

COVID-19 Anosmia Study  
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## Summary

### Objectives:

#### Research Questions:

1. What is the natural history of COVID-19 related olfactory dysfunction?
2. Is there a therapeutic benefit of omega-3 supplement administration for COVID-19 related olfactory dysfunction?

The aim of the study is to gain an understanding of the natural history of olfactory dysfunction associated with COVID-19 infection in addition to evaluating whether there is a therapeutic role for omega-3 supplementation during the subacute period. Through this study, we hope to provide anticipatory guidance regarding the prognosis for COVID-19 related olfactory dysfunction as well as assess a potential therapeutic intervention.

### Background:

Infection with the novel coronavirus (COVID-19) has been linked to new-onset olfactory dysfunction, often as the only presenting symptom.<sup>1-3</sup> In one multicenter European study, 85.6% of patients with mild to moderate symptoms reported hyposmia or anosmia with early recovery of olfactory function in just under half of patients.<sup>4</sup> However, the pathogenesis and natural history of COVID-19 related olfactory dysfunction is poorly understood.

Anosmia most commonly arises in association with sinonasal disease or post-infectious or post-traumatic disorders.<sup>5,6</sup> Notably, olfactory loss has been associated with impaired quality of life, higher rates of depression, and even increased mortality risk.<sup>5,7,8</sup> Spontaneous recovery has been observed in patients with post-infectious olfactory dysfunction, typically over a period of months to years, with an estimated one-third of patients demonstrating meaningful improvement after one year.<sup>9-12</sup>

Smell retraining therapy appears to be an effective therapeutic option for patients with post-infectious olfactory dysfunction, particularly for patients who initiate treatment within one year from onset of symptoms, but requires an intervention period of at least three to four months.<sup>5,13,14</sup> Various pharmacotherapies have been investigated in the treatment of post-infectious anosmia but none have clearly demonstrated utility with the exception of a possible benefit for nasal steroid irrigations in combination with smell retraining therapy.<sup>15-17</sup>

More recently, omega-3 polyunsaturated fat supplementation has emerged as a promising pharmacotherapy for olfactory dysfunction in patients without sinonasal disease. Omega-3 fatty acid deficient mice demonstrate evidence of olfactory dysfunction<sup>18</sup> and mice receiving omega-3

fatty acids have improved recovery after peripheral nerve injury, which has been linked to neuroprotective effects mediated through anti-oxidant and anti-inflammatory pathways.<sup>19,20</sup> In humans, a large cross-sectional study found that older adults with higher dietary fat intake had lower incidence of olfactory impairment.<sup>21</sup> From a clinical perspective, patients without sinonasal disease receiving postoperative omega-3 fatty acid supplementation after endoscopic endonasal skull base surgery in a randomized control trial demonstrated a significantly greater rate of return of normal olfactory dysfunction.<sup>22</sup>

Little is known about either the natural history of olfactory dysfunction associated with COVID-19 infection or about the therapeutic efficacy of omega-3 fatty acid supplementation in patients with post-viral anosmia. We hope to gain a better understanding of each through a randomized double-blind placebo control study that assesses both objective and subjective perception of olfactory dysfunction over a period of 6 weeks after infection.

- 1 Vaira, L. A., Salzano, G., Deiana, G. & De Riu, G. Anosmia and ageusia: common findings in COVID-19 patients. *Laryngoscope*, doi:10.1002/lary.28692 (2020).
- 2 Eliezer, M. *et al.* Sudden and Complete Olfactory Loss Function as a Possible Symptom of COVID-19. *JAMA Otolaryngol Head Neck Surg*, doi:10.1001/jamaoto.2020.0832 (2020).
- 3 Vukkadala, N., Qian, Z. J., Holsinger, F. C., Patel, Z. M. & Rosenthal, E. COVID-19 and the otolaryngologist - preliminary evidence-based review. *Laryngoscope*, doi:10.1002/lary.28672 (2020).
- 4 Lechien, J. R. *et al.* Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Otorhinolaryngol*, doi:10.1007/s00405-020-05965-1 (2020).
- 5 Boesveldt, S. *et al.* Anosmia-A Clinical Review. *Chem Senses* **42**, 513-523, doi:10.1093/chemse/bjx025 (2017).
- 6 Fonteyn, S. *et al.* Non-sinonasal-related olfactory dysfunction: A cohort of 496 patients. *Eur Ann Otorhinolaryngol Head Neck Dis* **131**, 87-91, doi:10.1016/j.anorl.2013.03.006 (2014).
- 7 Croy, I., Nordin, S. & Hummel, T. Olfactory disorders and quality of life--an updated review. *Chem Senses* **39**, 185-194, doi:10.1093/chemse/bjt072 (2014).
- 8 Ekstrom, I. *et al.* Smell Loss Predicts Mortality Risk Regardless of Dementia Conversion. *J Am Geriatr Soc* **65**, 1238-1243, doi:10.1111/jgs.14770 (2017).
- 9 Cavazzana, A., Larsson, M., Munch, M., Hahner, A. & Hummel, T. Postinfectious olfactory loss: A retrospective study on 791 patients. *Laryngoscope* **128**, 10-15, doi:10.1002/lary.26606 (2018).
- 10 Reden, J. *et al.* Recovery of olfactory function following closed head injury or infections of the upper respiratory tract. *Arch Otolaryngol Head Neck Surg* **132**, 265-269, doi:10.1001/archotol.132.3.265 (2006).
- 11 Hendriks, A. P. Olfactory dysfunction. *Rhinology* **26**, 229-251 (1988).
- 12 Reden, J., Herting, B., Lill, K., Kern, R. & Hummel, T. Treatment of postinfectious olfactory disorders with minocycline: a double-blind, placebo-controlled study. *Laryngoscope* **121**, 679-682, doi:10.1002/lary.21401 (2011).
- 13 Sorokowska, A., Drechsler, E., Karwowski, M. & Hummel, T. Effects of olfactory training: a meta-analysis. *Rhinology* **55**, 17-26, doi:10.4193/Rhin16.195 (2017).
- 14 Pekala, K., Chandra, R. K. & Turner, J. H. Efficacy of olfactory training in patients with olfactory loss: a systematic review and meta-analysis. *Int Forum Allergy Rhinol* **6**, 299-307, doi:10.1002/alr.21669 (2016).
- 15 Damm, M. *et al.* Olfactory training is helpful in postinfectious olfactory loss: a randomized, controlled, multicenter study. *Laryngoscope* **124**, 826-831, doi:10.1002/lary.24340 (2014).
- 16 Yan, C. H., Overvest, J. B. & Patel, Z. M. Therapeutic use of steroids in non-chronic rhinosinusitis olfactory dysfunction: a systematic evidence-based review with recommendations. *Int Forum Allergy Rhinol* **9**, 165-176, doi:10.1002/alr.22240 (2019).
- 17 Nguyen, T. P. & Patel, Z. M. Budesonide irrigation with olfactory training improves outcomes compared with olfactory training alone in patients with olfactory loss. *Int Forum Allergy Rhinol* **8**, 977-981, doi:10.1002/alr.22140 (2018).
- 18 Greiner, R. S., Moriguchi, T., Slotnick, B. M., Hutton, A. & Salem, N. Olfactory discrimination deficits in n-3 fatty acid-deficient rats. *Physiol Behav* **72**, 379-385, doi:10.1016/s0031-9384(00)00437-6 (2001).
- 19 Gladman, S. J. *et al.* Improved outcome after peripheral nerve injury in mice with increased levels of endogenous omega-3 polyunsaturated fatty acids. *J Neurosci* **32**, 563-571, doi:10.1523/JNEUROSCI.3371-11.2012 (2012).
- 20 Figueroa, J. D. & De Leon, M. Neurorestorative targets of dietary long-chain omega-3 fatty acids in neurological injury. *Mol Neurobiol* **50**, 197-213, doi:10.1007/s12035-014-8701-1 (2014).

- 21 Gopinath, B., Sue, C. M., Flood, V. M., Burlutsky, G. & Mitchell, P. Dietary intakes of fats, fish and nuts and olfactory impairment in older adults. *Br J Nutr* **114**, 240-247, doi:10.1017/S0007114515001257 (2015).
- 22 Yan, C. H. *et al.* Effect of Omega-3 Supplementation in Patients With Smell Dysfunction Following Endoscopic Sellar and Parasellar Tumor Resection: A Multicenter Prospective Randomized Controlled Trial. *Neurosurgery*, doi:10.1093/neuros/nyz559 (2020).

### Primary and Secondary Study Endpoints:

The primary endpoint of this study is a Brief Smell Identification Test, a standardized and validated objective measure of olfactory function, administered 6 weeks from symptom onset.

The secondary endpoints of this study include patient-reported outcome measure surveys, a modified Brief Questionnaire of Olfactory Dysfunction - Negative Statements (QOD-NS) survey and Sino-Nasal Outcome Test (SNOT-22), administered at time points of 1, 2, 4, and 6 weeks after symptom onset.

### **Settings and Resources**

#### Specify Other Setting of Human Research

This study will be executed at the Icahn School of Medicine at Mount Sinai. Patients will be recruited from the practices of faculty in the Department of Otolaryngology – Head and Neck Surgery and via the STOP COVID NYC web-based application (IRB 20-03271). All research will be conducted at the Icahn School of Medicine at Mount Sinai. No research will be conducted outside of the Icahn School of Medicine at Mount Sinai.

#### Feasibility of Meeting Recruitment Goals

Given the current 2020 COVID-19 pandemic and the high prevalence of this condition in the New York City area, combined with the high incidence of anosmia with COVID-19 infection, we anticipate relative ease in meeting recruitment goals.

#### Facilities To Be Used for Conducting Research

A portion of the patients will be recruited at Otolaryngology Faculty Practice Associates via telemedicine or through the STOP COVID NYC web-based application.

#### Involvement of the Community in the Design and Conduct of Research

There is no anticipated involvement of the community in the design and conduct of this research project.

### **Subjects**

#### Inclusion Criteria

Adults ( $\geq 18$  years of age) with self-reported new-onset olfactory dysfunction and a positive COVID-19 diagnosis will be deemed eligible for inclusion.

#### Exclusion Criteria

- Patients  $< 18$  years of age
- Patients who are unable to provide informed consent
- Patients without a positive COVID-19 PCR result obtained through nasopharyngeal swab
- Patients with a COVID-19 diagnosis but without self-reported anosmia
- Patients with severe COVID-19 disease as defined by the Mount Sinai Health System Treatment Guidelines for SARS-COV-2 (requiring high flow nasal cannula, non-rebreather, CPAP/BIPAP, or mechanical ventilation OR patients requiring pressor medication OR patients with evidence of end organ damage)
- Patients with pre-existing self-reported olfactory dysfunction
- Patients with a history of chronic nasal/sinus infections (rhinosinusitis) or history of endoscopic sinus surgery
- Patients using nasal steroid sprays or irrigations for any reason
- Patients who are prisoners of the state
- Patients who have psychiatric or developmental disorder conditions that may impair ability to provide informed consent

#### Other Aspects that Could Increase Subjects' Vulnerability

Patients who are minors, prisoners, or those who have a psychiatric or developmental disorder that may impair their ability to provide informed consent will be excluded from the study.

Personal health information will be protected in order to ensure that subjects' vulnerability is not increased. All research data will be accessible only to the research team members, and all data will be de-identified, encrypted, and password protected. This data will be stored on a Mount Sinai hospital computer located in the Otolaryngology Resident Library on the 10th floor of the Annenberg building. The library is locked at all times and requires a password for entry.

#### Safeguard to protect Subjects' rights and welfare

The principal and co-investigators will maintain communication with the subjects in order to help identify any issues that arise. The PI, co-investigator, or a delegate will inquire about adverse events throughout the study via phone calls and in-office visits. The PI will maintain records of all adverse events and will use the NCI Common Terminology Criteria for Adverse Events (CTCAE) for documentation. Adverse events occurring during the study will be reported to the Mount Sinai Program for the Protection of Human Subjects (PPHS). Any suspension of the study will be reported to the PI and the IRB. Additionally, a data and safety monitoring committee (DSMC) will be established and consist of the principal investigator and co-investigators. Adverse events will be reviewed every three months.

## **Participation**

### Procedures for Subjects to Request Withdrawal

Patients can request to be withdrawn from the study at any time during the recruitment or data collection period. Patients will be withdrawn from the study as requested. If a patient withdraws, all the information collected and stored will be immediately deleted.

### Procedures for Investigator to Withdraw Subjects

A subject will be withdrawn from the study if the subject requests to be withdrawn for any reason, if the subject does not follow study protocol regarding administration of the blinded intervention, if the subject is unable to continue due to deteriorating clinical status (related to COVID-19 or otherwise), or if the study is prematurely ended for any reason. The patient will continue with routine care per primary physician otherwise.

### Specify Other Recruitment Method

Patients will be recruited (utilizing inclusion and exclusion criteria outlined above) through the Otolaryngology Faculty Practices and the Mount Sinai Data Warehouse list of COVID-19 positive patients diagnosed at Mount Sinai Hospital as well as the web based application *STOP COVID NYC* (IRB 20-03271).

### How Participants Will Be Identified

Participants who are > 18 years of age, have self-reported anosmia and a positive COVID-19 diagnosis will be identified through the Mount Sinai Otolaryngology Faculty Practices and through the web-based application *STOP COVID NYC* (IRB 20-03271).

### How Research Will Be Introduced to Participants

Once participants are identified, the attending physician or another member of the research team will reach out to the patient to discuss the study and obtain informed consent.

### How Participants Will Be Screened

Subjects will be recruited via the Otolaryngology Faculty Practices or the web-based application *STOP COVID NYC* (IRB 20-03271) who have consented to be contacted for future studies.

Participants will be screened for inclusion and exclusion criteria by the attending physician or another member of the research team during the same session that the research is being explained to the participant.

## **Risk and Benefits**

## Risks to Subjects

Patients will be randomized into treatment and control groups. The treatment group will receive omega-3-fatty acid supplementation (1000 mg of omega-3 fatty acid blend including 683 mg Eicosapentaenoic Acid and 252 mg Docosahexaenoic Acid) to be taken daily for 6 weeks. The control arm will receive a placebo pill to be taken twice daily.

The main risks to subjects that choose to participate are as following:

-BSIT: This 12-item version of the Smell Identification Test™ is useful for quantifying smell loss in situations where less than five minutes of time are available. The odors are well known in most cultures. There are no side effects known to occur from this test. Patients could theoretically experience some nausea, vomiting, or headache from the different smells.

-Omega-3 fish oil has been deemed "generally regarded as safe" by the Federal Drug Administration and is considered to be very rarely associated with significant adverse side effects. Side effects of omega-3 fatty acid supplementation are typically mild and include gastrointestinal discomfort, heartburn, headache, and unpleasant taste. Patients also sometimes note a fishy odor or taste in their mouth that they find unpleasant. Taking high doses of fish oil supplements can potentially increase the risk of bleeding. However this is associated with much higher dosing and duration than what will be utilized during this study.<sup>1</sup> A 2018 Chang et al. meta-analysis of 21 randomized clinical trials involving a total of 12,750 patients receiving omega-3 fatty acid supplementation found no serious adverse events, concluding that they are generally safe and well-tolerated but are associated with these mild side effects.<sup>2</sup> No patient-reported adverse events were reported in the 2020 Yan et al. randomized control study on omega-3 fatty acid supplementation after skull base surgery.<sup>3</sup>

1 Mazereeuw, G., Lanctot, K. L., Chau, S. A., Swardfager, W. & Herrmann, N. Effects of omega-3 fatty acids on cognitive performance: a meta-analysis. *Neurobiol Aging* 33, 1482 e1417-1429, doi:10.1016/j.neurobiolaging.2011.12.014 (2012).

2 Chang, C. H. et al. Safety and tolerability of prescription omega-3 fatty acids: A systematic review and meta-analysis of randomized controlled trials. *Prostaglandins Leukot Essent Fatty Acids* 129, 1-12, doi:10.1016/j.plefa.2018.01.001 (2018).

3 Yan, C. H. et al. Effect of Omega-3 Supplementation in Patients With Smell Dysfunction Following Endoscopic Sellar and Parasellar Tumor Resection: A Multicenter Prospective Randomized Controlled Trial. *Neurosurgery*, doi:10.1093/neuros/nyz559 (2020).

### Description of Procedures Taken to Lessen the Probability or Magnitude of Risks

Patients randomized to the treatment arm will be administered omega-3-fatty acid supplementation daily, as described previously. Patients will be provided a contact number to the research team to report any adverse effects and be directed to appropriate medical care. Patients may drop out of the study for any reason at any time.

### Provisions for Research Related Harm/Injury

Significant adverse reactions to treatment will lead to immediate termination of treatment. Medical care will be provided by a Mount Sinai physician or a physician of the participant's choosing. Participant insurance will be charged for medical care related to treatment.

### Expanded Direct Benefit to Subjects

Participants may not receive any benefit from participation in the study. There is a possibility that participants in the treatment arm regain a greater degree of olfactory function or experience recovery at a faster rate as the result of the intervention.

### Benefit to Society

Given the extent of the current COVID-19 outbreak and the high prevalence of anosmia in patients, it is important to gain an understanding of this symptomatology. As outlined in the background, olfactory dysfunction has been linked to impaired quality of life, higher rates of depression, and increased morbidity and mortality. The proposed study aims to elucidate the natural history of COVID-19 associated olfactory dysfunction and investigate omega-3-fatty acid supplementation as a potential therapeutic intervention. Such information will help guide future research and treatment of COVID-19 associated olfactory dysfunction.

### Provisions to Protect the Privacy Interests of Subjects

Data will be saved on a master list of subjects kept on a secure department-owned computer. Subjects will be deidentified and assigned a code, with which all other communication and data will be saved. Subjects will be able to decide whether or not to discuss their participation in the study with individuals outside of the research study. The patient will be able to decide what private information to disclose to research personnel provided the information is not necessary for the study. Additionally, subjects will be able to decide which research personnel they would like to communicate with. Study personnel will respect subjects' decisions. All saved data will be permanently destroyed at the end of this study.

### Economic Impact on Subjects

There is no anticipated cost to research subjects. The cost of omega-3-fatty acid treatment and the placebo control will be covered by the Division of Rhinology and Sinus Surgery within the Department of Otolaryngology - Head and Neck Surgery. All additional procedures and office visits are standard of care and do not incur any additional cost to the patient. Patients are

encouraged to call the Mount Sinai Otolaryngology FPA service phone system in case they experience any side effects.

## **Procedures**

### Description of the Study Design

This is a prospective, double-blind, randomized controlled trial.

### Description of Procedures Being Performed

Patients will be recruited (utilizing inclusion and exclusion criteria outlined above) through the Otolaryngology Faculty Practices as well as the web based application STOP COVID NYC. Current recruitment goals are one hundred seventy six patients, with eighty eight patients in each group. After recruitment the patients will be block-randomized by a computer-generated sequence in a 1:1 allocation to treatment or control arms. Patients randomized to the treatment group will be allocated a supply of 1000 mg capsules of omega-3 fatty acid blend including 683 mg Eicosapentaenoic Acid and 252 mg Docosahexaenoic Acid) to be taken daily for 6 weeks. Patients randomized to the control group will receive a placebo and will follow the same regimen as the treatment group. Collection of data (described below) will occur through the use of the EPIC electronic medical record system, through phone conversations between investigators and subjects, and through information collected during office visits. The primary outcome studied will be the Brief Smell Identification Test (BSIT) which will be administered 6 weeks after symptom onset. The secondary outcomes include patient-reported outcome measure surveys, a modified Brief Questionnaire of Olfactory Dysfunction - Negative Statements (QOD-NS) survey and Sino-Nasal Outcome Test (SNOT-22), administered at time points of 1, 2, 4, and 6 weeks after symptom onset. After the conclusion of data collection a statistical analysis will be conducted to compare outcomes in the treatment and placebo arms.

### Description of the Source Records that Will Be Used to Collect Data About Subjects

The EPIC electronic medical record used at the Mount Sinai Hospital and FPA will be used to collect subject data.

### Description of Data that Will Be Collected Included Long-term Follow-Up

Patient identifying information (which will be then de-identified and exchanged with a Subject ID), demographics, history of present illness, past medical history, past surgical history, medication list, medication allergies, Brief Smell Identification Test (BSIT) score, modified Brief Questionnaire of Olfactory Dysfunction - Negative Statements (QOD-NS) Score, and Sino-Nasal Outcome Test (SNOT-22) score. Patients will be followed for a period of six (6) weeks with repeat collections of interval patient history as well as QOD-NS and SNOT-22 survey scores at the one, two, four, and six week follow-up periods.

## **Consent**

### Where and When Consent Will Be Obtained

Patients who have been identified for the study and meet inclusion criteria and do not meet exclusion criteria will be contacted to discuss the research study by the attending physician or another member of the research team. They will be sent a copy of the consent form to read over. Due to the current pandemic and inability for individuals to attend the office in-person to sign the consent form, participants will have the opportunity to sign the consent form virtually.

### Waiting Period for Obtaining Consent

The participant will have the opportunity to spend time reading the consent form to learn more about the study. If the participant decides to enroll in the study, they may do so by calling the PI to schedule a time to sign the consent.

### Consent form (see google doc link):

<https://docs.google.com/document/d/1221wtQ5oiaUmNQYi7963URNUkxk9lszQbfl8rQzLLFM/edit?usp=sharing>

## **Data**

### Description of Health Information that Will Be Viewed, Recorded, Or Generated

1. Data at the initial visit will include:
2. Documentation that patient meets all inclusion criteria and no exclusion criteria
3. Patient Identifying information (DOB, Name, MRN) and a Subject ID will be assigned
4. Patient's home address will be obtained in order to send BSIT kit and placebo or supplement.
5. Demographic information including age, gender, race and ethnicity
6. Patient history - history of present illness (including presence of symptoms, onset and duration of symptoms, associated symptoms, past medical history, past surgical history)
7. Past medical history
8. Past surgical history
9. List of medications and medication allergies
10. Brief Questionnaire of Olfactory Dysfunction - Negative Statements (QOD-NS) Score
11. Sino-Nasal Outcome Test (SNOT-22) Score
12. Follow-up visits at 1 week, 2 weeks and 4 weeks:
13. Patient interval history
14. Brief Questionnaire of Olfactory Dysfunction - Negative Statements (QOD-NS) Score
15. Sino-Nasal Outcome Test (SNOT-22) Score
16. Follow-up visit at 6 weeks:
17. Patient interval history
18. Brief Smell Identification Test (BSIT) Score
19. Brief Questionnaire of Olfactory Dysfunction - Negative Statements (QOD-NS) Score

## 20. Sino-Nasal Outcome Test (SNOT-22) Score

Follow-up visits at 1 week, 2 weeks and 4 weeks:

1. Patient interval history
2. Brief Questionnaire of Olfactory Dysfunction - Negative Statements (QOD-NS) Score
3. Sino-Nasal Outcome Test (SNOT-22) Score

Follow-up visit at 6 weeks:

1. Patient interval history
2. Brief Smell Identification Test (BSIT) Score
3. Brief Questionnaire of Olfactory Dysfunction - Negative Statements (QOD-NS) Score
4. Sino-Nasal Outcome Test (SNOT-22) Score

### Description of Non-Health Information that Will Be Viewed, Recorded, Or Generated

Contact information including telephone number and email address.

### **Safety Monitoring:**

Patients will be asked to report adverse effects related to omega-3 use. Minor side effects are not uncommon, and typically include gastrointestinal distress or fishy test. Serious adverse events are exceedingly rare. Patients will be instructed to report any potential adverse events to the PI which will be recorded. Patients will be screened for adverse events at each of the data collection check-points (1 week, 2 weeks, 4 weeks, and 6 weeks).

### **Drugs/Biologics**

### Study Fund Account