ORIGINAL RESEARCH ARTICLE

Drug Saf 2011; 34 (10): 849-859
0114-5916/11/0010-0849/$49.95/0

Drug-Induced Taste and Smell Alterations

A Case/Non-Case Evaluation of an Italian Database of Spontaneous Adverse Drug Reaction Reporting

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Abstract

Background: The frequency and clinical features of drug-related taste and/or smell impairments are currently unclear.

Objective: The aim of this study was to identify major drug classes associated with taste and smell alterations reported to the Italian spontaneous adverse drug reaction (ADR) reporting database.

Methods: The association between drug and altered taste or smell was investigated by case/non-case methodology. The reporting odds ratio (ROR) was used as a measure of disproportionality. Cases were defined as patients with at least one ADR related to taste or smell impairments. The non-cases included all patients without any ADRs related to taste or smell alterations.

Results: According to the selection criteria, 52 166 reports were included in the analysis. Overall, 182 cases of drug-related taste and/or smell dysfunctions were identified. Statistically significant unadjusted RORs were reported for macrolides (n = 31; 7.1; 95% CI 4.8, 10.5), terbinafine (the only drug reported within the group of antimycotics belonging to the Anatomical Therapeutic Chemical class D01AE) [n = 17; 76.4; 95% CI 44.0, 132.6], fluoroquinolones (n = 15; 1.7; 95% CI 1.0, 2.8) and protein kinase inhibitors (n = 10; 4.0; 95% CI 2.1, 7.7). When RORs were adjusted for sex and age category, the disproportion remained statistically significant for all of the previously mentioned drug classes.

Conclusions: Taste and/or smell abnormalities are common, sometimes unexpected and often persistent complaints of patients during pharmacological treatments. Physicians should be aware of the impact of these ADRs on patients' quality of life.

Background

Drug-induced taste and smell disorders seem to represent common adverse drug reactions (ADRs) in clinical practice. Several drugs and drug classes, such as ACE inhibitors, β-lactam antibiotics, biguanides, chlorexidine, opioids, protease inhibitors and antivirals, have been associated with these adverse events, which are usually documented anecdotally by case reports and, more rarely, by clinical studies.[1] Although a number of reviews have been published in an attempt to summarize the available evidence on these ADRs,[2-7] their actual frequency and clinical features remain largely unclear.

Since taste and smell disturbances are not regarded as life-threatening conditions, they are probably underestimated and often neglected by caregivers. However, they can result in significant impairments of the patient's quality of life.[8] Indeed, obtaining pleasure from food and the ability to maintain social eating habits may be impeded by food aversion and may entail mood disturbances as well as decreased social functioning.[9,10] Gustatory and olfactory disturbances may also play an important role in the aetiology of malnutrition and wasting, which affect approximately 40% of hospitalized patients.[11] Moreover, the detection of taste and smell alterations can be very difficult. Although some diagnostic tools are available to verify the status of taste and smell perception,[12-15] their use is very limited in clinical practice. Accordingly, in several published cases, diagnosis was based merely on subjective descriptions made by patients.[12,16-21]

The first aim of the present study was to identify major drug classes associated with the development of taste and smell impairments by means of quantitative signal analysis of reports to an Italian spontaneous ADR reporting database. The second aim was to describe the main pharmacological mechanisms and clinical features of these ADRs, with a particular focus on outcome information.

Methods

Data Source

The study was based on data recorded up to December 2008 by the Italian national database of spontaneous ADR reporting (Italian Drug Agency – Agenzia Italiana del Farmaco [AIFA]), which includes ADR reports from 1988. All ADR reports were coded using the WHO Adverse Reaction Terminology (WHO-ART). All drugs were grouped using the Anatomical Therapeutic Chemical (ATC) classification. The majority of reports in the database are contributed by physicians (approximately 90%). Each ADR report is verified both by the respective regional pharmacovigilance centre and AIFA in order to ensure completeness of information on concomitant medications and appropriate causality assessment of ADR according to the WHO criteria.[22] Only those reports scored as 'certain', 'probable' or 'possible' for causality assessment, and recorded in the database up to December 2008, were included in the present analysis. ADRs were classified as 'serious' when they resulted in death, were life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in a persistent or significant disability/incapacity, or represented a congenital anomaly/birth defect.

Design

Association between a drug and altered taste or smell was assessed by the case/non-case methodology, calculating the reporting odds ratio (ROR) and 95% confidence intervals (CIs) as a measure of disproportionality. ROR compares the frequency of an ADR reported for a particular

drug with the frequency of reports of the same ADR for all other drugs.[23] Cases were defined as patients who experienced at least one ADR related to the WHO-ART preferred term associated with taste ('taste loss' and 'taste perversion', including the lower-level terms 'gustatory sense diminished', 'taste absent', 'ageusia', 'taste bitter', 'taste garlic', 'taste metallic', 'taste peculiar', 'parageusia', 'taste alteration', 'dysgeusia') or smell impairments ('parosmia', including the lower-level terms 'smell alterations', 'smell change', 'smell peculiar', 'anosmia', 'dysosmia', 'hyperosmia', 'smell loss'). The non-cases included all patients who did not experience any ADR related to taste or smell alterations. Index reports included all ADR reports involving a drug class (ATC level 3) with at least five reports of smell or taste alterations, while reports involving all other drug classes were taken as the comparison group. Since the population of patients with vaccine-related adverse reactions differ largely from that with drug-related adverse reactions (i.e. healthy individuals, more children involved, etc.), reports of vaccine-related adverse events were excluded from the analysis in order to avoid biases. Taste and/or smell impairments were considered as expected for each drug when labelled in the respective Italian authorized summary of product characteristics by the end of December 2008. Available literature was also reviewed to explore possible pharmacological mechanisms supporting the occurrence of drug-induced chemosensory alterations identified in the present analysis.

Statistical Analysis

Statistical analysis was carried out using the software Stata version 10.0 (Stata Corporation, College Station, TX, USA). Categorical variables were evaluated using frequency distribution. To compare the characteristics of cases against non-cases, the chi-squared test (Fisher's Exact test when appropriate) was applied, while unadjusted ROR with 95% CI was calculated with the aim of exploring the potential 'signals of alarm'. Subsequently, a multivariate logistical model was fitted to estimate adjusted ROR, thus confirming the previously provided 'signals'. To avoid model instability, only drug classes with at least ten cases of gustatory and/or olfactory impairments were considered as a co-variate. Each potential confounder was retained in the final model wherever a change of at least 5% was observed for the ROR of interest.[24,25] Finally, for categorized variables, the linearity assumption was evaluated by computing the likelihood ratio test (LRT). As a result, the variable 'age' was taken as a continuous variable if the LRT rejected the null hypothesis when the model with categorical variables was nested in the alternative one including the continuous variable.

Results

According to the selection criteria, 52 166 reports (mean age ± SD 53.3 ± 22.2; females 58.9%) were included in the analysis. The causality assessment was scored as certain in 1328 reports (2.5%), probable in 18 442 (35.3%) and possible in 32 396 (62.1%). Unlikely, unassessable and unclassifiable reports (n = 2380; four cases of taste and/or smell impairments) had been already excluded from the analysis.

Overall, 182 cases (100%) of taste and/or smell impairments were identified (mean age 56.2 ± 14.8; females 66.5%); 4 were scored as certain, 53 as probable and 125 as possible. Taste alterations alone were reported in 137 patients (75.3%) and smell impairments alone in 20 patients (11.0%); 25 patients (13.7%) experienced both taste and smell alterations. The drugs suspected of having induced expected or unexpected taste and/or smell alterations in more than three reports are displayed in table I.

Drug classes with more than five reports of taste and/or smell disturbances are summarized in table II. Statistically significant unadjusted ROR was reported for macrolides, antimycotics (terbinafine is the only drug reported in the database belonging to the ATC class D01AE), fluoroquinolones and protein kinase inhibitors, although reports of taste and smell impairments for fluoroquinolones presented weak statistical evidence of disproportion (the CI may contain the null hypothesis) within the ADR reports in our database.

Table I. Number of cases of chemosensory impairments (overall chemosensory dysfunctions, at least taste, at least smell, concomitant taste and smell) classified on the basis of drugs most frequently reported as possible causative agents

Drug	Overall chemosensory dysfunctions	At least taste	At least smell	Concomitant taste and smell dysfunction
Clarithromycin	23	22	8	7
Terbinafine	17	15	3[a]	1
Sunitinib	8	8	0	0
Moxifloxacin	7	6	2[a]	1
Ramipril	4	4	0	0
Amoxicillin + clavulanic acid	4	3[a]	2[a]	1
Levofloxacin	4	3	2	1
Simvastatin	3	3	0	0
Azithromycin	3	2	2[a]	1
Roxithromycin	3	2	3[a]	2
Beclometasone	3	2[a]	2[a]	1

a Not labelled.

All of the previously mentioned drug classes achieved the threshold of ten reports of gustatory and/or olfactory alterations established in this study for signal detection by multivariate analysis. The characteristics of patients exposed to these drug classes, along with the overall population and the population with ADRs to other medications, are summarized in table III. Significant differences were detected among these populations with regard to sex, age category, number of concomitant medications, category and proportion of serious ADRs ($p < 0.001$). When RORs were adjusted for sex and age category, the disproportion remained statistically significant for all the drug classes included in this analysis (table II).

Macrolides (Anatomical Therapeutic Chemical (ATC) Classification J01FA)

The drug class most frequently involved in reports of taste and/or smell impairments was that of macrolides (31 reports; mean age 53 ± 13 years; 25 females). Among them, clarithromycin was suspected in the majority of reports (23), followed by azithromycin (3), roxythromycin (3) and telithromycin (2). Macrolides were suspected in 11 cases of combined taste and smell alterations (44% of total cases with simultaneous impairment of both senses). The median time to event onset since the first drug intake was 3 days (range 1–23 days; 70% of ADRs occurred while the treatment was ongoing and the remaining 30% within 7 days after the treatment was stopped). The outcome resulted as completely resolved within a period of 2–6 days from discontinuation of the suspected drug in 11 reports (10 clarithromycin, 1 azithromycin). However, 20 reports described an ongoing outcome at the last available follow-up (median time to follow-up 35 days; range 7–245 days). Notably, in two cases, taste and smell impairments had not resolved after a period of 140 days. In the first case, ageusia and anosmia developed in a 33-year-old Caucasian female after 5 days of treatment with oral clarithromycin 1 g/day for bronchitis. No concurrent medications were reported. This ADR had not resolved at follow-up 161 days later. The second case occurred in a 55-year-old Caucasian female receiving oral clarithromycin 500 mg/day for acute bronchitis. Five days after starting this treatment, she reported ageusia and anosmia, which were still present at follow-up 245 days later. Paranasal sinuses and encephalic CT scan, blood analysis and specialist visits (neurological, endocrinological and otolaryngological) did not reveal any relevant finding. Smell impairments are not expected for azithromycin and roxythromycin.

Other Antifungals for Topical Use (ATC D01AE)

Second to macrolides, the ATC class designated as 'other antifungals for topical use' was

suspected of inducing the highest number of taste and/or smell impairments (n = 17). The only drug reported within this class was terbinafine (n = 17; mean age 53 ± 13 years; 13 females). The median time to event onset was 24 days (range 4–95 days). In six cases the ADR led to treatment discontinuation, and in five cases taste and smell impairments were detected after the end of scheduled therapy. Five reports indicated a resolved outcome after a period of 35–140 days from the end of terbinafine intake. Twelve reports displayed an ongoing outcome at the last available follow-up (median time to follow-up 12 days; range 1–81 days). Smell alterations are not labelled for terbinafine.

Fluoroquinolones (ATC J01MA)

Fluoroquinolones were involved in 15 reports (mean age 53 ± 18 years; ten females) of taste and/or smell impairment, including seven cases associated with moxifloxacin intake, four with levofloxacin, two with norfloxacin, one with lomefloxacin and one with ciprofloxacin. The median time to event onset since the first drug intake was 2 days (range 1–16 days; 84% of ADRs occurred while the treatment was ongoing). In four cases, the ADR led to treatment discontinuation. Only three reports described complete ADR recovery within 1, 2 and 38 days from drug withdrawal, respectively. In 12 cases, the ADR was ongoing at the last available follow-up (median time to follow-up 7 days; range 2–147 days). Notably, a 91-year-old Caucasian woman developed anosmia after the first day of treatment with levofloxacin 500 mg/day for a flare of chronic bronchitis. The treatment was discontinued 5 days later. Smell impairment was considered as improving 147 days later. Smell impairments are not expected for moxifloxacin, norfloxacin and lomefloxacin.

Protein Kinase Inhibitors (ATC L01XE)

Protein kinase inhibitors were recorded as suspected drugs in ten reports of taste and/or smell impairments (mean age 61 ± 9; five females). Sunitinib was the most reported drug (n = 8), followed by erlotinib (n = 1) and imatinib (n = 1). The median time to event onset since the first drug intake was 48 days (range 1–410; all events occurred while the treatment was ongoing and none required drug discontinuation). In one report, ipogeusia developed in an 80-year-old man 5 days after dose titration of sunitinib from 400 to 800 mg/day for stromal gastrointestinal cancer (the treatment was ongoing from more than 400 days). Only one report described spontaneous complete recovery (time to recovery 21 days). In two cases, a recovery with unspecified sequelae was reported after 24 and 180 days, respectively. Seven reports described an ongoing ADR (two events were improving, while five reactions were

Table II. Drug classes most frequently reported with taste and/or smell alterations with unadjusted (≥5 reports) and adjusted reporting odds ratio (ROR) [≥10 reports][a]

Drug classes (ATC 3)	Reports of taste and/or smell impairments (n = 182)	Other ADR reports (n = 51 984)	Unadjusted ROR (95% CI)	Adjusted ROR[b] (95% CI)
Macrolides	31 (17.0)	1446 (2.7)	7.1 (4.8, 10.5)	8.3 (5.5, 12.4)
Antimycotics	17 (9.3)	70 (0.1)	76.4 (44.0, 132.6)	77.0 (44.2, 134.2)
Fluoroquinolones	15 (8.2)	2602 (5.0)	1.7 (1.0, 2.8)	1.7 (1.0, 2.9)
Protein kinase inhibitors	10 (5.4)	727 (1.4)	4.0 (2.1, 7.7)	4.6 (2.4, 8.9)
ACE inhibitors	6 (3.2)	1701 (3.3)	1.0 (0.4, 2.2)	NC
HMG-CoA reductase inhibitors ('statins')	6 (3.2)	1933 (3.7)	0.8 (0.3, 1.9)	NC
Proton pump inhibitors	5 (2.7)	1083 (2.0)	1.3 (0.5, 3.2)	NC

a All values are expressed as n (%)

b Adjusted for age category and sex.

ADR = adverse drug reaction; **ATC** = Anatomical Therapeutic Chemical; **NC** = not calculated (overall number of reports <10).

Table III. Main features of the populations exposed to the four drug classes achieving at least ten reports of taste and/or smell impairments[a]

	Overall (n = 52 166)	Macrolides (n = 1462)	Antimycotics (n = 87)	Fluoroquinolones (n = 2617)	Protein kinase inhibitors (n = 737)	Other medications (n = 47 236)
Sex[b]						
Females	30 727 (58.9)	886 (60.6)	54 (62.0)	1491 (56.9)	259 (35.1)	28 037 (59.3)
Age category (y)[b]						
0–15	2 804 (5.3)	207 (14.1)	1 (1.1)	36 (1.3)	2 (0.2)	2 558 (5.4)
16–30	5 510 (9.8)	293 (20.4)	12 (13.7)	232 (8.8)	6 (0.8)	4 607 (9.7)
31–45	8 646 (16.5)	349 (23.7)	17 (19.5)	460 (17.5)	32 (4.3)	7 778 (16.4)
46–60	11 717 (22.4)	279 (19.8)	32 (36.7)	536 (20.4)	195 (26.4)	10 675 (22.5)
61–75	15 709 (30.1)	218 (14.9)	20 (22.9)	771 (29.4)	385 (52.2)	14 315 (30.2)
76+	8 140 (15.6)	116 (7.9)	5 (5.7)	582 (22.2)	117 (15.8)	7 320 (15.4)
Concurrent medications[b]						
0–2	43 157 (82.7)	1317 (90.0)	82 (94.2)	2099 (80.2)	637 (86.4)	39 022 (82.5)
3–5	5 761 (11.4)	91 (6.2)	3 (3.4)	304 (11.6)	79 (10.7)	5 284 (11.1)
6–8	2 358 (4.5)	32 (2.2)	2 (2.3)	154 (5.8)	17 (2.3)	2 153 (4.5)
9–11	438 (0.8)	10 (0.6)	0	26 (0.9)	3 (0.4)	399 (0.8)
12+	452 (0.9)	12 (0.8)	0	34 (1.3)	1 (0.1)	405 (0.9)
Seriousness[b]						
No	39 434 (75.5)	1227 (83.9)	71 (81.6)	2013 (76.9)	605 (82.0)	35 518 (75.1)
Yes	12 732 (24.4)	235 (16.1)	16 (18.3)	604 (23.0)	132 (17.9)	11 745 (24.8)

a All values are expressed as n (%)

b $p < 0.001$.

not yet resolved) at the last available follow-up (median time to follow up 31 days; range 4–287 days). Among these reports, only one, involving a 62-year-old man, indicated disgeusia as a concomitant symptom of oral mucositis 42 days after starting sunitinib administration to treat renal cancer. The event was not yet resolved 287 days later. Smell alterations are not expected for any drug within the class of protein kinase inhibitors. Taste disorders are labelled for all protein kinase inhibitors except erlotinib.

Discussion

The present analysis supports the hypothesis that some drug classes are more frequently associated with taste and smell disturbances than others. For some drugs these adverse events are unexpected (in particular, the olfactory disorders), but for the majority of drugs these events are labelled as transient conditions. Of note, several cases among those recorded in our database were characterized by long-term recovery or appeared to be permanent. The clinical features varied appreciably among drug classes, possibly reflecting different aetiopathogenic pathways.

In general, the mechanisms underlying drug-induced taste and/or smell alterations can be classified into two groups: (i) primary mechanisms, resulting from a direct action of the drug; and (ii) secondary mechanisms, in which the altered perception is consequent to collateral effects of the drug. Examples of primary mechanisms include drug-receptor interaction (i.e. agonism or antagonism); disturbance of action potential propagation in cell membranes of afferent and efferent neurons (i.e. influence on calcium flux); alteration of the neurotransmitter function (i.e. inhibition of reuptake from synaptic cleft); and changes in interplays between neural networks in brain regions associated with sensory coding and modulation. Secondary mechanisms include limiting the access of chemicals to sensing receptors (i.e. drying the mucosa, increasing nasal engorgement, closing off taste pores, favouring inflammatory or infections), and changing the chemical or

ionic milieu in the environment of sensing receptors (i.e. altering the constituents of mucous or saliva).[6]

The specific mechanism underlying taste and smell disorders elicited by macrolides remains unknown. As for other antibiotics, macrolides are endowed with a bitter taste.[26] When taken systemically, these drugs can access both nasal and salivary secretions.[27] In this setting, a direct stimulation of taste and smell receptors or an alteration of the salivary taste can be hypothesized. However, such mechanisms would be consistent with transient events associated with short-term treatments. On the other hand, a high rate of persistent impaired perceptions was recorded in the present study. Moreover, macrolides were associated with the higher percentage of concomitant taste and smell alterations (44%). Although the three systems involved in the control of somatosensory transmission (trigeminal, gustatory and olfactory nerves) mediate different functions, such as eating, breathing or drinking, these nerve pathways often work simultaneously. Consequently, olfactory, trigeminal and gustatory fibres can be concomitantly activated. At peripheral level, olfactory and trigeminal fibres are intimately intermingled within the olfactory cleft region, and taste and trigeminal fibres are intermingled at the tip of tongue.[28] As a consequence, in healthy subjects these three modalities can interact.[29,30] Hence, some authors hypothesized that a loss or alteration of one modality could negatively affect the other chemical senses.[31] Based on these considerations, it has been proposed that macrolides might directly affect the neural transmission in one of these three systems, thus causing a direct damage to sensory fibres, which can be persistent and result in a simultaneous alteration of both taste and smell. However, in contrast with this contention, a recent study has suggested that there is little anatomical reason to believe that damage to one of these two senses should impair the other one, and that more relevant factors, favouring the simultaneous deterioration of both chemosensory systems, include age category, sex and aetiology.[32]

Terbinafine is a drug for which taste alterations are well documented in the medical literature. Adverse events involving taste are expected with a frequency of 0.6–2.8% in terbinafine recipients. Case reports suggest that taste loss commonly occurs after 4–6 weeks of drug use. On a subjective basis, recovery has been reported to occur after 4 months from symptom onset, although long-lasting losses have been described.[6,33-36] The pathophysiological mechanisms responsible for terbinafine-induced loss of taste function remain unclear. However, low body mass index (BMI) is recognized as a risk factor for terbinafine-induced taste alterations.[34] In particular, it has been suggested that terbinafine can accumulate in the adipose tissue because of its lipophilic nature. As a consequence, patients with reduced BMI can experience taste disturbances more frequently because the drug becomes more available at the site of injury.[34] In fungal cells, terbinafine inhibits squalene epoxidase, which is responsible for the production of sterols needed for maintaining the integrity of cell membrane. Since, in humans, this enzyme is involved in cholesterol biosynthesis, it has been suggested that terbinafine can alter the structure or function of neurons deputed to taste sensing by interference with cholesterol pathway.[36] This hypothesis is supported by the observation that HMG-CoA reductase inhibitors ('statins'), which are known to decrease cholesterol biosynthesis via inhibition of HMG-CoA reductase in the mevalonate pathway, can be associated also with taste dysfunctions (three cases associated with simvastatin in our database).[5] In contrast with literature data on taste, smell alterations are not expected for terbinafine. In addition, findings of a small study, evaluating taste and smell perception impairments by means of quantitative tests, excluded terbinafine-induced olfactory disturbances.[36] However, in our database three patients reported parosmia, and two of them complained of these symptoms in the absence of taste impairments.

Taste alterations have been reported for many fluoroquinolones, although information about the clinical features of these reactions is poorly documented. Unpleasant taste has been reported during clinical trials, especially with grepafloxacin. These events appeared to be dose related, with an

incidence of 17% in patients receiving grepafloxacin at the highest dose (600 mg/day).[37] Taste perversion has been reported also for levofloxacin and enoxacin.[38,39] So far, the mechanisms underlying these ADRs remain undetermined. It has been suggested that such disturbances might depend on the flavour of the drug, which has been described as bitter or metallic. However, in rare cases,[37] taste dysfunctions lasted for several months (one case was ongoing at 5 months of follow-up in the present study), thus suggesting a different aetiopathogenic mechanism.[39] Of note, to the best of our knowledge, smell alterations have not been specifically described for fluoroquinolones in the medical literature, although these reactions are labelled for some drugs in this class.

Taste and smell alterations are major daily concerns for cancer patients, and several antineoplastic treatments have been associated with chemosensory impairments.[40,41] Notably, these adverse effects can be confounded by several variables associated with antineoplastic care (i.e. pureed food administered to facilitate feeding in patients with mouth ulcerations, nausea and vomiting, etc.).[42] In our study, protein kinase inhibitors emerged as the most frequent anticancer drug class associated with reporting of gustatory and olfactory dysfunctions in Italy. The mechanisms underlying these adverse effects are unknown. It can be speculated that these disturbances are secondary to mucosal injuries (mucositis, stomatitis, xerostomy, etc.), which are commonly observed with these anticancer agents.[43] However, since only one patient in our database developed taste impairments concomitantly with mucositis, other mechanisms should probably be taken into account and investigated. Studies on the electrical conduction of the glossopharyngeal nerve during and after anticancer chemotherapy have highlighted an increment of taste threshold.[44-46] Although an increase in the taste threshold to electrical stimulation may not necessarily reflect the clinical severity of the impairment, electrogustometric investigations should be performed to gain knowledge on chemosensory disturbances during treatments with protein kinase inhibitors.

The present study suggests that different drugs are suspected as causative agents of long-term or permanent gustatory and olfactory dysfunctions, leading to significant alterations of patients' quality of life. However, these findings should be interpreted with caution because of limitations that are typical of spontaneous ADR reporting systems. In particular, taste and smell alterations were reported by patients as subjective symptoms, since objective measurements of chemosensory deficiencies by means of appropriate tools are not commonly available in primary care. In this regard, we were not able to assess whether reports of taste and/or smell disturbance in our database were validated by appropriate taste or smell testing, but it is reasonable to assume that specific tests were performed only in very rare conditions. This circumstance could have led to both misclassification of drug-related taste and smell alterations, and estimations of the time to recovery. Moreover, several confounders, putatively accounting as effect modifiers or alternative causative agents (i.e. smoking and dietary habits, concomitant respiratory disturbances, etc.), for these adverse events could not be disclosed. In particular, viral and bacterial infections are among the most frequent causes of taste and smell alterations, and these diseases are commonly treated with antibiotics.[47] Since in our study antibiotics were found to be most frequently involved in taste and smell dysfunctions, we cannot exclude that, at least in some cases, the diseases and not their drug treatments were the sources of the reported adverse events.

Further methodological issues associated with the study design deserve consideration. Databases containing spontaneous reports of adverse events represent important sources of data for drug safety monitoring in the general population. For initial studies aimed at signal detection, such as in the present case, a primary goal must be the estimation of the magnitude of the adverse effect, with as low as possible influence by biases. However, computing an unbiased effect measure from spontaneous reports is not straightforward. For instance, completeness of case finding is always a concern, and it is rarely possible to estimate the underlying population of users since, therefore, neither the incidence rates nor the risks can be calculated. Consequently, proportional

reporting ratio (PRR) has been suggested as an effect measure.[48] The strength of PRR stems from its lack of influence by under-reporting. ROR, as used in the present study, provides a better measure than PRR. The calculation of ROR considers the database as the population of a case-control study, thus allowing the exclusion from the control series those categories of adverse events for which reporting is suspected to be related to the medication under evaluation. This exclusion is consistent with the principle that in a case-control study the selection of controls should be independent from the exposure.[50] In general, two sources of bias that are known to affect PRR can be removed by means of ROR. One bias stems from a control series for which the exposure distribution differs from that of the source population for cases. This bias is a classic issue occurring in case-control study design and can be removed provided that event categories responsible for non-representativeness can be identified. The second bias stems from the inclusion of cases in the denominator of the proportion used to calculate PRR. This bias is usually of modest relevance unless the cases under study represent a large proportion of all reported cases, and it can be completely removed by using ROR instead of PRR.[49] Even with this improvement, variability in reporting proportions over time and across categories of drugs and adverse events will still make inferences from such data problematic. Indeed, the reporting fractions can vary as a consequence of notoriety, surveillance and market size effects.[50] These concerns will continue to pose problems when interpreting the results of data analysis using spontaneous report databases, and cannot be mitigated by estimating ROR in place of PRR.[49]

Conclusions

Taste and/or smell abnormalities are common, and sometimes unexpected, complaints of patients during pharmacological treatments. The present study suggests that the drug classes most frequently suspected of playing a causative role in gustatory and olfactory alterations are macrolides, terbinafine (as the only drugs among selected cases within the antimycotics ATC class D01AE), fluoroquinolones and protein kinase inhibitors. Some of these impairments may be suggested as class effects, although further investigations are needed to confirm this hypothesis. In several cases, these ADRs appear to be as long-lasting or permanent events. However, our study has important limitations and should be interpreted as an exploratory investigation. In particular, the present findings need to be verified by *ad hoc* observational studies in which drug-related taste and smell disorders are measured using validated tools for the assessment of chemosensory functions. Physicians should be aware of the clinical significance of these ADRs, their consequence on patients' quality of life and the importance of their reporting to health authorities.

Acknowledgements

The present research was funded by the Servizio Sanitario Regionale Toscano. The funding organization had no role either in the conduct of the present study or in the writing of the present manuscript. None of the authors have any conflicts of interest to declare.

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