Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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REVIEW ARTICLE

Olfactory Dysfunction in COVID-19, a Review of the Evidence and Implications for Pandemic Management☆

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Abstract There is debate as to whether olfactory dysfunction should be considered a symptom of COVID-19 infection, given the implications for managing the symptom itself, for diagnostic testing, and for implementing isolation measures. We undertook a systematic literature review of the articles indexed in PubMed on olfactory disorders in viral respiratory tract conditions, with special emphasis on COVID-19. The main objective was to find evidence of clinical interest to support the relationship between anosmia and COVID-19. Olfactory disorders in upper respiratory tract infections are frequent, most caused by obstruction due to oedema of the nasal mucosa. Occasionally, post-viral sensorineural olfactory dysfunction occurs, with a variable prognosis. The evidence on anosmia in COVID-19 patients is extremely limited, corresponding to a level 5 or D of the Centre for Evidence-Based Medicine. According to the various medical societies that have issued reports on the subject, it seems reasonable to apply isolation, hygiene and social distancing measures in patients with recent olfactory disorders as the only symptom, although the usefulness of diagnostic tests for this type of patient should be studied.

PALABRAS CLAVE
Anosmia;
Disfunción olfatoria posviral;
COVID-19

Alteraciones del olfato en el COVID-19, revisión de la evidencia e implicaciones en el manejo de la pandemia

Resumen Existe debate sobre si las alteraciones en el olfato deberían considerarse un síntoma de infección por COVID-19, dadas las implicaciones en el manejo del propio síntoma, en la realización de pruebas diagnósticas y en la aplicación de medidas de aislamiento. Se realizó una revisión sistemática bibliográfica de los artículos indexados en PubMed sobre alteraciones del olfato en cuadros virales de vías respiratorias, con especial énfasis en el COVID-19. El objetivo

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principal fue encontrar evidencia de interés clínico que apoye la relación entre ansomia y COVID-19. Las alteraciones del olfato en procesos infecciosos de vías altas son frecuentes, en su mayoría responden a una causa obstructiva por edema de la mucosa nasal. Ocasionalmente aparece una disfunción olfatoria post-viral de tipo neurosensorial, de pronóstico variable. La evidencia acerca de la anosmia en pacientes con COVID-19 es muy limitada, correspondiente a un grado 5 o D del Centre for Evidence-Based Medicine. En acuerdo con las distintas sociedades médicas que han emitido comunicados al respecto, parece razonable aplicar medidas de aislamiento, higiene y distanciamiento social a los pacientes con alteraciones del olfato de reciente aparición como único síntoma, aunque se debería estudiar la utilidad de la realización de pruebas diagnósticas a este tipo de pacientes.

Introduction

The advent of the global SARS-CoV-2 coronavirus pandemic has prompted debate about whether olfactory dysfunction should be considered a symptom of infection. According to a review by the Centre for Evidence-Based Medicine at the University of Oxford,[1] media reporting of alleged dozens of cases of anosmia, in the absence of other nasal or respiratory symptoms in patients who are positive for COVID-19, is not an acceptable level of evidence in the scientific literature. The review authors found only one article, without peer review, describing the presence of anosmia in 5.1% of patients with confirmed SARS-CoV-2, without finding significant differences in the proportion of patients with this symptom based on clinical severity.[2] Several otolaryngology societies, including the American, French, British and Spanish societies, have published reports on anosmia in COVID-19 based on anecdotal and non-peer reviewed cases. Therefore, according to the guidelines of the Centre for Evidence-Based Medicine, the degree of evidence supporting anosmia as a characteristic symptom of COVID-19 would be ñon-conclusiveï (grade 5 or D).

Given this situation of uncertainty, the possibility that olfactory dysfunction is a symptom attributable to COVID-19 may have implications for the way the symptom itself is handled, in diagnostic testing for the virus and for the application of isolation measures. The aim of this literature review is to seek an answer to the following questions:

a) What do we consider olfactory dysfunction and how do we objectify it? Is there a minimum intensity required to consider olfactory dysfunction secondary to coronavirus?
b) Is the relationship between anosmia and COVID-19 plausible?
c) What would be the prognosis and treatment of olfactory dysfunction in patients with COVID-19?
d) Which patients with olfactory dysfunction should be tested for COVID-19?
e) Can patients with confirmed COVID-19, in whom olfactory dysfunction persists after resolution of the clinical picture or after the isolation period, transmit the virus?

Material and Methods

A systematic literature search was performed on the Medline database using the following search expressions:

- (*Olfaction disorders* [MESH] OR *anosmia* [TI]) AND (*COVID-19* [MESH] OR *SARS-CoV-2* [MESH] OR *COVID-19* [ALL FIELDS] OR *CORONAVIRUS* [ALL FIELDS] OR *NOVEL CORONAVIRUS* [ALL FIELDS]).
- (*Diagnosis* [MESH] OR *signs and symptoms* [MESH] OR *respiratory tract infections* [MESH]) AND (*COVID-19* [MESH] OR *SARS-CoV-2* [MESH] OR *coronavirus* [MESH] OR *COVID-19* [ALL FIELDS] OR *coronavirus* [ALL FIELDS] OR *novel coronavirus* [ALL FIELDS]).
- *Post-viral olfaction disorder* [ALL FIELDS] OR *Post-viral olfactory disorder* [ALL FIELDS] OR (*olfaction disorders* [MESH]) AND *virus* [MESH]).
- (*Olfactory disorders* [ALL FIELDS] OR *olfactory disorder* OR *olfaction impairment* [ALL FIELDS] OR *olfaction disorders* [MESH]).
- (*Testing* [ALL FIELDS] OR *detection* [ALLFIELDS]) AND (*COVID-19* [MESH] OR *SARS-CoV-2* [MESH] OR *coronavirus* [MESH] OR *COVID-19* [ALLFIELDS] OR *coronavirus* [ALL FIELDS] OR *novel coronavirus* [ALL FIELDS]).

To increase the sensitivity of the search in the Medline database, a free search was also performed with the following expressions:

- COVID-19 detection.
- COVID-19 anosmia olfaction disorders.
- COVID-19 symptoms clinical presentation.
- COVID-19 review.
- Post-viral anosmia olfaction disorder.
- Neurological manifestations COVID-19.

The following terms were also consulted via the Google search engine: anosmia, COVID-19 and evidence-based medicine, symptoms, neurological.

Result Discussion

The expression search (*olfaction disorders* [MESH] OR *anosmia* [TI]) AND (*COVID-19* [MESH] OR *SARS-CoV-2* [MESH] OR *COVID-19* [ALL FIELDS] OR *coronavirus* [ALL FIELDS] OR *novel coronavirus* [ALL FIELDS]) yielded 11 results, 10 of them in English. Of these 10 articles, 6 were discarded for review, as they were case reports or letters to the editor. The article with an earlier publication date, in 2007, related olfactory dysfunction with the previously described coronavirus, but not with SARS-CoV-2. The rest of the articles found, 4 in total, were cross-sectional observational studies and were published in April 2020. The search with the expression (*Post-viral olfaction disorder* [ALL FIELDS] OR *post-viral olfactory disorder* [ALL FIELDS] OR (*olfaction disorders* [MESH]) AND (*virus* [MESH]) yielded 10 results, of which 4 were relevant as they directly address anosmia in viral infections (not SARS-CoV-2) of the upper respiratory tract.

The search expression (*Diagnosis* [MESH] OR *signs and symptoms* [MESH] OR *respiratory tract infections* [MESH]) AND (*COVID-19* [MESH] OR *SARS-CoV-2* [MESH] OR *COVID-19* [ALL FIELDS] OR *novel coronavirus* [ALL FIELDS]) yielded more than 1000 references and those corresponding to recent review articles or meta-analyses were selected.

The remaining search expressions in the Medline database and Google were used to obtain complementary information to review olfactory disturbances in upper respiratory tract infections and the recommendations of the different scientific societies.

Anatomo-physiological Memory

The olfactory epithelium is located in what is termed the olfactory groove, lining the cribriform plate. Under normal conditions it can extend to the mucosa of the upper third of the nasal septum and the middle and upper turbinates. It is columnar pseudostratified neuroepithelium whose basal cells have the capacity to regenerate in response to direct injury and can generate epithelial and neuronal cells. Olfactory neurons (first neuron of the olfactory pathway), whose body is located in the parabasal region of the epithelium, emit dendrites ending in cilia containing the olfactory receptors. The neuronal somas of the olfactory neurons, which are located in the parabasal region of the epithelium, emit the olfactory axons that emerge from the epithelium forming fascicles called the *fila olfactoria* (cranial nerve I), which in turn cross the lamina propria and make the first synapse in the olfactory bulb.[3] Sensitive innervation of the nasal cavity by trigeminal branches has the capacity to detect many chemical compounds in sufficiently high concentrations. Thus, subjects with a complete loss of function of the first cranial nerve can retain the ability to detect trigeminal-activating substances such as menthol and ammonia.[3]

Semiology of Olfactory Disorders

Olfactory disorders comprise a spectrum of dysfunction in the ability to smell and can be classified in different ways. From the quantitative point of view, with regard to the intensity of the dysfunction, we differentiate between *hyposmia* (increase in the threshold of detection of odours) and *anosmia* (total incapacity). Qualitative alterations of smell, understood as the capacity to correctly identify odours, are collectively termed *dysosmias*. Within these we distinguish *parosmia* (altered perception of an odour when the stimulus is present) and *phantosmia* (perception of an odour without any real stimulus). They can also be classified from an anatomical point of view into conductive olfactory disorders (secondary to nasal obstruction) and neurosensorial disorders (due to disturbances in the olfactory pathway). Olfactory disorders are frequently accompanied by impaired taste, in the form of *ageusia* or *dysgeusia*, although it is believed that the main component of this sensation is the olfactory dysfunction itself, which prevents the development of the subjective sensation we call *taste*.[3,4]

Exploration and Assessment of Olfactory Function

The study of olfactory function in the clinical environment is mainly semi-quantitative by means of kits of smell strips or vials, which are presented to the patient with the aim of determining olfaction thresholds. Some of the most used are the University of Pennsylvania Smell Identification Test-40 and the Barcelona Smell Test-24, which present 40 and 24 different olfactory stimuli respectively, and are therefore laborious and slow to administer.[5] There are abbreviated versions of olfactory tests, with between 4 and 12 stimuli, which make them even easier to use to assess large series of patients, such as the 4-item Pocket Smell Test and the 12-item Brief Smell Identification Test.[6] Despite their good levels of sensitivity and specificity, these abbreviated tests are still not applicable in conditions where there is a lack of time and resources. Another strategy, duly validated, is to use specific questionnaires,[7] such as the Questionnaire for Olfactory Dysfunction[8] or, even more simple, the use of a visual analogue scale, which can also be applied to the sense of taste.[9] The use of analogue scales can be complemented with the use of ethanol, ammonia and menthol, substances that are easily accessible, to assess trigeminal function.[7]

Aetiology, Clinical Characteristics and Prognosis of Olfactory Dysfunction Related to Viral Infections

Among the different causes of olfactory dysfunction are viral infections of the upper respiratory tract, which would account for between 17% and 36% of the olfactory dysfunction studied in specialist consultations.[4] In upper respiratory tract infections there is a component of rhinosinusitis (acute viral) that causes swelling of the nasal mucosa and increased secretion of mucus, which manifests as nasal obstruction, rhinorrhoea and hyposmia or conduction anosmia, which remit once the infection has been resolved. Thus, olfactory dysfunction in the course of upper respiratory tract infections is very frequent and considered an inherent symptom of these processes. There is no literature on impaired smell as an isolated symptom, or as a prodrome of an upper respiratory tract infection. However, it is known that in some cases the infectious agent itself generates direct damage to the neuroepithelium and produces hyposmia or neurosensory dysosmia, which persists for some time after resolution of the infectious picture. The intensity and duration of

this dysfunction, termed post-viral olfactory dysfunction (PVOD), are highly variable depending on the capacity and rate of regeneration of the neuroepithelium.

PVOD is more common in women and in individuals aged 50 and over. It can last from weeks to one or two years. It is accepted that if it lasts longer, expectations of recovery of olfactory function are very limited.[10,11] One third of patients usually improve completely after 13 months, although they notice symptoms of recovery after a few months.[11,12] The chances of full recovery are inversely proportional to the severity of the initial PVOD.[11,13] In addition to the involvement of the first cranial nerve, an impairment in the chemosensitivity of the nasal branch of the trigeminal has also been demonstrated.[13,14] The main problem for the study of this type of alteration is that most patients, in the context of catarrhal symptoms, attach no importance to this symptom and recover spontaneously, and therefore do not seek medical attention. Consequently, the available data on the real incidence of these disturbances and their progression over time are very scarce. Most series are limited to recruiting and analysing patients with established PVOD that has not improved spontaneously,[13] who delay consulting for months.[11] Due to this delay, and given that the damage is considered established, treatment with corticosteroids or antivirals is usually ruled out, and therefore there is no clear evidence to support these treatments.[10,12]

It has been suggested that the incidence peaks of DOPV, which are between the months of May and June, coincide with parainfluenza virus type 3 (PIV3) incidence peaks. Following this reasoning, Suguiura et al.'s group related DOPV with parainfluenza virus infections and demonstrated elevated antibody titres against PIV3 in the serology of 127 patients with DOPV.[15] Along the same lines, and with a more solid methodology, Wang et al. showed that 88% of nasal epithelium samples from patients with DOPV, PCR tested, were positive for PIV3, compared to 9.1% of those of the controls.[16] Subsequently, PCR has demonstrated the presence of other viruses causing DOPV, such as rhinovirus, parainfluenza virus, Epstein Barr virus and coronavirus,[17] the latter being found in 15% of those affected. Attempts have been made to reproduce DOPV in a murine model infected with Sendai virus, which is considered equivalent to human influenza virus in mice. Tian et al. showed that infection by Sendai virus in the murine model altered olfactory function, reducing regenerative capacity and preventing the physiological function of the olfactory neuroepithelium. They also demonstrated the persistence of genetic material of the virus in the cells of the epithelium and olfactory bulb at least 60 days after infection.[18]

Evidence Available in the Scientific Literature of Olfactory Dysfunction in Patients With Coronavirus Disease 2019

The first article, without peer review, that mentioned and quantified the presence of anosmia in patients with COVID-19 was published by Mao et al.[19] on February 22, 2020. This study analysed the presence of neurological manifestations in a series of 214 patients in a hospital in China, differentiating between central and peripheral nervous system symptoms. The authors reported the presence of symptoms that they classified as belonging to the central nervous system in 53 patients (24.8%), of which the most frequent were very non-specific symptoms such as dizziness (36 patients [16.8%]), headache (28 patients [13.1%]) and impaired level of consciousness (16 patients [7.5%]). Within the peripheral nervous system manifestations, hypogeusia was reported in 12 patients (5.6%) and hyposmia in 11 patients (5.1%). The authors of this study suggest that the presence of olfactory dysfunction could explain involvement of the central nervous system, by a hypothetical retrograde pathway from the olfactory mucosa. The assessment of these symptoms was retrospective, based on the data recorded in the patients' clinical histories, and therefore an information bias is highly likely. The only method of validating the information mentioned in the article was the supposed review of the data entered in the clinical history by 2 independent neurologists. There is no mention of how the presence of hyposmia or hypogeusia was assessed, or whether all the patients were systematically asked about these symptoms. Furthermore, at no time is the possibility assessed that impaired taste and smell may be due to a conduction mechanism, nor are other rhinological symptoms, such as nasal obstruction and rhinorrhoea, assessed simultaneously.

A new multi-centre study conducted in multiple countries in Europe was subsequently published on 6 April 2020.[20] Four hundred and seventeen patients with PCR-confirmed COVID-19, excluding patients admitted to ICU and with previous olfactory dysfunction. The assessment of clinical data was heterogeneous; in some cases, it was done in person in medical consultations or hospital and in others remotely, by telephone and through self-completed online surveys. The impact of olfactory dysfunction on quality of life was assessed by means of a previously validated short version of the Questionnaire of Olfactory Disorders-Negative Statements (sQOD-NS), and olfactory and taste function was assessed with an unvalidated adaptation of questions selected by a group of experts. The authors reported 85.6% (357/417) of COVID-19 patients with olfactory impairment, of which 284 were classified as anosmic (68%) and 73 as hyposmic (18%). Of the patients, 11.8% presented olfactory dysfunction before the onset the rest of the symptoms, 65.4% after and 22.8% during the course of the clinical picture. In 63% of the cases the olfactory dysfunction persisted after the resolution of the rest of the symptoms, although 72.6% recovered their sense of smell in the following 8 days. The important limitations of the study are the great heterogeneity in the data collection, the use of non-validated questionnaires and the lack of validation of the information, and therefore an information bias is likely.

Later, a cross-sectional observational study was published in which 2428 online surveys were conducted in patients with flu-like symptoms compatible with COVID-19.[21] In this paper, aetiological confirmation by PCR was not required and the methods do not specify the questions used to assess the symptoms or the criteria for electronic invitation to take part in the survey. They reported 74.4% of patients with anosmia, 17.3% of patients with hyposmia and 90% of patients with taste alterations. The serious methodological shortcomings of this publication mean we must view the results with extreme caution.

Only one day later, the group of Yan et al.[22] published a cross-sectional study in which an invitation to complete

an online survey was sent to 1480 patients who had consulted their centre with pseudo-flu symptoms. Of these 1480 patients contacted, 102 were PCR-positive for SARS-CoV-2, of whom 59 (58%) responded to the survey, while 1378 were negative, of whom 203 (15%) responded to the survey. The survey consisted of 27 questions related to alterations in taste and smell and their temporal relationship with symptoms, including a self-assessment of the subjective degree of olfactory or taste function on a scale from 0 (anosmia or ageusia) to 10 (no impairment). The authors reported 68% olfactory dysfunction and 42% impaired taste in COVID-19 positive patients, while the corresponding percentages in COVID-19 negative patients were 16% and 17% respectively. Thus, they calculated that COVID-19 positive patients had an odds ratio of 10.9 (95% CI: 5.6–20) of presenting anosmia and 11.9 (95% CI: 6.1–23.2) of presenting ageusia. The percentage of COVID-19 positive patients who reported improvement in taste and smell at the time of the survey was 72.5%, and this improvement correlated with the disappearance of other symptoms of the disease. Its results should be taken with caution, since there are important qualitative limitations in the collection of information (information bias), lack of an exact definition of what criteria were used to define olfactory or gustatory dysfunction, and a low participation rate (selection bias).

A more modest, cross-sectional, single-centre study was published on 16 April 2020, with 114 patients PCR-positive for coronavirus.[23] The information was obtained by reviewing the clinical histories of the patients, who were visited in the hospital and followed up by telephone. The percentage of patients with anosmia was 47%, and its duration was more than 7 days in 55% and more than 14 days in 20%. In no case was the onset of anosmia the first symptom of the disease. According to their results, anosmia debuted a mean of 4.4 days (95% CI: 2.5–6.3) after the onset of symptoms. Nasal obstruction and rhinorrhoea were present in 30% and 57% of patients, respectively. Again, this study has the limitation of the quality of the information, not systematised, obtained from the review of medical records, and no information is provided on the criterion for assessing the impaired smell.

On the other hand, there is evidence that nasal and oropharyngeal swabs from patients with COVID-19, studied by PCR, become negative about 15 days after the onset of symptoms,[24,25] and we know that patients without symptoms can be positive. Case reports of patients who have recovered from COVID-19 with positive swabs have generated interest in the infectious potential of these subjects. Xing et al. published a follow-up study with periodic swabs in 62 patients from the medical staff of their institution, of which 2 (3.23%) were positive after discharge from hospital, more than 15 days after the onset of symptoms.[26] Again, none of these studies mentioned the relationship between olfactory dysfunction and possible persistence of the virus in nasal or oropharyngeal swabs.

With the information found in the review we tried to answer the questions posed in the objectives:

a) What do we consider olfactory dysfunction and how do we objectify it? Is there a minimum intensity required to consider olfactory dysfunction secondary to coronavirus?
   - Olfactory disorders vary in intensity (hyposmia, anosmia) and in quality (parosmia, phantosmia). They can be conductive, neurosensory or mixed. Clinical assessment usually takes place in specialist consultations with kits of different olfactory stimuli presented to patients, although if not available it might be appropriate to use visual analogue scales.
   - We have no solid evidence to establish specific characteristics of anosmia in COVID-19, although recent studies put the presence of anosmia at between 5.1% and 85.6%. Only one study mentions anosmia as a symptom prior to the onset of the clinical picture.
   - In all studies on olfactory disorders in patients with COVID-19 there is a high risk of information and selection bias.

b) Is the relationship between anosmia and COVID-19 plausible?
   - Conduction anosmia is common in patients with upper respiratory viral processes and has been associated with different families of viruses such as rhinovirus, parainfluenza virus and coronavirus. A low proportion of patients present DOPV, whose duration and recovery is variable. Coronaviruses may be responsible for approximately one-sixth of all cases of DOPV. Parainfluenza virus has been shown to be present in the cells of the olfactory epithelium for up to several months after the infection has resolved. Published studies suggest that anosmia is a common symptom in COVID-19.

c) What would be the prognosis and treatment of olfactory dysfunction in patients with COVID-19?
   - There are no reliable data available to categorically assess the prognosis of olfactory disorders in COVID-19, although the evidence suggests that functional recovery is the norm. The available evidence on other viruses affecting the nasosinusal mucosa reveals that most patients have a transient olfactory disorder, possibly conductive, which disappears when the remaining symptoms resolve. Patients who develop DOPV recover their sense of smell completely in one third of cases within a year of the infection. The chances of recovery appear to be more limited in long-term, older, and female patients.
   - Despite the fact that empirical treatment of post-viral olfactory disorders is by topical nasal or systemic corticosteroids, there are doubts as to the efficacy of these drugs in DOPV. We also recommend avoiding the administration of corticosteroids in patients with COVID-19 and we should therefore also advise against them in the treatment of DOPV.

d) Which patients with olfactory dysfunction should be tested for COVID-19?
   - Ideally, for research purposes, and given the lack of solid data available, the recommendation should be to take nasal swabs from any patient with recent onset anosmia who has been duly assessed. Pragmatically, the scarcity of diagnostic tests make it necessary to consider whether it is worthwhile to take nasal swabs from patients who present with anosmia as an isolated symptom, or whether it is sufficient to follow the usual recommendations of isolation, hygiene and social distancing (hand washing, use of a mask, minimum separation distance of 1–2 metres), although it could be justified in some groups, such as health professionals.

e) Can patients with confirmed COVID-19, in whom olfactory dysfunction persists after resolution of the clinical picture or after the isolation period, transmit the virus?
   - Although there is evidence that genetic material of the virus persists in the epithelial cells of the nasal mucosa up to several months after para-influenza infection, we do not have data on whether the same is true for COVID-19. Furthermore, the presence of genetic material in the cells does not necessarily mean that the affected individual has the ability to transmit the virus.
   - The limited evidence available on DOPV shows that it is likely that neuroepithelial damage persists after resolution of the infection, which resolves slowly as the neuronal component of the olfactory mucosa regenerates. Therefore, there are no data to support the hypothesis that patients with DOPV are potential sources of virus transmission, although this cannot be ruled out either.
   - The only way to determine whether patients with DOPV are capable of transmitting the virus would be to take PCR nasal swabs. Given the scarcity of these tests, and the central role of health personnel as vectors, it should be seriously considered whether repeat swabs in health personnel with DOPV are necessary, at least in selected cases.

Conclusions

The existence of olfactory dysfunction in infectious processes of the upper airways is not surprising, and it is known that there is obstructive type dysfunction, which resolves when other acute symptoms resolve. In some cases, post viral olfactory dysfunction of a neurosensorial type may appear, which takes weeks or months to disappear. In patients with COVID-19 it seems that anosmia is a common symptom, although limitations in the available evidence make decision-making difficult at the clinical level and highlight the need for reliable data collection about these symptoms. Although in our setting it is advisable to apply measures of isolation, hygiene and social distancing (hand washing, use of a mask and minimum separation distance of 1–2 metres) in patients with recent olfactory dysfunction as an isolated symptom, it does not seem appropriate to perform diagnostic tests on all these subjects. A subgroup of patients where swabs should be considered are those cohabiting with people at high risk of mortality (the immunosuppressed, elderly or chronically ill). Nor does it seem advisable to take swabs systematically in patients in whom the DOPV persists after the resolution of the rest of the symptoms, although their use in certain groups, such as health professionals, could be justified.

Conflict of Interests

The authors have no conflict of interests to declare.

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