REVIEW ARTICLE

Drug Safety 2008; 31 (3): 199-215
0114-5916/08/0003-0199/$48.00/0

Drug-Induced Taste Disorders

Richard L. Doty,[1] *Muhammad Shah*[1] and *Steven M. Bromley*[1,2]

1 Smell and Taste Center, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA
2 Cooper University Hospital, University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School, Camden, New Jersey, USA

Contents

Abstract

Numerous drugs have the potential to adversely influence a patient's sense of taste, either by decreasing function or producing perceptual distortions or phantom tastes. In some cases, such adverse effects are long lasting and cannot be quickly reversed by drug cessation. In a number of cases, taste-related adverse effects significantly alter the patient's quality of life, dietary choices, emotional state and compliance with medication regimens. In this review, we describe common drug-related taste disturbances and review the major classes of medications associated with them, including antihypertensives, antimicrobials and antidepressants. We point out that there is a dearth of scientific information related to

this problem, limiting our understanding of the true nature, incidence and prevalence of drug-related chemosensory disturbances. The limited data available suggest that large differences exist among individuals in terms of their susceptibility to taste-related adverse effects, and that sex, age, body mass and genetic variations in taste sensitivity are likely involved. Aside from altering drug usage, management strategies for patients with taste-related adverse effects are sorely needed. Unfortunately, stopping a medication is not always an easy option, particularly when one is dealing with life-threatening conditions such as seizures, cancer, infection, diabetes mellitus and uncontrolled hypertension. Hopefully, the information contained in this review will sensitize physicians, researchers and drug manufacturers to this problem and will result in much more research on this pressing topic.

At least 90% of physician office visits result in a drug prescription.[1,2] Prescription drugs, as well as many over-the-counter medications, vitamins, minerals and herbal preparations, can produce chemosensory disturbances, in addition to adversely affecting oral health.[3] According to the *Physician's Desk Reference*[4] (PDR), hundreds of prescription medications produce such disturbances, either by altering acuity (e.g. by lessening sensitivity) or by producing perceptual distortions. Disorders of taste and smell function can negatively influence appetite, food intake, quality of life, emotional state and, importantly, medication regimen compliance.

The limited data available suggest that drug-induced chemosensory disturbances disproportionately occur in the elderly. Patients >65 years of age currently comprise 13% of the population, yet they consume approximately one-third of all prescribed drugs, with polypharmacy being the norm.[2,5] In a study of 1163 patients followed in the Oral Health: San Antonio Longitudinal Study of Aging, 33% reported drug-related alterations in taste and 57% the presence of dry mouth.[6] In 4163 patients surveyed in the Piedmont Health Survey of the Elderly, 11% reported drug-related taste changes and 56% dry mouth.[6]

Despite such reports, the true incidence and prevalence of drug-related chemosensory disturbances remain unclear. This reflects a number of factors, including: (i) the lack of uniformity as to how chemosensory disturbances are described and reported; (ii) little or no quantitative measurement or clinical documentation in validating chemosensory complaints; (iii) a failure to distinguish between the chemosensory effects and potential interactions among the underlying medical conditions and the medications used to treat them; (iv) variability in the doses and duration of medication treatments; (v) a lack of patient-specific data that may alter baseline chemosensory function, such as age, bodyweight, diet, genetic factors, co-morbid medical conditions and concurrent medication use; and (vi) failure to take into account spontaneous resolution of the dysfunction – resolution that may be high for some classes of drugs. Unfortunately, specific information regarding drug-induced chemosensory disturbances is often limited to isolated case reports in specialty journals, even after 3 years of drug cessation.

It is important to emphasize that physicians commonly make the error of accepting a patient's report of chemosensory loss without quantitative verification, despite the ready availability of tests that can achieve this end.[7,8] Such verification is critical, since many patients do not accurately gauge the degree of their dysfunction, and physicians and patients alike often erroneously attribute loss of such flavour sensations as chocolate, lemon, meat sauce and strawberry to gustatory dysfunction.[9] In fact, such losses reflect reduced stimulation of the olfactory receptors via the retronasal route.[10] True taste loss reflects taste-bud-mediated sensations such as sweet, sour, bitter, salty, umami (e.g. monosodium glutamate sensations), and perhaps chalky (e.g. cal-

Table I. Medications that reportedly alter smell and/or taste[a]

Drug class	Agent
Antianxiety agents	Alprazolam, buspirone, flurazepam
Antibacterials	Ampicillin, azithromycin, ciprofloxacin, clarithromycin, enoxacin, ethambutol, metronidazole, ofloxacin, sulfamethoxazole, ticarcillin, tetracycline
Antidepressants	Amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline
Antiepileptic drugs	Carbamazepine, phenytoin, topiramate
Antifungals	Griseofulvin, terbinafine
Antihistamines and decongestants	Chlorphenamine, loratadine, pseudoephedrine
Antihypertensives and cardiac medications	Acetazolamide, amiodarone, amiloride, amiodarone, bepridil, betaxolol, captopril, diltiazem, enalapril, hydrochlorothiazide, losartan, nifedipine, nisoldipine, nitroglycerin, propafenone, propranolol, spironolactone, tocainide
Anti-inflammatory agents	Auranofin, beclometasone, budesonide, colchicine, dexamethasone, flunisolide, fluticasone propionate, gold, penicillamine
Antimanic drugs	Lithium
Antimigraine agents	Dihydroergotamine mesilate, naratriptan, rizatriptan, sumatriptan
Antineoplastics	Cisplatin, carboplatin, cyclophosphamide, doxorubicin, fluorouracil, levamisole, methotrexate, tegafur, vincristine
Antiparkinsonian agents	Anticholinergics, levodopa
Antipsychotics	Clozapine, trifluoperazine
Antiviral agents	Aciclovir, amantadine, ganciclovir, interferon, pirodavir, oseltamivir, zalcitabine
Bronchodilators	Bitolterol, pirbuterol
CNS stimulants	Amfetamine, dexamfetamine, methylphenidate
Hypnotics	Eszopiclone, zolpidem
Lipid-lowering agents	Atorvastatin, fluvastatin, lovastatin, pravastatin
Muscle relaxants	Baclofen, dantrolene
Pancreatic enzyme preparations	Pancrelipase
Smoking cessation aids	Nicotine
Thyroid drugs	Carbimazole, levothyroxine sodium and related compounds, propylthiouracil, thiamazole

a The evidence for the involvement of many of these drugs in chemosensory disturbance comes from the *Physician's Desk Reference*.[4]

cium salts), metallic (e.g. iron and metal salts) and fatty.

This review focuses on the major classes of medications associated with clearly defined taste disturbance as an adverse effect. Discussion of the potential pathophysiological mechanisms, along with suggestions towards management, is provided whenever possible. Understanding the potential taste-related adverse effects of a given medication is of practical importance, because this allows the medical practitioner to more accurately counsel patients about what to expect when taking a medication, thereby ensuring better compliance and allaying future fears about its use. Simply stopping a medication is not always an easy decision, particularly when one is dealing with sometimes volatile and life-threatening conditions such as seizures, cancer and infection.

The breadth of drugs reportedly associated with chemosensory disturbance is enormous, as shown in table I. However, evidence for such involvement is highly variable, and a number of descriptive categories do not distinguish between sensory loss, which can be quantified, and distortions or phantom tastes, which are not easily quantified. For example, the majority of drugs are listed in the PDR[4] and other authoritative sources[11] as producing 'altered taste' without defining the nature of such alterations. The major classes of drugs that are most strongly implicated in altering taste function are listed in the following sections.

1. Antimicrobials

1.1 Antibacterials

Although it has long been known that a number of antibacterials have the potential to alter taste function, their relative influences on taste and smell have rarely been empirically established.[12] A case in point is an early report that griseofulvin produced 'tastelessness' to all foods and flavours, although neither smell nor taste testing was performed.[13] The potential for routine use of antibacterials to alter the normal oral, gastric and intestinal flora is significant and may lead to superimposed infections (e.g. candidiasis, caries) and periodontal disease that can influence taste function adversely.[3,14] Overuse of antibacterials can also lead to resistance and further treatment complications.

Many antibacterials taste bitter, metallic and/or sour at concentrations that occur in salivary secretions, implying a direct influence on the taste system.[15,16] Metronidazole is well known to produce a metallic taste that can affect patient compliance. Empirical studies indicate that, with the exception of pyrimidines (i.e. pyrimethamine and trimethoprim), a number of antibacterials change the taste of sodium, potassium and/or calcium salts when applied locally to the tongue. Ampicillin and pentamidine, for example, decrease sodium chloride perception; tetracycline, pentamidine and ethambutol decrease potassium chloride perception; and ampicillin, pentamidine, aciclovir, ethambutol and sulfamethoxazole reduce calcium chloride perception.[16]

It is generally assumed that antimicrobial agents access nasal and salivary secretions from the general circulation. The concentration of the fluoroquinolone enoxacin, a drug that induces both taste and smell alterations, is over one and a half times higher in nasal secretions than in plasma.[16] Intravenous injection of pentamidine produces, in some persons, an almost immediate bitter or metallic sensation, possibly via direct stimulation of taste receptors via blood- or saliva-borne routes.

It is of interest that the taste of antibacterials can be influenced by the medium in which they are ingested. Thus, some antibacterials taken together with acidic foods or suspended in acidic sports drinks taste more bitter than when taken with water. This reflects the fact that these drugs dissolve more rapidly in acidic conditions and their bitterness is not blocked by sweet tastants.[15]

1.2 Antifungals

Perhaps the best documented case of an antifungal agent influencing taste function is that of terbinafine, a drug introduced in 1991. In one clinical trial, terbinafine produced adverse taste effects in 2.8% of 465 patients who received the drug compared with 0.7% of 137 patients who received placebo.[4]

In the first case report on this topic, a 46-year-old woman progressively lost her ability to taste after taking terbinafine (250 mg/day) for long-standing *Trichophyton rubrum* infection of the toenail.[17] The taste loss was first noticed around 6 weeks after drug initiation, and followed a distinct progression, with salty and bitter tastes first disappearing, followed by sweet and sour ones. After drug cessation, taste sensations recovered in the same order they had disappeared, with subjective recovery of sweet sensations taking about 5 weeks. Similar reports subsequently appeared, with most indicating recovery within several months after drug discontinuance.[18,19] In one such report, taste dysfunction did not resolve completely even after 3 years of taking the drug.[19]

In the only study to quantitatively assess taste and smell function in patients complaining of terbinafine-related taste disturbance (250 mg/day), olfactory function was normal.[20] However, taste function was abnormal in all of the six patients evaluated (three male and three female non-smokers; 44–83 years of age). Relative to matched normal controls, sour (citric acid) and bitter (caffeine) perception was more severely altered than sweet (sucrose) and salty (sodium chloride) perception, as measured by a forced-choice taste-identification test. A non-significant positive correlation was present between the test measures and the length of time since treatment cessation (Pearson $r = 0.52$; $p = 0.29$).

Terbinafine-related taste problems appear to be much more common in older patients and in patients with lower body mass. In a case-control study, 87 cases of self-reported terbinafine-induced taste loss and 362 control patients who reported no such loss were identified from a pharmacy prescription listing.[21] The mean latent period between first intake of terbinafine and reported taste loss in the cases was 35 days. Subjective return of function usually occurred within 4 months of drug discontinuance. Cases were found to be significantly older than controls and had lower average body mass indices (BMIs). The risk of taste loss in patients ≥55 years of age with a BMI of <21 kg/m^2 was 12.8 times higher than in patients <35 years of age.

Since terbinafine is highly lipophilic, the aforementioned association between lower BMI and greater risk for terbinafine-related taste loss could reflect higher, more injurous, drug concentrations. Older patients may be more vulnerable to drug-related taste alterations than younger ones if they have fewer or less functional taste afferents.[22] Thus, proportional damage to such afferents would result in larger functional deficits. As with the other allylamines, terbinafine inhibits ergosterol biosynthesis via inhibition of squalene epoxidase.[23] Squalene epoxidase is an element of the fungal sterol synthesis pathway essential for the creation of sterols needed for the fungal cell membrane. Since squalene epoxidase also catalyzes the second and likely rate-limiting step in cholesterol biosynthesis from farnesyl pyrophosphate, and since cholesterol-reducing drugs such as atorvastatin induce disturbances in taste function in humans,[24] it is conceivable that terbinafine alters the cell structure or function of taste-related neurons via the cholesterol pathway. Some have speculated that the taste-related adverse effects associated with terbinafine reflect inhibition of cytochrome P450 enzymes at the receptors.[17]

Support for the idea that the effects of terbinafine occur at the level of the afferent gustatory pathway comes from two observations: (i) this drug seems to produce greater alterations in bitter- and sour-taste perception than in sweet- and salty-taste perception; and (ii) more sucrose-best and sodium chloride-best fibres are present in the primate chorda tympani nerve than citric acid-best and caffeine-best fibres.[25] Assuming a similar situation in humans, it may be that the fewer fibres and/or receptors dedicated to a given taste sensation, the larger the adverse effects of terbinafine on their function.

1.3 Antivirals

As with a number of antibacterials, some antiviral agents have marked taste-related adverse effects, often described as bitter. For example, the protease inhibitors, which are widely used in the treatment of HIV and AIDS, exhibit such adverse effects, and appear to adversely modify the taste perception of other taste compounds. Highly active antiretroviral therapies (HAARTs) reportedly produce a high incidence of taste perversions in HIV-positive adults, including oily aftertastes.[26,27]

At least two of the four licensed influenza antiviral agents available in the US, namely amantadine and oseltamivir, have been reported to taste bitter in oral suspension, with amantadine being the most bitter.[15] As with antibacterials, the bitterness is increased when the milieu in which they are delivered is more acidic.[15] The bad taste of aciclovir is the basis for poor medication compliance by children, for whom the tablets must be crushed for ingestion because of their size.[28] It should be noted that aciclovir is commonly used to treat Bell's palsy, a medical condition with a direct adverse effect on taste function on the side of the tongue ipsilateral to the facial weakness.[14]

Several anti-rhinovirus preparations designed for intranasal spray application have been associated with transient unpleasant tastes.[29,30] For example, intranasal introduction of pirodavir, a capsid-binding antipicornaviral agent, induced an unpleasant taste in 59% of 66 patients tested compared with 27% of 65 patients who received the carrier component alone.[29] The taste sensations, which are reported as being relatively mild, usually began within 4–15 minutes after nasal spraying and lasted <1 hour, typically <5 minutes. This temporal pattern suggests that the effects are likely local and prob-

ably related to movement of the drug within the nasal secretions via the nasal pharynx to the taste buds.

Recently maribavir, a member of a new class of antivirals, benzimidazole ribosides, has undergone clinical trials. In the phase I trial, this drug was administered at increasing doses to 13 healthy and 17 HIV type 1-infected patients in a double-blind protocol.[31] The only consistent adverse effects were taste disturbance (83%) and headache (53%). The taste disturbance, the intensity of which was dose related, was characterized as a bitter, metallic, chemical or 'altered oral taste sensation', and may have reflected salivary secretion of the drug onto the taste receptors after systemic absorption.

Oral zinc lozenges have long been sold as an over-the-counter remedy for mitigating the length and symptoms of common colds. Several studies have reported that such lozenges produce bad-taste sensations.[32,33] For example, one randomized, double-blind, placebo-controlled study found that bad-taste sensations were reported by 80% of the zinc group and by only 30% of the placebo group ($p < 0.001$).[34] An aftertaste was also noted, with 41% of the zinc recipients and 6% of the placebo recipients reporting the aftertaste as moderate to severe. A mild aftertaste was noted by 45% of the zinc group compared with 24% of the placebo group. While zinc lozenges can adversely influence taste function, zinc repletion reportedly improves the symptoms of hypogeusia and xerostomia in cases of zinc deficiency.[35]

2. Antiproliferatives and Antimetabolites

Chemotherapeutic agents can lead to olfactory and gustatory receptor destruction, and patients undergoing these modes of therapy are at risk for impairment of chemosensory function. Although receptive elements can be regenerated from basal (stem) cells,[36-38] if antiproliferatives alter the stem cell population, permanent damage can occur. Commonly involved drugs include cisplatin, carboplatin, cyclophosphamide, doxorubicin, fluorouracil, levamisole and methotrexate. Antineoplasatic agents that interfere with cellular function by incorporating into either DNA or RNA (purine and pyrimidine nucleotides) are termed antimetabolites.

The antimetabolite tegafur is commonly reported to alter taste. Whether taste *per se* is the factor is not clear, since this drug produces olfactory dysfunction and severe degeneration within the olfactory mucosa, influencing a range of cell types including the olfactory receptor cells.[39] Initial infusion of a number of antiproliferatives can result in an immediate bitter taste, as well as taste alterations that can continue for months, in some cases reflecting direct passage of the drug into the saliva.[40] In a study of cisplatin, 77% of the 284 infused patients developed a metallic taste that lasted from a few hours to 3 weeks.[41] Immunosuppression secondary to chemotherapy can also lead to candidiasis, as well as a host of other problems including oral bleeding and dental disease that may further compromise function and contribute to dysgeusia.[42]

Ageusia was recently reported in a patient with multiple myeloma receiving pegylated liposomal doxorubicin.[43] This 67-year-old man with a history of arterial hypertension and persisting left bundle-branch block was initially treated with cyclophosphamide 200 mg/m^2 (days 1–4), pegylated liposomal doxorubicin 20 mg/m^2 (day 1), and dexamethasone 40 mg (days 1–4) [CLAD]. The treatment was followed by high-dose melphalan therapy and autologous peripheral stem-cell transplantation. The disease recurred 18 months later, and renal failure developed. The patient was again treated with the CLAD protocol. After the first cycle, almost complete ageusia occurred, along with weight loss and severe depression. Chemotherapy was continued, but pegylated liposomal doxorubicin was replaced by conventional doxorubicin. Within 12 weeks of discontinuance of the pegylated liposomal doxorubicin, the patient's sense of taste returned to normal. The authors concluded that a probable connection exists between reversible ageusia and the use of pegylated liposomal doxorubicin.

3. Antithyroid Drugs

It has been known since the early 1950s that thiamazole adversely influences the ability to taste.

In the first report of this phenomenon, Hallman and Hurst[44] described a patient who, after 4 weeks of being on a 40-mg dose of thiamazole, lost his ability to identify sweet, sour, bitter and salty tastants. The patient's taste function returned 3 weeks after cessation of therapy.

Hypothyroid patients who receive thyroid replacement medication are more likely to complain of taste dysfunction than non-hypothyroid patients.[9] The relative roles of the medication, the underlying thyroid problem, and other factors are not clear in these thyroxin-replete individuals, and some such patients actually perform better on a whole-mouth test of taste identification and perceived intensity than non-hypothyroid patients.[9] Early studies employing more localized presentation of taste stimuli to the tongue reported that hypothyroid patients exhibit heightened detection thresholds to tastants, most particularly bitter-tasting ones, and that thyroxine replacement returns the thresholds to normal.[45]

The influences of thioamides are not confined to taste. Indeed, carbimazole and thiamazole inflict significant damage to the olfactory mucosa of rats, altering to some degree their ability to smell.[46-48] However, anosmia is not induced.[47] Hypothyroidism induced in rats by administration of propylthiouracil alters taste preferences for salty, sour and bitter tasting stimuli, but not sweet tasting ones, resulting in greater intake of these substances. Sensitivity *per se* appears not to be altered.[49]

4. Cardiovascular Medications

Nearly all classes of cardiovascular medications have been associated with altered taste function, including antilipaemic agents, adrenergic stimulants, α- and β-adrenergic receptor antagonists, ACE inhibitors, angiotensin II antagonists, calcium channel antagonists, group I–IV antiarrhythmics, combination diuretics and coronary vasodilators. Indeed, over one-third of all the current blood pressure modifying agents have taste-related adverse effects.[24] Described in the following sections are those classes for which the most data are available.

4.1 ACE Inhibitors

ACE inhibitors are the most common antihypertensive drugs to have chemosensory adverse effects, mainly gustatory ones. Seventy percent of the ACE inhibitors listed in the PDR[4] are associated with altered taste perception (i.e. classified specifically as producing loss of taste, sweet taste, metallic taste, taste disturbance or taste distortion).[24] When combined with calcium channel blocking or diuretic drugs, 11 of 17 (65%) ACE inhibitors are associated with such taste disturbances.[24]

Captopril, the first orally active ACE inhibitor, was introduced in 1977. This drug engenders more frequent complaints of ageusia and dysgeusia than any other drug in its class.[50] Captopril can make sweet-tasting foods taste salty and can produce a persistent bitterness or saltiness in the mouth. In one study, this drug was found to reduce the perceived intensity of sucrose and potassium chloride.[51] The effects of captopril are dose-related, with reports of disturbance increasing from 1.6% at dosages of <150 mg/day to 7.3% at dosages >150 mg/day.[52] Although the sulfhydryl group, which is present in captopril but absent in most other ACE inhibitors, may contribute to this drug's adverse effects, non-sulfhydryl-containing ACE inhibitors, such as enalapril, can also produce similar adverse chemosensory affects, albeit at much lower frequencies.[53]

In some cases, alterations in taste attributed to captopril and other ACE inhibitors are self-reversing, disappearing a few months after the initiation of therapy. In most cases, discontinuance of the drug reverses the taste deficit. Grosskopf et al.[54] describe a patient with captopril-related nausea and altered taste. Within 48 hours of drug cessation, the nausea subsided and subjective taste function returned to normal. McNeil et al.[55] reported that three of 16 captopril-treated patients who reported having lost taste function recovered function within 2 weeks of stopping the medication.

In terms of adverse effects, patients may respond differently to medications within the ACE inhibitor class. For example, one case report describes a 66-year-old woman who had the common adverse event

of cough while taking quinapril. However, weeks later she was switched to enalopril and developed severe dysgeusia instead.[56]

4.2 Angiotensin II Antagonists

Angiotensin antagonists act by blocking the angiotensin receptors themselves. Losartan, the most widely used of these drugs, has been associated with ageusia and dysgeusia.[57,58] Although losartan has similar therapeutic efficacy to ACE inhibitors, it appears to have fewer adverse effects, conceivably reflecting no increase in bradykinin levels secondary to its use.[59,60]

4.3 Antihyperlipidaemics

Adverse chemosensory effects are noted in the PDR[4] for seven of the ten antihyperlipidaemic drugs that are in current clinical use. 'Altered taste' is named as an adverse effect for all six of the HMG-CoA reductase inhibitors ('statins'), and dysgeusia, ageusia and parosmia are listed as additional adverse effects for a number of these drugs. In a placebo-controlled study of atorvastatin, adverse effects of altered taste, parosmia and ageusia were noted.[4] Similar adverse effects were noted in clinical trials with cerivastatin, fluvastatin, pravastatin, lovastatin and simvastatin.

4.4 Calcium Channel Antagonists

More than half of the calcium channel antagonists in current clinical practice have been implicated, mainly in case reports, in the production of taste or smell disturbances. Agents containing nifedipine, amlodipine, diltiazem, bepridil and nisoldipine have all been said to induce dysgeusia.[61]

In addition to effects on taste, calcium channel antagonists variably and unpredictably affect the gingiva and are associated with the production of gingival hyperplasia in 20–83% of patients.[4,62] Whether such gingival alterations can indirectly alter taste function, e.g. via exudate secretion, is unknown.

4.5 Diuretics

There has been a resurgence of the use of diuretics, given that they are quite effective in blood pressure control and have a relatively low incidence of adverse effects.[63] The influences of diuretics on human taste function are not clear. According to a study reported in the PDR, amiloride is associated with 'bad taste' in <1% of 607 patients evaluated.[4] Amiloride itself has a bitter taste. Animal studies suggest that amiloride can block sodium channels on the taste cell, suggesting that this substance may alter the taste of some salts.[64,65] Indeed, psychophysical studies indicate that amiloride (100 μmol/L) placed on the tongue for 5 minutes reduces the perceived intensity of solutions of sodium chloride and lithium chloride, but not potassium chloride, in most subjects.[66] However, whole-mouth threshold values of patients who have been taking amiloride systemically for some period of time suggest hypersensitivity, not hyposensitivity, to sodium chloride. Those receiving amiloride had decreased sodium levels in their saliva tests, conceivably producing a perceptual imbalance between the stimulated and adapted states.[67]

Medications with carbonic anhydrase inhibiting properties (e.g. acetazolamide) have taste disturbance as a prominent adverse effect.[68] Mechanisms for acetazolamide influences on taste remain unclear, although there are known influences of this medication on electrolyte balance, salivary production, acid/base balance in the serum and central neurotransmitter receptor function.[69] Two of the newer antiepileptic medications are relatives of acetazolomide, namely zonisamide and topiramate.

5. Corticosteroids

Corticosteroids have the ability to alter the body's immune system and induce oral candidiasis, as well as stomatitis, glossitis, oral bleeding and dental disease, all of which can alter or contribute to taste dysfunction.[70] As a result of concern for poor compliance with the use of oral liquid corticosteroid preparations in children, Mitchell and Counselman[71] examined the relative palatability of dexamethasone, prednisone and prednisolone using adult

volunteers. Dexamethasone was preferred in all four categories evaluated, namely smell, texture, taste and aftertaste. Prednisone was least preferred. The prednisone was a brand name, whereas the other two corticosteroid preparations were generic, contrary to the notion that brand name drugs are always more palatable. In a randomized, double-blind, crossover, multicentre study of 95 patients that compared three different intranasal corticosteroid preparations for allergic rhinitis, aqueous triamcinolone was found to cause less irritation, less intense odour, a milder taste and less aftertaste than mometasone and fluticasone propionate.[72] Thus, it is clear that corticosteroid preparations considered to be equal on all levels may not be equal in terms of taste palatability.[73]

It is possible that high dose or long-term systemic use of corticosteroids may alter the taste system independently of immunosuppression, particularly if it is compromized for other reasons (e.g. as a result of age). It is known, for example, that dexamethasone potentiates the olfactotoxicity induced by the systemic olfactotoxin 3-methyl indole (3-MI) during the first 2 weeks after insult, an effect likely due, in part, to the inducing action of dexamethasone on the cytochrome P450 responsible for metabolic bioactivation of 3-MI.[74] Whether similar effects can occur within the taste system proper is unknown.

6. Psychoactive Drugs

6.1 Antidepressants

A variety of tricyclic antidepressants are associated with peculiar taste sensations. Drugs of this class include amitriptyline, clomipramine, desipramine, doxepin, imipramine and nortriptyline. Some of these drugs not only have a taste of their own, but may alter the intensity of other tastants (such as salt and sugar).[75] For example, in one study of 34 subjects, the widely used tricyclic antidepressant amytriptyline was continuously applied to the tongue.[76] Sensations from all four basic taste modalites were altered to some degree. When this drug was applied intermittently, only the taste for salts was diminished.

The reasons for the effects of amitriptyline on taste perception are unknown, although this agent may enter the lingual or the biochemical environment of the taste receptors via saliva or the lingual blood supply. It could then block sodium, potassium and calcium membrane channels, as well as alter the metabolism of second messenger systems. This and other members of the tricyclic class also have anticholinergic properties that may contribute to distortions of taste perception.[77] Dry mouth is a classic adverse effect of anticholinergic medications.

Another class of antidepressants, namely selective serotonin reuptake inhibitors, have also been associated with taste disturbances, such as taste loss and taste perversion. Drugs of this class include citalopram and fluoxetine, the latter of which is also associated with parosmia.[4,78] It is not known whether this is a misclassification or a true adverse effect of this widely used medication.

The atypical antidepressants, such as venlafaxine, duloxetine, mirtazapine, bupropion, trazodone and nefazodone, act on multiple brain receptors beside the serotonergic receptors, without activating unwanted sites such as histamine and acetylcholine. Bupropion, an atypical antidepressant, commonly produces taste disturbance by causing dryness of mouth. Johnston et al.[79] reported that dry mouth is positively associated with mean bupropion metabolite concentrations and inversely related to patient weight.

The possibility exists that antidepressants may alter taste problems induced by other drugs, such as antibacterials. For example, one case report describes an 84-year-old woman who developed a metallic taste after using levofloxacin for an ear infection.[80] The dysgeusia persisted even after discontinuation of levofloxacin, but resolved after her antidepressant medication was switched from fluoxetine to mirtazapine. However, it is conceivable that the resolution of the dysgeusia was spontaneous and that its apparent dependence upon the change in medication was purely coincidental.

6.2 Antianxiety Agents

Benzodiazepines, the most common antianxiety drugs, are widely used in clinical practice these days. Among this class of drugs are flurazepam and alprazolam, both of which are reported to cause dysgeusia.[4,81] However, there is evidence that benzodiazepines enhance taste palatability and may increase perceived sweetness of some foods.[82,83] Moreover, it should be noted that olfactory and gustatory disturbances in the form of hallucinations/auras can occur as a simple partial seizure phenomenon and, in cases where chemosensory disturbance is seizure-related, benzodiazepines may actually help.

6.3 Antipsychotics

Haloperidol, a butyrophenone and the prototypical traditional antipsychotic agent, has been implicated in several reports of taste disturbance, as has trifluperazine.[75]

Atypical antipsychotics have largely replaced traditional antipsychotics in the management of psychotic conditions marked by positive (productive) symptoms. Olanzapine, the prototype in the class, has been reported to produce dysgeusia.[84] Risperidone, another common antipsychotic, has also been reported as producing a bitter dysgeusia.[85]

6.4 Antimanics/Mood Stabilizers

According to some reports, lithium, the main stay of bipolar disorder treatment, can lead to distorted taste sensations.[86,87] However, it is not clear whether such effects are taste effects, olfactory effects or both. Duffield,[88] in the first case report of this phenomenon, described a 50-year-old physicist who began, after a few days of taking lithium carbonate (250 mg three times daily), noticing that certain foods took on "a strange and unpleasant taste". As noted by this patient, "The first to be affected were butter and celery; both had a strong flavour quite unlike anything else I have experienced. The 'new' flavour seemed superimposed on the original taste, and was the same for both these foods. Cooked celery also had a strong associated smell, which I found almost unpleasant; other vegetables tasted and smelt perfectly normal." This patient went on to state, "… even a trace of butter (for example, in cakes) rendered them very unpalatable."

This phenomenon was subsequently observed by others and occurred in approximately 5% of a group of 450 patients being treated with this drug.[89] In these cases, the taste reportedly disappeared 3 days after taking the drug. These authors pointed out that, in rats, lithium is particularly concentrated in the olfactory bulbs, caudate and pituitary, suggesting this effect may be olfactory related. Since lithium is commonly used as the illness-inducing unconditioned stimulus in conditioned taste-aversion studies in animals, it is not inconceivable that some patients could develop conditioned aversions to tastes or smells during lithium treatment.[90]

6.5 Antiepileptic Drugs

As a class, antiepileptic drugs are quite variable in their mechanisms of action and they can directly affect both central and peripheral neural function. Antiepileptic medications are known to affect such receptor targets as the sodium channel, calcium channel, GABA receptor and the glutamate system, as well as influence enzymatic clearance in the body, and thereby alter the metabolism of other medications.[91] The newer antiepileptic medications are considered to be 'cleaner' enzymatically, but their mechanisms of action are much less well defined.[92]

It is not clear whether or to what degree antiepileptic drugs alter chemosensory thresholds, although sensory thresholds in some other modalities are increased by antiepileptics (e.g. vibration perception). One report of ageusia following phenytoin does exist in the literature.[93] In this case, a 52-year-old man with a right parietal glioma was given intravenous phenytoin (750 mg) over a 3-hour period after he was admitted with simple focal and secondary generalized seizures. He soon developed an inability to detect solutions of saccharin, sodium chloride, citric acid and quinine hydrochloride. Two weeks later, the problem persisted and, because he

had a 10- to 25-fold increase in liver enzyme levels, the phenytoin was discontinued and replaced with phenobarbital. A week later he had regained his taste.

A commonly reported adverse effect of topiramate, a medication used for seizures and migraine prevention, is altered taste perception.[94] A recent study showed that such alteration occurred in 8% of 469 patients receiving this drug.[95] Patients complain occasionally of a topiramate-induced metallic taste that can fade over time or with a reduction in dose.[96]

Some antiepileptic medications (e.g. carbamazepine, oxcarbazepine) can produce hyponatremia as a major adverse effect, possibly through syndrome of inappropriate antidiuretic hormone secretion (SIADH) or salt-wasting processes. Several studies have shown that hyponatremia alone, as a complication of neoplasm and SIADH, can result in taste alterations such as a sweet dysgeusia.[97,98] It should be pointed out that patients who have seizures are susceptible to non-medicine causes of chemosensory distortions, such as olfactory and gustatory auras associated with partial seizures themselves.

Gingival hyperplasia is a well recognized complication of phenytoin, as well as calcium channel antagonists and ciclosporin;[99] however, to our knowledge there are no clear correlations between overgrowth of gingival tissue and taste perception, *per se*.

6.6 CNS Stimulants

CNS stimulants, namely amfetamines, dexamfetamines and related compounds such as methylphenidate, can produce dysgeusia (e.g. 'unpleasant taste') in some patients.[100] Additionally, amfetamine-based drugs such as methamfetamine ('speed') and methylenedioxymethamfetamine ('ecstasy') produce a wide range of aberrant oral sensations. For example, methamfetamine abusers report experiencing xerostomia, which cannot be explained by the direct peripheral action of this drug on the secretory acini. One proposed mechanism is that methamfetamine centrally inhibits salivatory nuclei via stimulation of adrenergic α_2 receptors.[101]

In rats, low doses of amfetamine likely enhance odour detection performance via dopamine D_1 receptors, whereas higher doses of amfetamine likely depress such performance via D_2 receptors.[102-104] Whether a similar dose-related effect of amfetamines on odour or taste perception occurs in humans is not known.

6.7 Hypnotics

Many sleep-inducing agents are associated with taste and, in rare instances, smell disturbances as potential adverse effects. Zolpidem, currently the most widely employed sleeping aid, is listed in the PDR as producing 'taste perversion' and, more infrequently, 'parosmia'.[4] Eszopiclone, a nonbenzodiazepine pyrrolopyrazine derivative of the cyclopyrrolone class, is associated with complaints of 'unpleasant taste'. In a 6-week placebo-controlled trial of this drug in non-elderly persons, 16% of 104 patients receiving the 2-mg dose experienced this adverse effect. This number doubled in those receiving the 3-mg dose (32%; 34/105). Only 3% of the 99 persons in the placebo group complained of this symptom. In a larger double-blind placebo-controlled study, 26.1% of 593 patients taking the 3-mg dose of eszopiclone for 6 months reported an unpleasant taste compared with 5.6% of 195 placebo controls.[105]

6.8 Substance Abuse Management Agents

A number of medications used in alcohol and drug abuse management affect taste perception. Acamprosate, an agent that decreases excitatory glutamergic neurotransmission during alcohol withdrawal, produces aversive tastes, whereas disulfiram, a drug that inhibits the activity of acetaldehyde dehydrogensase, produces metallic- or garlic-like aftertastes.[106] In one study, naltrexone, an opiate antagonist, decreased the pleasantness of glucose solutions, but not salt solutions,[107] whereas in another study this drug mitigated the normal tendency of foods to become more pleasant as a function of hunger.[108] The decrease in electric taste thresholds that occurs during presentation of food to fasted patients is eliminated by naltrexone.[109]

7. Other Substances

A number of agents in cigarette smoke, such as acrolein, acetaldehyde, ammonia and formaldehyde, can induce damage to olfactory mucosa, often in a dose-dependent manner.[110,111] Human studies suggest that smoking causes long-term, but reversible, deficits in smell ability, and persons who currently smoke are more likely to have an olfactory deficit than persons who have never smoked.[112] In animal studies, even relatively brief exposures to cigarette smoke (once or twice per day for 6–9 days) can cause physical changes in the olfactory epithelium, such as reduction in the size and number of vesicles and cilia.[113]

Acute ingestion of alcohol influences ethanol thresholds and was found in a double-blind study to have subtle influences on a standardized odour memory/discrimination test.[114] Chronic ethanol use has been associated with both reversible and non-reversible olfactory dysfunction, the latter being most extreme in cases of Korsakoff's psychosis, where CNS damage from thiamine deficiency is present.[115] Alcohol also affects taste in the form of reduced intensity ratings that persist even after detoxification. Alcohol ingestion may potentiate the influences of cigarette smoking on olfactory epithelial pathology.[116]

Botulinum toxin A, frequently used to treat dystonia, localized hyperhidrosis, migraine headaches and cosmetic rhytides, was reported in one case to result in a self-limiting metallic taste.[117] One proposed mechanism from these authors is zinc chelation: botulinum toxin works on zinc-dependent endoprotease to prevent acetylcholine release.

Among the migraine-specific triptan class of medications, sumatriptan was the first offered in the form of a nasal spray. Many patients reportedly do not tolerate the 'unpleasant' bitter taste of this drug, especially when it is administered incorrectly towards the back of the nasopharynx.

8. Management of Drug-Induced Taste Disorders

The mechanisms responsible for taste-related adverse effects are poorly understood. In some cases they are likely multiple and interactive. Thus, drug-induced adverse taste effects can reflect (i) the taste of the drug itself; (ii) damage to the taste receptors, either directly or via secondary processes, such as acid from gastroesophageal reflux; (iii) influences of immunosuppression and related sequellae (e.g. development of oral candidiasis); (iv) disturbed neuronal impulse propagation (e.g. by influencing calcium flux, inducing perineural inflammation or demyelinating neurons); (v) changes in neurotransmitter function; (vi) alterations in higher-order cortical processing of taste-related sensory information; (vii) drying of the oral mucosa, which limits access of chemicals to receptor sites; and (viii) altered production and chemical composition of saliva and mucosal elements. Although saliva serves the fundamental purpose to provide moisture and lubrication in the mouth, it is also essential to buffer acids and bases and to increase availability of solubilized chemicals to taste receptors.[118] Interestingly, patient expectations may also play a role in how medications relate to taste. Thus, if a patient expects a medicine to taste badly, this medication may be more likely to be experienced adversely.[119]

In light of such complexities and the general lack of understanding of the basis for most drug-related adverse effects, the management of drug-induced taste disorders can be difficult. The long-lasting adverse effects of medications conceivably reflect damage to the taste receptors, nerves or more central structures. Improved oral hygiene can minimize some drug-related effects, such as drug-induced gingival hyperplasia. In cases where the chemosensory problem is due to underlying illness targeted by the pharmacological intervention (e.g. epilepsy, hypothyroidism, cancer, infection), then removing the medication may actually make the smell or taste problem worse. However, in most cases, termination of drug therapy, employing an alternative medication or changing dose are the logical approaches to overcome taste-related adverse effects, although specific therapy to alleviate symptoms may be required in cases where the effects persist. Despite the fact that peak impairment may occur near the time of medication-dose administration, accumulation of an

underlying chemosensory altering metabolite is possible and may explain some cases of lingering disturbance. Secondary effects of pharmacological interventions, such as salivary gland impairment with resulting xerostomia or superimposed oropharyngeal and nasal cavity infections, can complicate chemosensory recovery.

Although the removal of the offending medication may alleviate the chemosensory adverse event in most cases, further efforts on the part of the clinician may help protect a patient from ongoing taste-related problems. As noted earlier, many medical conditions result in chemosensory processing problems and, if left unchecked, these medical conditions are likely to result in further dysfunction. A detailed history regarding all medications taken is important and examination of the oral cavity, head and neck region, and gustatory/olfactory functions is essential. In many cases, blood tests and neuroimaging techniques may be necessary. Oral hygiene needs to be discussed since chemosensory perception can be dramatically influenced by such factors as poor dental health, overuse of topical agents such as mouthwashes or peroxide and repetitive oral trauma (e.g. aggressive tooth brushing, misaligned dentures or braces). Artificial saliva can be beneficial in many cases of xerostoma exacerbated by medications.

It should be noted that, in some patients, a clinician needs to consider other factors when trying to determine if a resulting chemosensory complaint relating to a medication is truly an adverse event, as opposed to a distinctive experience coloured by cultural background and prior exposure. For example, the concept of 'bitter' has long been felt to represent an adaptive taste experience to avoid ingesting environmental toxins or poisons (since they usually taste bitter to humans).[120] Yet, coffee and beer would clearly lose their appeal without some bitter taste. How a particular person responds to a medication and labels it either 'good' or 'bad' tasting may be directly related to variation in (i) the multitude of bitter taste receptors in each patient; (ii) the person's exposure time to bitter-tasting substances in the past; and (iii) the complex interplay of personality traits.[121,122] We know that studies of animals show that they can vary tremendously in their tolerability of apparently toxic-tasting (bitter) substances. Thus, herbivorous animals (grazing and browsing) seem to have a higher threshold for bitter-tasting and toxic substances since they are more commonly encountered in their limited routine diet of wild plants and fruits. This is contrasted to the carnivore that typically has a lower threshold for bitter tastes and is on 'high alert' for poisonous non-meat substances.[120]

Repeated exposure to a particular taste quality may result in a changed preference for that quality. In one study, for example, children who were repeatedly exposed to sweet or sour tasting substances tended to prefer the sweet taste only after repeated exposure. Prior to the exposure they had an equal preference for both tastes.[123] It also appears that a high level of consumption of fruit in boys leads to a preference for high concentrations of citric acid in food substances.[124]

By inference from these data, it may be that although a medication produces an adverse chemosensory experience, initially as a result of prior exposures and cultural differences, repeated exposure may lead to tolerability and even a preference for this same medication. Unfortunately, there is a tremendous lack of data on this subject.

9. Conclusions

This paper presents a general overview of drugs that have the potential to adversely influence the sense of taste. It is apparent that a very wide range of oral medications have this potential, either by altering acuity or by producing perceptual distortions or phantom tastes. Such effects can be long lasting and, in many cases, significantly alter the patient's dietary choices, quality of life, emotional state and compliance with medication regimens.

Unfortunately, the lack of empirical studies largely compromises a true understanding of the nature, incidence and prevalence of drug-related chemosensory disturbances. Moreover, relatively little is known about the physiological basis of such effects and major initiatives on the part of drug

companies to correct such problems appear to be slow in forthcoming, if at all. The limited data suggest that considerable differences exist among patients in terms of their susceptibility to drug-related adverse taste effects, and that such susceptibility depends upon a number of individual factors, including sex, age and BMI. Surprisingly, little research has been performed to understand factors that make some patients susceptible to drug-related effects, including the influences of culture and prior experience.

It is clear from the studies reviewed in this paper that the main alternatives available to the physician to aid in mitigating drug-related adverse taste effects are drug discontinuance, drug substitution and dose adjustment. Hence, it is critical for the physician to become knowledgeable as to which drugs are most likely to produce chemosensory disturbances and what alternatives are available. Unfortunately, the time course of the reversibility of many taste-related adverse effects is unknown, and short-term discontinuance often proves ineffectual.

It is clear that without the use of medications in many circumstances, underlying medical conditions can progress to distort and/or damage chemosensation (e.g. infection, seizures, neoplasm, etc.). However, one inevitable risk with some medications is a resulting adverse effect on chemosensory function. This 'balancing act' of knowing when to treat a patient with a medication that can potentially cause adverse effects encompasses much of the art of medical practice. While the clinician tries to 'do no harm', many medical therapies unfortunately leave a bad taste in the mouth.

Acknowledgements

This work was supported, in part, by Grants RO1 DC 004278 and RO1 AG 27496 from the National Institutes of Health, Bethesda, MD, USA. Dr Doty is a major shareholder in Sensonics, Inc., a manufacturer and distributor of tests of smell and taste function, and has served as a consultant to GlaxoSmithKline and Sepracor. Dr Bromley has participated on advisory panels and speaker bureaus for GlaxoSmithKline, Eli Lilly and Company, Pfizer, Cephalon and Forest Pharmaceuticals.

References

1. Guggenheimer J. Oral manifestations of drug therapy. Dent Clin North Am 2002; 46 (4): 857-68
2. Marks HM. Revisiting the origins of compulsory drug prescriptions. Am J Public Health 1995; 85 (1): 109-15
3. Ciancio SG. Medications' impact on oral health. J Am Dent Assoc 2004; 135 (10): 1440-8
4. Physicians' Desk Reference. Montvale (NJ): Medical Economics Company, Inc., 2005
5. Lewis IK, Hanlon JT, Hobbins MJ, et al. Use of medications with potential oral adverse drug reactions in community-dwelling elderly. Spec Care Dentist 1993; 13 (4): 171-6
6. Shinkai RS, Hatch JP, Schmidt CB, et al. Exposure to the oral side effects of medication in a community-based sample. Spec Care Dentist 2006; 26 (3): 116-20
7. Ahne G, Erras A, Hummel T, et al. Assessment of gustatory function by means of tasting tablets. Laryngoscope 2000 Aug; 110 (8): 1396-401
8. Doty RL. Office procedures for quantitative assessment of olfactory function. Amer J Rhinol 2007; 21 (4): 460-73
9. Deems DA, Doty RL, Settle RG, et al. Smell and taste disorders, a study of 750 patients from the University of Pennsylvania Smell and Taste Center. Arch Otolaryngol Head Neck Surg 1991; 117 (5): 519-28
10. Burdach KJ, Doty RL. The effects of mouth movements, swallowing, and spitting on retronasal odor perception. Physiol Behav 1987; 41 (4): 353-6
11. Byrne BE. Oral manifestations of systemic agents. In: Ciancio SG, editor. ADA®/PDR® guide to dental therapeutics. 4th ed. Montvale (NJ): Thomson PDR, 2006: 835-9
12. Keiser HR, Henkin RI, Bartter FC, et al. Loss of taste during therapy with penicillamine. JAMA 1968; 203 (6): 381-3
13. Fogan L. Griseofulvin and dysgeusia: implications? Ann Intern Med 2007; 74: 795-6
14. Bromley SM, Doty RL. Clinical disorders affecting taste: evaluation and management. In: Doty RL, editor. Handbook of olfaction and gustation. New York: Marcel Dekker, 2003: 935-57
15. Ishizaka T, Miyanaga Y, Mukai J, et al. Bitterness evaluation of medicines for pediatric use by a taste sensor. Chem Pharm Bull 2004; 52 (8): 943-8
16. Schiffman SS, Zervakis J, Westall HL, et al. Effect of antimicrobial and anti-inflammatory medications on the sense of taste. Physiol Behav 2000; 69 (4-5): 413-24
17. Juhlin L. Loss of taste and terbinafine [letter]. Lancet 1992; 339 (8807): 1483
18. Beutler M, Hartmann K, Kuhn M, et al. Taste disorders and terbinafine [letter]. BMJ 1993: 307: 26
19. Bong JL, Lucke TW, Evans CD. Persistent impairment of taste resulting from terbinafine. Br J Dermatol 1998; 139 (4): 747-8
20. Doty RL, Haxel BR. Objective assessment of terbinafine-induced taste loss. Laryngoscope 2005; 115 (11): 2035-7
21. Stricker BH, Van RM, Sturkenboom MC, et al. Taste loss to terbinafine: a case-control study of potential risk factors. Br J Clin Pharmacol 1996; 42 (3): 313-8
22. Granger EM, Glendinning JI, Smith JC, et al. Behavioral and electrophysiological responses to NaCl in young and old fischer-344 rats. Chem Senses 1993; 18 (4): 419-26
23. Balfour JA, Faulds D. Terbinafine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in superficial mycoses. Drugs 1992; 43 (2): 259-84

24. Doty RL, Philip S, Reddy K, et al. Influences of antihypertensive and antihyperlipidemic drugs on the senses of taste and smell: a review. J Hypertens 2003; 21 (10): 1805-13
25. Hellekant G, Danilova V, Ninomiya Y. Primate sense of taste: behavioral and single chorda tympani and glossopharyngeal nerve fiber recordings in the rhesus monkey, Macaca mulatta. J Neurophysiol 1997; 77 (2): 978-93
26. Eiznhamer DA, Creagh T, Ruckle JL, et al. Safety and pharmacokinetic profile of multiple escalating doses of (+)-calanolide A, a naturally occurring nonnucleoside reverse transcriptase inhibitor, in healthy HIV-negative volunteers. HIV Clin Trials 2002; 3 (6): 435-50
27. Johnson MO, Stallworth T, Neilands TB. The drugs or the disease? Causal attributions of symptoms held by HIV-positive adults on HAART. AIDS Behav 2003; 7 (2): 109-17
28. Eksborg S, Pal N, Kalin M, et al. Pharmacokinetics of acyclovir in immunocompromized children with leukopenia and mucositis after chemotherapy: can intravenous acyclovir be substituted by oral valacyclovir? Med Pediatr Oncol 2002; 38 (4): 240-6
29. Hayden FG, Andries K, Janssen PA. Safety and efficacy of intranasal pirodavir (R77975) in experimental rhinovirus infection. Antimicrob Agents Chemother 1992; 36 (4): 727-32
30. Hsyu PH, Pithavala YK, Gersten M, et al. Pharmacokinetics and safety of an antirhinoviral agent, ruprintrivir, in healthy volunteers. Antimicrob Agents Chemother 2002; 2002 Feb; 46 (2): 392-7
31. Wang LH, Peck RW, Yin Y, et al. Phase I safety and pharmacokinetic trials of 1263W94, a novel oral anti-human cytomegalovirus agent, in healthy and human immunodeficiency virus-infected subjects. Antimicrob Agents Chemother 2003; 47 (4): 1334-42
32. Macknin ML, Piedmonte M, Calendine C, et al. Zinc gluconate lozenges for treating the common cold in children: a randomized controlled trial. JAMA 1998; 279 (24): 1962-7
33. Marshall S. Zinc gluconate and the common cold. Review of randomized controlled trials. Can Fam Phy 1998; 44: 1037-42
34. Mossad SB, Macknin ML, Medendorp SV, et al. Zinc gluconate lozenges for treating the common cold: a randomized, double-blind, placebo-controlled study. Ann Intern Med 1996; 125 (2): 81-8
35. Tanaka M. Secretory function of the salivary gland in patients with taste disorders or xerostomia: correlation with zinc deficiency. Acta Otolaryngol Suppl 2002; (546): 134-41
36. Bergman U, Ostergren A, Gustafson AL, et al. Differential effects of olfactory toxicants on olfactory regeneration. Arch Toxicol 2002; 76 (2): 104-12
37. Oakley B, Riddle DR. Receptor cell regeneration and connectivity in olfaction and taste. Exp Neurol 1992; 115 (1): 50-4
38. Zain RB, Hanks CT. Morphological changes in taste buds of the fungiform papillae after a single dose of x-ray irradiation in rats. Malays J Pathol 1989; 11: 57-64
39. Nakamura H, Nonomura N, Fujiwara M, et al. Olfactory disturbances caused by the anti-cancer drug tegafur. Eur Arch Otorhinolaryngol 1995; 252 (1): 48-52
40. Epstein JB, Phillips N, Parry J, et al. Quality of life, taste, olfactory and oral function following high-dose chemotherapy and allogeneic hematopoietic cell transplantation. Bone Marrow Transplant 2002; 30 (11): 785-92
41. Wickham RS, Rehwaldt M, Kefer C, et al. Taste changes experienced by patients receiving chemotherapy. Oncol Nurs Forum 1999; 26 (4): 697-706
42. Bergström U, Giovanetti A, Piras E, et al. Methimazole-induced damage in the olfactory mucosa: effects on ultrastructure and glutathione levels. Tox Path 2003; 31: 379-87
43. Kiewe P, Jovanovic S, Thiel E, et al. Reversible ageusia after chemotherapy with pegylated liposomal doxorubicin. Ann Pharmacother 2004; 38 (7-8): 1212-4
44. Hallman BL, Hurst JW. Loss of taste as a toxic effect of methimazole (tapazole) therapy: report of three cases [letter]. J Amer Med Assoc 1953; 152: 322
45. McConnell RJ, Menendez CE, Smith FR, et al. Defects of taste and smell in patients with hypothyroidism. Am J Med 1975; 59 (3): 354-64
46. Genter MB, Owens DM, Carlone HB, et al. Characterization of olfactory deficits in the rat following administration of 2,6-dichlorobenzonitrile (dichlobenil), 3,3′-iminodipropionitrile, or methimazole. Fundam Appl Toxicol 1996; 29 (1): 71-7
47. Xu W, Slotnick B. Olfaction and peripheral olfactory connections in methimazole-treated rats. Behav Brain Res 1999; 102 (1-2): 41-50
48. Sitzia J, North C, Stanley J, et al. Side effects of CHOP in the treatment of non-Hodgkins's lymphoma. Cancer Nurs 1997; 20 (6): 430-9
49. Brosvic GM, Doty RL, Rowe MM, et al. Influences of hypothyroidism on the taste detection performance of rats: a signal detection analysis. Behav Neurosci 1992; 106 (6): 992-8
50. Boyd I. Captopril-induced taste disturbance [letter]. Lancet 1993; 342: 304
51. Zervakis J, Graham BG, Schiffman SS. Taste effects of lingual application of cardiovascular medications. Physiol Behav 2000 Jan; 68 (3): 405-13
52. Griffin JP. Drug-induced disorders of taste. Adverse Drug React Toxicol Rev 1992; 11 (4): 229-39
53. DiBianco R. ACE inhibitors in the treatment of heart failure. Clin Cardiol 1990; 13 (6 Suppl. 7): VII32-8
54. Grosskopf I, Rabinovitz M, Garty M, et al. Persistent captopril-associated taste alteration [letter]. Clin Pharm 1984; 3 (3): 235
55. McNeil JJ, Anderson A, Christophidis N, et al. Taste loss associated with oral captopril treatment. BMJ 1979; 2: 1555-6
56. Unnikrishnan D, Murakonda P, Dharmarajan TS. If it is not cough, it must be dysgeusia: differing adverse effects of angiotensin-converting enzyme inhibitors in the same individual. J Am Med Dir Assoc 2004; 5 (2): 107-10
57. Heeringa M, van PE. Reversible dysgeusia attributed to losartan [letter]. Ann Intern Med 1998; 129 (1): 72
58. Schlienger RG, Saxer M, Haefeli WE. Reversible ageusia associated with losartan [letter]. Lancet 1996; 347 (8999): 471-2
59. Goldberg AI, Dunlay MC, Sweet CS. Safety and tolerability of losartan potassium, an angiotensin II receptor antagonist, compared with hydroclorothiazide, atenolol, felodipine ER, and angiotensin-converting enzyme inhibitors for the treatment of systemic hypertension. Am J Cardiol 1995; 75 (12): 793-5
60. Goa KL, Wagstaff AJ. Losartan potassium: a review of its pharmacology, clinical efficacy and tolerability in the management of hypertension. Drugs 1996; 51 (5): 820-45
61. Levenson JL, Kennedy K. Dysosmia, dysgeusia, and nifedipine. Ann Intern Med 1985; 102 (1): 135-6
62. Guggenheimer J. Oral manifestations of drug therapy. Dent Clin North Am 2002; 46: 857-68
63. Appel LJ. The verdict from ALLHAT: thiazide diuretics are the preferred initial therapy for hypertension. JAMA 2002; 288 (23): 3039-42

64. Roitman MF, Bernstein IL. Amiloride-sensitive sodium signals and salt appetite: multiple gustatory pathways. Am J Physiol Regul Integr Comp Physiol 1999; 276 (6): 1732-8
65. Roper SD. Signal transduction and information processing in mammalian taste buds. Pflugers Arch 2007; 454 (5): 759-76
66. Anand KK, Zuniga JR. Effect of amiloride on suprathreshold NaCl, LiCl, and KCl salt taste in humans. Physiol Behav 1997; 62 (4): 925-9
67. Mattes RD, Christensen CM, Engelman K. Effects of therapeutic doses of amiloride and hydrochlorothiazide on taste, saliva, and salt intake in normotensive adults. Chem Senses 1988; 13: 33-44
68. McMurdo ME, Hutchinson GL, Lindsay G. Taste disturbance with acetazolamide. Lancet 1990; 336 (8724): 1190-1
69. Leaf A, Schwartz WB, Relman AS. Oral administration of a potent carbonic anhydrase inhibitor (Diamox): I. Changes in electrolyte and acid-base balance. N Engl J Med 1954; 250 (18): 759-64
70. Kennedy WA, Laurier C, Gautrin D, et al. Occurrence and risk factors of oral candidiasis treated with oral antifungals in seniors using inhaled steroids. J Clin Epid 2000; 53 (97): 696-701
71. Mitchell JC, Counselman FL. A taste comparison of three different liquid steroid preparations: prednisone, prednisolone, and dexamethasone. Acad Emerg Med 2003; 10 (4): 400-3
72. Bachert C, El Akkad T. Patient preferences and sensory comparisons of three intranasal corticosteroids for the treatment of allergic rhinitis. Ann Allergy Asthma Immunol 2002; 89 (3): 292-7
73. Regan TD, Lewis D, Norton SA. Taste comparison of corticosteroid suspensions. J Drugs Dermatol 2006; 5 (9): 835-7
74. Kratskin IL, Kimura Y, Hastings L, et al. Chronic dexamethasone treatment potentiates insult to olfactory receptor cells produced by 3-methylindole. Brain Res 1999; 847 (2): 240-6
75. Schiffman SS, Graham BG, Suggs MS, et al. Effect of psychotropic drugs on taste responses in young and elderly persons. Ann NY Acad Sci 1998; 855: 732-7
76. Schiffman SS, Zervakis J, Suggs MS, et al. Effect of medications on taste: example of amitriptyline HCl. Physiol Behav 1999; 66 (2): 183-91
77. Ackerman BH, Kasbekar N. Disturbances of taste and smell induced by drugs. Pharmacotherapy 1997; 17: 482-96
78. Hunter KD, Wilson WS. The effects of antidepressant drugs on salivary flow and content of sodium and potassium ions in human parotid saliva. Arch Oral Biol 1995; 40 (11): 983-9
79. Johnston JA, Fiedler-Kelly J, Glover ED, et al. Relationship between drug exposure and the efficacy and safety of bupropion sustained release for smoking cessation. Nicotine Tob Res 2001; 3 (2): 131-40
80. Padala KP, Hinners CK, Padala PR. Mirtazapine therapy for dysgeusia in an elderly patient. J Clin Psychiatry 2007; 8: 178-80
81. Scharf MB, Roth PB, Dominguez RA, et al. Estazolam and flurazepam: a multicenter, placebo-controlled comparative study in patients with insomnia. J Clin Pharmacol 1990; 30 (5): 461-7
82. Berridge KC, Peciña S. Benzodiazepines, appetite, and taste palatability. Neurosci Biobehav Rev 1995; 19 (1): 121-31
83. Caldwell EE, Wallace P, Taylor SP. Use of an analog task to study effects of diazepam on taste perception, consummatory behaviors, and risk taking in a social context. J Gen Psychol 2004; 13 (2): 101-17
84. Abdullahi M, Radfar M. A review of drug induced oral reactions. J Cont Dent Prac 2005; 4 (1): 1-22
85. Tyssen A, Remmerie B, Eng C, et al. Rapidly disintegrating risperidone in subjects with schizophrenia or schizoaffective disorder: a summary of ten phase I clinical trials assessing taste, tablet disintegration time, bioequivalence, and tolerability. Clin Ther 2007; 29 (2): 290-304
86. Bressler B. An unusual side-effect of lithium. Psychosomatics 1980; 21 (8): 688-9
87. Vestergaard P, Poulstrup I, Schou M. Prospective studies on a lithium cohort: 3. Tremor, weight gain, diarrhea, psychological complaints. Acta Psychiat Scand 1988; 78 (4): 434-41
88. Duffield JE. Side effects of lithium carbonate [letter]. BMJ 1973; 1 (5851): 491
89. Himmelhoch JM, Hanin I. Letter: Side effects of lithium carbonate. BMJ 1974; 4 (5938): 233
90. Grupta KD, Jefferson JW. Lithium and "accidentally" induced food aversion [letter]. J Clin Psychiatry 1980; 41 (10): 364
91. Mizielinska SM. Ion channels in epilepsy. Biochem Soc Trans 2007; 35 (Pt 5): 1077-9
92. Onat F, Ozkara C. Adverse effects of new antiepileptic drugs. Drugs Today 2004; 40 (4): 325-42
93. Zeller JA, Machetanz J, Kessler C. Ageusia as an adverse effect of phenytoin treatment. Lancet 1998; 352: 68
94. Brandes JL, Saper JR, Diamond M, et al. Topiramate for migraine prevention: a randomized controlled trial. JAMA 2004; 291 (8): 965-73
95. Silberstein S, Loder E, Forder G, et al. The impact of migraine on daily activities: effect of topiramate compared to placebo. Curr Med Res Opin 2006; 22: 1021-9
96. Storey JR, Calder CS, Hart DE, et al. Topiramate in migraine prevention: a double-blind, placebo-controlled study. Headache 2001; 41 (10): 968-75
97. Nakazato Y, Imai K, Abe T, et al. Unpleasant sweet taste: a symptom of SIADH caused by lung cancer. J Neurol Neurosurg Psychiat 2006; 77 (3): 405-6
98. Panayiotou H, Small SC, Hunter JH, et al. Sweet taste (dysgeusia). The first symptom of hyponatremia in small cell carcinoma of the lung. Arch Intern Med 1995; 155 (12): 1325-8
99. Marshall RI, Bartold PM. A clinical review of drug-induced gingival overgrowths. Aust Dent J 1999; 44: 219-32
100. Mata F. Effect of dextro-amphetamine on bitter taste threshold. J Neuropsychol 1963; 4: 315-20
101. Saini T, Edwards PC, Kimmes NS, et al. Etiology of xerostomia and dental caries among methamphetamine abusers. Oral Health Prev Dent 2005; 3 (3): 189-95
102. Doty RL, Ferguson-Segall M. Odor detection performance of rats following d-amphetamine treatment: a signal detection analysis. Psychopharmacology 1987; 93 (1): 87-93
103. Doty RL, Li C, Bagla R, et al. SKF 38393 enhances odor detection performance. Psychopharmacology 1998; 136 (1): 75-82
104. Doty RL, Risser JM. Influence of the D-2 dopamine receptor agonist quinpirole on the odor detection performance of rats before and after spiperone administration. Psychopharmacology 1989; 98 (3): 310-5
105. Krystal AD, Walsh JK, Laska E, et al. Sustained efficacy of eszopiclone over 6 months of nightly treatment: results of a randomized, double-blind, placebo-controlled study in adults with chronic insomnia. Sleep 2003; 26 (7): 793-9
106. Enghusen PH, Loft S, Andersen JR, et al. Disulfiram therapy - adverse drug reactions and interactions. Acta Psychiatr Scand Suppl. 1992; 369: 59-65

107. Fantino M, Hosotte J, Apfelbaum M. An opioid antagonist, naltrexone, reduces preference for sucrose in humans. Am J Physiol 1986; 251 (1): R91-6

108. Bertino M, Beauchamp GK, Engelman K. Naltrexone, an opioid blocker, alters taste perception and nutrient intake in humans. Am J Physiol 1991 Jul; 261 (1 Pt 2): R59-63

109. Komorowski JM, Komorowska A. Naloxone modulates gustatory perception, but not insulin and c-peptide release, in sham-fed human-subjects. Int J Obes 1986; 10 (2): 83-9

110. Gaskell BA. Nonneoplastic changes in the olfactory epithelium: experimental studies. Environ Health Perspect 1990; 85: 275-89

111. Reed CJ. Drug metabolism in the nasal cavity: relevance to toxicology. Drug Metab Rev 1993; 25 (1-2): 173-205

112. Frye RE, Schwartz BS, Doty RL. Dose-related effects of cigarette smoking on olfactory function. JAMA 1990; 263 (9): 1233-6

113. Matulionis DH. Ultrastructure of olfactory epithelia in mice after smoke exposure. Ann Otolaryngol 1974; 83: 192-201

114. Patel SJ, Bollhoefer AD, Doty RL. Influences of ethanol ingestion on olfactory function in humans. Psychopharmacology 2004; 171 (4): 429-34

115. Mair RG, McEntee WJ, Doty RL. Olfactory perception in Korsakoff's psychosis: correlation with brain noradrenergic activity. Neurology 1983; 33 Suppl. 2: 64-5

116. Vent J, Robinson AM, Gentry-Nielsen MJ, et al. Pathology of the olfactory epithelium: smoking and ethanol exposure. Laryngoscope 2004; 114 (8): 1383-8

117. Murray C, Solish N. Metallic taste: an unusual reaction to botulinum toxin A. Dermatol Surg 2003; 29: 562-3

118. Mandel ID. The role of saliva in maintaining oral homeostasis. J Am Dent Assoc 1989; 119 (2): 298-304

119. Sarinopoulos I, Dixon GE, Short SJ, et al. Brain mechanisms of expectation associated with insula and amygdala response to aversive taste: implications for placebo. Brain Behav Immun 2006; 20 (2): 120-32

120. Glendinning JI. Is the bitter rejection response always adaptive? Physiol Behav 1994; 56 (6): 1217-27

121. Drewnowski A. The science and complexity of bitter taste. Nutr Rev 2001; 59 (6): 163-9

122. Mattes RD. Influences on acceptance of bitter foods and beverages. Physiol Behav 1994; 56 (6): 1229-36

123. Liem DG, De GC. Sweet and sour preferences in young children and adults: role of repeated exposure. Physiol Behav 2004; 83 (3): 421-9

124. Liem DG, Bogers RP, Dagnelie PC, et al. Fruit consumption of boys (8-11 years) is related to preferences for sour taste. Appetite 2006; 46 (1): 93-6

Correspondence: Dr *Richard L. Doty*, Smell and Taste Center, University of Pennsylvania School of Medicine, 5 Ravdin Building, 3400 Spruce Street, Philadelphia, PA 19104, USA.
E-mail: doty@mail.med.upenn.edu