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REVIEW

Investigational drugs for the treatment of olfactory dysfunction

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ABSTRACT

Olfactory dysfunction could be the sign of acquired or degenerative diseases. The loss of the sense can be caused by a damage in the nasal structure (olfactory epithelium) or a neuro inflammation/degeneration in the superior olfactory pathway. The understanding of the origin of the smell alteration would be desirable for appropriate management of the problem. Unfortunately, clinical investigations do not always allow to define the exact cause. This review discusses the treatments available and their mechanism of action based on the administration methods; in fact, just looking at the results obtained by the researcher using topic versus systemic treatment, might be possible to speculate about the peripheral or central origin of the olfactory disorder. Because COVID-19 causes olfactory loss and several treatments (topical and systemic) have been tested in this disease, we have decided to use this model of acquired olfactory loss to discuss the different therapeutical option. The authors believe these treatments might be an option also for treating olfactory disease related to neurodegeneration.

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Smell loss; olfactory; neuroepithelium; olfactory bulbs; olfactory cortex; neuroinflammation; cortisone; vitamin A; Palmitoylethanolamide; Luteolin; PEA; LUT; PEALUT

1. Introduction

Acute infection of the upper airways and chronic diseases of the nose as nasal polyposis and chronic sinusitis are the first causes of olfactory impairment [1]; in case of nasal polyposis, the alteration of smell is caused by mechanic obstruction that blocks odor perception; in chronic sinusitis, the persistence of inflammation damages both respiratory and olfactory mucosa causing the inability to perceive odors [1].

In this review, we aim to analyze the drugs that can be used for treating the loss of smell caused by damage of the olfactory cells (olfactory mucosa/olfactory neuroepithelium) [2] and/or due to the inflammation of superior olfactory pathways (from the olfactory bulbs to the cortex) [3,4]. Diseases of the olfactory neuroepithelium cause a peripheral smell loss, while lesions in the superior olfactory pathways are responsible of a central smell loss [3,4]. There are also conditions, in which both the peripheral and central pathways are affected by the disease with consequent smell loss [5,6].

Identifying correctly the origin (peripheral or central) of the smell alteration is very complex due to the lack of valid investigation methods. Moreover, the ones available, for example Sniffin' sticks, are subjective and not objective. Nasal endoscopy could offer more info about the state of mucosa, but only in the presence of macroscopic alteration. When possible additional and more informative tests as magnetic resonance imaging (MRI) should be performed to support the identification of the origin of the olfactory disorders; in fact, although a local treatment can be successful for neuroepithelium damage, won't be in case of olfactory bulbs inflammation. Unfortunately, still today identifying the real cause of the olfactory loss is only speculative and deductible by the results obtained after therapy.

The incorrect identification of the area (s) from which the concern originates might be a problem especially in the case of smell disorders of recent onset. An early treatment could: i) stop the progression of the disease [5] and ii) allow rapid tissue/function recovery [6], thanks to the support and stimulation of natural cells turnover [5,6].

This review will discuss the therapeutic options for the treatment of smell disorders based on the treatments that have been tried and the results obtained. The result of 'ex-adjuvantibus treatments' could indirectly support understanding of the origin of the smell alteration.

2. Methods

This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) checklist and statement recommendations (Figure 1). The nature of this review did not require Institutional Review Board approval.

2.1. Search strategy

A comprehensive search strategy, developed in partnership with a medical librarian, was performed on PubMed, Scopus and Google Scholar without time restrictions. The keywords used in combination were: 'olfactory dysfunction and treatment,' 'smell disorder and treatment,' 'smell disorders and topic treatment,' 'olfactory disorders and topical treatment,'

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'olfactory dysfunction and drugs,' and 'smell disorder and drugs.' Only articles in the English language were considered for the analysis.

Two independent investigators reviewed the articles extracted from the literature review. Duplicates were removed, then each reviewer singularly filled in an Excel data sheet (Microsoft Corporation, USA) including information extracted from the articles. Files were then compared and disagreements on the inclusion/exclusion papers were debated until complete agreement of both researchers. Only papers that received full consensus were considered.

PRISMA guidelines were followed to conduct the systematic review and the full list of references was screened for potentially relevant articles.

2.2. Study selection criteria

We included articles with the following characteristics: patients (0–99 years) affected by smell disorders, treated with topic, or systemic treatment, written in English language, with full-text available. The articles that discussed olfactory rehabilitation as treatment of the olfactory disorder, where excluded as not pertinent to the aim of this work. The selected articles were read in full to assess the study objectives and the results.

3. Results

3.1. General

Table 1 summarizes the studies that were considered in this review.

3.2. Topical treatment of olfactory dysfunction for olfactory epithelium inflammation

The olfactory epithelium (OE) is located in the upper part of the nasal cavity (close to cribriform lamina) and has a jeopardy distribution (Figure 1); this particular (jeopardy) distribution puts the neuroepithelium in contact with the nasal (respiratory) mucosa; the latter is commonly affected by infections and inflammations which can easy spread in these neuronal areas [7].

The OE consists of three primary components: epithelium, basement membrane and lamina propria; in addition, the olfactory pit is formed by the invagination of OE into the underlying connective tissue [8]; the olfactory pit prolongs the association of odorant with receptors by creating a pouched environment and providing specific niches for specialized neurons. The OE contains five cell types: olfactory receptor neurons (ORN), sustentacular cells (SC), basal cells (BC), microvillar cells (MC), and finger-like microvillar cells (FMC) [8]. Damage to ORN, SC, or BC causes alteration of the olfactory function and, depending on the severity of the damage, can lead to permanent loss of the sense of smell [9]. Di Stadio et al. hypothesized that after an acquired viral infection causing neuroinflammation, the natural regenerative capacity of the ORN may be altered inducing aberrant regeneration of the cells with the onset of parosmia [6]. The authors discussed the topic hypothesizing peripheral (neuroepithelium) and central (olfactory bulb) olfactory pathways involvement [6].

The neuroepithelium is easily accessible through the nose, so local therapy with nasal spray could be potentially beneficial, as shown by recent studies [10,11]. Nasal irrigation with cortisone (budesonide) administered immediately after infection reduced local inflammation and blocked the spread of the inflammatory process and associated progressive neuroepithelial dysfunction [11]. Varricchio et al. used a nasal spray with saline solution containing high molecular weight sodium hyaluronate, and 5% xylitol [12] to treat virus-related olfactory dysfunctions. The authors showed that the solution, which has anti-inflammatory (sodium hyaluronate) and antiseptic (xylitol) capacity, was able to decrease viral aggressiveness reducing (according to the authors' hypothesis) the spread of the virus into the olfactory bulb, as evidenced by the resolution of the smell alteration after the application of the nasal spray. In another study, a nasal spray solution with vitamin A was tested. This vitamin, which possesses strong antioxidant capacity, can directly act on local inflammation by reducing the reactive oxygen species (ROS) production [10] and, when sprayed into the nose improves the local immune response. The improved immune response stops the viral infection and limits the viral damage to the neuroepithelium [10]. Reden et al. also showed the improvement of the olfactory function using oral administration of vitamin A [13]. However, the study was conducted including patients with peripheral olfactory (viral infection) and with central (traumatic brain injury), damage to the sense of smell, making difficult to understand whether vitamin A acted at the peripheral or central level. In fact, the olfactory neuroepithelium can be a good route of delivery agents to the brain [14]. Through this retrograde transport (from neuro-epithelium to the olfactory bulb) the drugs can reach the olfactory bulb and then the brain [15]; this route can solve the problem of passing drugs from the blood through the brain blood barrier (BBB) which is one of the major concerns in the treatment of neuroinflammatory and neurodegenerative disorders [16]. The intranasal route is composed of two pathways, one intracellular while the other extracellular. The intracellular pathway begins with endocytosis by olfactory sensory cells, followed by axonal transport to their synaptic clefts in the olfactory bulb where the drug is exocytosed. In the extracellular mechanism, drugs are transported directly into the cerebral spinal fluid by first passing through the paracellular space across the nasal epithelium, then through the perineural space to the subarachnoid space of the brain [17]. However, today to fully benefit of this route it is necessary to vehiculate the drugs by nanoparticles [18]. So although intriguing to think about possible central effect of the nasal spray used in the studies, we think that it is unlikely that they could reach olfactory bulbs because they have limited concentration of active not vehiculated elements.

3.3. Systemic treatment of olfactory dysfunction which arise from superior olfactory pathways

The neuroepithelium is connected through the axons of the ORN to the olfactory bulb, which contains glomerulus, mitral

Table 1. Results of the literature review

PMID	Title of work	Author Name	Year of publication	Type of study	Sample size	Drug used	Dosage	Administration method	Results
33,728,831	Smell recovery in patients with COVID-19: an experience with nebulized nasal treatment	Varricchio A, La Mantia I, Brunese FP, Ciprandi G.	2021		42 (18 hyposmia, 24 anosmia)	Hypertonic saline (3% NaCl), high-molecular-weight sodium hyaluronate and xylitol (ALUNEB)	Twice a days for 7 days in hyposmiatwice a days for 10 days in anosmia	Nasal nebulization with medical device (MAD Nasal). Nebulize particles ranging 30 to 10 mm	All patients with hyposmia/ hypogeusia improved after treatment and achieved normal sensory function ten days from treatment starting.All anosmic/ ageusic patients recovered normal smell and taste between 10 and 20 days after treatment
21,287,560	Treatment of postinfectious olfactory disorders with minocycline: a double-blind, placebo-controlled study	Reden J, Herting B, Lill K, Kern R, Hummel T.	2011	Randomized, prospective, double-blind, placebo-controlled.	55(26 the verum 29 received the placebo)	Minocycline	Minocycline was given in a dose of 100 mg/d, one capsule twice a day, for a period of 21 days	Oral tablet	After treatment, 58% and 48% reported an improvement of the patients in the verum and placebo group, respectively (P = .54). The mean TDI score after therapy was 20.8 and 21.5, respectively. Change of TDI score was 1.8 (verum) and 2.5 (placebo). These improvements were statistically significant (P = .036 and P = .009, respectively). Nevertheless, medication had no significant effect on that improvement (P = .55).minocycline in the given dosage has little or no effect on the recovery of human olfactory function following postinfectious olfactory loss. However, spontaneous recovery is found in approximately 20% of the patients over an observation period of 7 months.
22,752,966	Olfactory function in patients with postinfectious and posttraumatic smell disorders before and after treatment with vitamin A: a double-blind, placebo-controlled, randomized clinical trial	Reden J, Lill K, Zahnert T, Haehner A, Hummel T.	2012	Double-blind, randomized, placebo-controlled clinical trial	52	Vitamin A (26 paz)Placebo (26 paz)	10,000 IU per day for 3 months	Oral tablet	Forty-four percent of all patients reported recovery of their sense of smell; 29% of the participants exhibited significant improvement in measured olfactory function. However, there was no significant difference between the outcome of patients receiving verum or placebo

(*Continued*)

Table 1. (Continued).

PMID	Title of work	Author Name	Year of publication	Type of study	Sample size	Drug used	Dosage	Administration method	Results
27,860,366	The effect of intranasal sodium citrate on olfaction in post-infectious loss: results from a prospective, placebo-controlled trial in 49 patients	Whitcroft KL, Ezzat M, Cuevas M, Andrews P, Hummel T.	2017	Prospective, single-blind, placebo-controlled trial.	49	Monorhinally with 1 mL sodium citrate solution. The contralateral nasal cavity was treated with 1 mL physiolog- ical sodium chloride solution, which acted as internal control	1 mL of sodium citrate solution	Intranasally	We demonstrated a statistically significant improvement in composite threshold + identification scores following treatment with sodium citrate, compared with placebo. This was true for all patients (mean improve- ment 0.87 2.68 points, P = 0.04), and on subgroup analysis in those with hyposmia (mean improvement1.15 2.37 points, P = 0.02)
28,434,127	Intranasal vitamin A is beneficial in post-infectious olfactory loss	Hummel T, Whitcroft KL, Rueter G, Haehner A.	2017		170	Olfactory training (46 paz) Olfactory training + vitamin A (124 paz)	Olfactory training using four stan- dard odorants [phenylethyl alcohol (rose), eucalyptol (eu-calyptus), citronellal (lemon), and eugenol (cloves)] for 12 weeks topical vitamin A. Patients were pseudo-ran- domly chosen to undergo such treatment. Vitamin A (Vi- tadralÒ, Aristo Pharma GmbH, Berlin, Germany) was administered intranasally at a dose of 10,000 IU once daily, for 8 weeks	Instill the vitamin A drops using a lying position with the head tilted back, which has been suggested to improve access to the upper nasal cavity	Treatment groups were then compared using a student's t test. In this way, any differences in pre-treatment olfactory scores were controlled for. For all patients, the change in odor discrimination score was significantly greater in the training vitamin A group compared with the training along group (1.4 points, p = 0.008)

(*Continued*)

Table 1. (Continued).

PMID	Title of work	Author Name	Year of publication	Type of study	Sample size	Drug used	Dosage	Administration method	Results
29,901,865	Budesonide irrigation with olfactory training improves outcomes compared with olfactory training alone in patients with olfactory loss	Nguyen TP, Patel ZM.	2018	Randomized, controlled trial	133	OT (olfactory training) with saline irrigations (67 paz) OT (olfactory training) with budesonide irrigations (66 Paz)	Olfactory training was carried out in a twice-daily fashion over a 6-month time period, with 4 specific patient-purchased essential oilsA NeilMedTM (NeilMed, Santa Rosa, CA) squeeze bottle and salt packets, along with distilled or filtered water, was used to deliver saline irrigations twice a day for 6 months. Budesonide respules in a 0.5-mg/2-mL dose were added to the irrigation bottles of those patients randomized to that arm	Nasal irrigation	Forty-seven patients (35.3%) had a clinically significant improvement in olfaction. Nearly double the patients in the budesonide irrigation group (43.9%) improved compared with the control group (26.9%) ($p = 0.039$).
33,423,106	Efficacy and safety of oral corticosteroids and olfactory training in the management of COVID-19-related loss of smell	Le Bon SD, Konopnicki D, Pisarski N, Prunier L, Lechien JR, Horoi M.	2021	Prospective study	27	Methylprednisolone (18 patients) methylprednisolone + olfactory training (OT) (9 patients)	10-day of 32 mg of methylprednisolone once daily combined with OT (9 pz) OT alone (18 pz)	Oral tablet	After 10 weeks, patients in the OCS + OT group had significantly improved their olfactory score by 7.7 points on average ($p = 0.007$), compared with a 2.1-point increase in the OT group ($p = 0.126$) (Figure 1). Additionally, a Mann–Whitney U Test confirmed the significant difference in ΔTDI scores between the OCS + OT group and the OT group ($p = 0.046$).

(*Continued*)

Table 1. (Continued).

PMID	Title of work	Author Name	Year of publication	Type of study	Sample size	Drug used	Dosage	Administration method	Results
33,471,169	Intranasal sodium citrate in quantitative and qualitative olfactory dysfunction: results from a prospective, controlled trial of prolonged use in 60 patients	Whitcroft KL, Gunder N, Cuevas M, Andrews P, Menzel S, Haehner A, Hummel T.	2021	Prospective, controlled study	60	Sodium citrate to the right nasal cavity (1 ml, 3.5 g/140 ml, pH 7.4, 298 mOsmol/L).	Two times per day for a period of 2 weeks	The application was with a glass pipette ('dropper'). Patients were instructed to apply the medication whilst lying in the 'Kaiteki' position, lying on the right side with neck turned laterally away from the bed by 20–30° and neck extended 20–40°. Following appli-cation, they were instructed to maintain this position for 1–2 min.	Significant improvement in TDI score after treatment (comparing best pre- with best post-treatment TDI of right and left monorhinal scores; improvement of 2.08 ± 3.82 points, $p < 0.0001$, see Figure 1). However, this improvement did not reach clinical significance (taken as ≥ 5.5 points).
34,156,697	Randomized clinical trial 'olfactory dysfunction after COVID-19: olfactory rehabilitation therapy vs. intervention treatment with Palmitoylethanolamide and Luteolin': preliminary results	D'Ascanio L, Vitelli F, Cingolani C, Maranzano M, Brenner MJ, Di Stadio A.	2021	Randomized-controlled clinical trial	12 patients (7 cases, 5 control)	Control group: olfactory rehab 30 daystreatment group: olfactory rehab + PEA and Luteolin	PEA 700 mg + Luteolin 70 mg	Oral tablet	Patients taking supplement had greater im- provement in Sniffin score than controls (mean change in Sniffin score = 2 for CG and 4 for TG; KW: $p = 0.01$)

(*Continued*)

Table 1. (Continued).

PMID	Title of work	Author Name	Year of publication	Type of study	Sample size	Drug used	Dosage	Administration method	Results
30,472,771	Therapeutic use of steroids in non-chronic rhinosinusitis olfactory dysfunction: a systematic evidence-based review with recommendations	Yan CH, Overdevest JB, Patel ZM.	2019	Systematic review	1394	Local and systemic steroids	Not applicable	Intranasal and oral steroids	Paucity of high-quality studies demonstrating efficacy of either topical or oral steroids for olfactory dysfunction unrelated to sinonasal disease. The only level 1 evidence suggests using steroid rinses to improve olfactory outcomes in select patients, with weaker evidence supporting use of oral steroids. Topical steroid sprays do not improve olfactory dysfunction in this patient population and are not recommended.

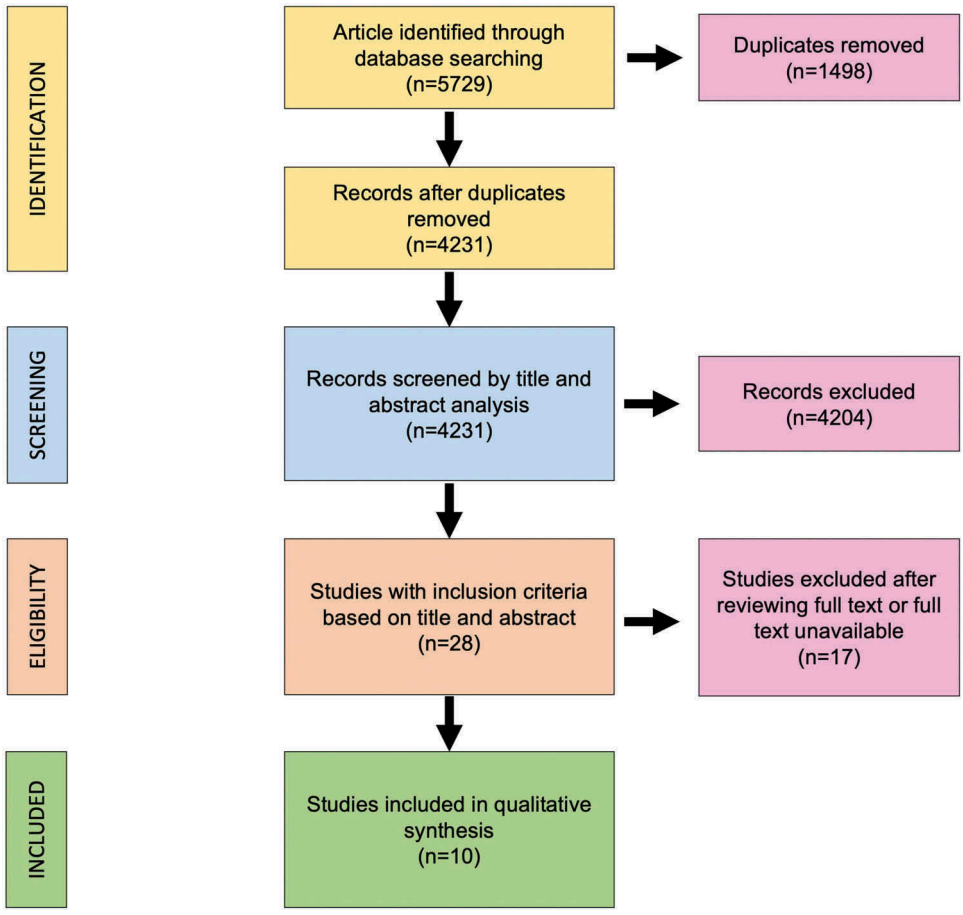

Figure 1. CONSORT Diagram.

cells and tufted relay neurons. The axons converge in the glomerulus to form the first cranial nerve (olfactory nerve). The glomerulus is connected by synapses to the mitral cells; the latter together with the tufted relay neurons forms the olfactory tract. This structure bifurcates in the medial and lateral olfactory stria (y inverted-shaped). The olfactory stimulus is conducted through these structures up to the piriform cortex, the periamygdaloid cortex, the olfactory tuberculosis and the anterior olfactory nucleus. The primary olfactory cortex is formed by the medial and lateral olfactory stria and the anterior perforated substance. The lateral olfactory stria is extended posteriorly giving origin to the entorhinal area which, together with the uncus, forms the secondary olfactory cortex, also known as the orbitofrontal cortex (Figure 2). This area is straightly related to memory. The primary cortex is responsible for the active perception of the sense of smell, while the secondary one is the portion where the smell perception is integrated with emotions and memory.

Aggressive viral infections inflame the neuroepithelium, and this inflammatory process can spread through the cells up to the olfactory bulb [6] due to its closeness (local spread of the inflammatory phenomenon) [19]; then, if the host immune system is not able to stop the inflammation and its diffusion in the surrounding tissue, this event can reach the primary cortex [20]. It has been speculated that some patients have a less effective ability to modulate the inflammation and neuroinflammation that makes them a very susceptible population; the researcher identified the downregulation of 2′-5′-Oligoadenylate Synthetase 1 (OAS1) as cause of this increased susceptibility [20]. Patients suffering from persistent anosmia following COVID-19 infection could be a valid human model for acquired central neuroinflammation, often characterized by memory impairment, as shown in several papers [5,20,21]. Although Sars-Cov2 does not directly spread from the neuroepithelium in the olfactory bulb [22], the virus is able to cause neuroinflammation [23], which, if it is not correctly managed [24], can affect other part of the brain [25], as showed in the patients who were suffering from COVID-19 [26].

The neuroinflammation refers to the activation of microglia and astrocytes, release of cytokines and chemokines, production of reactive oxygen species, and oftentimes the infiltration of peripheral leukocytes into the central nervous system (CNS) [26].

Because neuroinflammation, despite for different causes [27], seems to be relevant in COVID-19, and it is also responsible of the olfactory loss [19,27], we think that it is worth to discuss drugs able to modulate this phenomenon.

In a pilot study, Le Bon et al. [28] used a systemic cortisone treatment (32 mg of methylprednisolone once daily) in 9 patients suffering from persistent olfactory dysfunction COVID-19 related, as diagnosed by the Sniffin's stick test. The patients included in the study were affected by smell alteration for the previous 5 weeks at the time of enrollment.

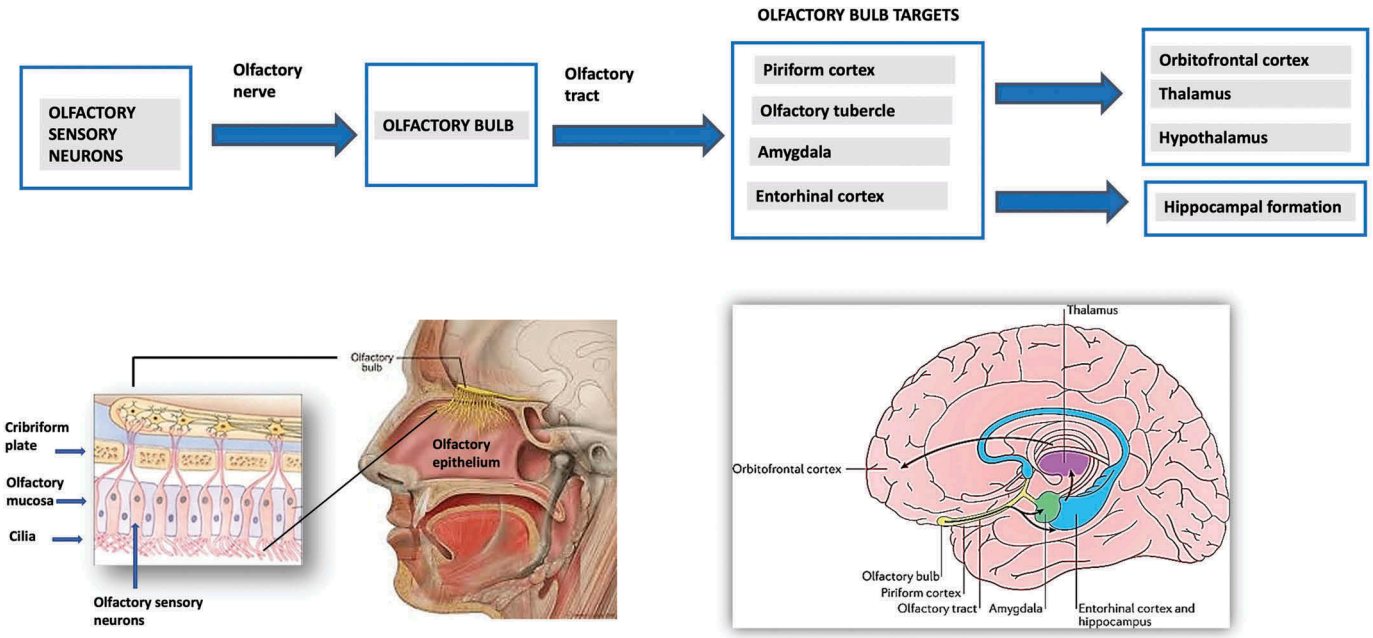

Figure 2. The image shows the olfactory pathways. In the nose the neuroepithelium. Then once the neurons go in the glomeruli the olfactory stimulus arrives up to the olfactory cortex.

Patients in the treatment group (9 subjects) who received combined treatment with cortisone and olfactory training were compared with a control group (18 patients), who underwent olfactory rehab only. The authors noted an improvement in olfactory functions after 10 weeks only in those patients treated with cortisone. The authors affirmed that the treatment was safe. Unfortunately, no information about the patient's age and comorbidities were available.

Cortisone is a potent anti-inflammatory drug and, when administered as systemic treatment, it can act peripherally on the neuroepithelium [29] and centrally on olfactory bulbs reducing the inflammation [30]. Systemic cortisone reduces the inflammation into the nose both reducing pro-inflammatory cytokines [31] and the recruitment of the inflammatory cells by an inhibited expression of adhesion molecules such as ICAM-1 and VCAM-1 [32]. Due to the local and systemic effect of this drug, it might be complex to fully understand on which portion of the olfactory pathways it is active. Probably, the efficacy observed by the researchers was combination of central and peripheral efficacy.

The beneficial effect of cortisone for treating the acute form of neuroinflammation in the brain is well known; in fact, high doses of cortisone are used in the treatment of relapses of Multiple Sclerosis (MS), when the definitive diagnosis is not yet clear [33]. Anyway, cortisone has several side effects and, although safe when used as a spray for prolonged treatment, can be dangerous when used by oral administration.

D'Ascanio, Di Stadio et al. presented the preliminary results of their national clinical trial with a design like the one of Le Bon [28]. They compared patients treated with ultra-micronized Palmitoylethanolamide (PEA) and Luteolin (Lut) (PEA-LUT) plus olfactory rehab to a control group (olfactory rehab alone). Patients included in the study suffered from the loss of smell for at least 5 months (average of affection 9.7 months) and considered long-COVID patients [34].

The authors found statistically significant improvement in the olfactory functions of the patients treated with ultra-micronized PEA-LUT(700 + 70 mg after one month of treatment compared to controls. The result showed that in case of non-spontaneous recovery-generally within 6 months after the onset of smell alteration, the use of PEA-LUT allowed to recover the olfactory capacities. In this study, the patients were quite equally distributed in the two groups, seven in the treatment group and five in the control group. To note, the authors found that patients affected by smell alteration for a longer period recovered better olfactory function than those with a shorter illness.

Recently, Di Stadio et al. [35] observing 185 patients confirmed the efficacy of PEA-LUT plus olfactory rehabilitation compared to olfactory rehab only as treatment for COVID-19 related olfactory. In total, 92% of patients improved their olfactory functions after treatment and 55% of them recovered normal olfactory functions. PEA-LUT in its ultra-micronized form was well tolerated by the patients and determined clinical improvement of the olfactory disorder. Moreover, thanks to its ability to mediate and modulate neuroinflammation, it improved the micro-environment facilitating the regenerative process in the olfactory pathways, as clinically evidenced by the recovery of the sense of smell [5]. The effects of this association are due to the properties of ultra-micronized PEA of i) downregulating the mast cells activation and ii) attenuating the activation of M1 microglia in the brain increasing the triggering of the M2 phenotype [5] and of Lut to inhibiting the activation of the Toll-like receptor 4 (TLR4)/TNF receptor-associated factor 6 (TRAF6)/nuclear transcription factor-κB (NF-κB) signaling pathway, thereby reducing inflammation [5]. Because PEA-LUT down-regulates

the activation of mast cells, and these cell proliferates during induces nasal inflammation [36], their down-regulation might reduce local inflammation [37] and supports the recovery of the sense working at peripheral level also.

Despite only speculative, PEA-LUT, as well as systemic cortisone, could act both in the central and peripheral olfactory pathways allowing the recovery of the smell functions.

4. Expert opinion based on the systematic review evidence

The identification of the origin of the olfactory dysfunction is extremely important to decide the best treatment for the smell loss. In cases of peripheral damage, local medications are useful and beneficial, especially in the early stages of the disease because can limit the inflammation and its spread in the surrounding (neuroepithelium) tissues. However, the age and the cause (viral, trauma, exposure to toxic agents) responsible for peripheral neuroinflammation are two aspects that may negatively affect the success of treatment. Generally, peripheral olfactory dysfunctions have a viral origin and commonly occur in the elderly. Despite for different reason both aging and virus cause the death of the olfactory cells. In these cases, a nasal spray containing vitamins, hyaluronic acid, and/or substances to improve nasal clearance and local immune response could be beneficial. Treatment should be considered in the early phase (viral infection) or as a preventive measure (in the elderly).

In the case of a central cause, the discussion about choosing the right treatment becomes more complex. If we exclude the acute causes of olfactory dysfunction, such as COVID-19 infection, head trauma and stroke, loss of the sense of smell reflecting central neuroinflammation is generally caused by a chronic neurodegenerative event.

Loss of smell is associated with age, male gender, and non-Hispanic black ethnicity [38]. On the other hand, women are more likely affected by microvascular brain disease and Alzheimer's disease (AD) than men [15] and both conditions, which cause chronic neuro-inflammation, might negatively impact on women' olfactory capacities. The olfactory deficits have been identified as an early sign of other pathologies characterized by neuroinflammation, such as Parkinson's disease (PD) and, in some cases, MS [9]. The neuro-inflammation is common denominator of all these diseases [39–41]; the phenomenon is chronic in neurodegenerative disorders [39,40] and acute (relapsing) in MS [41].

Recently, due to COVID-19 pandemic, we identified Sars-CoV2 infection as clear cause of acute neuro-inflammation [26]; the researchers have hypothesized that this acute neuro-inflammation might increase the long-term risk of presenting neurodegenerative diseases [19].

Although treatment with PEA-LUT was studied in COVID-19 patients, the subjects included in the study suffered from a 'persistent' loss of smell over a 11-month period, which could be considered as onset of chronic inflammation. This molecule, unlike systemic cortisone, has no adverse effects and can be used over a long period of time without causing discomfort to patients.

Based on current evidences, we do not know whether the treatment could also be beneficial for olfactory dysfunctions caused by chronic neuroinflammation, but it could be useful in the early phase of neurodegenerative disorders to prevent the worsening of the process. Treating chronic neuroinflammation is a challenge because it has a 'no-return point' from which it is not possible coming back.

Because today it is still not possible to correctly identify the real causes of the olfactory loss, especially in case of manifest nasal diseases, our opinion is that in the absence of a well-identified origin, the combination of topical nasal cortisone and anti-neuroinflammatory molecules as PEA-LUt could be helpful to early stop the olfactory damage, both in case of peripheral or central origin.

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