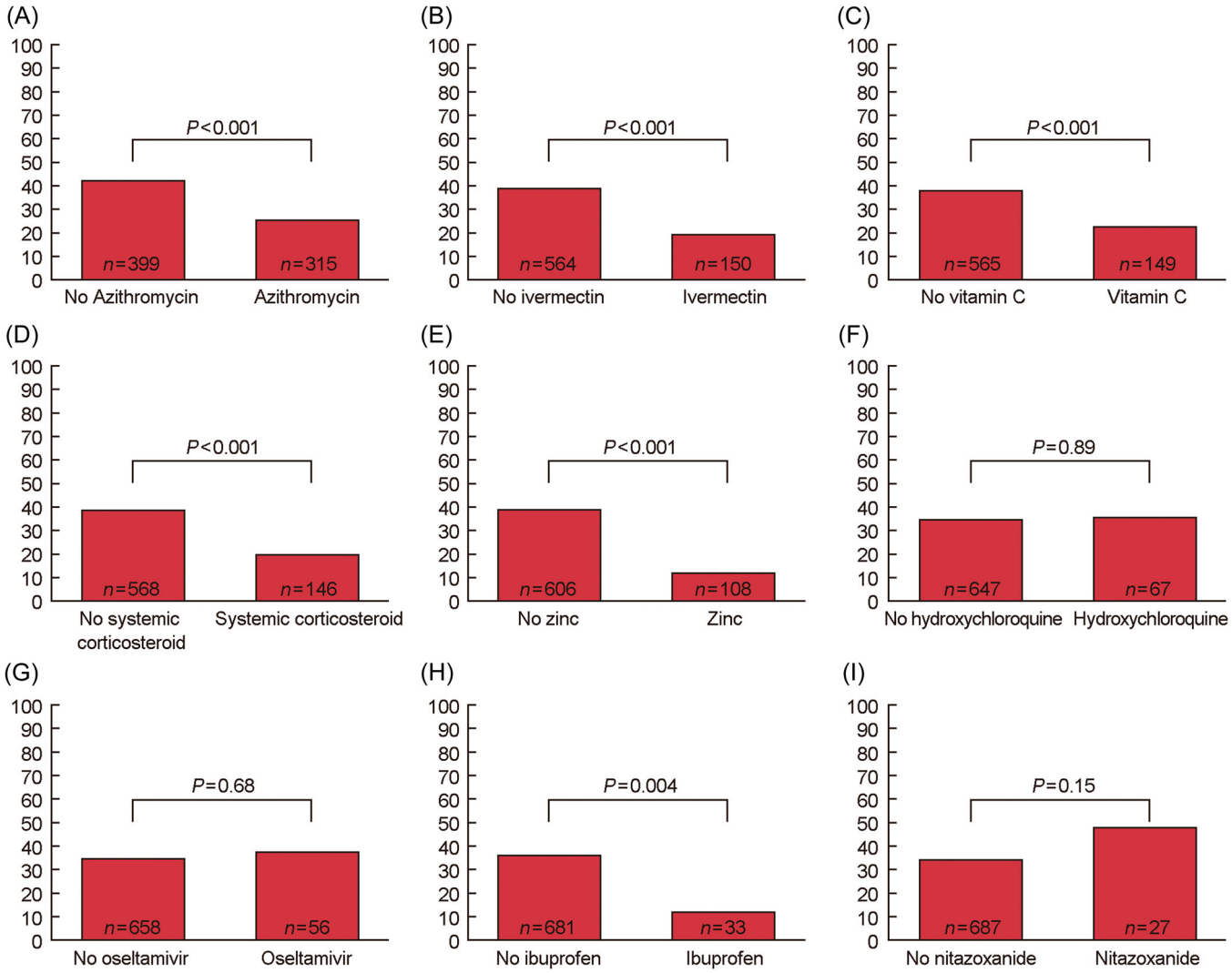

FIGURE 2 Percentages of total taste and smell recovery and univariate comparisons between patients who used or did not use different medications (A-I) after severe acute respiratory syndrome coronavirus-2 infection.

respiratory infections.[14] Several in vitro studies confirmed its efficacy against viruses such as influenza, rotavirus, and coronavirus, mainly when used at higher concentrations.[15,16] Recently, in a double-blind clinical trial, nitazoxanide (600 mg, twice a day, for 7 days) showed superiority against a placebo in clinical and virological outcomes in COVID-19 patients hospitalized with mild respiratory insufficiency.[17] More clinical data on the usefulness of this drug for preventing olfactory and taste disturbances is needed.

As with nitazoxanide, more research is needed to determine the efficacy of corticosteroids in protecting against COVID-19 damage to the olfactory system. We observed a higher severity of taste impairment in those who used systemic corticosteroids, but this medication did not influence smell severity in our sample. The detrimental effect of systemic corticosteroids on taste function must be interpreted with caution as the marginal effect was relatively small, no taste test was employed, and the negative effect was not present in self-reports of smell deficit severity. Both beneficial and nonbeneficial effects of steroids have been reported in the literature. In one study, a short course of systemic corticosteroids and OT suggested benefit for recovery in patients with persistent olfactory loss after 5 weeks of COVID-19.[18] However, another study comparing OT plus topical mometasone found no greater benefit than OT alone.[19] Another study showed a better initial improvement at 1-month posttreatment with oral corticosteroids compared to controls; however, this improvement did not reach statistical significance after 2 months.[20] Thus, the benefit or harm of systemic corticosteroids in COVID-19 chemosensory dysfunction still needs more clinical trial studies.

TABLE 2 Logistic models showing the adjusted effect of the medications in the complete self-reported improvement of the chemosensory complaints.

Variables	OR	95% CI	*p* Value
Female sex	0.46	0.32–0.67	<0.001[a]
Non-White	0.73	0.48–1.11	0.142
Interval onset symptoms and interview (days)	0.99	0.99–1.00	<0.001[a]
Systemic corticosteroid	0.52	0.32–0.84	0.008
Azithromycin	0.60	0.41–0.89	0.010
Nitazoxanide	3.30	1.35–8.20	0.009
Zinc	0.24	0.12–0.47	<0.001[a]
Ibuprofen	0.43	0.14–1.32	0.010
Hydroxychloroquine	1.66	0.89–3.08	0.110

Note: Values lesser than 1 indicate a worse chance of total recovery, whereas positive values indicate a higher chance. OR, change in the odds associated with a change in each of the independent variables.

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Statistically significant measures. Significant *p* value after Bonferroni correction: 0.002.

TABLE 3 Multiple linear models showing the effect of the medications on the self-reported severity of smell dysfunction (0 = *no olfaction*, 10 = *olfaction as before COVID-19*).

Variables	ME	95% CI	*p* Value
Female sex	−1.16	−1.68 to −0.65	<0.001[a]
Interval onset symptoms and interview (days)	−0.01	−0.02 to −0.01	<0.001[a]
Azithromycin	−0.70	−1.20 to −0.20	0.006
Nitazoxanide	1.10	−0.07 to 2.30	0.070
Zinc	−0.92	−1.70 to −0.20	0.020
Ibuprofen	−0.90	−1.90 to 0.17	0.100
Ivermectin	−0.43	−1.00 to 0.18	0.170
Vitamin C	−0.48	−1.10 to 0.17	0.150
Hydroxychloroquine + syst. ce	−3.30	−5.90 to −0.70	0.010
Hydroxychloroquine + syst. ce + azithromycin	3.70	0.72 to 6.68	0.020

Note: Values lesser than 0 indicate a worse chance of total recovery, whereas positive values indicate a higher chance.

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; ME, marginal effect; syst. ce, systemic corticosteroids.

[a]Statistically significant measures. Significant *p* value after Bonferroni correction: 0.002.

Almost all subjects of our study complained of taste and smell losses, but only 0.8% reported only taste dysfunction. It is likely that an olfactory test of these individuals would have identified a smell disorder[1,2] given that patients often do not know the relationship between smell and taste function.[21]

As shown in Supporting Information S1: Table 1, the group of individuals who did not take any medication had a higher educational level, were more likely to be men, and reported fewer comorbidities. We found chemosensory recovery rates of 31% and 44% after 30 days or more than 60 days, respectively. This percentage is lower than previously reported rates of subjective olfactory recovery.[3] However, it is important to note that we considered recovery to have occurred only if the return was considered to be as good as before the disease. Many studies calculate subjective recovery rates without establishing whether the recovery is equivalent to what was perceived before the SARS-CoV-2 infection. It is observed in the clinic that patients are anxious to know when they will smell and taste normally, not just a little better than what they experienced in the acute phase of COVID-19. It is conceivable that our recovery rate may have been influenced by our social media enrollment method, since it is possible that a dispropriate number of persons with intractable smell or taste losses may have been recruited. Participating in research is always a source of hope to obtain ideas or new approaches for quelling deficits in people with persistent symptoms. This could also explain why total recovery was lower in the patients recruited 90 days after the first symptom than in those between 60 and 90 days from this date point.

Women have a better olfactory capacity than men and are more sensitive to small alterations in the chemosensory function. This may explain their 54% lower chance of self-reported total recovery compared to men. As cited above, patients with more severe or longer periods of symptoms may be more likely to seek research opportunities for improvement. This persistent olfactory or taste dysfunction could be one reason why, in our sample, there is no relationship between the probability of recovery and the time between our survey and their acute symptoms. Also, among the three factors related to a worse olfactory outcome are the older age of the patient, the severity of the initial loss, and the duration of its presence.[22]

Despite the concern of adverse events and limitations of treatments that have been reported in the literature, none have included the combination of double-blinding, contemporaneous nontreated controls,[23] there were no reported severe reactions in the patients of our sample who survived COVID-19. It is noteworthy that we did not have access to the electrocardiogram of our patients that might show other side effects, such as QT prolongation in those using hydroxychloroquine. One must view the present study as exploratory in nature, since a multitude of variables could not be evaluated. A better study design would be to follow patients from the beginning of the SARS-CoV-2 diagnosis and subsequently compare quantitative smell and taste test results from cohorts receiving different treatments. Nonetheless, cross-sectional studies such as ours can provide important insight and directions for determining which agents or interventions would be most fruitful to study.

TABLE 4 Multiple linear regression models on the effect of medications on the self-reported severity of taste dysfunction (0 = *no taste*, 10 = *taste as before COVID-19*).

Variables	ME	95% CI	*p* Value
Female sex	−0.72	−1.20 to −0.25	0.003
Non-White	−0.74	−1.23 to −0.25	0.003
Years of schooling	0.08	−0.04 to 0.19	0.180
Interval onset symptoms and interview (days)	−0.01	−0.02 to −0.01	<0.001[a]
Azithromycin	−0.62	−1.10 to −0.18	0.006
Systemic corticosteroid	−0.88	−1.41 to −0.35	0.001[a]
Zinc	−0.58	−1.17 to −0.01	0.050
Ibuprofen	−0.74	−1.71 to 0.22	0.130

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; ME, marginal effect.

Note: Values lesser than 1 indicate a worse chance of total recovery, whereas positive values indicate a higher chance.

[a]Statistically significant measures. Significant *p* value after Bonferroni correction: 0.002.

CONCLUSION

In conclusion, except nitazoxanide, our data strongly suggests that a number of therapies used to manage COVID-19 symptoms do not have a meaningful impact on the recovery of smell and taste deficits. Our findings also highlight the potential harm that oral zinc may have on the return of chemosensation from a SARS-CoV-2 infection.

AUTHOR CONTRIBUTIONS

Marco A. Fornazieri, José L. B. da Silva, Deusdedit Brandão Neto, and Fábio D. R. Pinna conceptualized and designed the study, conducted the data collection, conducted the analyses, drafted the initial manuscript, and revised the manuscript. Bruno Machado Cunha, Marco A. Fornazieri, Samuel P. Nicácio, Lucas K. Anzolin, José L. B. da Silva, Aristides Fernandes Neto conducted the data collection and drafted the initial manuscript. Richard L. Voegels critically reviewed the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Please contact the author (M. A. F.) to provide anonymized data for the present study.

ETHICS STATEMENT

The local ethics committee approved this study. All patients confirmed their willingness to participate in the study, were presented with the consent form, and had their acceptance recorded.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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