

# Recovery from 3 Years of Daily Olfactory Distortions after Short-Term Treatment with GABA-Analogue

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## Keywords

Olfactory disorder · Phantosmia · Treatment

## Abstract

This case report describes a healthy 47-year-old man with a 3 years history of daily unpleasant olfactory distortions with severe negative effects on the quality of life. The distorted smoke-like smell occurred every day and was most prominent in the evenings resulting in severe discomfort as the patient felt suffocated by the smoke when falling asleep. The distorted smell had no odour triggers and was classified as phantosmia. Patient history, nasal endoscopy, neurological and otolaryngological examination, depression screening, cognitive testing, and CT scan revealed no obvious aetiology, resulting in the diagnosis of idiopathic phantosmia. Quantitate olfactory function was normal. Based on anecdotal evidence in the literature, the patient was treated with a GABA-analogue (pregabalin 50 mg × 3) for 4 weeks. During this treatment, the olfactory distortions completely disappeared for the first time in 3 years and had not reoccurred after 7 months of follow-up. GABA-analogues may be a potential treatment for some of the patients suffering from olfactory distortions. While this constitutes a single case report

without controls and phantosmia can disappear spontaneously, there is no proof of causality. However, given the long duration of symptoms, temporal relationship with treatment on the sudden disappearance of phantosmia, and long follow-up without recurrence, this highlights the need for further studies on GABA-analogues as a potential treatment of idiopathic phantosmia. Consequently, larger studies and systematic evaluation of potential effects in different patient groups are warranted before routine treatment with GABA-analogues is advised.

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## Introduction

Olfactory deficits are common and have gained a high level of attention following COVID-19, where olfactory dysfunction was identified as a common acute symptom of infection with a potentially poor prognosis of recovery [1]. However, olfactory deficits have for decades been known to be common as olfactory loss affects around 15% and olfactory distortions affect 4% of the general population [2, 3]. While sino-nasal causes of olfactory dysfunction can have both medical and surgical options for treat-

ment [4, 5], other causes of olfactory dysfunction currently rely on olfactory training as the main evidence-based treatment for a reduced or diminished sense of smell (hyposmia and anosmia) [6]. Currently, there are no recommended treatments for olfactory distortions, which entails both distortions of perceived odours (parosmia) and distorted perceptions of smell without an odour source (phantosmia). Although anecdotal descriptions of the potential effects of GABA-analogues on olfactory distortion have been mentioned in the literature [7], no data or case reports on this treatment have previously been published. This case report describes the patient history, clinical evaluation, treatment, outcome, and follow-up of a patient with 3 years of daily phantosmia after 4 weeks of treatment with pregabalin.

## Case Report

A 47-year-old man with no previous medical history or regular medication was referred to a tertiary smell and taste clinic due to a 3-year history of daily smell distortions. Prior to symptom onset, the patient had experienced a reduction of his hearing bilaterally after a scuba-diving ascent, which normalized during the following weeks. Furthermore, at the time of debut, the patient had experienced mild stress symptoms, which also waned over time without improvement of olfactory symptoms. There were no symptoms of depression or anxiety before or after debut of phantosmia. There was no history of head trauma, new medications, infections, or dental operations prior to debut. The patient had never been a smoker and had low weekly consumption of alcohol (4 units/week). The distorted smell was unchanged since its debut and was described by the patient as a highly unpleasant smoky odour that occurred without an apparent odour source (phantosmia). The patient rated the phantosmia as 10 of 10 on a VAS scale on negative impact on quality of life. The general perception of odours and aromas was not affected in quality or quantity (no parosmia or hyposmia), but the unpleasant distorted smell was particularly dominant in the evenings and had an aggravating effect on the ability to fall asleep as the patient felt suffocated by the perceived smoke.

The patient had not experienced allergic symptoms (sneezing, nasal irritation, affected conjunctivae or skin), or symptoms of chronic rhinosinusitis (no nasal discharge, nasal blockage, headache/-pressure, or reduced sense of smell). Distortions were present in different surroundings and were therefore not suspected to have a specific trigger in the patient's residence.

The patient had after symptom debut been evaluated by a practising otolaryngologist where nasal endoscopy revealed normal nasal anatomy and mucosae. A cerebral 1.5 T MRI had been performed without pathological findings. Two months of treatment with nasal steroids was attempted without improvement of symptoms.

Upon referral, the patient underwent a sino-nasal CT scan which revealed no sino-nasal blockage, tumours, or mucosal swelling. A skin test for allergies revealed no signs of allergy. Nasal endoscopy was still normal. Neurological examination and neuro-

psychiatric screening (MDI, MMSE, and clinical assessment) were conducted without further deficits.

Olfactory testing (Sniffin' Sticks; Burghart GmbH, Holm, Germany) was conducted with a threshold score (T) of 7.5, discrimination score (D) of 16, and an identification score (I) of 15, constituting an overall TDI score of 35.5, representing a quantitatively normal sense of smell (>30) [8]. The sino-nasal outcome test (SNOT-22) questionnaire representing sino-nasal symptoms affecting the quality of life was 16, i.e., within normal limits. Taste screening with taste sprays indicated a normal sense of taste with correct identification of sweet, salty, sour, and bitter. Depression screening with Major Depression Inventory (MDI) revealed no cardinal signs of depression and a total score of 18. As such, the patient had no clear aetiology or sino-nasal symptoms that could explain the sudden debut of phantosmia and no explanation of the permanent distortions, resulting in a diagnosis of idiopathic phantosmia.

The patient conducted nasal lavage after the initial visit to the smell and taste clinic for a month without any effects on the occurrence or severity of phantosmia. Although no published data were available for medical treatment of distorted olfactory disorders, a recent commentary article described experiences with potential benefits of GABA-analogues on olfactory distortions [7]. The patient was presented with the possibility of treatment with pregabalin after consulting with the Danish Medicines Agency and agreed to initiate treatment. With an initial daily dose of 25 mg × 3, the patient had no effect on phantasmic symptoms after a week and the dose was increased to 50 mg × 3. After 2 weeks of treatment with this dose, the phantosmia suddenly disappeared completely. The patient continued the treatment an additional week. Phantosmia did not reappear after discontinuation and the patient did not suffer from any side effects during the treatment. At 7 months of follow-up after ending pregabalin treatment, the patient had not experienced any side effects or recurrence of phantosmia and reported an improved subjective quality of life.

## Discussion/Conclusion

Although olfactory distortions are rather common, affecting up to four percent of the population [3] and indications of a possible effect of GABA-analogues have been published [7], there are no prior published data or case reports on the effects of GABA-analogues on olfactory distortions. As such, this case report is the first to describe the treatment and effects of this potential treatment in a single case.

Pharmacologically, GABA-analogues inhibit presynaptic voltage-gated calcium channels and thereby decrease the release of neurotransmitters to the synaptic cleft. There are two possible mechanisms for GABA-inhibitors to exhibit alterations in odour perception. This can occur in the olfactory bulb and/or the primary olfactory cortex as these structures (in contrast to the olfactory epithelium) have a substantial number of GABAer-

gic interneurons. In the olfactory bulb, GABAergic cells including granule cells have been shown to regulate the magnitude of olfactory receptor neuron input through presynaptic inhibition [9]. In the primary olfactory cortex, GABAergic interneurons are directly excited by mitral cell axons, thereby inhibiting affected action potential firing in pyramidal cells [10]. As such, the potential effect of GABA-analogues may also offer a new possibility to study the mechanisms of olfactory processing and odour coding in a clinical population.

In previous case reports, other pharmacological interventions of idiopathic phantosmia and olfactory reference syndrome have been reported with successful outcomes after treatment with antidepressants or sodium valproate [11–13]. As such, the GABAergic neurons are not the only potential target for treating phantosmia. The effects and pharmacological targets of these treatments in different aetiologies of phantosmia may not only improve the treatment of phantosmia but may also offer insights into the underlying mechanisms of phantosmia.

With the high incidence of olfactory distortions following COVID-19 [14], there is an urgent demand for more case reports, case-control studies, and most importantly RCT studies to shed light on the potential effects of GABA-analogues and other pharmacological interventions on different olfactory distortions. This case report can serve as inspiration for the potential dosage and treatment duration of such GABA-analogue studies. However, it is critical that a systematic evaluation of the potential treatment in different phantosmia aetiologies is conducted before treatment is initiated on a broader scale.

### Key Points

- GABA-analogues have been described in the literature as a potential treatment of olfactory distortions, but so far, no data or case reports have been published.
- This case report describes how a patient with 3 years of daily unpleasant phantosmia was cured with 4 weeks of GABA-analogue treatment.
- At 7 months follow-up, no recurrence of phantosmia had occurred.
- GABA-analogues may offer potential for treating olfactory distortions, but larger studies are needed to evaluate the effect before treatment is initiated on a broader scale.

### Statement of Ethics

The study was conducted according to the Declaration of Helsinki on Biomedical Research Involving Human Subjects. Written informed consent was obtained from the patient for publication of the details of their medical case. The conduction of the study was approved by the Central Denmark Region Ethics Committee (1-10-72-1-21).

### Conflict of Interest Statement

The author has no conflicts of interest to disclose.

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### Author Contributions

Alexander Wieck Fjaeldstad conducted the clinical assessment, treatment, and follow-up of the patient, wrote the manuscript, and reviewed the manuscript prior to submission.

### Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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