Neuromodulators do not appear effective for post-viral parosmia

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Dear Editor:

The COVID-19 pandemic brought attention to post-viral smell distortion, or parosmia, which is defined as a qualitative dysfunction resulting from distorted odor perception in the presence of an odorous medium [(1)]. Very often, qualitative and quantitative alterations occur simultaneously. Patients severely affected by qualitative odor disorders find that their quality of life has deteriorated [(2)]. For quantitative loss from viruses, the role of olfactory training has been emphasized [(3)], along with high volume steroid nasal irrigations [(4)], and even injections with platelet-rich plasma [(5)]. However, there has been no high-level evidence demonstrating an effective treatment for qualitative olfactory disorders. Considering the need for correct synaptic signaling to perceive smell appropriately, neuromodulators have long been discussed as a potential treatment option [(6)]. The purpose of this study was to analyze the therapeutic potential of neuromodulators like gabapentin, pregabalin, or amitryptiline in the treatment of parosmia from viral upper respiratory illnesses.

A retrospective medical record review initially identified 21 patients presenting to a tertiary academic smell disorder center with post-viral parosmia who were treated with a neuromodulatory agent (PwN) between June 2015 and December 2022, 17 of which completed a 6 month follow up data set. This cohort was then compared with a cohort of 18 patients with post-viral parosmia over the same period who were not treated with a neuromodulatory agent (PsN). All subjects in both groups had quantitative olfactory impairment. The mean value of the UPSIT test in the PwN group was 24.23 (SD=8.16) and in the PsN group 24.22 (SD=9.20). In the PwN group, gabapentin was used in 11 cases, pregabalin in 1 case, and amitriptyline in 5 cases. VAS (to assess for subjective score and change over time of smell distortion) started at an average of 7.61 in both the PwN group and the PsN, (range 3-10; 0 - no changes 10 - very significant changes. VAS on follow-up was an average of 5.55 in the PwN group and 4.89 in the PsN group, (range 0-9). 7 patients of the PwN group and 6 patients of the PsN group had a >5 point improvement in the VAS. There was no significant difference between VAS scores between the two groups ($p = 0.51$), or in duration of parosmia prior to presentation, time to follow-up (Figure 1).

Although neuromodulating agents have been suggested and used for decades by physicians to attempt treatment of parosmia [(7)], the first report on the treatment of parosmia with gabapentin was presented by Garcia et al. [(6)]. In their report, the authors suggested potentially promising treatment effect for parosmia, however, they acknowledged an extremely small nine person sample, with additional limitations of no control group, no validated testing measure used as an outcome, and the patients being on other treatments for smell dysfunction at the same time, such as budesonide irrigations and olfactory training. In our case control study, we did not observe such a significant improvement in the subjective sensation of parosmia with use of these agents. Although our findings could represent a type 2 error, this result is supported by a recent prospective study randomizing patients with parosmia to either gabapentin or placebo, where, they also found no benefit compared to the control group [(8)] (Table 1).

Treatment of post-viral parosmia with neuromodulators such as gabapentin, pregabalin or amitriptyline, whether induced by COVID-19 or other viruses, did not show a significant effect on the outcome of smell distortion, when compared directly to those not receiving neuromodulator treatment. Although larger, randomized, placebo-controlled studies may elucidate a role for neuromodulators in this patient population, there is no current indication for their use in post-viral parosmia.

Abbreviations

COVID-19: coronavirus disease 2019; PwN: parosmia group who were treated with a neuromodulatory agent; PsN: parosmia group who were not treated with a neuromodulatory agent; SNOT-22: Sino-nasal Outcome Test; VAS: Visual Analogue Scale.

Table 1. Comparison of data from neuromodulator studies for parosmia.

Study	Total n	Control group?	Median baseline UPSIT	Dosage	Number of people	Duration of parosmia	Duration of treatment	Conclusion
Garcia et al.	9	No	21 (Range 13-35)	gabapentin 300 mg bid	2	11 months	6 months	Found benefit but no control group for comparison
				gabapentin 300 mg qd	(Range 13-35)	12 months	6 months	
					1	11 months	1 month	
					1	15 months	1 month	
				gabapentin 200 mg qd	2	10 months	2 months	
						6 months	3 weeks	
Mahadev et al.	68	Yes	25 (Range 7-34)	gabapentin 300mg tid	1	At least 3 months but not individually reported	8 weeks with on and off taper	No benefit over placebo control group
				gabapentin 600mg tid	3	At least 3 months but not individually reported	8 weeks with on and off taper	
				gabapentin 900mg tid	4	At least 3 months but not individually reported	8 weeks with on and off taper	
					10	At least 3 months but not individually reported	8 weeks with on and off taper	
Present study	35	Yes	23 (Range 9-33)	amitryptiline 100mg qd	1	4 months	6 months	No benefit over control group
				amitryptiline 100mg qd	1	6 months	6 months	
				amitryptiline 100mg qd	1	7 months	6 months	
				amitryptiline 100mg qd	1	8 months	6 months	
				amitryptiline 100mg qd	1	11 months	6 months	
				pregabelin 75mg bid	1	4 months	6 months	
				gabapentin 400mg tid	2	2 months	6 months	
				gabapentin 300 mg tid	1	1 month	6 months	
				gabapentin 100mg tid	3	7 months	6 months	
				gabapentin 100mg bid	4	6 months	6 months	
				gabentin 100mg qd	1	12 months	6 months	

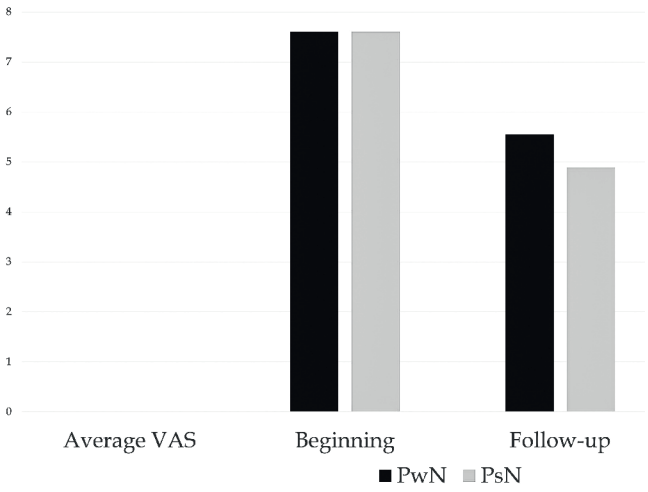

Figure 1. Change in parosmia VAS in patients with and without neuromodulator use.

Authorship contribution

KR: acquisition, analysis, and interpretation of data for the work; drafting the work; BRC: acquisition of data for the work; drafting the work; ZMP: conception of the work; analysis and interpretation of data for the work; reviewing it critically for important intellectual content and final approval.

Conflict of interest

None.

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SUPPLEMENTARY MATERIAL

Protocol and registration

The Institutional Review Board approved this study.

Materials & Methods

The following data were extracted: whether the virus was proven as COVID-19 or some other viral illness, duration of parosmia, age, gender, comorbidities, University of Pennsylvania Smell Identification Test (UPSIT) results obtained at the first visit, and Sinonasal Outcome Test-22 (SNOT-22). A retrospective medical record review initially identified 21 patients presenting to a tertiary academic smell disorder center with post-viral parosmia who were treated with a neuromodulatory agent (PwN) between June 2015 and December 2022, 17 of which were able to complete a 6 month follow up data set. This cohort was then compared with a cohort of 18 patients with post-viral parosmia over the same time period who were not treated with a neuromodulatory agent (PsN). The follow-up period was at least 6 months for all patients (range of 6-24 months). A visual analog scale (VAS) was used to assess subjective outcome and change over time of odor distortion.

Statistical analysis

A paired t-test was used to compare outcomes between the two groups, with $p<0.05$ considered significant.

Results

There were 9 women, 1 transgender person, and 7 men in the PwN group, aged 20-91 (mean of 44) and 14 women and 4 men in the PsN group, aged 25-68 (mean of 47). None of the subjects had chronic rhinosinusitis. SNOT-22 value in the PwN group ranged from 8-64 (mean 31.11; SD=18.37) and for the PsN group 8-90 (mean 32.38; SD=26.92). Accompanying taste disorders were present in 13 PwN and 6 PsN subjects. There were two active cigarette smokers in each of the two groups.
Olfactory training was used by 4 subjects in the PwN group and 5 in the PsN group. No one in either group showed a change in body weight due to their parosmia over the time of the study. Depressive or anxiety disorders were previously established diagnoses in 6 people from the PwN group and 3 from the PsN group. There was no significant difference between co-morbidities or demographic data between the two groups.

Limitations

Limitations of our study include that patients were first identified in a retrospective manner, although some of the follow up data was prospectively collected, and there are inherent biases to any retrospective study. Another limitation is that this was a relatively small number of patients, a limitation we tried to balance by tightly controlling the two cohorts so they were able to be matched and compared much more precisely than in other published studies.