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Review Article

Influence of medications on taste and smell

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Abstract Medications frequently have chemosensory side effects that can adversely affect compliance with medical treatment regimens. Hundreds of drugs have been reported to induce unpleasant tastes and/or odors as well as altered chemosensations when administered alone or in combination with other medications. Some chemosensory complaints are due to the sensory properties of the drug itself such as aversive bitter and metallic tastes. However, most chemosensory side effects of drugs are due to alterations in the transduction pathways, biochemical targets, enzymes, and transporters by the offending medications. Studies of chemosensory perception in medicated older individuals have found that taste and smell loss is greatest for those consuming the largest number of prescription drugs. There are no standard treatments for drug-induced chemosensory disorders because each drug has unique biological effects. However, there are a few treatment options to ameliorate chemosensory alterations including addition of simulated flavors to food to compensate for losses and to override offending tastes and smells.

Introduction

In the last 75 years there have been fundamental advancements in the treatment of disease as thousands of new drugs were introduced by the pharmaceutical industry. In the United States, for example, over 1300 new drugs were approved between 1950 and 2013 by the United States Food and Drug Administration.[1] Although most of these drugs have efficacious or even life-saving properties, a significant portion has adverse chemosensory side effects.

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Reviews of clinical reports, drug reference books, medication inserts, and clinical trials have identified over 350 drugs in all major drug categories that elicit taste complaints and over 70 drugs with olfactory effects.[2–6] Fifty percent (50%) of the top 100 drugs of 2017 in the United States have the potential to induce chemosensory complaints and side effects (see Table 1). Functional measurements of chemosensory processes have not yet been performed in systematic well-controlled clinical trials that evaluate the side effects of a wide range of medications so

Table 1 Drugs from top 100 in the United States in 2017[8] that elicit taste or smell complaints or disorders in some individuals.[2–6]

Drug class	Drugs from top 100 in the US in 2017[8]	Taste disorders[2–5]	Smell disorders[6]
Anti-infectives	Amoxicillin	Yes	Yes
	Azithromycin	Yes	Yes
	Ciprofloxacin	Yes	Yes
Anti-inflammatory anti-pyretic and/or analgesic agents	Aspirin	Yes	
	Diclofenac	Yes	
	Ibuprofen	Yes	
	Acetaminophen	Yes	
	Tramadol	Yes	
Antihistamines and antiallergenic agents	Loratadine	Yes	
	Fluticasone	Yes	Yes
	Prednisone		Yes
Antihypertensives and cardiovascular agents	Amlodipine	Yes	Yes
	Diltiazem	Yes	Yes
	Enalapril	Yes	Yes
	Furosemide	Yes	
	Hydrochlorothiazide	Yes	
	Lisinopril	Yes	
	Losartan	Yes	
	Metoprolol	Yes	
	Propranolol	Yes	
	Spironolactone	Yes	
	Triamterene	Yes	
Antilipidemics	Atorvastatin	Yes	Yes
	Lovastatin	Yes	Yes
	Pravastatin	Yes	Yes
	Simvastatin	Yes	
CNS drugs/Sympathomimetics	Amphetamine	Yes	
Endocrine and diabetes drugs	Glipizide	Yes	
	Insulin	Yes	
	Metformin	Yes	
	Levothyroxine	Yes	Yes
Gastrointestinal drugs	Omeprazole	Yes	
	Ranitidine	Yes	
Psychopharmacologic agents	Amitriptyline	Yes	
	Bupropion	Yes	
	Citalopram	Yes	
	Fluoxetine	Yes	
	Paroxetine	Yes	
	Sertraline	Yes	
	Trazodone	Yes	
	Venlafaxine	Yes	
	Alprazolam	Yes	
	Clonazepam	Yes	
	Diazepam	Yes	
	Zolpidem	Yes	
Nose throat and pulmonary agents	Albuterol	Yes	
Vitamins minerals nutrients and related compounds	Ergocalciferol	Yes	
	Potassium	Yes	

CNS: central nervous system.

the incidence of drug-induced chemosensory disorders is not known. However, based on current information, the incidence of adverse chemosensory effects from drugs depends upon the specific medication with an average of 5% across most medications[4] but up to 66% for the drug eszopiclone used to treat insomnia.[7]

Drug-induced taste disorders were the most frequent cause of taste disturbances in patients evaluated at a Taste and Smell Clinic in Tokyo, Japan.[9,10] Taste alterations from drugs accounted for up to 25% of the diagnoses with the preponderance of taste disorders occurring in older patients. The fact that older individuals were most vulnerable to medication-induced chemosensory disorders is due to their disproportionate use of prescription and nonprescription drugs relative to younger individuals.[11] In addition, adverse drug reactions, including chemosensory disorders, occur at a higher rate in a geriatric population.[12,13] An example of the elevated burden of drug-induced chemosensory disorders in older persons is taste loss due to terbinafine.[13] Patients who were 65 years of age or more were 4.4 times more likely to experience taste loss than those 35 years of age or younger.

Chemosensory complaints from drugs include adverse sensations such as bitter or metallic tastes, reduced acuity, and perceptual distortions. However, classifications of these adverse sensations from drugs and other causes have not been globally standardized in the medical literature. The most common terms for chemosensory disorders are: ageusia (total loss of taste), hypogeusia (decreased taste sensation), hypergeusia (heightened sensitivity to taste), dysgeusia (distorted taste sensation), phantogeusia (taste that occurs without oral stimulation), anosmia (total loss of smell), hyposmia (decreased smell sensation), hyperosmia (heightened sensitivity to smell), dysosmia (distorted smell sensation), and phantosmia (odor that occurs in absence of stimulation). The majority of taste dysfunction from medications cited in the scientific literature involves hypogeusia or dysgeusia. Most complaints of smell functioning from drugs involve hyposmia, hyperosmia and dysosmia. These disturbances of taste and smell are not simply an annoyance but can significantly reduce compliance with medication use and quality of life as well as impact food intake and nutritional status, particularly in the elderly.[2,14,15]

The purpose of this article is to describe some of the factors and mechanisms responsible for taste and smell complaints from medications. These include adverse sensory properties of the drug itself as well as biochemical disruption of normal taste and smell signals caused by medications. Current data indicate that there are significant individual differences in the vulnerability to drug-related chemosensory disturbances. Individual differences in chemosensory disturbances result from drug interactions caused by polypharmacy and drug—homeopathic combinations, differences in dosage, as well as patient-specific variables such as genetic factors, age, and concomitant medical conditions.

Adverse sensory properties of the drug itself are the cause of some complaints

The active drugs in the majority of oral pharmaceutical products have unpleasant bitter tastes.[4,16,17] Bitter taste sensations serve as a biological warning that drugs are xenobiotic compounds with biochemical and potentially adverse effects. Orally ingested drugs in liquid formulations (or chewed solid forms) directly stimulate taste receptors on the tongue and the first third of the esophagus during ingestion. Schiffman et al[17] studied the taste effects of topical application of 62 drugs to the lingual surface in human subjects. These drugs were representatives of the following classifications: psychotropic, cardiovascular, analgesic, anti-inflammatory, antihistamine, sedatives, antiemetic, antimicrobial, and antiviral. They found that the vast majority of these drugs had a bitter taste while some had metallic and sour components. The taste thresholds ranged widely from as low as 2.9 μmol/L (0.0029 mmol/L) for the antiretroviral drug saquinavir (Invirase) to 24 mmol/L for the HIV/AIDS drug didanosine. Even brief unpleasant bitter tastes can induce physiological side effects. For example, a single presentation of saquinavir significantly elevated plasma norepinephrine levels, a hormone associated with the fight and flight response.[17]

Drugs can also induce bitter tastes after absorption from the gut into the general circulation where they are ultimately transported to the oral cavity. That is, drugs are transferred into saliva after diffusion from the lingual blood vessels where they can directly activate taste receptors post absorption. For some drugs, the concentrations in the plasma and saliva exceed the taste threshold which explains their bitter taste. An example is saquinavir; after a 600 mg dose, the concentration of saquinavir in saliva is 0.0127 mmol/L, and in plasma, 0.22 mmol/L. These concentrations in saliva and plasma exceed the taste thresholds of 0.0029 mmol/L in uninfected patients and 0.0061 mmol/L in unmedicated HIV patients.[18] For other drugs, the concentrations in plasma and saliva do not exceed the taste threshold. However, with chronic use, drugs can accumulate in taste buds over time to levels high enough to induce a bitter taste. Another factor that plays a role in taste perception of drugs secreted into saliva is xerostomia; hyposalivation, which commonly occurs in elderly persons taking xerostomia-inducing medications,[19] can elevate the concentration of some drugs in saliva leading to intense adverse tastes.

There are considerable individual differences in intensity of bitterness of drugs reported by patients. The variability among patients in the perceived aversiveness of bitter drugs is due in part to genetic polymorphisms in the 25 genes comprising the human taste 2 receptor gene family (TAS2R) that mediate bitter taste perception.[20,21] For example, variability in the hTAS2R38 gene (also called the phenylthiocarbamide or PTC gene) determines whether a person is susceptible to the bitterness of thiourea compounds. Persons called "tasters" are very sensitive to the bitter taste of PTC while those with a different genetic makeup called "nontasters" find the taste of PTC to be bland. The antithyroid medication methimazole is a representative drug that is more bitter to "tasters" than "nontasters."[22,23] Variation in the hTAS2R31 gene predicts the sensitivity to bitterness of the artificial sweetener acesulfame-K that is used as an excipient in some drug formulations.[24]

Some orally ingested medications elicit aversive metallic sensations (with or without associated bitterness) due to

topical activation of receptors on the oral cavity. Examples include enoxacin (antibiotic), fenoprofen (nonsteroidal anti-inflammatory), and baclofen (muscle relaxant).[4] Medicinal herbs such as the hemostatic Ankaferd Blood Stopper (ABS) used in dental procedures also elicit temporary metallic complaints.[25] Mineral supplements also elicit metallic sensations when they contact the lingual surface. It is not yet established whether "metallic" is a taste sensation mediated by taste receptors or a sensation induced by activation of TRPV1 (the transient receptor potential cation channel subfamily V member 1) located in sensory nerve endings in the oral cavity.[26] Genetic polymorphisms that occur in the TRPV1 gene[27] likely account for the variability among patients in the perceived aversiveness of metallic sensations.

Some drugs induce metallic or bitter taste sensations within seconds to minutes when administered by the intravascular rather than the oral route.[4] Intravenous injections of lidocaine (local anesthetic, antiarrhythmic), ropivacaine (local anesthetic), iron preparations (iron deficiency), thyrotropin-releasing hormone (thyroid stimulating hormone release), nicotinic acid (B-vitamin), and arginine (amino acid) all invoke metallic taste complaints. Intravascular administration of the semi-synthetic bile acid sodium dehydrocholate produces a bitter taste. The mechanisms responsible for "intravascular taste" are not well-understood. There are multiple mechanisms by which intravenously administered drugs can produce metallic or bitter tastes including: 1) permeation into the saliva from the basolateral side of the lingual epithelium, 2) interaction with free nerve endings on the basolateral side of taste cells, and/or 3) interaction with downstream signaling mechanisms inside of taste cells that are normally activated by interaction with apical taste receptors.

Some drugs alter normal taste and smell signals

Drugs not only induce tastes of their own but can also disrupt normal signals from other taste stimuli including food and beverages. Schiffman and colleagues[17,28,29] performed a series of experiments to determine the effect of brief topical application of drugs to the tongue. These experiments were designed to determine the degree to which the presence of drugs in saliva distorts taste perception. Distortion of taste has been shown to be associated with blood plasma and saliva concentrations.[7] Exposure of the tongue to the diuretic amiloride, which blocks the epithelium sodium channel (ENaC), reduced the taste intensity of NaCl and other sodium salts, LiCl, and sweeteners including saccharides, glycosides, and dipeptides.[28] However, topical amiloride did not alter the taste of sour and bitter tastes, potassium or calcium salts. The selective blockage saltiness and sweetness by amiloride with no effect on bitterness and sourness can lead to aversive taste complaints about food and beverages. Brief lingual exposure to the antifibrillary drug bretylium tosylate was found to increase the taste intensity of NaCl and LiCl without any effects on sweet, sour, or bitter compounds.[29] The selective increase in the taste intensity of NaCl from bretylium tosylate can lead to complaints of excess salty taste. In an additional set of experiments,[17] drugs reported in the medical literature to invoke taste dysfunction were evaluated for their effect on nine oral stimuli: NaCl, KCl, $CaCl_2$, sucrose, quinine HCl (QHCl), citric acid, capsaicin (pungent), WS-3 (n-ethyl-p-menthane-3-carboxamide) which has a menthol-like "taste", and FeSO4 (metallic). The main finding of these set of experiments was that lingual application of most of these drugs altered the intensity in some but not all of the nine test stimuli. These non-uniform alterations across the stimuli may play a role in complaints of altered taste or dysgeusia.

While some of the taste alterations measured in the above studies likely occur from direct interaction with channels and receptors on the apical taste cell, other mechanisms may also play a role. Drugs can permeate or accumulate in phospholipid membranes of cell because most of them are amphipathic compounds, that is, they contain both hydrophobic and hydrophilic domains. The antidepressant sertraline is an example of a drug that accumulates in phospholipid membranes leading to transformation of the biochemical properties of the cell.[30] Furthermore, permeation of the phospholipid membrane of taste cells by drugs can alter taste signals by interacting with downsteam signaling mechanisms on the cytosolic of side of the membrane such as G-proteins and TRPM5,[31,32] as well as G protein-coupled receptor (GPCR) kinase.[33] Alteration of taste signals may occur within seconds or minutes of exposure to drugs at the apical level.

Taste alterations resulting from drug—drug interactions and polypharmacy

A significant number of chemosensory disturbances are a consequence of drug—drug interactions from polypharmacy rather than intake of a single drug.[34] When two drugs are taken concomitantly, one drug can alter the bioavailability and/or pharmacological effects of a co-administered drug. In a study of elderly cardiovascular patients, those taking the greatest number of medications had the largest taste losses at the threshold level as well as the most complaints of altered taste.[35] Polypharmacy is a prominent aspect of global medical practice. In China, for example, polypharmacy is typical in psychiatric treatment as well a Traditional Chinese Medicine where use of a single medicine is uncommon.[36] In the United States, 29% of community-dwelling persons aged 57—85 years used at least 5 medications simultaneously.[38] Polypharmacy is also a common problem in treatment of HIV infection.[39]

Polypharmacy can affect the bioavailability of drugs due to interactions with components of "first pass metabolism" in the gut and liver (also called presystemic metabolism). During first pass metabolism, drugs are metabolized by enzymes called cytochromes P450 (CYP) and effluxed by transporters (such as P-glycoprotein) that reduce the concentration of the drug that reaches the systemic circulation. Certain drugs are also known to inhibit P450 enzymes and P-glycoprotein. If a drug (drug 1) that is a substrate of CYP (i.e. is metabolized by CYP) is coadministered with a drug (drug 2) that is inhibitor of the analogous CYP enzyme, elevated plasma concentrations of drug 1 will occur. For some medications such as mexiletine, diazepam, donepezil, fentanyl, pimozide, sertraline, and trazodone, drug

blood-plasma levels that are only 1.1 to 1.2 times greater than normal can be toxic. Elevated blood-plasma levels beyond therapeutic concentrations play a major role in taste disorders.[34]

Pharmacokinetic factors that may be causative factors in taste disorders

Currently, the pharmacokinetic factors (including targets, enzymes, and transporters) that may contribute to taste and smell disorders are not well understood. Examples of the pharmacokinetic factors for the tricyclic antidepressant amitriptyline,[40,41] a drug that frequently causes taste disorders, are shown in Table 2. Amitriptyline interacts with 33 targets, 9 enzymes, and 1 transporter, and it is not known which of these[43] factors play a role in chemosensory alterations. Furthermore, amitriptyline also interacts with two carriers, serum albumin and alpha-1-acid glycoprotein, and is involved in 48 biointeractions (drug—drug interactions). It is not yet known which one or combination of these many targets, enzymes, transporters, carriers, and/or biointeractions are responsible for the taste aberrations caused by amitriptyline.

The representative drugs in Table 3 interact with over different 175 targets, enzymes, and transporters,[40,41] which illustrates the magnitude of the difficulty of determining the precise mechanism by which a particular drug or drug combination causes taste or smell aberrations. Furthermore, a drug can have toxic consequences that are unrelated to their pharmacokinetic effects involving targets, enzymes, and transporters. Experimental studies are needed to obtain empirical data regarding the mechanisms by which drugs alone and in combination disrupt chemosensory perception.

Some drugs can amplify the sense of smell

Drug effects on olfaction have received little experimental attention. The limited literature on this topic suggests that

Table 2 Pharmacokinetic factors (including targets, enzymes, and transporters) involved in the disposition of the antidepressant amitriptyline in the body.[40,41]

Targets (33)	Enzymes (9)	Transporters
Sodium-dependent noradrenaline transporter	Cytochrome P450 2D6	Multidrug resistance protein 1
Sodium-dependent serotonin transporter	Cytochrome P450 1A2	
5-hydroxytryptamine 1A, 1B, 1D, 2A, 2C, 6, 7 receptor	Cytochrome P450 2C19	
Delta-, Kappa-, and Mu- type opioid receptors	Cytochrome P450 2C9	
High affinity nerve growth factor receptor	Cytochrome P450 3A4	
Brain-derived neurotrophic factor (BDNF)/neurotrophin-3 growth factor receptors	Cytochrome P450 3A5	
Alpha-1A, 1B, 1D, and 2A adrenergic receptors	Cytochrome P450 2B6	
Histamine H1, H2, and H4 receptor	Cytochrome P450 2C8	
Muscarinic acetylcholine receptors M1, M2, M3, M4, and M5	Cytochrome P450 2E1	
Potassium voltage-gated channels subfamily KQT members 2 and 3, subfamily A member 1, subfamily D member 2, and subfamily D member 3.		
Beta adrenergic receptor.		
Sigma non-opioid intracellular receptor 1.		

Table 3 Representative drugs reported to induce taste alterations: the number of targets, enzymes, and transporters with which each drug interacts according to DrugBank Canada.[41]

Drug and category	Targets	Enzymes	Transporters	Biointeractions
Antihypertensives, cardiovascular, and related agents				
Amiodarone	7	10	1	20
Amlodipine	10	10	1	21
Nifedipine	9	11	3	29
Antineoplastic and immunosuppressant drugs				
Tamoxifen	9	19	4	36
CNS drugs/Sympathomimetics				
Cimetidine	1	12	12	33
Psychopharmacologic agents				
Diazepam	19	11	1	35
Midazolam	19	7	2	32
Triazolam	21	5	0	25

CNS: central nervous system.

some medications cause hyposmia or dysosmia.[2–6] However, several medication types have also been reported to increase sensitivity to odors. In an exploratory study, Lötsch et al[42] delivered a 12-item odor identification test to 1006 outpatients ranging in age from 18 to 92 years at a general practitioner's office. They found that persons who took unrelated drugs that targeted α_{1A} adrenergic blockade had slightly but significantly higher olfactory scores. They also reported that one drug levothyroxine was associated also with a significantly better (but clinically irrelevant) olfactory score. The N-methyl-D-aspartate (NMDA) antagonist caroverine reportedly led to increased sensitivity to the odor of n-butanol and improved ability to identify odors.[42] Methacholine has been reported to increase olfactory sensitivity.[2]

Exacerbation of drug-induced chemosensory disorders by normal aging and disease

The alteration in chemosensory functioning from medications can be exacerbated by taste and smell deficits associated with certain diseases (such as cancer) as well as normal aging. Taste and smell losses occur in cancer patients and normal aging in the absence of medication use or other medical treatments. Longitudinal and cross-sectional studies have found that taste and smell losses tend to become noticeable after 60 years of age with greater severity after age 70 years.[44,45] The gustatory system is more robust than the olfactory system until therapeutic drug use is introduced. The mean taste thresholds for elderly individuals taking 3 or more medications were an average of 5.4 times higher than for non-medicated younger individuals across a range of salts, sweeteners, acids, amino acids, and bitter compounds.[3] These losses were due to the combined effect of age and medications. Some elderly persons were not consciously aware of these losses but attributed their reduced sensations of smell and taste to outside sources such as inferior food quality.

Altered chemosensory functioning has been reported in untreated cancer patients.[3,46] It is thought that these losses in function are due to metabolic changes induced by the neoplasm itself. These changes are exacerbated by chemotherapy and radiation therapy that damage the periodic turnover and replication of gustatory and olfactory receptors. In addition, patients undergoing treatment for cancer often report heightened awareness of taste and smell along with altered taste and smell perception and aversions to food. The "heightened sensitivity" to taste and smell is not caused by improved acuity but rather altered hedonic perception from robust learned or conditioned aversions in which taste and odor are associated with the toxic side effects of chemotherapy and radiation. Acquired taste and smell aversions can be reduced if patients do not eat for several hours before or after chemotherapy. Antiemetic drugs including scopolamine, cyclizine, prochlorperazine, and trimethobenzamide and the antihistamine chlorpheniramine may also be helpful in attenuating taste aversions.[2] For cancer patients with taste and smell aversions from chemotherapy, cold sources of protein such as cold meats can be tolerated better than warm ones.

Assessment and treatment of drug-induced taste and smell disorders

There are no standard treatments for drug-induced chemosensory disorders because each drug has unique biological effects and, for the most part, the biochemical mechanisms responsible for the complaints are not known. However, it is frequently possible to identify the offending drug, drug combination, or drug—food interaction that may be responsible and thus eliminate it. For example, the temporal onset of taste or smell dysfunction may coincide with the introduction of a new drug or drug combination. Cessation of the new drug(s) will, in many cases, diminish and ultimately reverse the chemosensory complaints over time. Interactions between the prescription drugs, over-the-counter drugs, herbal medications, and foods that commonly cause adverse interactions (and potentially chemosensory disorders) can be often identified in pharmaceutical databases such as DrugBank Canada.[41] Some drugs are more likely than others to be causes of chemosensory complaints. These include antiproliferative drugs used in cancer treatment that affect the normal cycle of turnover of taste receptor cells on the tongue and olfactory receptors in the nose. Drugs with sulfhydryl groups (—SH) in their molecular structure such as penicillamine and captopril are also likely candidates for chemosensory complaints due to their potential for many types of chemical reactions in the body.[2]

Several approaches have been used to treat or ameliorate taste and smell disorders with variable success.[2,3,14,35] Zinc salts (e.g. zinc sulfate) may be helpful if they interact with —SH groups in the offending drug or compensate for zinc deficiency. Vitamin supplements such as vitamins A and B3 (niacin) may also improve chemosensory functioning in states of deficiency. Eliminating the artificial organochlorine sweetener sucralose from the diet can be helpful because it can potentially remove life-saving drugs from the body[47] and exacerbate medical conditions. For patients with hyposmia and hypogeusia, the flavor of foods and beverages can be amplified by addition of simulated food flavors (available from flavor manufacturers) that compensate for taste and smell losses. For example, simulated bean flavor can be added to beans, and simulated pork flavor can be added to pork. These simulated flavors contain odorous molecules that are extracted from natural products or synthesized in the laboratory based on chemical analysis of natural products. Some simulated flavors, particularly meat flavors, contain nonvolatile compounds such as amino acid salts (e.g. monosodium glutamate) as well as volatile odorous molecules. Enhancement with simulated flavors differs from conventional cooking techniques that utilize spices and herbs that impart different flavors to the food rather than intensify a food's own unique odor. Flavor amplification of foods has been reported to improve food palatability, increase salivary flow, increase secretion rate of salivary immunoglobulin A (sIgA), and improve lymphocyte counts. Several other practical

measures may be helpful in some cases. Patients should be instructed to achieve as much flavor as they can from their food by chewing well (releasing flavor molecules so they can interact with taste and smell receptors) and switching among foods as they eat. In addition, alternating among the foods on the plate counteracts the phenomenon of sensory adaptation in which each successive bite of the same food tastes and smells weaker and weaker with repetitive ingestion. Chewing gum or ice, rinsing the mouth with sodium bicarbonate, or applying local anesthetics can sometimes provide temporary relief from taste dysfunction.

Final comment

As more and more new drugs are introduced as treatment options for disease by the pharmaceutical industry, the incidence and prevalence of medication-induced chemosensory disorders will continue to escalate. Going forward, comprehensive clinical trials are necessary to better understand the magnitude of the problem including the complicated cascades and cellular events that produce losses in taste and smell from medications.

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