Pharmacology of the Respiratory, Gastrointestinal and Genitourinary Drugs: Clinical Implications

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CE Credits: 2 hours
Intended Audience: Dentists, Dental Hygienists, Dental Assistants, Dental Students, Dental Hygiene Students, Dental Assistant Students
Date Course Online: 01/02/2018 Last Revision Date: N/A Course Expiration Date: 01/01/2021
Cost: Free Method: Self-instructional AGD Subject Code(s): 10
Online Course: www.dentalcare.com/en-us/professional-education/ce-courses/ce540

Disclaimer: Participants must always be aware of the hazards of using limited knowledge in integrating new techniques or procedures into their practice. Only sound evidence-based dentistry should be used in patient therapy.

Introduction
This course will identify therapeutic agents commonly prescribed for the treatment of respiratory, gastrointestinal (GI), and genitourinary (GU) disorders, present their mechanisms of action, discuss indications for their use, and correlate the information to clinical dentistry.

Conflict of Interest Disclosure Statement
• Dr. Terézhalmy has done consulting work for Procter & Gamble and has served on the dentalcare.com Advisory Board.

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Overview

This continuing dental education course is intended to provide a clinical frame of reference when patients present in the oral healthcare setting with a history of taking drugs for the treatment of respiratory, gastrointestinal (GI), and genitourinary (GU) disorders. Based on the Top 300 Prescription Drugs dispensed by U.S. community pharmacies, common respiratory, GI, and GU disorders are identified and discussed, including implications to clinical dentistry.

Learning Objectives

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

- Discuss the relevance of the top 300 drugs dispensed by U.S. community pharmacies.
- Identify common respiratory, gastrointestinal, and genitourinary drugs.
- Discuss the mechanism of action of respiratory, gastrointestinal, and genitourinary drugs and indications for their use.
- Discuss prevalent respiratory, gastrointestinal, and genitourinary disorders with reference to the practice of dentistry.

Introduction

A patient’s overall health status determines the patient’s ability to undergo and respond to dental care. Consequently, patient-specific problems that may interfere with the clinical process must be identified. In determining perioperative risk, clinicians must consider past and present illnesses, major hospitalizations, history of drug allergies and other adverse drug reactions (ADRs), dietary supplements and special diets, and medications taken by the patient.

In the United States there are approximately 500 Food and Drug Administration (FDA)-approved active ingredients (therapeutic agents) in several thousand different formulations. ClinCalc DrugStats provides prescription drug utilization data estimates based on the annual Medical Expenditure Panel Survey (MEPS). The list of the Top Prescription Drugs of 2017 reflects data collected in 2014 and is based on more than 3.187 billion out-patient prescriptions.

The Top 200 Prescription Drugs of 2017 represent 40% of the available 500 active ingredients and comprise 90% of all prescription drugs taken by ambulatory patients in 2014. The Top 300 Prescription Drugs of 2017 represent 60% of the available 500 active ingredients and comprise 97% of all prescription drugs taken by ambulatory patients in 2014. These data are invaluable in identifying patient-specific risks factors in ambulatory settings.

The Top 300 Prescription Drugs of 2017 include 38 agents, prescribed primary by physicians, for the treatment of respiratory, gastrointestinal (GI), and genitourinary (GU) conditions. In relation to these drugs, minimum competency by oral healthcare providers assumes knowledge in the following four areas: (1) recognition of drugs by name (brand/generic); (2) indications for their use; (3) familiarity with potential ADRs; and (4) the use of reliable informational resources.

DailyMed, a useful online resource, is the official repository for FDA-approved package inserts, i.e., for individual drug-approved, clinically relevant...
The posted information is the most recent submitted to the FDA by pharmaceutical companies and includes strengthened warnings undergoing FDA review. The information is accurate; whenever possible, it is based on human experience, and does not contain promotional or misleading information such as implied claims.

Respiratory, Gastrointestinal, and Genitourinary Drugs in the Top 300 Prescription Drugs
Based on the Top 300 Prescription Drugs of 2017 (dispensed in 2014), 17 of the therapeutic agents (Table 1) are indicated for the treatment of respiratory abnormalities and represent nearly 185 million prescriptions; 13 of the drugs (Table 2) are indicated for the treatment of GI conditions and represent over 160 million prescriptions; and 8 of the drugs (Table 3) are indicated for the treatment of GU dysfunction and represent nearly 393 million prescriptions.

Prevalent Respiratory Disorders
Based on the mechanisms of action of respiratory drugs in the Top 300 Prescription Drugs of 2017 dispensed by U.S. community pharmacies in 2014, the most common respiratory disorders encountered in an ambulatory patient population include allergic rhinitis; asthma; chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema; and sneezing and coughing, often associated with the above and other diagnoses.

Allergic Rhinitis
Allergic rhinitis occurs when an allergen such as dust mites, insect waste, animal dander, molds, pollens, and other pollutants (e.g., cigarette smoke) penetrate the nasal mucosa, enters the underlying tissue, and interacts with IgE antibodies on the surfaces of previously sensitized mast cells and basophiles. The allergen cross-links IgE/Fc receptor-complexes and causes the release of histamine, which binds to histaminergic receptors in the nasal mucosa and surrounding tissues.

Histamine-induced venule dilation engorges the local microvasculature with blood and the contraction of vascular endothelial cells allows the escape of plasma proteins and fluid from capillary venules. The accompanying itchy palate, sneezing, coughing, and runny nose; and allergic conjunctivitis result from the combined action of histamine and the release of other chemical mediators of inflammation (e.g., kinins, prostaglandins, and leukotrienes).

Patients should be informed about their condition and advised to avoid known allergens. Intranasal corticosteroids are the most common treatment for persistent symptoms. Patients with more severe disease that does not respond to intranasal corticosteroids may be taking an antihistamine, and a cysteinyl leukotriene (CysLT)-receptor antagonist. Other therapies may include decongestants such as pseudoephedrine; and intranasal cromolyn, an agent that inhibits mast cell degranulation.

Allergic rhinitis is a systemic illness and may be associated with fatigue and malaise. Symptoms may be mild, i.e., do not interfere with the patient’s quality of life; or severe, i.e., they may affect participation in sports, sleep, and school or work performance; and in susceptible patients exacerbate asthma. Severe allergic rhinitis may interfere with the clinical process. Patients with an uncertain diagnosis or severe symptoms require a medical referral.

Asthma
Asthma is primarily an inflammatory disorder of the airway, with inflammation caused by allergens or other stimuli leading to bronchial hypersecretion and bronchospasm. Airborne substances, such as pollens, dust mites, mold spores, animal dander, and insect waste have been implicated. Other factors include viral infections, physical activity (exercise-induced asthma), and cold air. In recent decades, environmental and work-related pollutants are becoming increasingly implicated.

Coughing, shortness of breath and wheezing are the sine qua non of asthma. In a moderate to severe attack, tightness or pain in the chest occurs due to spasm of the bronchial tubes. In severe cases the individual may use the accessory muscles of respiration (sternocleidomastoid, trapezius, and scalenus)
Table 1. Respiratory Drugs in the Top 300 Prescription Drugs of 2017.²

<table>
<thead>
<tr>
<th>Drug*</th>
<th>Mechanisms of Action*</th>
<th>Indication*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluticasone (nasal spray)</td>
<td>Synthetic trifluorinated corticosteroid with anti-inflammatory activity</td>
<td>Allergic rhinitis</td>
</tr>
<tr>
<td>Cetirizine Loratadine</td>
<td>Selective histaminergic H₁-receptor antagonists</td>
<td>Allergic rhinitis</td>
</tr>
<tr>
<td>Albuterol (inhaler) Levalbuterol inhaler</td>
<td>Selective short-acting beta₂-adrenergic receptor agonists</td>
<td>Bronchospasm with reversible obstructive airway disease</td>
</tr>
<tr>
<td>Montelukast</td>
<td>Cysteinyl leukotriene (CysLT)-receptor antagonist</td>
<td>Allergic rhinitis, Asthma, Exercise-induced bronchoconstriction</td>
</tr>
<tr>
<td>Budesonide (inhaler) Beclomethasone (inhaler)</td>
<td>Anti-inflammatory corticosteroid that exhibits potent glucocorticoid activity</td>
<td>Asthma</td>
</tr>
<tr>
<td>Mometasone w/formoterol (inhaler)</td>
<td>Mometasone furoate is a corticosteroid demonstrating potent anti-inflammatory activity; Formoterol is a long-acting, selective beta₂-adrenergic agonist</td>
<td>Asthma</td>
</tr>
<tr>
<td>Fluticasone w/salmeterol (inhaler)</td>
<td>Fluticasone is a synthetic trifluorinated corticosteroid with anti-inflammatory activity; Salmeterol is a long-acting, selective beta₂-adrenergic agonist</td>
<td>Asthma, COPD</td>
</tr>
<tr>
<td>Budesonide w/formoterol (inhaler)</td>
<td>Budesonide is an anti-inflammatory corticosteroid that exhibits potent glucocorticoid activity; Formoterol is a long-acting, selective beta₂-adrenergic agonist</td>
<td>Asthma, COPD (including chronic bronchitis and/or emphysema)</td>
</tr>
<tr>
<td>Ipratropium</td>
<td>Long-acting, muscarinic M₃-receptor antagonist</td>
<td>Long-term, once-daily, maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema</td>
</tr>
</tbody>
</table>
Table 1. Continued.

<table>
<thead>
<tr>
<th>Drug*</th>
<th>Mechanisms of Action*</th>
<th>Indication*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albuterol w/ipratropium (inhaler)</td>
<td>Albuterol is a selective, short-acting beta2-adrenergic receptor agonist; Ipratropium is a long-acting, muscarinic M3-receptor antagonist</td>
<td>Bronchospasm associated with COPD in patients requiring more than one bronchodilator</td>
</tr>
<tr>
<td>Benzonatate</td>
<td>Anesthetizes the stretch receptors located in the respiratory passages, lungs, and pleura thereby reducing the cough reflex at its source</td>
<td>Symptomatic relief of cough</td>
</tr>
<tr>
<td>Guaifenesin</td>
<td>An expectorant that promotes or facilitates the removal of secretions from the respiratory tract by increasing sputum volume and making sputum less viscous</td>
<td>To loosen phlegm (mucus) and thin bronchial secretion, to drain bronchial tubes, and to make coughs more productive</td>
</tr>
<tr>
<td>Guaifenesin w/codeine phosphate</td>
<td>Guaifenesin is an expectorant that promotes or facilitates the removal of secretions from the respiratory tract by increasing sputum volume and making sputum less viscous; Codeine, an opioid-receptor agonist that elevates the threshold for cough</td>
<td>To temporarily control cough due to minor throat and bronchial irritation as may occur with the common cold or inhaled irritants</td>
</tr>
</tbody>
</table>

*FDA-approved information on specific agents is available at DailyMed - the website is a user-friendly, look-up-and-download resource that provides comprehensive, up-to-date information on individual drugs.*

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Table 2. Gastrointestinal Drugs in the Top 300 Prescription Drugs of 2017.²

<table>
<thead>
<tr>
<th>Drug*</th>
<th>Mechanisms of Action*</th>
<th>Indication*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>Proton pump inhibition - suppress the final step in gastric acid production by covalently binding to the (H⁺, K⁺)-ATPase enzyme system at the secretory surface of gastric parietal cells</td>
<td>Peptic ulcer disease (PUD) Active duodenal ulcer Active gastric ulcer Symptomatic gastroesophageal reflux disease (GERD) Erosive esophagitis (EE) due to acid-mediated GERD Pathological hypersecretory of H⁺ (e.g., Zollinger–Ellison syndrome) Risk reduction of NSAID-associated gastric ulcer</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esomeprazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lansoprazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexlansoprazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ranitidine</td>
<td>Reversibly inhibit the action of histamine a histaminergic H₂-receptors on gastric cells</td>
<td></td>
</tr>
<tr>
<td>Famotidine</td>
<td></td>
<td>Short-term treatment of duodenal ulcers</td>
</tr>
<tr>
<td>Sucralfate</td>
<td>Accelerate healing of ulcer by forming a complex with proteinaceous exudate at the ulcer site and inhibits pepsin activity</td>
<td></td>
</tr>
<tr>
<td>Docusate Polyethylene glycol 3350</td>
<td>Osmotic agents – soften stool by increasing the amount of water the stool absorbs in the gut, making the stool softer and easier to pass.</td>
<td>To relieve occasional constipation</td>
</tr>
<tr>
<td>Meclizine</td>
<td>Blocks the vasodepressor response to histamine by histaminergic H₁-receptor antagonism</td>
<td>Nausea Vomiting Motion sickness Vertigo</td>
</tr>
<tr>
<td>Dicyclomine</td>
<td>Potent anticholinergic effect – relieves smooth muscle spasm in the GI tract</td>
<td>Irritable bowel syndrome</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>Sensitize tissues to the action of acetylcholine – stimulates motility of the upper gastrointestinal tract</td>
<td>GERD Acute and recurrent diabetic gastroparesis</td>
</tr>
</tbody>
</table>

²FDA-approved information on specific agents is available at DailyMed - the website is a user-friendly, look-up-and-download resource that provides comprehensive, up-to-date information on individual drugs.³
and may be found sitting down, leaning forward against a support in order to fix the shoulder muscles so that these accessory muscles may obtain better leverage on the chest wall.\textsuperscript{7,8}

The treatment of asthma is a stepwise approach based on current impairment and the anticipated risk of an acute attack.\textsuperscript{9,10} In patients with intermittent asthma an inhaled short-acting beta\textsubscript{2}-adrenergic receptor agonist such as albuterol is preferred (Step 1).\textsuperscript{2,3,9,10} For patients with persistent mild asthma, daily medication with low-dose inhaled corticosteroid such as budesonide is preferred (Step 2); montelukast, a cysteinyl leukotriene (CysLT)-receptor antagonist, is an alternative.\textsuperscript{2,3,9,10}

The treatment of patients with persistent moderate asthma is reflected in the recommendations in Steps 3 and 4. Treatment is Step 3 is less aggressive with low-dose inhaled corticosteroid plus an inhaled long-acting, selective beta\textsubscript{2}-adrenergic receptor agonist such as fluticasone w/salmeterol or medium-dose inhaled corticosteroid; low-dose inhaled corticosteroid plus montelukast, a cysteinyl leukotriene (CysLT)-receptor antagonist, is an alternative regimen.\textsuperscript{2,3,9,10}

Treatment of persistent moderate asthma in Step 4 is more aggressive with medium-dose inhaled corticosteroid plus inhaled long-acting selective beta\textsubscript{2}-adrenergic receptor agonist; or medium-dose inhaled corticosteroid plus montelukast, cysteinyl leukotriene (CysLT)-receptor antagonist, as an alternative regimen.\textsuperscript{2,3,9,10} Persistent severe asthma (Step 5) is treated with high-dose inhaled corticosteroid plus inhaled long-acting selective beta\textsubscript{2}-adrenergic receptor agonist.\textsuperscript{2,3,9,10}
In oral healthcare settings consider strong emotions and stress as potential factors that may precipitate an acute asthma attack during the perioperative period. In susceptible patients metabisulfite, an antioxidizing agent included in local anesthetics to minimize oxidation of the vasoconstrictor, may exacerbate asthma; and NSAIDs such as ibuprofen and naproxen increase endogenous leukotriene concentrations and may precipitate symptoms of asthma (intolerance).

Mild exacerbation of asthma is characterized by dyspnea only with activity. The patient experiences prompt relief with inhaled short-acting beta₂-adrenergic receptor agonist such as albuterol. Moderate exacerbation is characterized by dyspnea that interferes with or limits physical activity. The patient experiences prompt relief with inhaled short-acting beta₂-adrenergic receptor agonist and requires routine referral for a medical evaluation.

Severe exacerbation is characterized by dyspnea at rest that interferes with conversation. The patient experiences partial relief from frequent inhaled short-acting beta₂-adrenergic receptor agonist and should be referred to an emergency room. The patient with severe, life-threatening asthma is diaphoretic and is unable to speak because of dyspnea. Frequent inhaled short-acting beta₂-adrenergic receptor agonist provides mild/no relief and the patient requires hospitalization.

**Chronic Obstructive Pulmonary Disease**

Chronic obstructive pulmonary disease (COPD) is chronic airway irritation, mucus production, loss of elasticity in lung parenchyma, and airflow obstruction. The terms chronic bronchitis and emphysema are no longer included in the formal definition. Chronic bronchitis, a clinical term, describes a productive cough and sputum production for ≥ three months during two successive years. Emphysema, a pathological term, describes destruction of alveolar capillary membrane.

Exposure to tobacco smoke is the most significant risk factor for COPD. Other risk factors include advanced age; secondhand cigarette smoke; chronic exposure to occupational pollutants such as silica, coal, and concrete dust; chronic exposure to environmental pollutants such as cotton, hemp, and grain dust and welding fumes; alpha₁-antitrypsin deficiency (a genetic anomaly); childhood history of recurrent respiratory infections; and family history of COPD.

On exertion (physical or emotional stress), patients with COPD typically experience coughing, dyspnea (air hunger), and wheezing (a high-pitch whistling sound). Other signs and symptoms include the use of accessory muscles of respiration, pursed-lip breathing (air is inhaled slowly through the nose and exhaled slowly through pursed lips); pulmonary hyperinflation (widened anteroposterior chest diameter and diminished breath sounds); and, less commonly, cyanosis.

COPD is a systemic disease with important non-pulmonary components such as weight loss, and respiratory and skeletal muscle abnormalities. Weight loss is related to increased circulating inflammatory mediators and pulmonary cachexia; respiratory muscles are overworked and fatigued; and skeletal muscles are underworked and atrophied. Persistent pulmonary damage can lead to right-sided heart failure, peripheral edema, jugular vein distention, and hepatomegaly.

Treatment delays/reduces the risk of acute exacerbations, i.e., sustained worsening of dyspnea, cough and/or sputum excretion. Maintenance therapy may include an inhaled corticosteroid with a long-acting selective beta₂-adrenergic receptor agonist such as fluticasone w/salmeterol or an inhaled long-acting muscarinic M₂-receptor antagonist, such as ipratropium. Long-term oxygen therapy, indicated if O₂ saturation is ≤88%, corrects hypoxemia.

When a patient with COPD presents in an oral healthcare setting determine residual respiratory and physical impairment and restriction of normal activities. Patient with mild disease reports shortness of breath when hurrying on flat ground or climbing a slight hill or a flight of stairs. The exacerbation can be controlled with an increase in the dosage of the regular...
medication, i.e., an inhaled corticosteroid with a long-acting selective beta₂-adrenergic receptor agonist.\textsuperscript{2,3,15}

Patients with moderate disease stop to breath after walking 100 meters on flat ground. The exacerbation cannot be controlled with an increase in dosage of regular medication.\textsuperscript{15} The patient requires medical referral and treatment with systemic corticosteroids and/or antibiotics. The patient with severe disease is short of breath when dressing and, in general, is housebound from breathlessness. Patient requires evaluation in an emergency room and, likely, hospitalization.

Patients with COPD placed in a supine position may experience orthopnea soon after reclining. Treat patients in a semi-reclining position and monitor oxygen saturation with a pulse oximeter. Severe exacerbation of COPD (i.e., fast, labored breathing, hypoxemia, signs of right-sided heart failure such as peripheral edema and cyanosis, arrhythmia, chest pain, altered mental status, and sudden extreme dyspnea) warrants immediate medical referral.

\textbf{Sneezing and Coughing}

A sneeze is a sudden, forceful, uncontrolled burst of air from the lungs. The soft palate and uvula are depressed, the tongue elevates to partially close the passage to the mouth, and the air ejected from the lungs is expelled mostly through the nose. Sneezing typically occurs when irritants and foreign particles reach the nasal mucosa and trigger the release of histamine that initiates the sneeze reflex by activating sensory fibers of the trigeminal nerve.

Coughing is an explosive respiratory maneuver, which reflexively or deliberately is intended to clear irritants, foreign particles, and secretions from the airway.\textsuperscript{16,17} It consists of three sequential phases: inhalation; forced exhalation against a closed glottis; and, following opening of the glottis, violent release of air from the lungs. Common causes of acute cough include upper respiratory tract infections, exacerbation of COPD and asthma, and pneumonia.\textsuperscript{16}

Common causes of chronic cough include chronic bronchitis and gastroesophageal reflux disease, treatment with an angiotensin-converting enzyme inhibitor, and obstructive sleep apnea.\textsuperscript{16,17} When persistent and excessive, cough can seriously impair quality of life and lead to vomiting, muscle pain, rib fractures, urinary incontinence, tiredness, syncope, and depression.\textsuperscript{16,17} It also has psychosocial effects, such as embarrassment and negative impact on social interactions.\textsuperscript{16,17}

Symptomatic treatment may include the administration of guaifenesin or guaifenesin w/codeine.\textsuperscript{2,3,17} Guaifenesin, an expectorant, promotes or facilitates the removal of secretions from the respiratory tract by increasing sputum volume and making sputum less viscous. Codeine phosphate, an antitussive agent, temporarily controls cough due to minor throat and bronchial irritation that may occur with the common cold or inhaled irritants.

\textbf{Prevalent Gastrointestinal Disorders}

Based on the mechanisms of action of gastrointestinal drugs in the Top 300 Prescription Drugs of 2017 dispensed by U.S. community pharmacies in 2014, the most common gastrointestinal disorders encountered in an ambulatory patient population include peptic ulcer disease (PUD), gastroesophageal reflex disease (GERD), nausea and vomiting; constipation; irritable bowel syndrome (IBS); and diabetes-induced gastroparesis.

\textbf{Peptic Ulcer Disease}

Parietal cells of the gastric mucosa contain receptors for gastrin (G) and acetylcholine (M\textsubscript{3}), both of which activate cellular mechanisms that increase intracellular calcium ion concentrations. In the presence of calcium ions, increased concentrations of cyclic AMP activate the proton pump (H\textsuperscript{+}/K\textsuperscript{+}-ATPase) of parietal cells to secrete hydrogen ions against a large concentration gradient in the gastric lumen in exchange for potassium ions.

Histamine, released from mast cells, interacts with H\textsubscript{2}-receptors on parietal cells and also activates adenylate cyclase resulting in increased concentrations of intracellular cyclic AMP and contributes to the secretion of hydrogen ions. In addition, under the influence of the neurotransmitter acetylcholine,
the mucous neck cells and peptic (chief) cells secrete pepsinogen. Pepsinogen, following contact with gastric acid, is converted to pepsin, an active proteolytic enzyme.

The normal gastroduodenal mucosa resists injury from acid and pepsin in the gastric juice by several homeostatic defense mechanisms. Surface epithelial cells secrete mucus and bicarbonate creating a pH gradient in the mucus layer from the highly acidic gastric lumen to the nearly neutral surface of the mucosa. Gastric mucosal cells have a specialized apical-surface membrane, which resists the diffusion of acid back into mucosal cells.

Mucosal cells also resist injury by intrinsic mechanisms, such as extrusion of back-diffused acid by means of sodium-hydrogen or sodium-bicarbonate exchange. In addition, surface epithelial cells continually slough and proliferating cells rapidly repair mucosal injury. Prostaglandins also enhance mucosal resistance to injury by maintaining mucosal blood flow to remove acid that has diffused across the compromised mucosa and by stimulating the secretion of mucus and bicarbonate.

PUD is characterized by erosion of the gastric or duodenal mucosa by acid and pepsin. The principal symptom is pain. The patient often has periods of remissions, with complete freedom from symptoms for weeks or months. The patient with PUD is predisposed to hemorrhage, perforation, and pyloric stenosis. Hemorrhage may vary from slight bleeding to massive hemorrhage and the patient may vomit variable quantities of blood. Blood in the stool makes it black and tarry (melena).

Perforation of gastric or duodenal mucosa, results in the discharge of gastric or duodenal contents into the peritoneal cavity causing an inflammatory reaction (peritonitis) characterized by severe generalized abdominal pain and board-like rigidity of the abdominal muscles. Pyloric stenosis is the most common complication of duodenal ulcers and results from contraction of scar tissue laid down at the base of the ulcer.

Although PUD may be associated with increased secretion of acid (Zollinger-Ellison syndrome) and peptic activity is an indispensable component of the pathogenesis of ulcers, peptic ulcers generally develop only when mucosal defense mechanisms are also altered. Two major factors, Helicobacter pylori infection and NSAIDs appear to disrupt mucosal resistance to injury. Stress, alcohol, cigarette smoking, and genetic factors further exacerbate the injury.

The medical management of PUD associated with H. pylori includes various antibacterial combinations, which leads to rapid healing of active peptic ulcers and low recurrence rates. The antibacterial agents used most often include bismuth subsalicylate, tetracycline, metronidazole, amoxicillin, and clarithromycin. Two or three of these agents are usually given in combination with an H₂-receptor blocker (e.g., ranitidine) or a proton pump inhibitor (e.g., omeprazole).

Sucralfate, a cytoprotective agent, is effective in healing peptic ulcers and for prevention of relapse. Other strategies include antacids consisting of mixtures of magnesium hydroxide, aluminum hydroxide, and calcium carbonate. Sodium bicarbonate compounds can be effective in promoting the healing of duodenal ulcers and prostaglandin analogs can prevent gastric ulcers in patients on chronic NSAID therapy by increasing mucin and bicarbonate release.

When documenting the medical history be cognizant that patients with PUD often have periods of remission, with complete freedom from symptoms for weeks or months. Patients in remission may respond negatively to questions related to PUD. Be specific, ask patients “do you now have or have you ever had PUD.” When managing odontogenic pain consider the well-established ulcerogenic effect of NSAIDs and use alternative analgesics, e.g., acetaminophen-containing formulations.

**Gastroesophageal Reflux Disease**

The squamous epithelium of the esophagus is not designed to resist the digestive action of the acidic gastric juice and it frequently becomes inflamed and eroded in patients with GERD. The primary determinant of GERD appears to be transient relaxations of the
lower esophageal sphincter not induced by swallowing.\textsuperscript{20,21} Episodes of transient relaxation are more common after meals. Slow gastric emptying and increases in intra-abdominal pressure may also induce reflux.

A hiatal hernia, i.e., a small hernial pouch, can serve as a reservoir for gastric contents. Transient relaxation of the lower esophageal sphincter is more likely to be followed by an episode of reflux when there is a hiatal pouch with retained gastric acid. GERD is further exacerbated by obesity and smoking (nicotine relaxes the lower esophageal sphincter). The extent of damage will depend on the intrinsic resistance of the esophageal epithelium to the digestive action of gastric acid.

Other modulating factors include the characteristics of the refluxed fluids: acid and pepsin together are more damaging to the esophageal epithelium than either one alone, the presence of bile, and the duration of contact between the refluxed gastric acid and the mucosa. The duration of contact depends on the number of reflux episodes per unit time, salivary neutralization of the refluxed acid, and the efficiency of esophageal peristalsis to remove the refluxed bolus of gastric acid.

Typical symptom associated with GERD is substernal burning pain radiating up to the neck (relieved immediately by antacids) brought on by positional changes of the body, e.g., lying flat in a supine position or stooping after a meal, which encourage gastroesophageal reflex.\textsuperscript{21} Esophageal pain may sometimes mimic cardiac pain. Bleeding is rare, presenting as hematemesis (vomiting of blood), which sometimes may cause severe, at first, obscure anemia.

Complications of GERD include peptic strictures due to scarring of inflamed tissue, asthma, hoarseness, and dental erosions. Additionally, prolonged acid injury may lead to metaplastic transformation of the esophageal squamous epithelium (Barrett’s esophagus) with a potential for malignant transformation.\textsuperscript{20} Medical treatment for GERD includes histaminergic H\textsubscript{2}-receptor blocking agents such as ranitidine and/or proton pump inhibitors such as omeprazole.\textsuperscript{2,3,20,21}

Other strategies include the administration of metoclopramide; a prokinetic drug that sensitzes tissues to the action of acetylcholine and thereby stimulates motility of the upper gastrointestinal tract that effectively decreases the contact time between gastric acid and the esophageal mucosa.\textsuperscript{2,3,20,21} Sucralfate, a cytoprotective agent, which electrostatically binds to positively charged proteins in ulcerative tissue retards acidic and proteolytic damage.\textsuperscript{2,3,20,21}

When treating patients with a history of GERD recognize that these patients may experience episodes of reflux in a supine position - they tend to do better in the perioperative period in a semi-reclining position. Patient may report substernal pain radiating up to the neck (relieved by antacids) mimicking pain of cardiac origin (relieved by nitroglycerin). When managing odontogenic pain keep in mind the well-established ulcerogenic effect of NSAIDs.

Nausea and Vomiting

The physiologic purpose of nausea is to prevent food intake; that of vomiting is to expel food or other toxic substances present in the upper part of the GI tract.\textsuperscript{22,23} The vomiting center, located in the lateral reticular formation of the medulla is the origin of the final common pathway along which different impulses induce emesis. The second important medullary site is the chemoreceptor trigger zone located in the area postrema.

The chemoreceptor trigger zone, which is outside the blood-brain barrier is accessible to humoral stimuli (chemicals, toxins, viruses, ions) circulating either in the blood or in the cerebrospinal fluid. However, the chemoreceptor trigger zone can only initiate emesis through stimulation of the vomiting center. The vomiting center may also be activated directly by impulses that originate in the pharynx, the GI tract and the cerebral cortex.

Indeed, emotional trauma and unpleasant olfactory and visual stimuli may cause nausea and vomiting. Finally, stimulation of the vestibular apparatus (movements of the head, neck, and eye muscles) may cause nausea and vomiting by stimulating the vomiting center.
Irritable Bowel Syndrome

IBS or spastic colon is the most frequent functional disorder of the GI tract. It is viewed as a biopsychosocial disorder characterized by altered GI motility, GI hypersensitivity, and psychosocial factors (anxiety, depression, stress). Other factors that may be involved include neurotransmitters such as serotonin, which may stimulate intestinal secretion and peristalsis and visceral pain receptors via 5-HT₃ and 5-HT₃-serotonergic pathways.

Patients with IBS experience an exaggerated gastrocolic reflex, altered gastric emptying, and increased small bowel contractions, all of which are exacerbated by food intake and/or stress. Abdominal pain relieved by defecation and pain associated with looser or more frequent stools are the hallmark of IBS. Patients may experience bloating, flatulence, dyspepsia, atypical chest pain; and diarrhea or constipation, or alternating diarrhea and constipation.

Many patients find it helpful to increase dietary fiber, drink plenty of water, avoid carbonated drinks, and eat smaller meals. To relieve pain, dicyclomine, a potent anticholinergic agent that relieves smooth muscle spasm of the GI tract may be helpful. Diarrhea-predominated IBS may respond to loperamide, which binds to opiate receptor in the gut wall, inhibits the release of acetylcholine and prostaglandins, reduces peristalsis, and increases intestinal transit time.

Diabetes-induced Gastroparesis

GI complications of diabetes mellitus (DM) and their symptoms are often caused by abnormal GI motility, which is a consequence of diabetic autonomic neuropathy caused primarily by impaired vagal control. About one in ten patients with DM report symptoms consistent with gastroparesis characterized by nausea, vomiting, bloating, postprandial fullness (satiety), and upper abdominal pain. Delayed gastric emptying contributes to poor blood glucose control.

Dietary modifications such as increasing liquid intake for patients with delayed solid emptying and eating smaller meals minimize...
postprandial fullness. Fiber supplements, foods that are high in fat and alcohol impair gastric emptying and their intake should be reduced. The use of tobacco products should be discontinued. Metoclopramide, a prokinetic agent that stimulates motility of the upper GI tract is useful to minimize the symptoms of postprandial fullness and nausea.2,3,28

Prevalent Genitourinary Disorders
Based on the mechanisms of action of genitourinary drugs in the Top 300 Prescription Drugs of 2017 dispensed by U.S. community pharmacies in 2014, the most common GU disorders encountered in an ambulatory patient population include benign prostatic hypertrophy (BPH), erectile dysfunction (ED), and urinary incontinence (i.e., overactive bladder with urinary incontinence, urgency, and increased urinary frequency).

Benign Prostatic Hypertrophy
Benign prostate hypertrophy is a common age-related, nonmalignant adenomatous overgrowth of the peri-urethral prostate gland. As the lumen of the prostatic urethra narrows, urinary outflow is progressively obstructed. Symptoms include urgency, incomplete emptying, increased frequency, weak stream, hesitancy, overflow incontinence, nocturia; and, potentially, complete urinary retention. Patients with mild symptoms do not require treatment.

Patients with moderate to severe symptoms are managed by lifestyle modification, medications, and surgery. Lifestyle modifications include losing weight, decreasing evening fluid intake; avoiding alcohol, caffeine, or highly seasoned food; and limiting medications known to cause lower urinary tract symptoms (e.g., incomplete emptying) such as anticholinergic agents, antidepressants, antihistamines, sympathomimetic drugs, and opioid analgesics.  

Alpha1-adrenergic receptor antagonists such as terazosin and tamsulosin, which cause smooth muscle relaxation in the prostatic urethra and bladder neck, are the first-line of treatment for moderate-to-severe symptoms. If monotherapy with an alpha1-adrenergic receptor antagonist is not effective, a 5α-reductase inhibitor (e.g., finasteride or dutasteride) that reduces testosterone-associated androgenic effects and gradually decreases prostatic volume is added to the regimen.2,3,29,30

Erectile Dysfunction
A normal sexual erectile response is initiated by parasympathetic and sympathetic neuronal triggers that integrate physiologic stimuli of the penis with sexual desire. In associations with parasympathetic stimuli, nitric oxide produced by endothelial cells triggers a molecular cascade that results in smooth muscle relaxation and arterial influx of blood into the corpus cavernosum. This is followed by compression of venous return, which produces the erection.

ED is defined as the inability to achieve or maintain an erection sufficient for satisfactory sexual performance. ED may result from advancing age, cardiovascular diseases, hypertension, diabetes mellitus, hormonal disorders, prescription and recreational drug use, neurologic conditions (e.g., Alzheimer's disease, Parkinson's disease), psychological problems (e.g., anxiety, depression), obesity, sedentary lifestyle, cigarette smoking, and many drugs.  

First-line therapy for ED is aimed at lifestyle changes directed at increased physical activity, weight loss, and smoking cessation; and modifying pharmacotherapy that may contribute to ED. Pharmacotherapy with sildenafil or tadalafil, which inhibit phosphodiesterase type 5 (PDE5) responsible for degradation of cGMP enhances the effect of nitric oxide and result in smooth muscle relaxation and inflow of blood to the corpus cavernosum.

Urinary Incontinence
Urinary incontinence (UI) is a common, age-related, involuntary loss of urine. With aging, bladder capacity decreases, the ability to inhibit urination declines, and detrusor muscle overactivity leads to frequent bladder contractions. In women, decreased estrogen levels lead to decreasing urethral resistance. In men, as
prostate size increases, it partially obstructs the urethra. Consequently, voiding becomes difficult to control and tends to become incomplete.

Urinary incontinence is classified as transient or chronic. Transient incontinence is defined as urinary leaking that spontaneously reverses after the underlying cause such as acute or chronic urinary tract infection, atrophic vaginitis, hyperglycemia, depression, reduced mobility (i.e., functional incontinence), or drug-induced urinary retention is resolved. Chronic incontinence may be characterized as stress-, urge-, mixed-, overflow-, or functional-incontinence.

Stress-incontinence is caused by sphincter weakness. Urge-incontinence is caused by detrusor over-activity, which may be sensory (e.g., local irritation, inflammation, or infection) or neurogenic (e.g., cerebral inhibition of detrusor contractions). Overflow-incontinence is caused by impaired detrusor contractility or bladder obstruction (e.g., BPH) that lead to leakage. Functional-incontinence is usually caused by physical or environmental barriers to use a toilet.

The severity of symptoms and their effect on the quality of life (e.g., effects of UI on work, daily activities, sleep, sexual activity, social interactions) determines treatment.

Treatment begins with bladder training, i.e., relaxation training aimed to reduce detrusor activity. Drug therapy includes an alpha₁-adrenergic receptor agonist that increase sphincter tone and anticholinergic agents such as solifenacin and tolterodine that relax the detrusor muscle in urge- and stress-incontinence.

Some patients with UI may experience near-constant dribbling or intermittent voiding with or without awareness of the need to void. Others may experience extreme urgency with little or no warning and may be unable to prevent voiding until reaching the bathroom. Provide ample opportunities for bathroom breaks during the clinical process. Also, note that opioids cause overflow-incontinence and NSAIDs increase fluid retention causing functional-incontinence.

**Summary**

Predicated on their mechanisms of action, 38 of the Top 300 Drugs of 2017 dispensed by U.S. community pharmacies are prescribed for the treatment of respiratory, GI, and GU disorders. Respiratory, GI, and GU abnormalities may be associated with mild to potentially life-threatening complications and may interfere with the quality of life of patients. Underling medical pathoses, their treatment, and quality of life issues may affect the clinical process in dentistry.
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/professional-education/ce-courses/ce540/start-test

1. Which of the following statements related to respiratory drugs in the Top 300 is correct?
   a. Synthetic trifluorinated corticosteroid with anti-inflammatory activity such as fluticasone nasal spray and selective histaminergic H₁-receptor antagonists such as cetirizine and loratadine are indicated for the treatment of allergic rhinitis.
   b. Selective short-acting beta₂-adrenergic receptor agonists such as albuterol and levalbuterol are indicated for the treatment of bronchospasm with reversible obstructive airway disease.
   c. Montelukast, cysteinyl leukotriene (CysLT)-receptor antagonist, may be taken by a patient for the treatment/prevention of allergic rhinitis, asthma, or exercise-induced bronchoconstriction.
   d. All of the above.

2. A patient with asthma may be taking which of the following medications?
   a. Fluticasone w/salmeterol
   b. Budesonide w/formoterol
   c. Mometasone w/formoterol
   d. All of the above.

3. Which of the following statements related to respiratory drugs in the Top 300 is correct?
   a. Fluticasone w/salmeterol or budesonide w/formoterol may be taken by a patient for the treatment of COPD.
   b. Long-acting, muscarinic M₁-receptor antagonists such as tiotropium and ipratropium are indicated for the long-term treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema.
   c. Albuterol w/ipratropium is indicated for the treatment of bronchospasm associated with COPD in patients requiring more than one bronchodilator.
   d. All of the above.

4. Which of the following statements related to respiratory drugs in the Top 300 is correct?
   a. Benzonatate anesthetizes the stretch receptors located in the respiratory passages, lungs, and pleura thereby reducing the cough reflex at its source.
   b. Guaifenesin is indicated to loosen phlegm (mucus) and thin bronchial secretion, to drain bronchial tubes, and to make coughs more productive.
   c. Guaifenesin w/codeine is indicated for the temporarily control cough due to minor throat and bronchial irritation as may occur with the common cold or inhaled irritants.
   d. All of the above.

5. Which of the following statements related to proton pump inhibitors and histaminergic H₂-receptor antagonists is correct? Proton pump inhibitors and histaminergic H₂-receptor antagonists are indicated for ____________.
   a. the treatment of both active duodenal and gastric ulcers
   b. short-term treatment of duodenal ulcers
   c. the treatment of symptomatic gastroesophageal reflux disease (GERD)
   d. risk reduction of NSAID-associated gastric ulcer
6. Which of the following GI drugs in the Top 300 accelerates healing of ulcers by forming a complex with proteinaceous exudate at the ulcer site and inhibits pepsin activity?
   a. Omeprazole
   b. Ranitidine
   c. Sucralfate
   d. Metoclopramide

7. Which of the following GI drugs in the Top 300 is indicated for the treatment of nausea, vomiting, motion sickness, and vertigo?
   a. Docusate
   b. Meclizine
   c. Dicyclomine
   d. Metoclopramide

8. Which of the following GU drugs in the Top 300 is selective prostate alpha1-adrenergic receptor antagonists indicated for the treatment of BPH?
   a. Tamsulosin and terazosi
   b. Finasteride and dutasteride
   c. Sildenafil and tadalafil
   d. Solifenacin and tolterodine

9. Which of the following statements related to allergic rhinitis is correct?
   a. Allergic rhinitis is characterized by itchy palate, sneezing, coughing, and runny nose; and allergic conjunctivitis that result from the combined action of histamine and the release of other chemical mediators of inflammation.
   b. Intranasal corticosteroids (e.g., fluticasone) are the most common treatment for persistent symptoms of allergic rhinitis.
   c. Patients with more severe allergic rhinitis that does not respond to intranasal corticosteroids may be taking an antihistamine, and a cysteinyl leukotriene (CysLT)-receptor antagonist, is an alternative.
   d. All of the above.

10. All of the following statements related to asthma are correct EXCEPT which one?
    a. Asthma is primarily an inflammatory disorder of the airway, with inflammation caused by allergens or other stimuli leading to bronchial hypersecretion and bronchospasm.
    b. In patients with intermittent asthma daily medication with low-dose inhaled corticosteroid such as budesonide is preferred (Step 2); montelukast, a cysteinyl leukotriene (CysLT)-receptor antagonist, is an alternative.
    c. Treatment of persistent moderate asthma may include medium-dose inhaled corticosteroid plus inhaled long-acting selective beta2-adrenergic receptor agonist; or medium-dose inhaled corticosteroid plus montelukast, cysteinyl leukotriene (CysLT)-receptor antagonist.
    d. Persistent severe asthma is treated with high-dose inhaled corticosteroid plus inhaled long-acting selective beta2-adrenergic receptor agonist.
11. **Which of the following statements related to COPD is correct?**
   a. On exertion (physical or emotional stress), patients with COPD typically experience coughing, dyspnea (air hunger), and wheezing (a high-pitch whistling sound).
   b. Maintenance therapy for COPD may include an inhaled corticosteroid with a long-acting selective beta<sub>2</sub>-adrenergic receptor agonist such as fluticasone w/salmeterol or an inhaled long-acting muscarinic M<sub>2</sub>-receptor antagonist, such as ipratropium.
   c. Patients with COPD placed in a supine position may experience orthopnea soon after reclining - treat patients in a semi-reclining position and monitor oxygen saturation with a pulse oximeter.
   d. All of the above.

12. **All of the following statements related to sneezing and coughing are correct EXCEPT which one?**
   a. A sneeze is an explosive respiratory maneuver, which reflexively or deliberately is intended to clear irritants, foreign particles, and secretions from the airway.
   b. Common causes of acute cough include upper respiratory tract infections, exacerbation of COPD and asthma, and pneumonia.
   c. Common causes of chronic cough include chronic bronchitis and GERD, treatment with an angiotensin-converting enzyme inhibitor, and obstructive sleep apnea.
   d. Symptomatic treatment of cough may include the administration of guaifenesin or guaifenesin w/codeine.

13. **All of the following statements related to PUD are correct EXCEPT which one?**
   a. Prostaglandins inhibitors enhance mucosal resistance to injury by maintaining mucosal blood flow to remove acid that has diffused across the compromised mucosa and by stimulating the secretion of mucus and bicarbonate.
   b. Peptic activity is an indispensable component of the pathogenesis of ulcers, but peptic ulcers generally develop only when mucosal defense mechanisms are also altered - two major factors, H. pylori infection and NSAIDs appear to disrupt mucosal resistance to injury.
   c. The medical management of PUD includes various antibacterial combinations and an H<sub>2</sub>-receptor blocker (e.g., ranitidine) or a proton pump inhibitor (e.g., omeprazole).
   d. When managing odontogenic pain consider the well-established ulcerogenic effect of NSAIDs and use alternative analgesics, e.g., acetaminophen-containing formulations.

14. **All of the following statements related to GERD are correct EXCEPT which one?**
   a. Symptoms associated with GERD include substernal burning pain radiating up to the neck, which is relieved immediately by nitroglycerin.
   b. Medical treatment for GERD includes histaminergic H<sub>2</sub>-receptor blocking agents such as ranitidine and/or proton pump inhibitors such as omeprazole.
   c. When treating patients with a history of GEDR recognize that these patients may experience episodes of reflux when in a supine position - they tend to do better in the perioperative period in a semi-reclining position.
   d. When managing odontogenic pain keep in mind the well-established ulcerogenic effect of NSAIDs.
15. **All of the following statements related to constipation are correct EXCEPT which one?**
   a. Major causes of constipation include functional abnormalities, colonic disease, rectal problems, neurological diseases and metabolic conditions, and the administration of many drugs.
   b. Osmotic agents such as docusate or polyethylene glycol 3350 soften stool by increasing the amount of water the stool absorbs and make it easier to pass.
   c. It is of note that opioid analgesics, by binding μ-receptors in GI tract, increase the tone of the anterior portion of the stomach, decrease gastric motility, and cause constipation.
   d. The risk of opioid analgesic-induced constipation is unavoidable, it is not dose related and patients develop tolerance.

16. **All of the following statements related to irritable bowel syndrome are correct EXCEPT which one?**
   a. IBS is an uncommon (rare) functional disorder of the GI tract characterized by altered GI motility, GI hypersensitivity, and psychosocial factors.
   b. Patients with IBS may experience bloating, flocculence, dyspepsia, atypical chest pain; and diarrhea or constipation, or alternating diarrhea and constipation.
   c. To relieve pain associated with IBS, dicyclomine, a potent anticholinergic agent that relieves smooth muscle spasm of the GI tract may be helpful.
   d. IBS with diarrhea may respond to loperamide, which binds to opiate receptor in the gut wall, inhibits the release of acetylcholine and prostaglandins, reduces peristalsis, and increases intestinal transit time.

17. **All of the following statements related to diabetes-related gastroparesis are correct EXCEPT which one?**
   a. GI complications of diabetes mellitus (DM) are often caused by abnormal GI motility, which is a consequence of diabetic autonomic neuropathy caused primarily by impaired vagal control.
   b. Symptoms consistent with gastroparesis include nausea, vomiting, bloating, postprandial fullness (satiety), upper abdominal pain, and delayed gastric emptying contributes to poor blood glucose control.
   c. Dietary modifications include fiber supplements and foods that are high in fat to increase gastric emptying.
   d. Metoclopramide, a prokinetic agent that stimulates motility of the upper GI tract is useful to minimize the symptoms of postprandial fullness and nausea.

18. **All of the following statements associated with benign prostatic hypertrophy are correct EXCEPT which one?**
   a. Benign prostate hypertrophy is a common age-related, nonmalignant adenomatous overgrowth of the peri-urethral prostate gland.
   b. Symptoms include urgency, incomplete emptying, increased frequency, weak stream, hesitancy, overflow incontinence, nocturia; and, potentially, complete urinary retention.
   c. Alpha₁-adrenergic receptor antagonists such as terazosin and tamsulosin, which cause smooth muscle relaxation in the prostatic urethra and bladder neck, are the first-line of treatment for moderate-to-severe symptoms.
   d. If monotherapy with an alpha₁-adrenergic receptor antagonist is not effective, a 5α-reductase inhibitor (e.g., finasteride or dutasteride) that increases testosterone-associated androgenic effects is added to the regimen.
19. **All of the following statements associated with erectile dysfunction are correct EXCEPT which one?**
   a. ED is defined as the inability to achieve or maintain an erection sufficient for satisfactory sexual performance.
   b. In associations with sympathetic stimuli, nitric oxide produced by endothelial cells triggers a molecular cascade that results in smooth muscle relaxation and arterial influx of blood into the corpus cavernosum.
   c. First-line therapy for ED is aimed at lifestyle changes directed at increased physical activity, weight loss, and smoking cessation; and modifying pharmacotherapy that may contribute to ED.
   d. Pharmacotherapy with sildenafil or tadalafil, which inhibit phosphodiesterase type 5 (PDE5) responsible for degradation of cGMP enhances the effect of nitric oxide and result in smooth muscle relaxation and inflow of blood to the corpus cavernosum.

20. **Which of the following statements related to urinary incontinence is correct?**
   a. Therapy includes an alpha-1-adrenergic receptor agonist that increase sphincter tone and anticholinergic agents such as solifenacin and tolterodine that relax the detrusor muscle.
   b. Some patients with UI may experience extreme urgency with little or no warning and may be unable to prevent voiding until reaching the bathroom.
   c. Opioid analgesics cause overflow-incontinence and NSAIDs increase fluid retention causing functional-incontinence.
   d. All of the above.
References

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Dr. Terézhalmy is Professor and Dean Emeritus, School of Dental Medicine, Case Western Reserve University. In addition, he is a Consultant, Naval Postgraduate Dental School, National Naval Medical Center. Dr. Terézhalmy earned a BS degree from John Carroll University; a DDS degree from Case Western Reserve University; an MA in Higher Education and Human Development from The George Washington University; and a Certificate in Oral Medicine from the National Naval Dental Center.

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