

Management of long-lasting phantosmia: a systematic review

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Background: Interest in the pathophysiology and management of phantom smells has increased rapidly over the last decade. A PubMed search for the term “phantosmia” demonstrated a near-doubling of articles published on phantosmia within the past 7 years. We aimed to systematically review the literature on the management of phantosmia.

Methods: The PubMed, EMBASE, and Cochrane databases were searched for articles published since January 1990, using terms combined with pertinent Boolean search operators. We included articles evaluating management of phantosmia written in the English language, with original data and a minimum of 6 months of follow-up, on at least 2 patients and with well-defined and measurable outcomes.

Results: A total of 2151 unique titles were returned upon the initial search. Of these, 146 abstracts were examined, yielding 7 articles meeting the inclusion criteria. All articles were predominantly level 4 evidence. One prospective level 3 study was included. The studies included a total of 96 patients, with follow-up ranging from 6 months to 11 years. Endpoints were primarily based on subjective patient

responses. Management options included observation and medical and surgical therapy. Olfactory mucosa excision was the only surgical intervention studied, with short-term symptomatic improvement in 10 of 11 patients. Forty-one patients were treated medically, which included antipsychotic, antimigraine, and antiseizure medications, transcranial stimulation, and topical cocaine application.

Conclusion: Despite increasing interest in the treatment of phantosmia and reports of successful therapies, there remains a paucity of data and lack of consensus regarding optimal management of this difficult condition. © 2018 ARS-AAOA, LLC.

Key Words:

olfactory disorders; parosmia; phantom smell; olfaction; olfactory excision

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Olfactory disorders encompass many clinical presentations and can often have devastating effects on quality of life.¹ There are many terms used to describe these disorders. *Dysosmia* is a general term used to describe an abnormality in olfactory sensation. This term can be further classified into qualitative and quantitative changes in the sense of smell. Quantitative changes are measurable

variations that include anosmia (complete loss of smelling ability) and hyposmia (decreased smelling ability), whereas qualitative changes are described as parosmia (ie, troposmia or cacosmia, describing a distorted perception of an odorant) or phantosmia (sensation of smell in the absence of an odorant). Quantitative changes may be measured by verified objective and physiologic testing, whereas qualitative changes in smell have no reliable verified tests, meaning their diagnosis depends primarily on patient history.² These disorders have been noted to follow upper respiratory infections or head trauma.^{3,4}

The clinical investigation and treatment of phantosmia has been evolving over the last 10 years. Landis et al provided a concise and valuable overview of idiopathic phantosmia in 2010.² At that time, a literature search of phantosmia in PubMed returned 25 articles. In 7 years, the number of articles returned for this term has nearly doubled, climbing to 48 articles. Over this time period, studies have investigated the etiology, pathophysiologic mechanisms, management, and interventions of this phenomenon.

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We performed a systematic review of the literature over the past 25 years on this topic, focusing on the management and treatment of phantosmia, aiming to delineate whether a consensus exists regarding optimal management.

Materials and methods

A systematic review of English-language published literature was conducted to investigate management of phantosmia. Our study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist and statement recommendations during the conduct of this qualitative systematic review.

In February 2017, we searched PubMed, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) databases for relevant publications, beginning after January 1990 through February 2017. A principal electronic search strategy was designed and utilized for each database. The search included combined key terms and exploded medical subject headings (MeSH). The following terms were used during our search: *phantosmia*; *phantom smell*; *olfactory hallucination*; *distorted olfactory perception*; and *unstimulated olfactory distortion*.

Eligibility criteria

The articles utilized in this review were limited to those written in the English language that included original data. These articles included limited case series and cohort studies, with an understanding of potential bias in the limited series of patients managed. Two members of the investigation team independently reviewed the articles to include in this study. The following inclusion criteria were applied: original data; therapeutic intervention performed with at least 6 months of follow-up; at least 2 patients included in the study; well-defined and measurable outcomes obtained; and published after January 1990. Studies with no measurable outcomes; no therapy offered; <6 months of follow-up; review articles; articles with little relevance to our study aims; and all basic science, cadaver, and animal-model studies were excluded. Publications were obtained by review of the titles, articles, and abstracts narrowed down from the criteria cited.

Data extraction

Data were extracted and reviewed independently. Any disagreement in inclusion or exclusion of articles was re-reviewed for a consensus between investigators. Articles were then evaluated for time of study, number of patients, age of patients, therapy provided, outcomes provided, length of follow-up, and statistical analysis. The level of evidence was then assigned based on the published guidelines by the Oxford Centre for Evidence-based Medicine, Levels of Evidence.⁴

Summary

The articles were organized based on the therapy offered, follow-up, and qualitative disease progression. Performing meta-analysis was not possible given the limited series of patients provided in each study and the qualitative measures and outcomes reported.

Results

The article selection process is illustrated in Figure 1. A total of 2151 unique titles were returned upon the initial search. Of the titles reviewed, 146 abstracts were selected and examined, yielding 29 full-text articles to review and ultimately 7 articles that met the inclusion criteria, as illustrated in Figure 1. No level 1 (randomized controlled trials) or level 2 studies were available for analysis; the study articles were predominantly level 4 evidence, and 1 prospective level 3 study was included.⁵ The studies included a total of 96 patients, with follow-up ranging from 6 months to 11 years (Table 1). Endpoints were primarily based on subjective patient responses. Management options included observation⁶ and medical^{7–9} and surgical^{9,10} therapy. No studies that met the inclusion criteria addressed the role of steroid therapy, and this may be the subject of future studies.

One article provided outcomes with observation alone,⁶ with 56.8% of patients reporting short-term improvement of symptoms but only 31.8% of patients reporting long-term relief (Table 1). Twenty-four patients were treated medically with antipsychotic medications,⁹ anti-seizure medications,⁸ topical cocaine,⁷ or antimigraine prophylactic medications.¹¹ Long-term symptomatic relief was achieved with antiseizure and antipsychotic medications in 4 of 4 patients,^{8,9} but none of the 6 patients treated with topical cocaine application had long-term resolution of their symptoms (Table 1).⁶ One study retrospectively investigating migraine patients with phantosmia linked to their headaches showed that 9 of 14 patients had improvement in their symptoms with antimigraine prophylactic therapy including topiramate, nortriptyline, and verapamil, and no patient had resolution of their headaches without a corresponding resolution of their phantosmia symptoms.¹¹ Two articles provided surgical management outcomes^{7,9}; olfactory mucosa excision was the only surgery performed on these patients, with symptomatic improvement in 10 of 11 patients (Table 1).

Morrissey et al⁹ addressed surgical and medical management in their series of 5 patients. They reported a battery of symptoms and exam findings that helped differentiate 2 etiologies of phantosmia in their patients: central and peripheral (Table 2, Table 3).⁹ In their series, patients were trialed with haloperidol for 3 months and, if symptoms did not resolve, surgery was offered.⁹ Three patients with phantosmia attributable to a peripheral cause underwent surgery, whereas 2 patients with phantosmia, likely stemming from a central cause, had resolution of their symptoms with medical therapy.⁹ In another study, 17 patients were treated

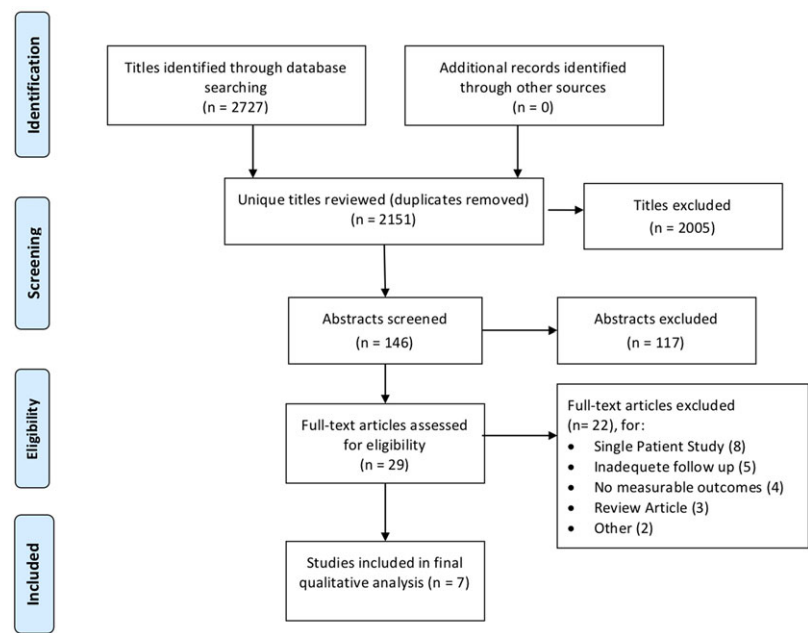


FIGURE 1. PRISMA Diagram Illustrating Literature Search Algorithm.

with transcranial stimulation; all patients had short-term relief of their symptoms, but only 2 of the 17 had long-term relief of their phantasmia (Table 1).⁵ Overall, in those treated with effective therapy (ie, antipsychotic, antiseizure, antimigraine, or surgical therapy), 73.3% of patients (23 of 29) had long-term relief, compared with only 31.8% of patients (14 of 44) treated with observation alone (Table 1).

Discussion

Phantasmia is an important phenomenon that can have a drastic impact on a patient’s quality of life, both in social and work-related activities.^{1,2,9} Although the

actual prevalence of phantasmia in the general population is unknown, the problem is present in almost 25% of patients reporting subjective olfactory dysfunction and seeking care in specialized olfactory outpatient centers.^{2,10} These patients require a multidisciplinary approach and thorough counseling, and it is prudent for the otolaryngologist to understand the causes, potential interventions, and outcomes of this phenomenon to provide adequate care to those in need.

Although phantasmia is often seen in patients who have lost olfactory ability, it is also found in people with a normal sense of smell. The cause of phantasmia is not completely understood, but it may be attributed to a

TABLE 1. Phantasmia treatment modalities and outcomes

Treatment modality	Number of patients	Age range (years)	Follow-up (years)	Patients reporting short-term improvement of symptoms (n)	Patients reporting complete resolution of symptoms after ≥ 6 months (%)	Studies referenced (level of evidence)
Observation	44	NA	6	25 of 44 (56.8%)	14 of 44 (31.8%)	Landis et al 2010 (4)
Medical (antipsychotic, antimigraine, antiepileptic)	18	20-62	1.5-3.5	13 of 18 (72.2%)	13 of 18 (72.2%)	Morrissey et al, 2016 (4); Majumdar et al, 2003 (4); Coleman et al, 2011 (4)
Medical (topical cocaine)	6	25-69	1.6	6 of 6 (100%)	0 of 6 (0%)	Leopold and Hornung, 2013 (4)
Surgical excision of olfactory mucosa	11	21-60	0.5-11	10 of 11 (91%)	10 of 11 (91%)	Morrissey et al, 2016 (4); Leopold et al, 2002 (4)
Transcranial magnetic stimulation	17	30-76	0.5-5	13 of 17 (77%)	2 of 17 (11.8%)	Henkin et al, 2011 (3)

NA = not available.

TABLE 2. Central vs peripheral phantasmia⁹

	Peripheral	Central
Duration of symptoms	Intermittent, often caused by odorant stimuli	Constant, unremitting
Localization	Often worse on 1 side	Bilateral
Effect of nasal obstruction	Lidocaine pledgets and nasal obstruction may relieve symptoms	No relief of symptoms
Effect of topical cocaine	Resolution of symptoms and development of anosmia	No relief of symptoms

TABLE 3. Summary of studies included in systematic review

Author	Year	Age range (years)	n	Therapy	Follow-up	Statistical analysis (yes or no)	Results/notes	Level of evidence
Morrissey et al ⁹	2016	20-60	5	Medical (2): haloperidol; surgical (3): olfactory mucosal excision	18 months to 5 years	No	Three-month trial of haloperidol on all patients. Two patients were successfully treated with haloperidol alone. Those who failed haloperidol underwent olfactory mucosa excision. All patients' phantasmia ultimately resolved.	4
Leopold and Hornung ⁷	2013	25-69	6	Topical cocaine	19 months	No	Five of 6 patients achieved transient loss of phantasmia over hours to days. One patient improved for 6 weeks. Phantasmia returned at long-term follow-up in all patients.	4
Landis et al ⁶	2010	Unclear	44	Observation	Mean 6 years observation	Yes	Phantasmia symptoms disappeared in 14 patients (31.8%), improved in 11 patients (25%), remained the same in 17 patients (38.7%), and worsened in 2 patients (4.5%). No association with gender nor TDI score (odor threshold [T], odor discrimination [D], and odor identification [I]).	4
Henkin et al ⁵	2011	30-76	17	Repetitive transcranial magnetic stimulation	6 months to 5 years	Yes	Of the patients, 80% responded to repetitive transcranial magnetic stimulation in the short term. Two patients continued with inhibition of distortion beyond 5 years, whereas the rest of the patients had return of their phantasmia.	3
Leopold et al ¹⁰	2002	21-54	8	Olfactory mucosa excision	1-11 years	Yes	Seven of the 8 patients had complete and permanent resolution of their phantasmia. The excised olfactory mucosa generally shows a decreased number of neurons, a greater ratio of immature to mature neurons, and disordered growth of axons with some intraepithelial neuromas.	4
Majumdar et al ⁸	2003	20-62	2	Sodium valproate or phenytoin sodium	3.5 years	No	Two patients treated successfully with valproate or phenytoin.	4
Coleman et al ¹¹	2011	26-58	14	Topiramate, verapamil, nortriptyline, gabapentin	30 months ^a	No	Nine of 14 patients had improvement in their phantasmia symptoms. All patients with resolution of their headaches also had resolution of phantasmia symptoms.	4

^aLength of study.

number of etiologies, including chronic rhinosinusitis, intracranial hemorrhage, epilepsy, psychiatric conditions, neurologic disorders, iatrogenic causes, and neurologic and neurodegenerative disorders.^{12–14} Furthermore, peripheral and central causes of phantosmia have been described. The phantosmia perception is likely central, and peripheral neurons may have a part in modulating the sensation in some people. Peripheral phantosmia is believed to be caused by a dysfunction at the level of the olfactory receptors and neurons, which may lead to inappropriate representation of an odor stimulus.^{15–17} Central phantosmia is more likely attributable to dysfunction or damage localized to the cortical olfactory pathways.^{18–21}

The critical distinction between central and peripheral etiologies of phantosmia is guided by key symptomatic differences between the 2 etiologies (Table 2), and this plays a role in treatment.⁹ Notably, in cases of peripheral phantosmia, medical therapy or observation may prove ineffective, and surgical intervention is an option in those who fail multiple trials of medication.^{9,10,15} As part of the research paradigm in the past, resection of the olfactory bulb through an open craniotomy approach was sometimes used to treat phantosmia²² and, more recently, endoscopic nasal approaches to the olfactory mucosa have been described.^{9,10} Morrissey et al's study, included in our systematic review, supports the notion that peripheral phantosmia is unlikely to respond to medical therapy,⁹ and a similar study showed that resection of the olfactory bulb was effective for a patient failing a trial of haloperidol.²² However, it should be noted that the authors of those studies are experts in the field with a high degree of familiarity with the problem, and surgical intervention was typically pursued only after exhausting all other options. Given the lack of strong evidence to date and the risks associated with olfactory cleft procedures, surgery should not be viewed as a definitive clinical tool but rather as an option within the research paradigm for managing phantosmia.

In our systematic review, we identified a few medical and surgical modalities that have been studied in the management of phantosmia. Interest in phantosmia has steadily risen in the past decade, but to date no large-scale, randomized, case-control studies have been performed on the phenomenon, and no consensus exists regarding optimal management. Moving forward, what is needed is a prospective, randomized trial of medical therapy vs surgery to delineate optimal management of phantosmia. At this time, no strong recommendations can be made on the therapeutic staging in patients presenting with phantosmia. In the setting of the limited literature available, we have attempted to summarize a basic stepwise therapeutic decision tree for these patients (Fig. 2). Until a better consensus can be achieved, we suggest that providers begin with a multidisciplinary and comprehensive diagnostic work-up for patients presenting with phantosmia. This work-up should include a smell test to determine the extent of olfactory dysfunction; magnetic resonance imaging to rule out neoplasm, sinus disease, or cerebrovascular disease; and a neurologic examination to

evaluate for memory loss, seizures, or motor and sensory impairment given that phantosmia may be an early indication of neurocognitive disorders.^{3,12,13,16,23,24} Altogether, an extensive work-up is indicated as medical therapy may depend on the underlying cause of a patient's phantosmia, and success rates for medical therapy may also vary in this regard. For instance, olfactory hallucinations associated with focal epilepsy may be treated with antiepileptic agents,^{16,25} whereas migraine-associated phantosmia can be treated with prophylactic antimigraine medications such as topiramate.^{11,16}

After completing a thorough work-up, providers may consider observation of symptoms vs a trial of medical therapy (eg, antimigraine, antipsychotic, antiepileptic) tailored to the most likely etiology of a patient's phantosmia. If multiple trials of medical therapy and observation are unsuccessful, the patient may be referred to an expert in the field for consideration of surgical excision of olfactory mucosa (Fig. 2). A candid discussion regarding the potential risks and benefits of this surgical intervention, such as worsening olfactory dysfunction and cerebrospinal fluid leak, is prudent. Further investigation may reveal better treatment modalities for phantosmia.

Notably, there were multiple case reports we did not include in our analysis as they did not meet the inclusion criteria. A discussion of some of these studies may be insightful despite their exclusion from our systematic review. One such study investigated the role of lamotrigine in managing phantosmia²⁶ and noted that 3 patients had significant improvement with lamotrigine monotherapy, but length of follow-up was unclear.²⁶ Another study noted that 2 patients with brain tumors and phantosmia had resolution of their phantosmia after radiation therapy.²⁷ One study investigated the role of steroid therapy in a patient with rhinosinusitis, noting that the patient had definitive resolution of symptoms when treated with oral and intranasal steroid therapy.²⁸ One study showed that gabapentin therapy was successful in 1 of 3 patients.¹¹ Another study described a patient with phantosmia and depression treated with venlafaxine, which led to a complete resolution of mood symptoms and phantosmia.²⁹ A similar study showed that aripiprazole augmentation of antidepressant therapy led to significant improvement in 1 patient.³⁰ These studies highlight the potential role of antidepressants and anxiolytics in the treatment of select phantosmia patients who may have underlying psychiatric illness. Studies such as these did not meet our inclusion criteria but may still shed light on potential treatment modalities. Overall, studies suggest that medical therapy may be more successful in patients with central etiologies of phantosmia, whereas surgical excision of olfactory mucosa may be beneficial in peripheral phantosmia patients.⁹ However, there remains a paucity of relevant data in the literature and no definitive treatment recommendations are possible at this time.

The potential role of olfactory training in the treatment of phantosmia is also intriguing and warrants discussion. Although no studies on olfactory training met our inclusion

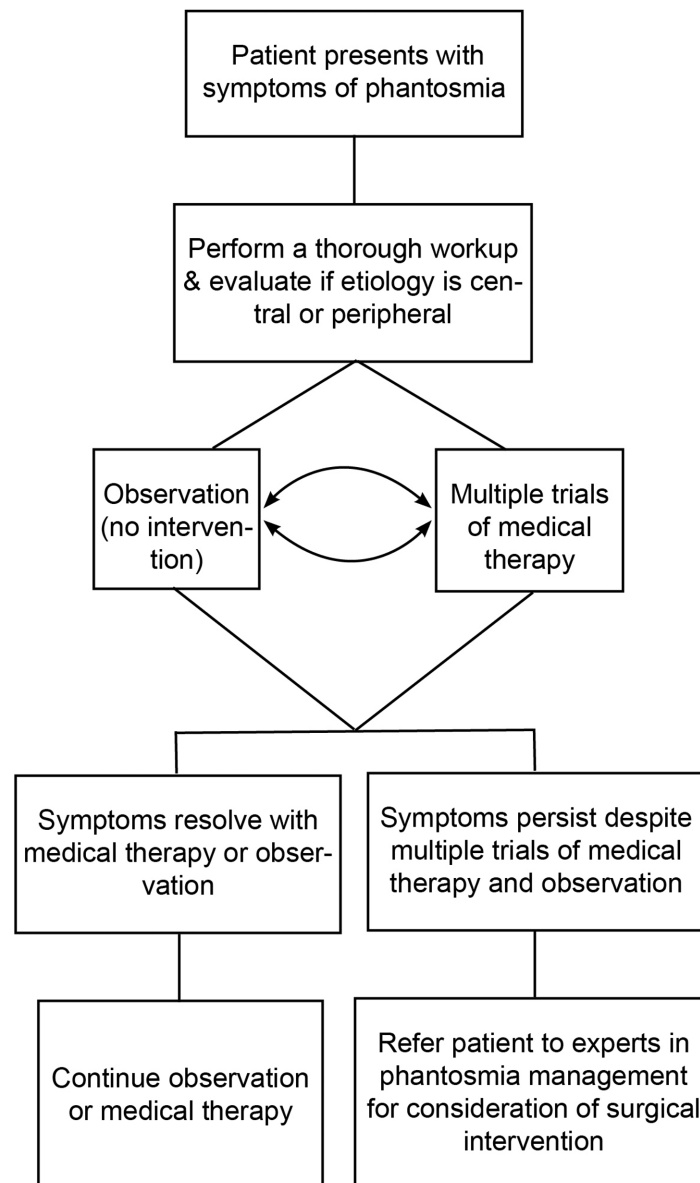


FIGURE 2. Management Algorithm for Patients Presenting with Phantosmia.

criteria, we encountered some studies that addressed the benefits of olfactory training in those with other forms of olfactory dysfunction.^{31–33} This olfactory training is a novel treatment modality in which patients are instructed to frequently sniff numerous scents representing major odor categories.³² A recent systematic review and meta-analysis showed that patients with hyposmia and anosmia benefit from olfactory training and demonstrate an overall improvement in TDI score (odor threshold [T], odor discrimination [D], and odor identification [I]) due to improvements in discrimination and identification, but not threshold.³² To our knowledge, the role of olfactory training in phantosmia patients has not been investigated specifically. However, we did find a case report describing a similar mechanism of therapy, in which olfactory counterstimulation was used effectively in a patient with phantosmia.³⁴ The patient was

given odorized pens with various odors (banana, garlic, cloves, turpentine) with instructions to sniff the pens during the onset of phantosmia; cloves and turpentine were effective in inhibiting phantosmia.³⁴ This study is promising despite its limitations, and future studies investigating the potential role of olfactory training in managing phantosmia would be beneficial.

There are limitations that prevent us from drawing generalizable conclusions based on our systematic review. First, despite including nearly 100 patients, we had to exclude the vast majority of studies due to inadequate follow-up, unclear outcome measures, and low patient numbers, limiting the overall power of our study. Although we did examine and discuss therapies described in case reports, these studies were not included in our systematic review due to their lack of power. Given the limited number of studies

investigating each modality of therapy and the retrospective nature of these studies, future prospective studies investigating the treatment of phantosmia would be beneficial. Overall, phantosmia is a challenging clinical problem, and to date no “gold standard” therapy has been identified. This systematic review highlights the importance of a comprehensive work-up in determining the etiology of phantosmia to help guide potential treatment options.

Conclusion

Despite increasing interest in the treatment of phantosmia and reports of successful therapies, there remains a paucity

of research and lack of consensus regarding the optimal management of this difficult and rare condition. Until a better consensus is achieved, we recommend a thorough work-up and a trial of medical therapy, with the consideration of surgical intervention in those who do not respond to the medical therapy. 🌐

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