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Background:

Olfactory dysfunction affects a significant proportion of the population but appears to be more common in the elderly population (>20% of adults over 60 years old). Unfortunately, many sufferers face an apparent lack of therapeutic options when consulting with medical professionals.

Method:

We searched various electronic medical databases for the treatment of non-conductive olfactory dysfunction. After careful review of the abstracts and the full articles, we included publications that fulfilled our inclusion criteria and analysed the results.

Results:

A total of 38 publications were included in our review including 6 randomised control trials, 14 cohort studies and 18 observational studies.

Conclusion:

Olfactory training appears to improve non-conductive olfactory dysfunction irrespective of the aetiology. Steroids appear to have some benefit, but this may be aetiology dependent and vitamin A and sodium citrate have shown some promise. Various other therapies have been investigated but high quality randomised control trials are still required to determine their place in managing this patient population.

Olfactory disorders present a common problem in the population with estimates of a prevalence of 1-5% and over 20% in the over 60's [1-5]. Although they have not typically been associated with any morbidity, recent studies have shown a clear association with dementia [6] and have now also shown anosmia to be an independent risk factor of early mortality [7] even when cognitive impairment is controlled for. It is certainly clear that these patients face a poorer quality of life [8] and that their plight has traditionally been neglected by the medical fraternity [9], however specialist smell and taste clinics are now emerging to help to address the unmet need [10]. Those patients with a conductive disorder such as chronic rhinosinusitis have a more established treatment pathway [11], albeit that there is certainly a need for more randomised controlled trials in terms of both the medical and surgical management of the latter [12-18]. Conversely the management of non-conductive olfactory disorders has remained a more controversial area with many patients left untreated due to a perceived lack of therapeutic options. Very recently, the management of olfactory disorders has been brought into focus through the publication of international guidelines, which finally gives clinicians a framework for diagnostic work up and treatment [19].

The anatomical classification of the aetiology of olfactory dysfunction provides an opportunity for patients to be risk stratified for appropriate management. Conductive olfactory dysfunction results from distortion to nasal anatomy which leads to mechanical obstruction of the olfactory cleft and prevents the odorant from reaching the olfactory cleft [20]. Non-conductive dysfunction is usually due to damage to olfactory neuroepithelium, olfactory nerve or a central dysfunction due to damage to the olfactory processing pathway of the central nervous system [21]. In practice, it is often more complex as in some cases conductive and non-conductive dysfunction can co-exist, for example in chronic rhinosinusitis. For the purposes of this review, we have focused only on treatment options for patients with non-conductive dysfunction. Although non-conductive olfactory dysfunction is a good anatomical classification, it may be more useful to consider the therapeutic options by aetiology [22]. The most common aetiologies for non-conductive olfactory loss are further discussed below.

Post-viral olfactory loss (PVOL) is the most common cause of olfactory dysfunction and usually follows an episode of upper respiratory tract infection. Viral pathogens such as rhinovirus, coronavirus and parainfluenza, have been detected in patients with PVOL [23]. Loss of cilia on receptor cells as well as remodelling and replacement of olfactory neuroepithelium with respiratory epithelium may be responsible for the reduced olfactory bulb volume and patchy distribution of neuroepithelia that has been demonstrated in PVOL patients [24,25].

olfactory loss [28]. PTOL occurs either immediately post injury or may be delayed reflecting an insidious pathology, possibly due to subsequent oedema [29]; in practice, patients with moderate to severe head injury often have delayed diagnosis of their olfactory sensory deficit as other life-threatening injuries take precedence. A third of patients with post-traumatic anosmia will spontaneously improve, perhaps due to secondary resorption of any haematoma [30]. Where symptoms persist for more than twelve months, treatment is often difficult and more likely to be unsuccessful [27].

Olfactory loss is well recognised in neurodegenerative conditions such as epilepsy, myasthenia gravis, Parkinson's disease (PD) and Alzheimer's disease [31,32]. The aetiology of olfactory dysfunction in these conditions remain unclear [33] and many of the treatments for these disorders are ineffective in improving olfactory function [34]. It has been reported that the olfactory loss in patients with PD occur more frequently than resting tremor and functional imaging has shown reduced activity in the hippocampus and amygdala of PD patients during odorous stimuli [35,36]. Histological studies have also shown pathological predisposition for central olfactory systems in patients with PD [37].

Congenital anosmia is a relatively rare condition characterised by a complete lack of olfactory perception with aplasia or hypoplasia of the olfactory bulb. Two main classifications have been described; type I which is associated with somatic, gonadal, and developmental abnormalities (e.g., Kallman syndrome) and tends to be familial and type II which presents as isolated olfactory dysfunction in a phenotypically normal patient [38,39]. Where olfactory bulb aplasia exists, treatment will not be relevant, although attempts at grafting olfactory bulbs in rats have proven successful and perhaps may provide an option in the future [40].

This systematic review aims to establish the rationale for medical and non-medical treatments for this group of patients and explores the evidence behind current treatment options for non-conductive olfactory dysfunction.

Methods

Based on the updated guidelines for systematic reviews of the Cochrane Collaboration Review Group, we performed a comprehensive electronic database search on medical and scientific databases (Pubmed, Google scholar, Cochrane database and Medline) using a specific search strategy. The Cochrane methodological filter for randomised control trials (RCTs) was utilised in addition to combing MeSH keywords and other relevant terms including, anosmia, hyposmia, pharmacotherapy,

publication and by following the modified GRADE quality assessment; the quality of evidence for the treatment option was graded

Inclusion Criteria

All published studies on treatment of non-conductive olfactory loss including:

- Randomised Control Trials
- Cohort studies
- Preliminary results on ongoing research

Exclusion Criteria

- Case reports
- Non-English publications

Results

The search resulted in 240 citations from which the relevant studies were selected for review and potential relevance. From this, 172 articles were excluded using the inclusion and exclusion criteria stated below, 68 abstracts were reviewed and the full articles of 38 citations fulfilled the criteria of inclusion. These articles were human studies primarily related to outcomes of management in patients with non-conductive olfactory dysfunction; 6 randomised controlled trials and 32 other outcome studies were included (Tables 1-5).

Table 1: Post Viral Olfactory Loss

Olfactory Training							
Study	**Study Design**	**Patients /Aetiology**	**Olfactory function Test**	**Intervention**	**Follow up (weeks)**	**Results**	**Level of evidence**
Polleti et al 2017 [41]	Prospective single blinded	PVOL, n=70 PTOL, n = 26	Sniffin sticks	Olfactory training with heavy molecular weight (HMW) odorant (>150g/mol, n=48) versus low molecular weight(LMW) odorant (<150g/mol, n=48) for 5months	20	Overall significant improvement in olfaction (PVOL>PTOL) No difference between HMW and LMW	2B
Sorokowska et al 2017 [42]	Meta-analysis	Mixed aetiology, 13 articles	variour	Olfactory training in a olfactory loss of different aetiologies		Significantly positive response to training	1
Konstantinidis et al 2016[43]	Prospective controlled	PVOL n=111,	Sniffin Sticks	Olfactory training (12 week training Vs 56 week training Vs Control)	56	Long term training yields better function	2B
Altundag et al, 2015 [44]	Prospective, controlled	PVOL, n=85	Sniffin Sticks	Olfactory training	36	Longer Olfactory training with change of odour was effective in terms of odour discrimination and identification	2B
Damm *et al,* 2014 [45]	prospective randomised single blinded controlled	PVOL, n=144	Sniffin' Sticks	High concentrations of 4 odours Vs Low concentrations	38	Olfactory training was significantly more effective with high concentration of odours and dysfunction <12 months	2B
Geißler *et al,* 2014[46]	Prospective study	PVOL, n=39	Sniffin' Sticks	suprathreshold concentations of 4 odours	32	Longer duration of training (≥32 weeks) increased effectiveness of training	2C

Medical Management							
Study	**Study Design**	**Patients /Aetiology**	**Olfactory function Test**	**Intervention**	**Follow up (weeks)**	**Results**	**Level of evidence**
Philpott et al 2017 [47]	Randomised control trial	Non-conductive olfactory loss (n=55)	Phenyl ethyl Alcohol (PEA)	0.5ml of 9 % sodium citrate versus placebo (sterile water)	120 minutes	32% improved odour sensitivity in treated arm	1B
Whitcroft et al 2017[48]	Randomised control trial	PVOL, n=49	Sniffin' Sticks	1 mL sodium citrate solution versus placebo (1 mL physiological sodium chloride solution)	30 minutes	statistically significant (but not clinically significant improvement in composite threshold + identification scores following treatment with sodium citrate,	1B

						compared with placebo.	
Hummel et al 2017 [48]	Retrospective cohort study	PVOL & PTOL (n=170)	Sniffin Sticks	Topical Vitamin A 10,000 IU/day for 8 weeks + olfactory training for versus olfactory training for 12 weeks	45	Significant improvement in Vitamin A group (37%)	2B
Henkin et al 2017 [49]	Prospective controlled	Multiple aetiologies PVOL= 11 Congenital =9	Olfactometry (odour detection and recognition for four odours)	Theophylline 200-800mg once a day for 2 to 10 months	40	Increased nasal mucus sonic hedgehog levels associated with improved detection and perception of smell	2B
Whitcroft et al, 2016 [50]	Prospective Randomised cohort Study	Hyposmia (n=57, 7 PVOL)	Sniffin Sticks	Topical sodium citrate versus placebo (sodium chloride)	30 minutes	Statistically significant improvement in PVOD	2B
Dai et al, 2016 [51]	Prospective cohort study	PVOL (n=50- Failed steroid and Vitamin B treatment)	University of Pennsylvania smell identification test	Traditional Chinese acupuncture with acupoints at the nasolabial grove and middle turbinates	12	Improved UPSIT score in TCA group from 18.24 to 22.08 compared to the observation group (17.36 to 18.64)	2B- High risk of bias
Kim et al, 2016 [30]	Retrospective study	Olfactory dysfunction (n=491, 178 PVOL)	Connecticut Chemosensory Clinical Research Center test (threshold test) and Cross-cultural Smell Identification Test	oral prednisolone 40mg reducing in third week by 5mg/day Vs mometasone furoate topical 2sprays Vs combination of oral and topical steroid	4	59.6% recovery in all group. Combination and single oral steroid statistically better than topical steroid alone	4
Blomqvist et al, 2013 [52]	Randomised Control Trial (RCT)	PVOL (n=40)	Butanol threshold test<8	40mg of prednisolone -reducing dose then topical fluticasone propionate for all patients, then randomised to placebo, control and continuation of flixonse	24	Initia40mg of prednisolone l improvement	2B
Henkin et al 2012 [53]	Open labelled prospective study	Multiple aetiologies n=10	Olfactometry (odour detection and recognition for four odours)	Patients who had sub-optimal response to oral theophylline (200-800mg) where treated with intranasal theophylline 20ug/day/nostril	4	Statistically significant improvement in olfactory function in this subgroup	2C
Reden et al, 2012 [54]	RCT	PVOL & PTOL (n=54)	Sniffin Sticks	Vitamin A (10,000iu capsule, once a day for 3 months Vs placebo)	20	No statistical significance in either PVOD or PTOL groups	1B
Schriever et al 2012 [55]	Retrospective cohort study	All aetiologies (n=425, 27 PVOL)	Sniffin Sticks	oral methylprednisolone 40mg reducing dose for 2weeks	2	Statistically significant improvement in sniffing sticks score by 6 points or more	2C

Reden et al, 2011[56]	RCT	PVOL, n=55	Sniffin Sticks	100mg BD monocycline Vs placebo	28	No statistical difference although 15% improved in treated group against 20% spontaneously improved	1B
Vent et al, 2010 [57]	Prospective study	PVOL, n=30	Sniffin Sticks	TCA (The following injection points were chosen: DuMai 16 and 20, Di20, Lu 7 and 9, Ma 36, and Ni3) repeated weekly for 10 weeks Vs Oral vitamin B complex for 12 weeks	12	Statistical improvement in TCA group (8/15) compared to Vitamin B group (2/15)	2C
Seo et al, 2009 [58]	RCT	PVOL, n=71	Butanol threshold test.(anosmia score between 0-3), cross culture smell identification test (CCSIT)	monotherapy(prednisolone-30 mg/d for the first 3 days, 20 mg/d for 4 days and 10mg/d for 7 days) combination (prednisolone/ginkgo biloba-80mg tds for 4 weeks) +All given mometasone furoate for 4/weeks	4	Statistically significant improvement BTT (4.8-6.9) and CCSIT	1B- No control group
Gudziol et al 2009 [59]	Prospective longitudinal pilot study	n=19, 4 functional hyposmia	Sniffin sticks	200mg IV or oral pentoxifylline	2days	Increased olfactory sensitivity in younger pateints	2C
Fukazawa et al, 2005 [60]	Prospective study	PVOL, n=133	T&T olfactometer and VAS	5mg intranasal injection of dexametasone or betametasone every 2 wks for 8wks	12	49.6% improvement using T&T olfactometer & visual analogue scales	2C
Heilmann et al, 2004 [61]	Prospective study	PVOL, Idiopathic, sinonasal disease, n=92	Sniffin Sticks	40mg oral prednisolone reducing dose for 3 wks Vs topical Mometasone Propionate for 3 months	12	oral steroids improved sig no sig in top	2C
Quint et al, 2002 [62]	RCT	non-conductive, n=77	Sniffin Sticks and BTT	120mg/day for 4 weeks caroverine vs zinc sulphate (control)	4	Anosmic patients improved but significant improvement in hyposmic patient	1B- No control group
Hummel et al. 2002 [63]	Prospective clinical trial	PVOL, n=23	Sniffin Sticks	alpha lipoic acid 600mg/day for 3 to 11 months	16	Statistically significant improvement in olfactory function especially younger patients	2B
Aiba et al, 1998 [64]	Retrospective cohort study	non-conductive , n=426 & PVOL, n=48	Visual Analogue Scale	300mg zinc sulphate/day for 1 month VS zinc + steroid (topical) + vitamin b Vs top steroid +Vitamin B	2	No sig4nificant improvement in PVOD group	2C

Table 2: Post traumatic Olfactory Loss

Study	Study Design	Patients /Aetiology	Olfactory function Test	Intervention	Follow up	Results	Level of evidence
Konstantinidis, et al, 2013	Prospective study	119, PTOL and PVOL	sniffin sticks	olfactory training group Vs control	16	significant improvement training groups	2C
Kim et al, 2016 [30]	Observational study	491 olfactory dysfunction, 96 PTOL	Connecticut Chemosensory Clinical Research Center test (threshold test) and Cross-cultural Smell Identification Test	oral prednisolone 40mg reducing in third week by 5mg/day Vs mometasone furoate topical 2sprays Vs combination of oral and topical steroid	4	12.5 % improvement mainly in those treated early	4
Jiang et al, 2015	Prospective randomised control study	145 PTOL	Odour discrimination test with phenyl ethyl alcohol	Group 1 = 39 (steroid-1mg/kg/day) -2 weeks tapering and zinc- 10mg TDS PO- 1 month, group 2=35 zinc , group 3 = 34 steroid, group 4 = 37 – no treatment	36	The recovery of olfactory function was observed in 11 patients (28.2%) in group 1, in 9 (25.7%) in group 2, in 4 (11.8%) in group 3, and in 1 (2.7%) in group 4. The recovery rates of olfactory function of groups 1 and 2 were significantly higher than the recovery rate of group 4	1B
Fujii et al, 2001	Prospective study	18 PTOL	T&T olfactometer(OT & IT) and Intravenous Alinamin	injection of dexamethasone (4mg/ 0.5mls) & Oral Vitamin B12 and Adenosine triphosphate	5 months	35% improvement in olfactory function	2C
Aiba et al, 1998 [64]	Retrospective cohort study	426 patient,95 PTOL	VAS	300mg zinc sulphate/day for 1 month VS zinc + steroid(topical) +vit b Vs top steroid +Vit B	2 weeks	significant improvement in PTOL group	2C

Ikeda et al, 1995 [65]	Observational study	17 PTOL	T&T olfactometer(OT & IT) and Intravenous 10mg thiamine propyl disulphide	12 intranasal betametasone/ 5 oral prednisolone 30-60mg OD 10-14 days	6-12 months	3 of 5 improved and 1 out of 12	4

Table 3: Olfactory loss in patients with Neurodegenerative conditions

Study	Study Design	Patients /Aetiology	Olfactory function Test	Intervention	Follow up	Results	Level of evidence
Haehner et al, 2013 [66]	Prospective study	70 Parkinson's Disease	sniffin sticks	olfactory training	12 weeks	significant improvement in those who had olfactory training	2C
Hummel et al 2005 [67]	Prospective study	11 Parkinson's patients	sniffin sticks	Deep brain stimulation	Not stated	Odour identification significantly increase with stimulation	4

Table 4: Idiopathic Olfactory Loss

Study	Study Design	Patients /Aetiology	Olfactory function Test	Intervention	Follow up	Results	Level of evidence
Mavrogeni et al, 2016 [68]	Observational study	5, non-conductive loss- idiopathic	Subjective	Monthly 1ml of platelet rich plasma via 30G needle, 1 cm from olfactory area over 3 months	Not stated	4 complete return of olfactory function. **THIS WAS A CASE SERIES WITH NO OBJECTIVE MEASURE OF OLFACTORY FUNCTION**	4
Duncan et al, 1962 [69]	Prospective non-randomised	56 patients with multiple aetiologies (21-PVOL, 17 idiopathic)	odour threshold	Vitamin A, subcutaneous injection (52) or oral tabs(3) or emulsion(1)	2years	Marked or perceptible improvement in 46 (injection) not randomised. Oral tablet group where given injection when it was felt that their treatment was failing	2C
Kim et al, 2016[30]	Observational study	491 olfactory dysfunction, 89 idiopathic	Connecticut Chemosensory Clinical Research Center test (threshold test) and Cross-cultural Smell Identification Test	oral prednisolone 40mg reducing in third week by 5mg/day Vs mometasone furoate topical 2sprays Vs combination of oral and topical steroid	4 weeks	No statistically significant improvement	4
Heilmann et al 2004 [61]	Prospective study	Differing aetiologies n = 192, (Idiopathic= 85, PVOL=72)	sniffin sticks	Oral prednisolone Vs local corticosteroids Vs Systemic Vitamin B	6months	Improvement following systemic and local corticosteroids; also improvement with systemic Vitamin B after 6 months	2C

Table 5: Congenital Olfactory loss

Study	Study Design	Patients /Aetiology	Olfactory function Test	Intervention	Follow up	Results	Level of evidence
Henkin et, 2016 [70]	Observational study	19 congenital hyposmia- non genetic	Detection thresholds (DT), recognition thresholds (RT), magnitude estimation (ME) and hedonics (H) for four odours [pyridine (pungent), nitrobenzene (bitter almond), thiophene (petroleum) and amyl acetate (banana)] using a standard three stimuli, forced choice staircase technique	theophylline, 200–800 mg daily for 2–36 months	36 months	63% significant initiation of smell function	2C

Table 6: Treatment options based on aetiology

a) Post viral olfactory loss

Intervention	Grade of Recommendation	Effect
Olfactory training	B	Positive
Steroid	B	Positive
Theophylline	B (Not specific to PVOL patients)	Positive
Sodium Citrate	B	Positive
N-methyl D-aspartate antagonist (caroverine)	C (hyposmic patients improved)	Positive
Traditional Chinese Acupuncture	C	Positive
Alpha lipoic acid	C	Positive
Vitamin A/B	C	Mixed
Monocycline	C	No effect
Zinc sulphate	C	No effect

b) Post traumatic olfactory loss

Intervention	Grade of Recommendation	Effect
Olfactory training	B	Positive
Steroid	B	Positive
Steroid + Zinc sulphate	C	Positive

c) Congenital olfactory loss

Intervention	Grade of Recommendation	Effect
Theophylline	D	Positive

d) Neurodegenerative olfactory loss

Intervention	Grade of Recommendation	Effect
Olfactory training	C	Positive
Deep brain stimulation	D	Positive

Table 7: Overall recommendation for various treatment options

Intervention	Number of publications	Double blinded	Summary of results	Expected therapy effect
Olfactory training	6	No	good effect	(+)
Steroid	12	yes	good effect	(+)
Theophylline	3	No	Good effect	(+)
Sodium Citrate	4	yes	anecdotal	(+)
Caroverine	1	No	anecdotal	(+)
Antibiotics (minocycline)	1	yes	No effect	nil
Vitamin A	3	No	inconsistent	(+)
Vitamin B	4	No	No effect	?
Vitamin C	0	/	?	
Vitamin E	0	/	?	
Strychnine	1	No	anecdotal	?
Traditional Acupuncture	2	yes	anecdotal	(+)
Alpha lipoic acid	1	No	anecdotal	?
Zinc sulphate	3	no	No effect	nil
Surgery	1	no	Good effect in patients with phantosmia	(+)

Discussion

Post-Viral (Infectious) Olfactory loss/dysfunction (PVOL)

Conservative management

Reden *et al,* 2006 studied 262 patients with PVOL and showed a 32% recovery rate without any treatment after 14 months of follow up; 6% of the patients in this cohort had worsening olfactory function [27]. In a study of 542 patients using the University of Pennsylvania smell identification test (UPSIT), London *et al* 2007 demonstrated that over one third of patients had spontaneous improvement of olfaction. Prognosis was found to be unrelated to aetiology and the rate of recovery was dependent on the degree of initial loss, age and the duration of olfactory loss [71]. Therefore, with all patients, a discussion about the prognosis and likelihood of spontaneous recovery should be undertaken as well as the possibility that in some individual circumstances, a conservative approach may avoid problems posed with medical options where contraindications or interactions exist due to their medical and drug history.

Olfactory Training

There is good evidence to suggest that olfactory training improves olfactory function in patients with PVOL. There is a single meta-analysis and several prospective controlled studies that have shown improved olfactory function in patients in whom long term (>32 weeks) and high concentrations of odorants have been used for olfactory training [41-46]. The classic olfactory training involves a five-minute exposure to four different odorants twice a day [43]. These four odorants (phenyl ethyl alcohol, eucalyptol, citronellal and eugenol) are said to define the six most significant odour qualities of the olfactory realm and have been shown to improve olfactory loss after training for 12 weeks or more. The modified olfactory training was first introduced by Altundag *et al* 2015. The four-odorant used in the classic odorant training was initially used for 12 weeks, followed by menthol, thyme, tangerine and jasmine for another 12 weeks and lastly green tea, bergamot, rosemary, and gardenia were used. This study was able to show better odour discrimination and identification in patients treated with the modified technique [44].

As olfactory training is a non-invasive low risk treatment strategy that can be self-directed, the vast majority of affected individuals can be advised to pursue this, however they will need encouragement in undertaking the full course of training as the results may not always be instantaneous. Patient forums such as those provided through the charity Fifth Sense [72] are useful ways for patients to engage with fellow sufferers who have adopted the same strategies.

Oral and Intranasal Corticosteroids

Studies exploring the use of various formulations, routes and doses of steroid in the treatment of PVOL patients have shown favourable outcomes [30,52,55,58]. There are however no large randomised control trials focused on this subset of patients. Various comparative studies have shown improvement in olfactory function in 25-55% of patients following treatment with steroids. In a randomised control trial by Seo *et al* 2016, 40mg oral prednisolone as monotherapy or combination with 80mg of ginkgo biloba for 4 weeks was shown to have significant improvement in olfactory function. This study did not include a control placebo group to ascertain if the improvement was statistically significant in comparison to an untreated group [58]. The question of oral versus topical steroids was exploited by Kim *et al* 2016, in a retrospective study and showed that combination of oral and topical steroids or oral steroid as monotherapy significantly improves olfactory function compared to montherapy with topical steroids [30]. Heilman *et al,* 2004 showed significant improvement in PVOL patients treated with oral prednisolone whilst adding topical mometasone propionate conferred no significant improvement in this group of patients. It has however been suggested that the technique of delivery of topical steroids may be the reason for the poor response to topical steroids; the Kaiteki position (patients lie on the side with their head tilted and chin turned upward) allows nasal drops to reach the olfactory cleft in 96% of decongested noses and 75% in the non-decongested nose [73]. Intranasal injection of steroid has also been shown to improve significantly the olfactory function in this group of patients [60].

Non-Steroid medical management

Theophylline: The mechanism of action of theophylline on olfactory neuroepithelium is not fully understood. Theophylline is postulated to inhibit phosphodiesterase and increase growth factors such as cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) therefore aiding olfactory neuroepithelium regeneration [74]. There are no specific studies on theophyllline in patients with PVOL. Henkin *et al,* 2009 evaluated 312 patients with hyposmia of multiple aetiologies treated with 200mg-800mg of theophylline and was able to show 50.3% of patients have statistically significant improvement in olfactory function. These patients were followed up between 6-72 months [49]. Henkin *et al* 2012 was also able to show improvement in olfactory function after treatment with intranasal theophylline in a pilot study [53]. Interpretation of these results should be viewed with caution as they have only been performed in one centre using non-standardised olfactory tests.

Sodium Citrate: Intranasal sodium citrate by its ability to buffer calcium ions has been shown to reduce mucosal calcium ions with subsequent reduction in negative feedback and increasing sensitivity to odorants. Whitcroft *et al* 2016 performed a prospective placebo controlled trial of monorhinal treatment of sodium citrate versus sodium chloride for patients with olfactory loss

(multiple aetiologies, n=57) and showed improved olfactory threshold and identification only in the PVOL cohort (n=7) [50] . Philpott *et al,* 2017 compared a single application of 0.5ml of 9% sodium citrate per nostril versus sterile water (n=55) in a randomised controlled trial and showed statistically significant improvement in olfactory function using olfactory thresholds for phenyl ethyl alcohol (PEA), 1-butanol and eucalyptol with thresholds measured up to 2 hours after intervention showing an effect lasting between 30 and 120 minutes after application [47]. In the latter study, the response rate was 1 in 3 of the treatment group as compared to none in the control group. Most recently the Dresden group performed a follow on study where they found some improvement in the treatment arm, but this did not reach clinical significance[48].

N-Methyl D-Aspartate (NMDA) antagonist: The mechanism of the NMDA antagonist, Caroverine on the olfactory neuroepithelium, is not entirely clear. Its mode of action is probably through its inhibition of the olfactory bulb feedback mechanism. Quinn *et al,* 2002 conducted a randomised control trial on 71 patients with non-conductive loss. The treatment group (n =51), had 120mg/day of caroverine and the control group (n=26), had 140mg/ day of zinc sulphate). Both groups were treated for 4 weeks and the treatment group had statistically significant improvement in olfactory function in both hyposmic and anosmic patients.

Alpha lipoic acid (ALA): Is a fatty acid mainly used in the treatment of diabetic neuropathy, it stimulates the expression of nerve growth factors; substance P and neuropeptide Y, and has anti-oxidative and neuroprotective capabilities. Uncontrolled prospective study of 23 patients with PVOL treated with 600mg/day of ALA for an average of 4.5 months by Hummel *et al* 2002 showed at least moderate improvement in olfaction in 61% of the participants.

Vitamin A: Vitamin A is known for its regenerative ability and it has been suggested that it improves olfaction by aiding regeneration of olfactory neuroepithelium. Duncan and Briggs in 1962, reported improvement in olfactory function in 50 of 56 patients following treatment with vitamin A. Reden *et al* in 2012 however, found no improvement in olfactory function in PVOL and PTOL patients following oral administration of 10000IU/day of vitamin A for 3 months in a double blinded, placebo-controlled trial using Sniffin' Sticks olfactory test [54]. More recently Hummel et al 2017, reported statistically improved olfaction in PVOL and PTOL patients in a retrospective cohort study (treatment group n=124, olfactory training with 10000 IU of intranasal Vitamin A and control group, n=46 had olfactory training) using sniffin sticks test assessment [48]. This study however has inherent problem of any retrospective study in that, the inability to control the differences between the groups may have confounded the results.

Minocycline and **Zinc sulphate:** Minocycline has been shown to act as an anti-apoptotic agent which may improve olfactory function. Randomised prospective placebo-control double blinded study by

Reden et al, 2011 using oral 50mg/bd of minocycline versus placebo for 3 weeks and found no statistical difference between the two groups [56].

Most of the studies using Zinc Sulphate have reported no statistically significant improvement in olfactory function post treatment especially in the PVOL group. Various doses have been used, ranging from 120mg daily to 300mg daily doses. Aiba et al, 1998 performed a randomised control trial with three groups (group A= treated with 300mg of oral zinc sulphate only, group B= Zinc sulphate 300mg + topical mometasone prioponate and group C= topical mometasone propionate + Vitamin B) and reported no improvement in PVOL group although the PTOL group statistically improved with zinc sulphate.

Non-Medical Management

Traditional Chinese Acupuncture: A non-randomised prospective study by Vent *et al*, 2010 was able to show significant improvement in PVOL patients with traditional Chinese acupuncture (n=15) compared with those treated with vitamin B [38]. This paper however had significant selection bias which may have affected the results. Dai et al, 2016 showed statistically significant improvement in olfactory function in PVOL patient who had failed to improve on steroid and vitamin B treatments following treatment with traditional Chinese acupuncture with acupoints along the nasolabial grove and the middle turbinate [39].

Post Traumatic Olfactory loss

Conservative Management

Spontaneous recovery of olfactory function is said to occur in a third of patients with post-traumatic olfactory loss (PTOL). The recovery may be due to secondary resorption of haematoma or resolution of initial nerve oedema [40]. Where symptoms persist for more than six months, treatment is often difficult and unsuccessful. Surgical management of obvious nasal deformities may improve the olfactory function, those who continue to be symptomatic, often have only a handful of options with little evidence.

Olfactory Training

Olfactory training has been shown to have significant effect in patients with PTOL. Training with low molecular weight molecules (<150g/mol) has been shown to be beneficial in this group of patients. Compared with PVOL patients, PTOL patients tend to benefit less from olfactory training possibly due to irreparable damage to the olfactory nerve [41].

Steroid Management

Studies have shown 10-30% improvement in olfactory function in patients treated with either oral or intranasal steroids [42,43]. Jiang *et al,* 2015 randomised 145 patients with PTOL into three treatment arms (Steroid, Zinc, combination of steroid and zinc) and a non-treatment arm and showed significant improvement in patients who had zinc sulphate as monotherapy and those treated with combination therapy (zinc sulphate and prednisolone) [44].

Non-Steroid Medical Management

Zinc sulphate has been shown to offer significant improvement in olfaction by Aiba et al 1998 in PTOL patients. This was a small prospective cohort study, there has been little randomised studies to support this, other than the Taiwanese study mentioned above.

Theophylline has been shown to improve olfactory function in PTOL patients. Oral theophylline and intranasal theophylline have been proposed for treatment, although as aforementioned, specific evidence for its use is confined to studies from only one centre without use of an internationally validated psychophysical olfactory test [45].

Olfactory loss in neurodegenerative disease

Neurodegenrative changes in the olfactory cortex are more commonly observed in patients with Parkinsons disease (PD) compared to age matched healthy individuals [75]. Severe hyposmia is a prodromal symptom of Parkinson Disease [76] and is considered one of the biggest risk factors of mortality in PD. Studies have demonstrated that olfactory disturbance in patients who were asymptomatic with the disease subsequently became symptomatic [75,78]. There is evidence to suggest that olfactory training with 4 odorants twice daily for 12 weeks significantly improves olfactory function compared to non-training group in PD patients [66,67].

Deep brain stimulation (DBS) has been added to the therapeutic armamentarium in the management of patients with PD. Hummel *et al,* 2005 found deep brain stimulation of the subthalamic nucleus of PD patients improved odour discrimination while having no effect on odour thresholds indicating a possible positive effect in cognitive processing of olfactory function [67].

Cholinesterase Inhibitor Velayudhan et al conducted an unblinded and uncontrolled study and demonstrated that the cholinesterase inhibitor, donepezil, could greatly improve olfactory function of Alzheimer's disease (AD) patients [79].

Congenital Anosmia

There is little literature on patients with congenital anosmia. It is widely accepted that syndromic patients with anosmia have little chance of gaining the ability to smell, although the idea of gene

therapy may prove to be useful in the future. Henkin *et al* 2016, however showed 63% improvement in olfactory function in 19 patients with isolated congenital anosmia (type II) following treatment with theophylline [70]; again this is the same caveat for the results from this one centre as above. In practice, the majority of patients with congenital anosmia have olfactory bulb aplasia regardless of whether they have Kallman syndrome or not [80].

Conclusion

Non-conductive olfactory loss can be challenging to manage and as evidence for the management of these disorders is limited and there is a growing need for good randomised control trials. Notwithstanding this, there is clear evidence for the use of olfactory training in the treatment of non-conductive olfactory loss irrespective of the aetiology[19]. The evidence for the use of other medical treatment according to aetiology is quite weak but it is clear from this review that there are additional management options available to them, albeit that a discussion with the patient about the potential limitations and pitfalls and also explaining that with certain medications they will not be licenced for the treatment of olfactory disorders. In terms of oral medications, steroids and theophylline have shown some promise in the treatment of PVOL and PTOL patients and with topical treatments, sodium citrate and vitamin A have also shown some good potential. The ENT research community now needs to convince funding bodies for the need to deliver more RCTs that can usefully inform clinicians on the place of these therapies and help to treat this much maligned group of patients. Initiatives such as the Generate project in the UK[81], may help take steps in this direction.

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Figure 1: **Schematic representation of the selection of studies for the systematic review**