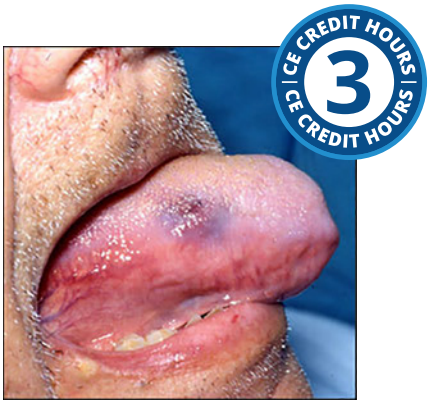
Adverse Drug Reactions - Part I



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Conflict of Interest Disclosure Statement

- The authors report no conflicts of interest associated with this course.

Introduction

This course presents the mechanisms of adverse drug reactions (ADRs), the 30 most common ADRs associated with the top 200 drugs dispensed by U.S. community pharmacies in 2008, and less common ADRs that relate to dental therapeutics and/or manifest in the head and neck area. Emphasis is on those ADRs that have a pharmacokinetic or a pharmacodynamic basis and, with the exception of overdose, are the result of drug-drug, drug-food, drug-herbal, and drug-disease interactions with therapeutic doses of drugs.

Please note this is Part I of a two-part series. *Adverse Drug Reactions – Part II* discusses common immune-mediated and idiosyncratic ADRs related to the top 200 drugs dispensed by U.S. community pharmacies in 2008, less commonly noted ADRs affecting oral tissues, and drug-related carcinogenesis and teratogenesis.

Course Contents

Overview

This course presents the mechanisms of adverse drug reactions (ADRs), the 30 most common ADRs associated with the top 200 drugs dispensed by U.S. community pharmacies in 2008, and less common ADRs that relate to dental therapeutics and/or manifest in the head and neck area. Emphasis is on those ADRs that have a pharmacokinetic or a pharmacodynamic basis and, except for overdose, are the result of drug-drug, drug-food, drug-herbal, and drug-disease interactions with therapeutic doses of drugs.

Learning Objectives

Upon completion of this course, the dental professional should be able to:

- Discuss in general terms the approval process of new drugs and its limitations as they relate to ADRs.
- Discuss "on-target," "off-target," and cytotoxic mechanisms of ADRs.
- Develop a clinical frame of reference related to ADRs.
- Discuss the spectrum of potential ADRs affecting the head and neck area and various organ systems associated with dental therapeutics and the top 200 drugs dispensed by U.S. community pharmacies.

Introduction

Clinicians and patients acknowledge the major role played by drugs in modern healthcare. Understanding how drugs affect body homeostasis at the molecular level serves as the foundation for developing new therapeutic agents and provides the basis for rational pharmacotherapy. However, drugs seldom exert their beneficial effects without also causing **adverse drug reactions** (ADRs). This therapeutic dilemma lends credence to the statement that there are no "absolutely" safe biologically active agents.

With the exception of overdose, an ADR is defined by the World Health Organization (WHO) and the U.S. Food and Drug Administration (FDA) as "a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function."[1,2] The phrase "response to a drug" means that a causal relationship between the therapeutic agent and the ADR is at least a reasonable possibility.

In a recently published study of over 1.5 million primary care patients, the authors determined the pooled prevalence of ADRs was 8.3%, of which 23% were deemed preventable.[3] The most frequently implicated drugs for all ages were cardiovascular agents (38%), nervous system agents (16.5%), and anti-infective agents (14.5%). For adults, the most frequently implicated drugs were cardiovascular agents (27.3%), nervous system agents (13.4%), and musculoskeletal agents (8.3%). For pediatric patients, anti-infectives accounted for 85% of ADRs. Other factors contributing to ADR risk were multimorbidity, increasing patient age, and polypharmacy (≥5 medications).

The FDA has one of the most rigorous approval requirements in the world to authorize the marketing of new drugs (Table 1).[4,5] However,

clinical trials cannot, nor are they expected to uncover every potential ADR. Pre-marketing study cohorts generally include less than 5000 subjects. ADRs that occur at a low frequency can easily be missed. In addition, pre-marketing clinical trials are of relatively short duration. ADRs that develop with chronic use and those that have a long latency period may also escape detection.

Most studies also exclude children, women, and the elderly and are seldom representative of the population exposed to the drug after FDA approval. Consequently, pre-marketing clinical trials detect only those ADRs that occur more frequently than 1 in 1000 subjects, which are then listed in the product's initial labeling (package insert) at the time of approval. To have a 95 percent chance of detecting an ADR with

Table 1. The Chronology of Testing and Introducing New Drugs.[4,5]

Preclinical testing (3 to 6 years)	Clinical trials (5 to 9 years)	Post-marketing surveillance (ongoing)
✓ Laboratory studies • Isolation or synthesis of a new chemical ✓ Animal studies • Assess safety and biological activity ✓ Pharmaceutical Company files an Investigational New Drug (IND) application with the FDA • FDA approval ✓ IND reviewed and approved by the Institutional Review Board where the studies will be conducted • Progress reports on clinical trials submitted to FDA annually	✓ Phase I (several months): • 20 to 100 healthy volunteers ○ Dosage range ○ Safety profile ✓ Phase II (several months to several years): • Several hundred volunteers with a specific disease ○ Short-term effectiveness ○ Adverse drug effects ✓ Phase III (1 to 4 years): • Several hundred to several thousand volunteers with a specific disease ○ Long-term effectiveness ○ Adverse drug effects ✓ Pharmaceutical Company files a New Drug Application (NDA) with the FDA • FDA approval	✓ Monitoring for safety during post-marketing clinical use to determine the true risk-benefit profile of the new drug • Pharmaceutical Company must continue to submit periodic reports to the FDA ○ Case reports of adverse drug reactions ○ Quality control records • FDA may require additional clinical trials (Phase IV studies)
5000 to 10,000 biologically active agents evaluated	5 to 10 biologically active agents approved for clinical trials	1 biologically active agent approved for marketing

an incidence of 1 in 10,000 subjects, a study population of 30,000 would have to be exposed to the drug.

ADRs can range from mild to severe and potentially result in hospitalization, permanent disability, or death. The old term "side effect" as used in the past, described not only negative (unfavorable) reactions; but, at times, concurrent positive (favorable) effects as well. The FDA recommends that this term no longer be used and should not be regarded as synonymous with ADRs.[2] Oral healthcare providers should be aware of the spectrum of ADRs and be actively involved in monitoring for and reporting such drug effects.

ARDs may be explained by one of five mechanisms: (1) "on-target" adverse reactions, (2) "off-target" adverse reactions, (3) cytotoxic reactions, (4) immune-mediated reactions, and (5) idiosyncratic reactions, i.e., reactions of unknown mechanisms.[6] A drug or drug class may produce toxic or adverse reactions by one or several of these mechanisms. In Adverse Drug Reactions – Part I, the discussion is limited to mechanisms (1), (2), and (3). Mechanisms (4) and (5) are discussed in Adverse Drug Reactions – Part II.

"On-target" Mechanisms of ADRs

Drugs are intended to interact with specific receptors (intended receptors) in specific tissues (intended tissues). An "on-target" ADR occurs when a drug interacts with its intended receptor in the intended tissue.[6] With the exception of overdose, therapeutic doses of drugs may result in suboptimal or exaggerated responses because of drug-drug, drug-food, drug-herbal, and drug-disease interaction-related induction or inhibition of pharmacokinetic or pharmacodynamic processes.

Many drug targets are expressed in more than one cell type. An "on-target" ADR may also occur when a drug interacts with its intended receptor, but in an unintended tissue.[6] For example, intended targets for H_1-histamine receptor antagonists are found in peripheral tissues, i.e., vascular smooth muscle, vascular endothelial cells, lungs, and nerve fibers. However, H_1-histamine receptor antagonists with high lipid solubility can cross the blood brain-barrier, interact with H_1-receptors in the brain, and cause drowsiness.

A relevant example for oral healthcare providers relates to the use of local anesthetic agents (LAs) intended to block sodium channels in neuronal tissues at or near the site of administration. However, an overdose; or rapid absorption, unintentional intravascular injection, low plasma protein binding, and slow metabolism or clearance of LAs can lead to high plasma levels. This can cause sodium channel blockade in the heart and cardiac depression-induced ventricular arrhythmia, atrioventricular block, and cardiac arrest.[6]

"Off-target" Mechanisms of ADRs

Very few drugs are completely selective; consequently, they can interact with different receptor types. An "off target" ADR can occur when a drug interacts with an unintended receptor either in an intended or in an unintended tissue.[6] For example, a β_2-adrenergic receptor agonist used to treat asthma may interact with β_1-adrenergic receptors in the heart and increase heart rate; and β_1-adrenergic receptor blocking agents targeting the heart may also antagonize β_2-adrenergic receptors in lungs and cause bronchoconstriction.

Two other examples of "off-target" ADRs, uncovered during post-marketing surveillance, resulted in the withdrawal of both drugs from the market. Terfenadine, an H_1-histamine receptor blocking agent interacted with unintended receptors (potassium channels) in an unintended tissue (heart) to generate fatal cardiac arrhythmias.[6] The anorectic agent, fenfluramine, targeting 5-HT serotonin receptors in the brain also interacted with 5-HT_{2B} receptors in the heart causing myofibroblast proliferation and fatal valvular damage.[6]

Cytotoxic Mechanisms of ADRs

Most drugs undergo metabolism into inactive metabolites in the liver and/or other tissues. Other drugs are pro-drugs, that must be metabolized into active metabolites to produce an effect; subsequently, these may undergo further metabolism into inactive metabolites. In some cases, however, the metabolites are unstable or reactive. For example, therapeutic doses of acetaminophen (APAP) are metabolized by

conjugation into APAP-glucuronide and APAP-sulfate; these compounds are nontoxic and are readily excreted.

A small percentage of APAP undergoes oxidation by cytochrome P450 isoenzyme CYP2E1 into N-acetyl-p-benzoquinoneimine (NAPQI), a highly reactive metabolite. This toxic metabolite must undergo conjugation by glutathione. The APAP-glutathione conjugate is nontoxic and is readily cleared from the body. However, with supratherapeutic dosages glutathione stores are depleted. As NAPQI accumulates, it attacks cellular and mitochondrial proteins in the liver.[6] This, in a dose-dependent manner may lead to hepatic fibrosis or necrosis.

The main mechanisms responsible for fibrosis or necrosis include an oxidative pathway, which leads to the formation of reactive oxygen species (ROS) and a reductive pathway, which leads to the formation of reactive nitrogen intermediates (RNI).[6] Moderate doses of a toxic drug or metabolite activate mechanisms that result in programmed cell death (apoptosis) and tissue fibrosis. High doses of a toxic drug or metabolite activate mechanisms that lead to uncontrolled cell death and tissue necrosis.

Clinical Frame of Reference Related to ADRs

Two or more drugs administered in therapeutic concentrations at the same time or in close sequence may act independently, may interact to increase or diminish the effect of one or more drugs, or may act to cause an unintended effect. All "on-target," "off-target," and cytotoxic ADRs have a pharmacokinetic or a pharmacodynamic basis and include those ADRs which, with the exception of overdose, are precipitated by drug-drug, drug-food, drug-herbal, and drug-disease interactions with therapeutic doses of a drug.[6]

The risk of ADRs depends on the **margin of safety** between the dose of a drug required for efficacy and the dose that causes ADRs.[6] When the margin of safety is large, ADRs result primarily from overdose; when the margin of safety is small, ADRs may manifest at therapeutic doses. In addition to the dosage of the drug administered and drug-drug, drug-food, drug-herbal, and drug-disease interactions the margin of safety is also modulated by other patient-related variable such as genetic predispositions and age.[6]

Overdose

Drug overdose occurs when a person takes more than the medically recommended dose of a prescription or over-the-counter drug. Overdose may result when a young child or an adult with impaired mental abilities accidentally ingest a medication left within their reach. An adult, especially seniors or people taking multiple medications, can mistakenly ingest the incorrect medication or take the wrong dose of a medication. Some individuals may also be hyperresponsive to a medication and even a therapeutic dose may be toxic.

Pharmacokinetic Drug-drug Interactions

Duration and intensity of drug action in both target and non-target tissues is predicated on the drug's plasma level and ability to reach intended and unintended receptors. In addition to dosage, the plasma level of a drug is modulated by the drug's rate of absorption, distribution, metabolism, and clearance.[6] These rates may be altered, i.e., induced or inhibited by concomitant drug therapy (Table 2). Some pharmacokinetic drug-drug interactions may at times be harnessed to optimize a drug's therapeutic effect.

An example is the pharmacokinetic ADR between opioid analgesics and APAP. Opioids bind to μ-receptors in the gastrointestinal tract to increase the tone of the anterior portion of the stomach, decreases gastric motility, and delay the absorption of APAP, which takes place in the intestine.[7] The historically cited example of the metronidazole inhibition of alcohol metabolism resulting in severe nausea and vomiting has recently drawn scrutiny and is no longer considered relevant.[8]

Pharmacodynamic Drug-drug Interactions

Pharmacokinetic drug-drug interactions occur when one drug alters the response of target and non-target tissues to another drug.[6] The

Table 2. Pharmacokinetic Drug-drug Interactions.

Type	Examples of Mechanisms
Absorption	Drug A causes vasoconstriction at the site of administration and interferes with the systemic absorption of drug B administered at the same site
	Drug A delays gastric emptying and the systemic absorption of drug B absorbed primarily in the intestine
	Drug A neutralizes gastric acid (elevates gastric pH) and prevents the absorption of drug B
	Drug A forms chelates or complexes with drug B and prevents its absorption
Distribution	Drug A competes for plasma protein binding with drug B and increases its plasma level
	Drug A blocks the transport of drug B into hepatocytes and increases its plasma level
	Drug A blocks the transport of drug B into the intestinal lumen and increases its plasma level
Metabolism	Drug A induces a CYP450 isoenzyme responsible for the metabolism of drug B and decreases its plasma level
	Drug A, inhibits a CYP450 isoenzyme responsible for the metabolism of drug B and increases its the plasma level
	Drug A inhibits CYP450-independent oxidation and causes accumulation of toxic intermediary metabolites of drug B
Renal clearance	Drug A competes for renal tubular transport with drug B and increases its elimination half-life
Biliary clearance	Drug A increases the synthesis of biliary proteins involved in the conjugation of drug B and decreases its plasma level

intended or unintended effect produced by a given plasma level of a drug may result from chronic use or the presence of one or more drugs that lead to (1) changes in the number of available receptors or their ability to respond; or lead to (2) pharmacological, (3) physiological, and (4) chemical drug interactions, which at times may also be used to therapeutic advantage (Table 3).[6]

One example of a pharmacodynamic drug-drug ADR is the interaction between NSAIDs and antihypertensive agents. The inhibition of prostaglandin synthesis by NSAIDs

Table 3. Pharmacodynamic Drug-drug Interactions.

Type	Mechanisms
Receptor alteration	Drug A, when administered chronically, decreases the number of its own receptors or alters the adaptability of receptors to physiological events
	Drug A, when administered chronically, increase the number of its own receptors or alters the adaptability of receptors to physiological events
Pharmacological	Drug A (an antagonist) and drug B (an agonist) compete for the same receptor site and as a function of their respective concentrations either prevent (antagonist) or produce (agonist) an effect
Physiological	Drug A and drug B interact with different receptors and enhance each other's action via different cellular mechanisms
	Drug A and drug B interact with different receptors and produce opposing effects via different cellular mechanisms
Chemical	Drug A interacts with drug B and prevents drug B from interacting with its intended receptor

increases vascular tone, which decreases the efficacy of antihypertensive drugs.[9] Another example is the pharmacological drug-drug interaction between epinephrine and β1-adrenergic receptor blocking agents. Since the β1-adrenergic receptors are blocked, unopposed α1-adrenergic receptor activation by epinephrine, although apparently rare in the dental setting, can potentially result in a hypertensive reaction.[10]

Two examples of beneficial drug-drug interactions are as follows. Epinephrine activates α1-adrenergic-receptors causing vasoconstriction, thereby delaying the systemic absorption of LAs, and increasing LAs' duration of action.[10] Phentolamine mesylate, a competitive α1-adrenergic-receptor antagonist, when injected at the site of LA administration reverses the action of epinephrine as a function of its concentration causing vasodilation, increasing the rate of systemic absorption, and shortening the duration of soft tissues anesthesia.[11]

Drug-food Interactions

Nutrients can act as mechanical barriers and protect the gastric mucosa from irritants; but they can also prevent drug-access to mucosal surfaces and reduce or slow the absorption of some drugs. Other mechanisms such as chemical interactions or chelating reactions with food components can produce inactive complexes. Conversely, a meal with high fat content may increase the absorption of some lipid-soluble drugs.[12]

Drug-herbal Interactions

Components of **grapefruit** inhibit cytochrome P450 isoenzyme CYP3A4 and increase the plasma level of a number of drugs; for example, it can significantly enhance the anticoagulant effect of warfarin.[13] **Ginkgo biloba** inhibits platelet function; its use with acetylsalicylic acid (ASA), other nonsteroidal anti-inflammatory agents (NSAIDs), and clopidogrel, which also interfere with platelet aggregation, increases the risk of bleeding.[6]

St. John's wort induces the cytochrome P450 isoenzyme CYP3A4 and decreases the efficacy of many drugs, including some prescribed by oral healthcare providers, e.g., benzodiazepines and macrolides antibacterial agents.[12,13] Large doses of vitamin C acidify the urine, inhibit the excretion of weak acids such as NSAIDs, acetaminophen, and tetracyclines (e.g.,

doxycycline and minocycline) and thus increase the plasma levels of these and other drugs.

Drug-disease Interactions

Cardiac diseases can often result in reduced metabolic activity in general because of poor hepatic and renal perfusion.[13] **Hepatic dysfunction** can affect drug metabolism and biliary excretion.[13] **Renal insufficiency** can be expected to impair renal drug metabolism and clearance.[13] Uncontrolled **hypothyroidism** decreases the rate of drug metabolism and increases sensitivity to CNS depressants, while uncontrolled **hyperthyroidism** can increase the rate of drug metabolism and increases sensitivity to CNS stimulants.[13]

Cytotoxic Reactions

Depending on the severity of the toxic insult cytotoxicity may manifest as apoptosis - programmed cell death; or necrosis - uncontrolled cell death.[6] Apoptosis is the genetically directed self-destruction of DNA-damaged cells and, depending on the regenerating capacity of the tissue, may lead to fibrosis.If the toxic insult is severe, programmed cell death cannot be accomplished and the cells undergo necrosis. Necrosis is characterized by autolysis of damaged cells, inflammation, and damage to nearby healthy tissues.[6]

Clinical Manifestations of ADRs

The Council of International Organizations of Medical Sciences (CIOMS) in their publication "Reporting Adverse Drug Reactions: Definitions of Terms and Criteria for Their Use" established guidelines for the diagnosis of ADRs and basic requirements for standardized reporting.[14] This is especially relevant since most reporting of ARDs is the result of spontaneous identification of single cases. The CIOMS codified ADRs under 21 major headings (Table 4) and defined 179 conditions considered reportable.

This course primarily focuses on the 30 most common ADRs that occured with therapeutic doses of drugs in the top 200 dispensed by U.S. community pharmacies in 2008.[15] The top 200 drugs were associated with 9829 individual potential ADRs. The 30 most common ADRs were determined by multiplying each potential ADR by the prescription volume of each drug in the top 200 (Box A). In addition, less common ADRs that relate to dental therapeutics and/or manifest in the head and neck area are presented.

DailyMed is the official website for FDA-approved label (package insert) information.[16] The website provides a standard, comprehensive, up-to-date, look-up-and-download resource for package inserts. The labeling information on the website is the most recent submitted to the FDA by pharmaceutical companies. The information is formatted to make it easy to read, includes strengthened warnings undergoing FDA review, and it is a reliable resource for information on potential ADRs related to specific drugs.

Overdose - Clinical Manifestations

Generally, with overdose, the effects of drugs are exaggerated, ADRs become more pronounced, and other unexpected reactions may be observed. Large overdoses of some medications may cause only minimal ADRs; yet, with other medications even smaller overdoses may cause severe toxicity, to include death. A single dose of some medications can be lethal to a young child. Although clinical manifestations of drug overdose vary, the signs and symptoms in Box B are suggestive of medication-induced toxicity in general.

The U.S. is in the midst of an **opioid overdose** epidemic. From 1999 to 2020, more than 263,000 people died in the United States from overdoses involving prescription opioids.[17] During the same period, overdose deaths involving prescription opioids increased almost five-fold. In 2020, there were 91,799 drug overdose deaths in the United States, of which 68,630 (74.8%) were caused attributed to opioids.[17] An opioid overdose can reliably be identified by the presence of three clinical signs and symptoms referred to as the "opioid overdose triad": (1) pinpoint pupils (miosis), (2) unconsciousness, and (3) respiratory depression (less than 12 breaths/min).[18]

Combining opioid analgesics with alcohol and other central nervous system (CNS) depressants increases the risk of respiratory depression and death. Indeed, opioids, alcohol, and sedatives are often present in fatal drug overdoses. Risk factors for

Table 4. Major categories of ADRs.[14]

SOC 0100	Skin and Appendages Disorders	SOC 1020	Myocardial, Endocardial, Pericardial, and Valve Disorders
SOC 0200	Musculo-skeletal System Disorders	SOC 1030	Heart Rate and Rhythm Disorders
SOC 0300	Collagen Disease	SOC 1040	Vascular (Extra-Cardiac) Disorders
SOC 0410	Central and Peripheral Nervous System Disorders	SOC 1100	Respiratory System Disorders
SOC 0431	Vision Disorders	SOC 1210	Red Blood Cell Disorders
SOC 0432	Hearing and Vestibular Disorders	SOC 1220	White Blood Cell and RES (Reticulo-Endothelial System) Disorders
SOC 0500	Psychiatric Disorders	SOC 1230	Platelet, Bleeding, and Clotting Disorders
SOC 0600	Gastrointestinal System Sisorders	SOC 1300	Urinary System Disorders
SOC 0700	Liver and Biliary System Disorders	SOC 1500	Fetal Disorders
SOC 0800	Metabolic and Nutritional Disorders	SOC 1810	Body as a Whole – General Disorders
SOC 1010	Cardiovascular Disorders, General		

overdose with prescribed opioid analgesics include middle age; history of substance abuse, including prescription and illicit drugs and alcohol; comorbid mental and medical disorders; high opioid dose (particularly with added benzodiazepines); methadone use; benzodiazepine coprescribing; antidepressant coprescribing; and unemployment.[19] A history of substance abuse, high prescribed dosage, male gender, older age, mental health conditions, concurrent prescriptions of other CNS depressants (e.g., benzodiazepines), and lower socioeconomic status.

ADRs Affecting Oral Tissues

The CIOMS does not provide a specific code for ADRs associated with oral tissues; however, it does include stomatitis and ulcerative stomatitis under the category of ADRs related to the gastrointestinal system.[14] In addition, **xerostomia** (ADR #28) and **taste disturbance** (ADR #30) were among the 30 most common ADRs identified with the top 200 drugs dispensed by U.S. community pharmacies in 2008.[15] Included under this heading are those orally-related ADRs that are of special interest to oral healthcare providers.

Box A. The 30 Most Prevalent ADRs Associated With the Top 200 Drugs Dispensed in 2008.[15]

01. Dizziness[1]	11. Thrombocytopenia[1]	21. Anxiety[1]
02. Nausea[1]	12. Abdominal pain[1]	22. Palpitation[1]
03. Headache[1]	13. Somnolence[1]	23. Tremor[1]
04.Vomiting[1]	14. Allergic reactions[2]	24. Arthralgia[2]
05. Diarrhea[1]	15. Dyspepsia[1]	25. Anorexia[1]
06. Rash[2]	16. Urticaria[2]	26. Nervousness[1]
07. Constipation[1]	17. Dyspnea[1,2]	27. Anaphylaxis[2]
08. Fatigue[1]	18. Hypotension[1,2]	28. Xerostomia[1]
09. Insomnia[1]	19. Depression[1]	29. Fever[1]
10. Pruritus[2]	20. Paresthesia[1]	30. Taste disturbances[1]

1. Possible primary mechanisms of ARDs: "on-target," "off-target," cytotoxic reactions.
2. Possible primary mechanisms of ADRs: immune-mediated and idiosyncratic reactions.

Box B. General Signs and Symptoms of Drug Overdose.

- ✓ Patient's skin may be hot and dry; or cool and sweaty
- ✓ Patient may complain of nausea, vomiting, abdominal pain, and diarrhea
- ✓ Patient may be sleepy, confused, or in a coma (cannot be aroused)
- ✓ Breathing may be rapid or slow; deep or shallow
- ✓ Blood pressure and pulse rate may be increased or decreased; in some cases the pulse may be absent (e.g., not palpable); body temperature may be elevated
- ✓ Organs specific toxicity: for example, chest pain may suggest damage to the heart or lungs

Box C. Major Drug Classes Causing Xerostomia.[20-24]

Anticholinergics	Antineoplastic agents
Anticonvulsants	Antiparkinsonian drugs
Antidepressants	Anxiolytic agents
Antiemetics	Diuretics
Antihistamines	Muscle relaxants
Antihypertensive agents	Neuroleptic drugs
Antiinflammatory agents	Opioids

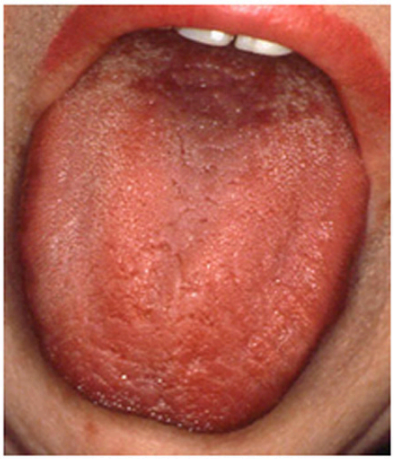


Figure 1. Antihistamine-induced Xerostomia.

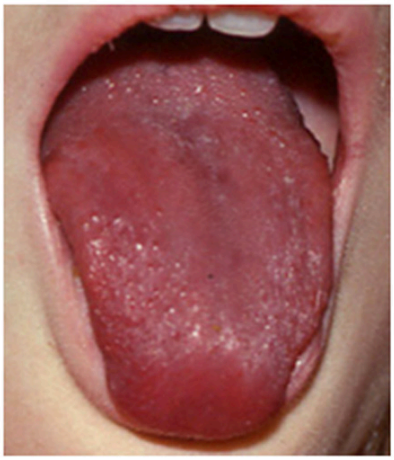


Figure 2. Neuroleptic Drug-induced Xerostomia.

Many drugs can cause **xerostomia** (Box C).[20-24] Reduced salivary flow may be related to a drug's parasympatholytic or antimuscarinic effect in the CNS at parasympathetic and some sympathetic ganglia, or at parasympathetic and some sympathetic effector junctions. Other drugs cause fluid and electrolyte imbalance; glandular vasoconstriction; or alter fluid movement from plasma through acinar cells to the ductal system and, ultimately, into the oral cavity (Figures 1 and 2).

Many drugs, e.g., chlorhexidine, metronidazole, benzodiazepines, oral hypoglycemic agents, angiotensin converting enzyme (ACE) inhibitors, diuretics, amiodarone, calcium-channel blocking agents, and H1-histamine receptor antagonist have been implicated in **taste disturbances** or **dysgeusia** characterized as bitter or metalic.[21,22,24] The mechanisms of action of these drugs related to taste disturbance are poorly understood, but appear to be associated with drug effects on trace metals (e.g., zinc) in plasma membranes.

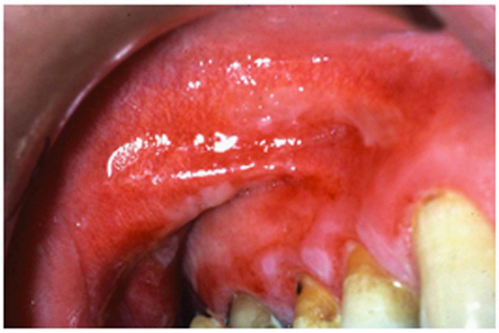


Figure 3. Topical ASA-induced Cytotoxic Reaction.

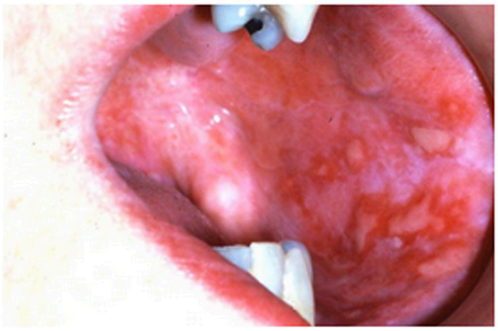


Figure 6. Methotrexate-induced Cytotoxic Reaction.

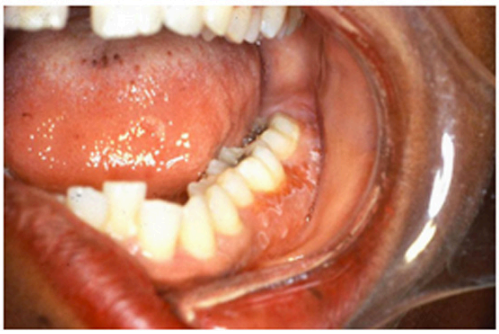


Figure 4. Lidocaine Ointment–induced Cytotoxic Reaction.

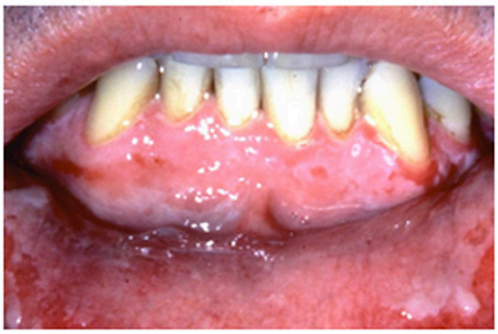


Figure 7. Antibacterial Agent-induced Pseudomembranous Candidiasis.

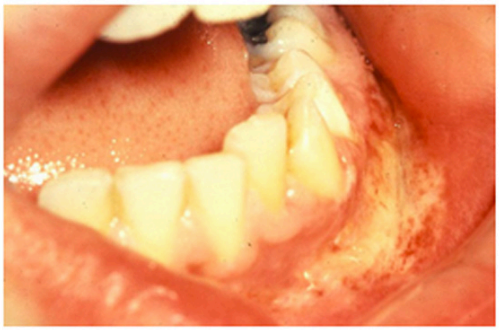


Figure 5. Hydrogen Peroxide-induced Cytotoxic Reaction.

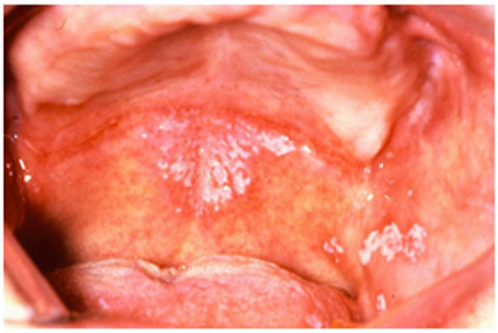


Figure 8. Inhaled (Topical) Corticosteroid-induced Pseudomembranous Candidiasis.

Stomatitis and **ulcerative stomatitis** represent cytotoxic reactions to topically applied agents, e.g., LAs; or may result from the systemic administration of cytotoxic drugs, e.g., antineoplastic agents, which damage not only tumor cells, but all rapidly dividing normal cell populations.[22,24] The degree of tissue damage depends on the specific agent, dosage, dosage schedule, and patient-related variables. The lesions may appear as erythematous macules, patches, papules, plaques, or diffuse ulcerations (Figures 3 and 4).

Antibacterial and corticosteroid therapy is often complicated by superinfection with candidal organisms in oral tissues.[21,22,24] Antibacterial agents kill bacteria allowing candidal species to successfully compete for nutrients. Corticosteroids promote gluconeogenesis and a hyperglycemic state facilitates the growth of the opportunistic candida species. **Candidiasis** typically presents as its pseudomembranous form characterized by the cottage cheese- or milk curd-like lesions that can be scraped off,

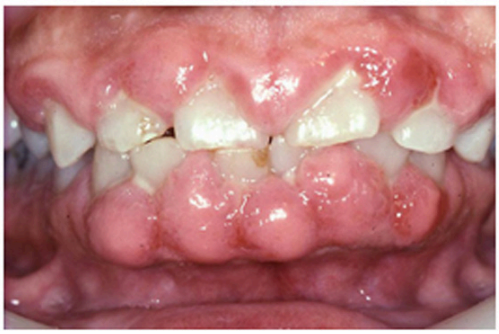


Figure 9. Calcium-blocking Agent-induced Gingival Enlargement.

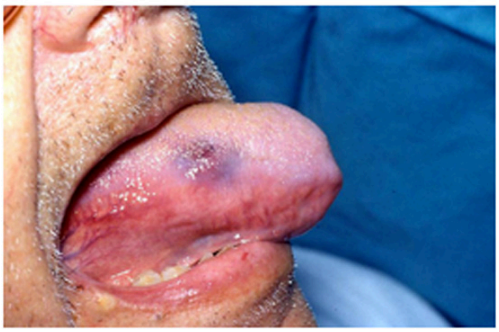


Figure 12. ASA/clopedogril-related Purpura.

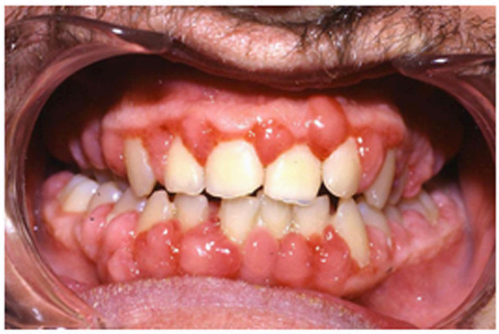


Figure 10. Cyclosporine-induced Gingival Enlargement.

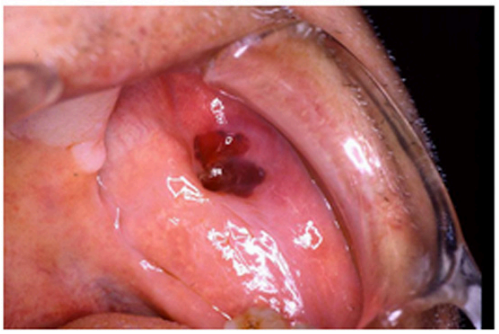


Figure 13. Warfarin-related Ecchymosis.

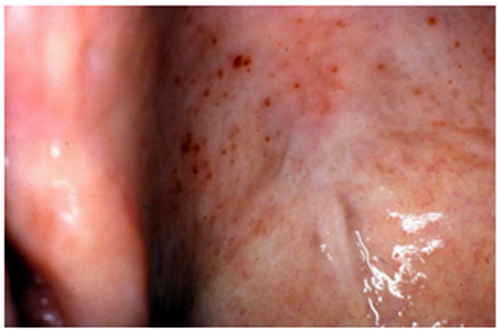


Figure 11. ASA-related Petechiae.

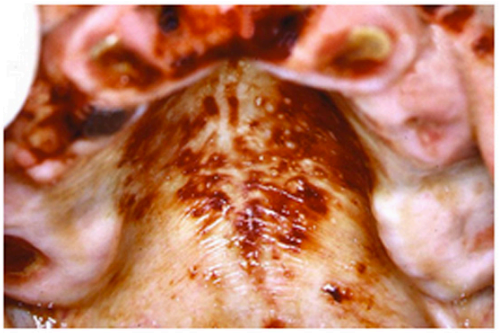


Figure 14. Heparin-related Spontaneous Bleeding.

leaving a red and sometimes hemorrhagic base.

Gingival enlargement may be associated with the administration of calcium-channel blocking agents, phenytoin, and cyclosporine.[20-22,24] The causative mechanisms are unclear, but they appear to be related to altered calcium metabolism and concomitant poor oral hygiene-related inflammation.[20] While the enlarged tissue is usually firm and painless, it may interfere with mastication; and, with significant inflammation, the patient may report pain and gingival bleeding (Figures 9 and 10).

ASA and other NSAIDs acetylate cyclooxygenase and inhibit platelet thromboxane A biosynthesis; clopidogrel inhibits adenosine diphosphate receptor-mediated platelet activity; and other medications such as antineoplastic agents may induce profound thrombocytopenia.[20] Clinical manifestations of platelet-related bleeding diatheses include **petechiae** (Figure 11), **purpura** (Figure 12), **ecchymosis** (Figure 13),

spontaneous gingival bleeding, and increased potential for **perioperative bleeding**.

The oral anticoagulants such as warfarin, the directs acting anticoagulants (DOACs), and heparin inhibit clot formation.[20] Warfarin which inhibits vitamin K-dependent clotting factors, primarily Factor VII. DOACs such as apixaban and rivaroxaban competitively block Factor Xa and heparin inhibits Factors II and X.[20] Clinical manifestations of anticoagulant-related bleeding diatheses include **hemorrhage**, which may be spontaneous or precipitated by trauma. Oral manifestations may include spontaneous gingival bleeding (Figure 14), submucosal bleeding with **hematoma** formation, and increased peri- and post-operative bleeding.

Prevention and treatment of osteoporosis include the administration of antiresorptive agents such as bisphosphonates (BPs). A rare ADR related to BPs is **medication-related osteonecrosis of the jaw** (MRONJ) precipitated by dentoalveolar trauma.[25] When BP molecules are released from the bone matrix some are internalized by osteoclasts resulting in inhibition of the mevalonate pathway essential for the synthesis of signaling proteins to activate osteoblast precursors. BPs also inhibit angiogenesis and are toxic to soft tissues.

ADRs Affecting the Gastrointestinal System

Nausea, vomiting, diarrhea, constipation, abdominal pain, dyspepsia, and anorexia were among the 30 most common potential ADRs associated with therapeutic dosages of the top 200 drugs dispensed by U.S. community pharmacies in 2008.[15] CIOMS does not list nausea and vomiting and considers abdominal pain an undesirable term to describe ADRs. When a patient complains of abdominal pain CIOMS recommends considering drug-induced colitis, pancreatitis, and peptic ulcer disease in the differential diagnosis.[14]

The physiologic purpose of **nausea** (ADR #2) is to prevent food intake and the purpose of **vomiting** is to expel food or other toxic substances present in the upper part of the gastrointestinal tract.[26] Nausea and vomiting occur in response to activation of the vomiting center either directly or through the chemoreceptor trigger zone (CRTZ). The CRTZ is outside the blood-brain barrier and is accessible to drugs circulating in the vascular compartment. NSAIDs, antibiotics, opioids, digitalis, and antineoplastic agents are examples of emetic drugs.[26]

Diarrhea (ADR # 5) and associated fecal urgency and incontinence may be defined as passage of loose, unformed stool with increased frequency.[14,27] Chronic diarrhea may be due to lactose intolerance, inflammatory bowel disease, malabsorption syndromes, endocrine disorders, irritable bowel syndrome, and the abuse of laxatives.[27] Common causes of acute diarrhea include viral and bacterial infections; and drugs such as antibacterial agents, Mg-containing antacids, antineoplastic agents, and colchicine.[27]

Constipation (ADR # 7) may be defined as the passage of excessively dry stool, infrequent stool, or stool of insufficient size.[14,28] It involves the subjective sensations of incomplete emptying of the rectum, bloating, flatus, lower abdominal discomfort, anorexia, malaise, headache, weakness, and giddiness. Common causes of acute constipation include antihistamines, opioid analgesics, neuroleptics, antidepressants, anticonvulsants, aluminum- and Ca-based antacids, Ca-channel blocking agents, and anti-parkinsonian drugs.[28]

Abdominal pain (ADR #12) is any pain in the topographical area of the abdomen. When describing an ADR, its relation to anatomical site and other symptoms should be specified.[29] For example, drug-induced **pancreatitis** is usually an acute condition characterized by upper abdominal pain accompanied by severe nausea and vomiting.[14,29] Some medications implicated in causing acute pancreatitis include corticosteroids, diuretics, oral hypoglycemic agents, estrogens, anticonvulsants, and antineoplastic agents.[29]

The principal symptom of **peptic ulcer disease** is also abdominal pain. Vomiting may also occur and the patient is predisposed to hemorrhage and perforation.[14,30] Hemorrhage may vary from slight bleeding to massive hemorrhage and the patient may vomit variable quantities of blood. If the blood goes down into the intestines, a large

amount of altered blood makes the stools black and tarry (melena). The ulcerogenic effect of NSAIDs is well established and is attributable to inhibition of prostaglandin synthesis.[30]

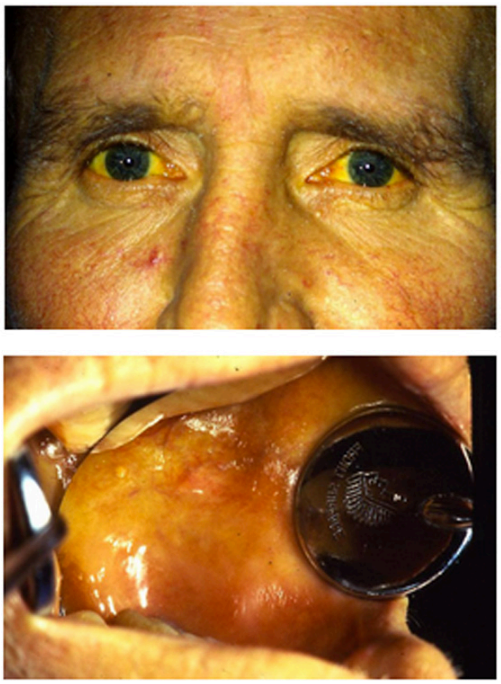
Of particular concern to oral healthcare providers should be the patient complaining of lower abdominal pain, acute diarrhea with blood in the stool that is currently taking or has been prescribed in the recent past clindamycin or a broader spectrum penicillin or cephalosporin. The signs and symptoms are likely due to bacterial superinfection, e.g., an overgrowth of *C. difficile* in the gastrointestinal tract, a serious presentation of which is termed **pseudomembranous colitis**.[31]

Dyspepsia (ADR # 17) is a sensation of discomfort or pain in the upper abdomen below the sternum. Patients may describe it as heartburn or indigestion and complain of feeling nauseous and bloated after eating and relate regurgitating (burping) food or liquid.[32] Drugs associated with acute dyspepsia include NSAIDs, opioids, antibacterial agents, oral hypoglycemic agents, ACE-inhibitors, angiotensin II-receptor antagonist, corticosteroids, estrogens, anti-parkinsonian drugs, digoxin, niacin, fenofibrate, and SSRIs.[32]

Anorexia (ADR #25) is defined as lack or loss of appetite for food.[14,15] It is to be differentiated from lack of appetite related to nausea, vomiting, or diarrhea; or hyporexia, decreased appetite; or anorexia nervosa, which is characterized by refusal to maintain normal body weight. With anorexia, limitation of food-intake and weight loss is not deliberate. Drugs that may have inhibitory effects on appetite and food intake include certain antibacterial agents, antineoplastic agents, fluoxetine, digoxin, quinidine, hydralazine, and vitamin A.

ADRs Affecting the Liver and Biliary System

A potential complication of nearly every medication is hepatocellular liver injury.[14] One such drug discussed at length earlier is APAP.[6] During the past decade it has been identified as the leading cause of **acute liver failure** (ALF) in the United States and up to 50% of APAP-related cases of ALF are due to unintentional overdose.[33] Clinical signs and symptoms of APAP overdose include nausea, vomiting, abdominal pain, anorexia, and a few days later, elevated bilirubin presents as jaundice (Figures 15 and 16).[34]



Figures 15 & 16. Hepatocellular toxicity in a patient with a history of alcohol abuse in association with therapeutic dosages of acetaminophen manifested as jaundice.

In response to the problem of APAP-related overdosing, the FDA called upon healthcare professionals to discontinue prescribing combination drug products with more than 325 mg of APAP per formulation.[33] Ultimately, the FDA and the pharmaceutical industry took action to protect consumers from the risk of ALF by formally withdrawing from the market all prescription combination analgesics containing more than 325 mg of APAP per unit dose.[33] When prescribed as a single agent analgesic, APAP, 650 mg per dose, q4h, may still be prescribed.

ADRs Affecting the Ears

Dizziness was the most common potential ADR associated with therapeutic dosages of the top 200 drugs dispensed by U.S. community pharmacies in 2008.[15] It is an imprecise term describing various related sensations such as faintness, a feeling of impending syncope;

light-headedness; and a feeling of imbalance.[35] A false sensation of movement of self or the environment is called **vertigo**.[14,35] Because these symptoms overlap, patients often use the terms dizziness and vertigo interchangeably.

Ototoxic drugs that affect the vestibular apparatus result in vertigo; cochlear ototoxicity results in **hearing loss**.[14] Ototoxic drugs may also cause **tinnitus** described by patients as noise in the ears such as buzzing, ringing, roaring, whistling, hissing, or pulsating.[14,35] Potentially ototoxic drugs include salicylates; antibiotics such as vancomycin, metronidazole, clindamycin, aminoglycosides (e.g., gentamycin and tobramycin), and macrolides; diuretics (e.g., furosemide); and antineoplastic agents (e.g., cisplatin).[35]

tADRs Affecting the Cardiovascular System

Hypotension (ADR #18) was the most common ADR related to the cardiovascular system in 2008.[15] It is defined as blood pressure (BP) below normal for the individual. Orthostatic hypotension is a decline from baseline of ≥ 20 mm Hg in the systolic BP and/or a decline of ≥ 10 mm Hg in the diastolic BP with symptoms of cerebral ischemia (syncope) following postural change.[14,36] Common drugs that produce orthostatic hypotension include diuretics, α1 and β1-receptor blockers, nitrates, digitalis, ACE-inhibitors, and calcium channel blockers.[36]

Syncope is defined as the sudden brief loss of consciousness due to decreased cerebral perfusion.[14,37] In a young adult it is usually precipitated by stressful situations (e.g., prolonged standing, crowded places, hot environment, severe pain, extreme fatigue and stress) followed by vasodilatation (sympathetic withdrawal) and bradycardia (parasympathetic activity). Prodromal signs and symptoms consist of blurred vision, diaphoresis, nausea, dizziness, weakness and eventual bradycardia, hypotension, and loss of consciousness. More worrisome causes of syncope include cardiovascular disorders (e.g., dysrhythmia, postural hypotension), hypoglycemia, anemia, or cerebrovascular insufficiency.[37]

Palpitation (ADR #22) is a general term used by patients to describe an unpleasant awareness of forceful, rapid, or irregular heartbeat.[8,38] The potential etiologies are extensive and include cardiac conditions, psychiatric, metabolic disorders, medications, and illicit drugs. Importantly, palpitations may indicate the presence of an arrhythmia. Atrial fibrillation is the most common arrhythmia resulting in hospitalization and is associated with an increased risk of stroke. All patients with palpitations should be medically evaluated to determine the etiology.[39]
Arrhythmia may result from drug-induced abnormal impulse generation or abnormal impulse conduction in the heart, and potentially lead to life-threatening torsades de pointes.[39] Implicated drugs include amphetamines, antiarrhythmics, anticholinergics, antihistamines, decongestants, diuretics, fluoroquinolones, macrolides antibiotics, phenothiazines, protease inhibitors, SSRIs, sympathomimetics, tricyclic antidepressants, and vasodilators.[39]

ADRs Affecting the Respiratory System

Dyspnea (ADR #17) is a symptom referring to shortness of breath, breathlessness, inability to take a deep breath, suffocating, air hunger, or pain on breathing.[14,40] Causes are numerous and include respiratory, cardiac, neuromuscular, psychogenic, and/or systemic illness.[40] Drugs that may induce dyspnea include opioids, cardioselective and nonselective β-adrenergic receptor antagonists, calcium channel blockers, dipyridamole, ASA, NSAIDs, and psychotropic drugs.[41]

ADRs Affecting the Urinary System

The kidneys provide the final common pathway for the clearance of most drugs and their metabolites. Consequently, they are exposed to high concentrations of potentially toxic metabolites that can cause renal damage, especially in the presence of pre-existing renal disease.[6] For example, the chronic use of NSAIDs can lead to direct nephrotoxicity called **analgesic nephropathy**, related to the inhibition of prostaglandin synthetase resulting in reduced glomerular blood flow and **acute renal failure**.[6,8,42]

Urinary incontinence is the involuntary loss of urine. Diuretics, alcohol, and caffeine increase urine production leading to increased frequency, urgency and nocturia.[43] Calcium-channel blocking agents,

anticholinergic drugs, alpha-adrenergic agonists, and skeletal muscle relaxants may cause urinary retention and **overflow incontinence**.[43] Opioid analgesics can cause urinary retention, and like psychotropic drugs such as sedative hypnotics, benzodiazepines, antidepressants, and antipsychotic agents may affect incontinence by blunting awareness to void.[43]

ADRs Affecting the Neuropsychiatric System

Somnolence (ADR #13), sleepiness or drowsiness, may be caused by numerous medications to include antihistamines, antidepressants, anxiolytics, antihypertensives, anticonvulsants, muscle relaxants, and opioids.[44] The use of alcohol and street drugs, such as marijuana and heroin, can cause drowsiness, as can some herbal teas and supplements, such as valerian.[45]

Insomnia (ADR #9) is a symptom characterized by difficulty in falling to sleep or to stay asleep. It is most often caused by psychiatric disorders, i. e., mood disorders and anxiety.[46] Drug-related insomnia may be associated with chronic use of drugs or result from drug withdrawal. The use of alcohol, anticonvulsants, antidepressants, and thyroid hormones therapy may interfere with sleep. The withdrawal of CNS depressants such as opioids analgesics, benzodiazepines, alcohol, cocaine, and heroin may also lead to insomnia.[46]

Depression (ADR #19) is a mental state dominated by a lowering of mood and it often includes other symptoms such as anxiety, agitation, sleep disturbances, alteration in appetite, and feelings of unworthiness, and suicidal thoughts.[14,47] It is a frequent consequence of treatment with β1-adrenergic receptor antagonists, digoxin, benzodiazepines, corticosteroids, levodopa, phenothiazines, and steroids.[47] It should be noted, however, that depression may be an appropriate response to transient life-stress situations.

Anxiety is the distressing experience of dread and foreboding; an unpleasant emotional experience characterized by nervousness, uneasiness, and fear.[48] Anxiety may be related to medical illnesses, psychiatric illness, or psychological illness. Symptoms of anxiety may be caused by antipsychotic drugs, anticholinergic agents, digitalis, amphetamines, caffeine, cocaine; as well as withdrawal of alcohol or sedative-hypnotics.[48]

ADRs Affecting the Peripheral and Central Nervous Systems

Headaches (ADR #3) may be primary or secondary.49 Primary headaches include migraine, cluster, and tension headaches. Secondary headaches may be related to extracranial causes (e.g., dental problems, sinusitis, and carotid artery disorders), intracranial causes (e.g., brain tumors and vascular disorders), and exposure to toxins and drugs. Secondary headache may be a symptom of exposure to monosodium glutamate (MSG); analgesic overdose; caffeine withdrawal; and treatment with estrogen and nitrates.[49]

Fatigue (ADR #8) or **weakness** is a subjective feeling of tiredness and may have physical or mental causes.[50] Mental fatigue is due to prolonged periods of cognitive activity. Physical fatigue may be due to normal muscle exertion; or it may be caused by endocrine/metabolic problems, cardiopulmonary abnormalities, psychiatric disorders, vitamin deficiencies, or drug withdrawal.[50] Fatigue is common with medications such as antihistamines and β1-adrenergic receptor antagonists.

Tremor (ADR #23) is unintentional, rhythmic muscle activity involving to-and-fro movements (oscillations) affecting most commonly the hands, arms, head, face, and legs.[51] Tremor may be a symptom of a neurological disorder; it is most often associated with Parkinson's disease. It is also a well-recognized adverse reaction to such drugs as amphetamines, cocaine, thyroid hormones, mercury poisoning, corticosteroids, SSRIs, and alcohol abuse; and alcohol and benzodiazepines withdrawal.[51]

Tardive dyskinesia (TD) is an ADR related to long-term dopamine2-receptor blockade by antipsychotic drugs such as haloperidol, chlorpromazine, thioridazine, trifluoperazine, fluphenazine, and perphenazine.[52] Symptoms include oral dyskinesia characterized by

involuntary lip-smacking, tongue protrusion, perioral movements, chewing movements, or a puffing of cheeks. Involvement of the neck and facial muscles, truncal musculature, and limbs may also occur.[52]

Paresthesia (ADR #20) is a form of neuropathy and refers to an unpleasant, abnormal sensation of tingling, numbness, or burning sensation.[53] Causes include diabetes mellitus, chronic alcoholism, nutritional deficiencies (e.g., B1, B6, B12, and vitamin E), hypothyroidism, autoimmune disease (e.g., Sjogren syndrome, lupus, rheumatoid arthritis), infections (e.g., Lyme disease, Epstein-Barr virus, hepatitis C, shingles, leprosy, HIV), toxins (heavy metals, chemicals), chemotherapy agents, medications (antibiotics, cardiovascular agents), and trauma/injury.[53]

Fever is elevated body temperature, i.e., > 37.8° C orally.[54] It is regulated by the hypothalamic thermoregulatory center that maintains the internal temperature within a maximum fluctuation of 0.6° C. Fever results when something raises the hypothalamic set point and triggers peripheral vasoconstriction to preserve heat and shivering, which increases heat production. Drugs that can increase heat production include amphetamines, cocaine, general anesthetics, and methylenedioxymethamphetamine (MDMA, or Ecstasy), antipsychotic agents, thyroxine, and interferons. Fever due to a hypersensitivity may occur with beta-lactam antibiotics, sulfa drugs, phenytoin, carbamazepine, procainamide, quinidine, and amphotericin B.[54]

ADRs Affecting the Endocrine/Metabolic System

The treatment of diabetes mellitus often includes the administration of insulin and/or an oral hypoglycemic agent to improve cellular glucose uptake.[55] The use of insulin, meglitinides, or sulfonylureas in the absence of adequate intake of carbohydrates is the most common cause of hypoglycemia. Conditions of increased metabolism such as fever, heavy exercise, anxiety, infection, and pain lead can lead to **hypoglycemia**.[55]

Signs and symptoms of hypoglycemia are neurogenic- and neuroglycopenia-related. Neuroglycopenic signs and symptoms result from the direct central nervous system (CNS) deprivation of glucose, and include behavioral changes, confusion, fatigue, seizure, coma, and potential death if not immediately corrected. Neurogenic signs and symptoms can either be adrenergic (e.g., tremors, palpitations, anxiety) or cholinergic (e.g., hunger, diaphoresis, paresthesias).[55]

Summary

"On-target," "off-target," and cytotoxic ADRs, with the exception of overdose, are related to the use of therapeutic dosages of drugs and are predicated on the same pharmacokinetic and pharmacodynamic pathways as the therapeutic effects of drugs. Prerequisites to considering ADRs in the differential diagnosis of a patient's signs and symptoms include awareness that an ever increasing number of patients are taking more and more medications (polypharmacy) and familiarity with relevant literature about ADRs.

Course Test Preview

To receive Continuing Education credit for this course, you must complete the online test. Please go to: *www.dentalcare.com/en-us/ce-courses/ce536/start-test*

1. All of the following statements related to adverse drug reactions (ADRs) are correct, EXCEPT for one. Which one is the exception?

A. Drugs seldom exert their beneficial effects without also causing ADRs – this therapeutic dilemma lends credence to the statement that there are no "absolutely" safe biologically active agents.
B. With the exception of overdose, an ADR is defined as "a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function."
C. The FDA has one of the most rigorous approval requirements in the world to authorize the marketing of new drugs and usually identifies the most important ADRs.
D. The phrase "response to a drug" means that a causal relationship between the therapeutic agent and the ADR is at least a reasonable possibility.

2. All of the following statements related to ADRs are correct, EXCEPT for one. Which one is the exceprtion?

A. In order to have a 95 percent chance of detecting an ADR with an incidence of 1 in 1,000 subjects, a population of 30,000 would have to be exposed to a drug.
B. The term "side effect," as used in the past, described not only negative (unfavorable) reactions; but, at times, concurrent positive (favorable) effects as well – the term should not be regarded as synonymous with ADRs.
C. ARDs may be explained by one of five mechanisms: (1) "on-target" adverse reactions, (2) "off-target" adverse reactions, (3) cytotoxic reactions, (4) immune-mediated reactions, and (5) idiosyncratic reactions.
D. A drug or drug class may produce toxic or adverse reactions by one or several of mechanisms of ADRs.

3. Which of the following statements related to "on-target" mechanisms of ADRs is correct?

A. An "on-target" ADRs may occur when a drug interacts with its intended receptor in the intended tissue.
B. An "on-target" ADR may also occur when a drug interacts with its intended receptor, but in an unintended tissue.
C. H1-histamine drugs that penetrate the blood-brain barrier may interact with H1-receptors in the brain to induce hyperexcitability
D. Local anesthetic agents intended to block sodium channels in neuronal tissues at the site of its administration with high plasma levels can cause sodium channel blockade in the heart.

4. All of the following statements related to "off-target" mechanisms of ADRs are correct, EXCEPT for one. Which one is the exception?

A. An "off target" ADR can occur when a drug interacts with an unintended receptor either in an intended or in an unintended tissue.
B. An example of an "off-target" ADR is when a β2-adrenergic receptor agonist used to treat asthma also interacts with β1-adrenergic receptors in the heart.
C. An example of an "off-target" ADR uncovered during post-marketing period, which resulted in the withdrawal of the drug from the market, occurred when terfenadine, an H1-histamine receptor blocking agent also interacted with unintended receptors (potassium channels) in an unintended tissue (heart).
D. β1-adrenergic receptor blocking agents targeting the heart may also antagonize β2-adrenergic receptors in lungs and cause bronchodilation.

5. All of the following statements related to cytotoxic mechanism of ADRs specific to APAP toxicity are correct, EXCEPT for one. Which on e is the exception?

A. When APAP undergoes oxidation by cytochrome P450 isoenzyme CYP2E1 into N-acetyl-p-benzoquinoneimine (NAPQI), this highly reactive metabolite is conjugated into APAP-glucuronide and APAP-sulfate.
B. When glutathione stores are depleted, NAPQI accumulates and attacks cellular and mitochondrial proteins in the liver, which may lead to hepatic fibrosis or necrosis.
C. Moderate doses of a toxic drug or metabolite activate mechanisms that result in programmed cell death (apoptosis) and tissue fibrosis.
D. High doses of a toxic drug or metabolite activate mechanisms that lead to uncontrolled cell death and tissue necrosis

6. All of the following statements related to "on-target," "off-target," and cytotoxic ADRs are correct, EXCEPT for one. Which one is the exception?

A. "On-target," "off-target," and cytotoxic ADRs have a pharmacokinetic or a pharmacodynamic basis.
B. "On-target," "off-target," and cytotoxic ADRs, with the exception of overdose, are precipitated by drug-drug, drug-food, drug-herbal, and drug-disease interactions with therapeutic doses of a drug.
C. The risk of ADRs depends on the margin of safety between the dose of a drug required for efficacy and the dose that causes ADRs.
D. When the margin of safety is small, ADRs result primarily from overdose; when the margin of safety is large, ADRs may manifest at therapeutic doses.

7. All of the following statements related to pharmacokinetic drug-drug interaction are correct, EXCEPT for one. Which one is the exception?

A. The plasma level of a drug depends on the dosage administered and the drug's rate of absorption, distribution, metabolism, and clearance.
B. Pharmacokinetic processes may be altered, i.e., induced or inhibited by drug-drug interactions.
C. The interaction between opioid analgesics and APAP is an example of a pharmacokinetic drug-drug interaction affecting the absorption of APAP.
D. Drug A competes for plasma protein binding with drug B and decreases it plasma level.

8. All of the following statements related to pharmacodynamic drug-drug interactions are correct, EXCEPT for one. Which one is the exception?

A. The intended or unintended effect produced by a given plasma level of a drug may result from chronic use of a drug or the presence of one or more drugs.
B. Pharmacodynamic ADRs are the result of receptor alterations, and pharmacological, physiological, and chemical drug-drug interactions.
C. The interaction between NSAIDs and antihypertensive agents is an example of a pharmacological drug-drug interaction.
D. An example of a beneficial pharmacodynamic drug-drug interaction is illustrated by the interaction between phentolamine mesylate and epinephrine.

9. All of the following statements related to drug-food and drug-herbal interactions are correct, EXCEPT for one. Which one is the exception?

A. Nutrients can act as mechanical barriers and protect the gastric mucosa from irritants; but they can also prevent drug-access to mucosal surfaces and reduce or slow the absorption of some drugs.
B. Components of grapefruit inhibit cytochromeP450 isoenzyme CYP3A4 and increase the plasma level of a number of drugs; for example, it can significantly enhance the anticoagulant effect of warfarin.
C. Ginkgo biloba inhibits platelet function; its use with acetylsalicylic acid (ASA), other nonsteroidal antiinflammatory agents (NSAIDs), and clopidogrel, which also interfere with platelet aggregation, increases the risk of bleeding.
D. St. John's wort inhibits the cytochrome P450 isoenzyme CYP3A4 and increases the efficacy of many drugs, including some prescribed by oral healthcare providers, e.g., benzodiazepines and macrolides antibacterial agents.

10. All of the following statements related to cytotoxic ADRs are correct, EXCEPT for one. Which one is the exception?

A. Depending on the severity of the toxic insult cytotoxicity may manifest as apoptosis, i.e., uncontrolled cell death.
B. Apoptosis is genetically directed self-destruction of DNA-damaged cells and, may lead to fibrosis.
C. If the toxic insult is severe, programmed cell death cannot be accomplished and the cells undergo necrosis.
D. Necrosis is characterized by autolysis of damaged cells, inflammation, and damage to nearby healthy tissues.

11. All of the following statements related to overdose are correct, EXCEPT for one. Which one is the exception?

A. Generally, with overdose, the effects of drugs are exaggerated, ADRs become more pronounced, and other, unexpected reactions may be observed.
B. From 1999 to 2020, more than 263,000 people died in the United States from overdoses involving prescription opioids.
C. From 1999 to 2020, overdose deaths involving prescription opioids doubled.
D. An opioid overdose can reliably be identified by the presence of three clinical signs and symptoms referred to as the "opioid overdose triad": (1) pinpoint pupils (miosis), (2) unconsciousness, and (3) respiratory depression.

12. All of the following statements related to ADRs affecting oral tissues are correct, EXCEPT for one. Which one is the exception?

A. Xerostomia (ADR #28) and taste disturbances (ADR #30) were among the 30 most common ADRs identified with the top 200 drugs dispensed by U.S. community pharmacies in 2008.
B. Stomatitis and ulcerative stomatitis represent cytotoxic reactions to topically applied agents, e.g., Las; or may result from the systemic administration of cytotoxic drugs, e.g., antineoplastic agents.
C. Antibacterial and corticosteroid therapy is often complicated by superinfection with candidal organisms in oral tissues.
D. Reduced salivary flow may be related to a drug's sympatholytic or muscarinic effect in the CNS.

13. All of the following statements related to ADRs affecting the gastrointestinal system are correct, EXCEPT for one. Which one is the exception?

A. Nausea, vomiting, diarrhea, constipation, abdominal pain, dyspepsia, and anorexia were among the 30 most common potential ADRs associated with therapeutic dosages of the top 200 drugs dispensed by U.S. community pharmacies in 2008.
B. Drug-induced pancreatitis is usually a chronic condition characterized by lower abdominal pain accompanied by severe nausea and vomiting.
C. The ulcerogenic effect of NSAIDs is well established and is attributable to inhibition of prostaglandin synthesis.
D. A major concern is a patient complaining of lower abdominal pain and bloody diarrhea who is currently taking or has recently taken clindamycin or a broader spectrum penicillin or cephalosporin.

14. All of the following statements related to ADRs affecting the liver and biliary system are correct, EXCEPT for one. Which one is the exception?

A. During the past decade APAP has been identified as the leading cause of acute liver failure (ALF) in the United States and up to 50% of APAP-related cases of ALF are due to unintentional overdose.
B. Clinical signs and symptoms of APAP overdose include nausea, vomiting, abdominal pain, anorexia, and a few days later, elevated bilirubin presents as jaundice.
C. The FDA formally withdrew from the market all prescription combination analgesics containing more than 650 mg of APAP per unit dose.
D. When prescribed as a single agent analgesic, APAP, 650 mg per dose, q4h, may still be prescribed.

15. All of the following statements related to ADRs affecting the ears are correct, EXCEPT for one. Which one is the exception?

A. Dizziness is the most common potential ADR associated with therapeutic dosages of the top 200 drugs dispensed by U.S. community pharmacies.
B. Dizziness is an imprecise term describing various related sensations such as faintness, a feeling of impending syncope; light-headedness; and a feeling of imbalance.
C. Vertigo is described by patients as noise in the ears such as buzzing, ringing, roaring, whistling, hissing, or pulsating.
D. Potentially ototoxic drugs prescribed by dentist include antibiotics such as metronidazole, clindamycin, and macrolides.

16. All the following statements related to ADRs affecting the cardiovascular and respiratory systems are correct, EXCEPT for one. Which one is the exception?

A. Common drugs that produce orthostatic hypotension include diuretics, α1 and β1-receptor blockers, nitrates, digitalis, ACE-inhibitors, and calcium channel blockers.
B. Macrolide antibiotics are known to cause cardiac arrhythmias that may potentially lead to life-threatening torsades de pointes.
C. Dyspnea may be caused by drugs prescribed by dentists such as opioids and NSAIDs.
D. Atrial fibrillation is an uncommon arrhythmia.

17. All of the following statements related to ADRs affecting the urinary system are correct, EXCEPT for one. Which one is the exception?

A. Urinary incontinence is the voluntary loss of urine – diuretics, alcohol, and caffeine increase urine production leading to increased frequency, urgency and nocturia.
B. The chronic use of NSAIDs can lead to direct nephrotoxicity called analgesic nephropathy, related to the inhibition of prostaglandin synthetase resulting in reduced glomerular blood flow and acute renal failure.
C. Calcium-channel blocking agents, anticholinergic drugs, alpha-adrenergic agonists, and skeletal muscle relaxants may cause urinary retention and overflow incontinence.
D. Opioid analgesics also can cause urinary retention, and like psychotropic drugs such as sedative hypnotics, benzodiazepines, antidepressants, and antipsychotic agents may affect incontinence by blunting awareness to void.

18. All of the following statements related to ADRs affecting the neuropsychiatric system are correct, EXCEPT for one. Which one is the exception?

A. Somnolence, sleepiness or drowsiness may be caused by numerous medications to include antihistamines, antidepressants, anxiolytics, antihypertensives, anticonvulsants, muscle relaxants, and opioids..
B. Insomnia is a symptom characterized by difficulty in falling to sleep or to stay asleep – drug-related insomnia may be associated with chronic use of drugs or result from drug withdrawal such as opioid analgesics of benzodiazepines.
C. Depression is never an appropriate response to a transient life-stress situation.
D. Anxiety is the distressing experience of dread and foreboding; unpleasant emotional experience characterized nervousness, uneasiness, and fear.

19. All of the following statements related to ADRs affecting the peripheral and central nervous systems are correct, EXCEPT for one. Which one is the exception?

A. Primary headache may be a symptom of exposure to monosodium glutamate (MSG); analgesic overdose; caffeine withdrawal; and treatment with nitrates.
B. Symptoms of tardive dyskinesia include dyskinesia characterized by involuntary lip-smacking, tongue protrusion, perioral movements, chewing movements, or a puffing of cheeks.
C. Drugs associated with paresthesia include Las, long-term exposure to nitrous oxide, mercury poisoning, led poisoning, anticonvulsant drugs; and withdrawal of benzodiazepines.
D. Drugs that can increase heat production, i.e., cause fever, include amphetamines, cocaine, general anesthetics, and antipsychotic agents.

20. All of the following statements related to ADRs affecting the endocrine/metabolic system are correct, EXCEPT for one. Which one is the exception?

A. The use of insulin, meglitinides, or sulfonylureas in the absence of adequate intake of carbohydrates is the most common cause of hypoglycemia..
B. Conditions of increased metabolism such as fever, heavy exercise, anxiety, infection, and pain lead can lead to hypoglycemia..
C. Neuroglycopenic signs and symptoms result from the direct central nervous system (CNS) deprivation of glucose, and include hyperacuity, excitation, and potential death if not immediately corrected.
D. Neurogenic signs and symptoms can either be adrenergic (e.g., tremors, palpitations, anxiety) or cholinergic (e.g., hunger, diaphoresis, paresthesias).

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