

Pulmonary Disorders and Smoking Cessation

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Learning Objectives

1. Classify, assess control, select, and monitor appropriate acute and preventive treatment for pediatric and adult patients with asthma, adult patients with chronic obstructive pulmonary disease (COPD), and adult patients with obstructive sleep apnea (OSA), depending on patient-specific factors.
 2. Educate patients about their therapy for asthma, COPD, OSA, and smoking cessation, including proper use of inhalers, holding chambers, positive airway pressure machines, and medications.
 3. Select and monitor appropriate pharmacotherapy and provide behavioral counseling to assist a patient in quitting smoking.
 4. Discuss public health, practice management, and patient advocacy issues as they pertain to asthma, COPD, OSA, and smoking cessation.
3. You are educating a patient who is now starting a new hydrofluoroalkane (HFA) MDI. Which is the most appropriate educational point to instruct the patient about?
 - A. A holding chamber is not necessary with HFA inhalers unless technique is inadequate.
 - B. Available HFA inhalers do not have counters.
 - C. HFA inhaler cases do not need to be cleaned.
 - D. HFA inhalers need to be primed before each use.
 4. A patient being initiated on the use of a DPI has only used MDIs in the past. Which is the most appropriate educational point to instruct the patient about?
 - A. When using a DPI, the puff will feel the same as that from an aerosol HFA inhaler.
 - B. DPIs require a quick and forceful inhalation technique.
 - C. DPIs should be shaken before each use.
 - D. DPIs should be used with a holding chamber.

Self-Assessment Questions

Answers and explanations to these questions can be found at the end of this chapter.

Questions 1 and 2 refer to the following case:

A 23-year-old woman has had wheezing and coughing for the past year. For the past few months, she has been using her boyfriend's albuterol inhaler about four times daily every day during the day and about twice weekly for coughing that awakens her during the night.

1. Which best classifies her asthma severity?
 - A. Intermittent.
 - B. Mild persistent.
 - C. Moderate persistent.
 - D. Severe persistent.
2. Which is the best controller therapy for her asthma?
 - A. Fluticasone (110 mcg/puff) 2 puffs twice daily by metered dose inhaler (MDI).
 - B. Montelukast one tablet orally daily.
 - C. Salmeterol one inhalation (50 mcg) twice daily by dry powder inhaler (DPI).
 - D. Fluticasone 250 mcg plus salmeterol 50 mcg one inhalation twice daily (DPI).
5. A 70-year-old woman reports a persistent shortness of breath, cough, and sputum production that has gradually worsened during the past year. Her COPD Assessment Test (CAT) score is 12. She has been using albuterol HFA 2 puffs several times daily for persistent shortness of breath. Her spirometry showed a forced expiratory volume in 1 second (FEV_1) of 70% of predicted and an FEV_1 /forced vital capacity (FEV_1/FVC) of 60% of predicted after bronchodilator administration. She has never had a COPD exacerbation. Which is the best medication with which to initiate therapy?
 - A. Tiotropium DPI.
 - B. Beclomethasone MDI.
 - C. Montelukast orally.
 - D. Fluticasone plus salmeterol MDI.

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6. A 65-year-old man with COPD (baseline FEV1 of 45% predicted) presents with a 3-day history of worsening shortness of breath and increased cough, which has been keeping him up all night. He has been bringing up a great deal more sputum when he coughs, which is mostly clear. He reports no cloudy, purulent sputum. In addition to albuterol by nebulization, which is the most appropriate treatment currently?
- A. No additional therapy needed.
 - B. Albuterol by nebulization.
 - C. Albuterol by nebulization plus oral prednisone burst.
 - D. Albuterol by nebulization plus oral prednisone burst plus oral antibiotics.
7. A 50-year-old man is given a diagnosis of OSA. He smokes, has newly diagnosed hypothyroidism (started levothyroxine 2 weeks ago), and gastroesophageal reflux disease (GERD), as well as hypertension (HTN) that is well controlled with lisinopril. Which condition/trigger is least likely to be causing or exacerbating his OSA?
- A. Hypothyroidism.
 - B. GERD.
 - C. HTN.
 - D. Smoking.
8. A 20-year-old woman wants to quit smoking. She is already overweight and has not tried to quit smoking before because she does not want to gain weight. She is highly motivated to quit smoking now, but she wants to use a treatment that will result in the least amount of weight gain. Which is the most appropriate therapy to recommend for her?
- A. Varenicline.
 - B. Bupropion.
 - C. Nicotine patch.
 - D. Nicotine patch plus nicotine gum.
9. A 40-year-old man presents to the clinic wanting to quit smoking. He rates how badly he wants to quit as 10/10 and believes he can quit with help. Together, you decide to use varenicline to help him quit smoking. Which is most accurate regarding medication use and counseling for this patient?
- A. A combination of behavioral counseling and drugs is more effective than either behavioral counseling or medication alone.
 - B. Most patients do not need to set a quit date; rather, they should cut down on cigarettes gradually before starting varenicline.
 - C. Varenicline has the same safety profile as nicotine replacement treatment products.
 - D. Use of varenicline longer than 3 months is not recommended.

I. ASTHMA

Guidelines

National Institutes of Health (NIH) National Heart, Lung, and Blood Institute (NHLBI). National Asthma Education and Prevention Program (NAEPP) Guidelines. NAEPP Expert Panel Report 3. NIH Publication 08-5846. July 2007. Available at www.nhlbi.nih.gov/guidelines/index.htm. Accessed September 12, 2014.

- A. Definition: Asthma is a common chronic inflammatory disorder of the airways characterized by airflow obstruction, bronchial hyperresponsiveness, and underlying inflammation causing recurrent variable episodes of wheezing, breathlessness, cough, and chest tightness, particularly at night or early in the morning. Increased bronchial hyperresponsiveness can occur to a variety of stimuli. Airway obstruction is often reversible spontaneously or with treatment.
- B. Diagnosis
 1. Episodic symptoms of airflow obstruction are present.
 2. Airway obstruction is reversible (defined as FEV₁ improvement by 12% or more for patients older than 12 years and 15% or more for those younger than 12 years after administration of short-acting β_2 -agonists [SABAs]).
 3. Alternative diagnoses are excluded. Asthma versus COPD as follows:
 - a. Cough is usually nonproductive with asthma and productive with COPD.
 - b. FEV₁ is reversible with asthma but COPD is irreversible.
 - c. Cough is worse at night and early in the morning with asthma; it occurs throughout the day with COPD.
 - d. Asthma exacerbation is often related to allergies/environmental triggers/viral respiratory infections; COPD has a common history of smoking.
 4. Exercise-induced bronchospasm
 - a. Presents with cough, shortness of breath, chest pain or tightness, wheezing, or endurance problems during exercise.
 - b. Can be confirmed by an exercise challenge, in which a 15% decrease in FEV₁ or peak expiratory flow (PEF) is seen before and after exercise, measured at 5-minute intervals for 20–30 minutes.

Table 1. Interpreting Spirometry

Component	What It Measures	Normal Values
FEV ₁	Volume of air exhaled forcefully in the first second of maximal expiration	Normal is 80% or greater of predicted value; reported in liters per minute and as a percentage of predicted value on the basis of sex, age, height, and race/ethnicity In asthma, reversibility is shown by an increase in FEV ₁ \geq 12% after SABA in patients older than 12 years and \geq 15% in those younger than 12 years
FVC	The maximum volume of air that can be exhaled after full inspiration	Reported in liters and as a percentage of predicted value on the basis of sex, age, height, and race/ethnicity Normal lungs can empty 80% of air in <6 seconds
FEV ₁ /FVC ratio	Differentiates between obstructive and restrictive disease	Normal: Within 5% of predicted range, which varies with age; usually 75%–80% in adults Decreased in obstructive disease (asthma, COPD) (<70%) Normal/high in restrictive disease (e.g., pulmonary fibrosis)

COPD = chronic obstructive pulmonary disease; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; SABA = short-acting β_2 -agonist.

C. Classification of Asthma Severity and Control

Table 2. Classification of Asthma Severity in Adults and Children^a

Components	Age Group, (years)	Intermittent	Mild Persistent	Moderate Persistent	Severe Persistent
Frequency of symptoms	All ages	≤2 days/week	>2 days/week, but not daily	Daily	Throughout the day
Nighttime awakening	≥12	≤2 times/month	3 or 4 times/month	More than once weekly, but not nightly	Often 7 times per week
	5–11				
	0–4	0	1 or 2 times/month	3 or 4 times/month	More than once weekly
SABA; used for symptom control	All ages	≤2 days/week	>2 days/week, but not daily	Daily	Several times a day
Interference with normal activity	All ages	None	Minor limitation	Some limitations	Extremely limited
FEV ₁ /FVC ^b	≥12	Normal	Normal	Reduced 5%	Reduced >5%
	5–11	>85%	>80%	75%–80%	<75%
	0–4	N/A			
FEV ₁ (% of normal)	≥12	>80% (normal)	>80% (normal)	>60% to <80%	<60%
	5–11				
	0–4	N/A			
Exacerbations requiring oral steroids	≥12	0 or 1/year	≥2/year	≥2/year	≥2/year
	5–11				
	0–4	0 or 1/year	≥2 in 6 months or ≥4 wheezing episodes a year ^c		
Recommended step for initiating treatment (see Table 3)	≥12	Step 1	Step 2	Step 3 ^d and consider short course of oral steroids	Step 4 or 5 and consider short course of oral steroids
	5–11				Step 3 ^d or 4 and consider short course of oral steroids
	0–4	Step 3 and consider short course of oral steroids			

^aThe patient's condition is classified according to the sign or symptom in the most severe category.

^bNormal FEV₁/FVC: 8–19 years of age: 85%, 20–39 years of age: 80%, 40–59 years of age: 75%, 60–80 years of age: 70%.

^cEpisodes lasting more than 1 day and risk factors for persistent asthma.

^dFor ages 5–11 years, initial step 3 therapy should be medium-dose ICS.

FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; ICS = inhaled corticosteroid; N/A = not applicable; SABA = short-acting β₂-agonist.

Adapted from NIH Asthma Guidelines. National Institutes of Health National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program (NAEPP) Guidelines. NAEPP Expert Panel Report 3. NIH Publication 08-5846. Available at www.nhlbi.nih.gov/guidelines/index.htm. Accessed September 12, 2014.

Table 3. Assessing Asthma Control in Adults and Children

Component	Age Group, (years)	Well Controlled	Not Well Controlled	Very Poorly Controlled
Symptoms	≥12	≤2 days/week	>2 days/week	Throughout the day
	5–11	≤2 days/week but not	>2 days/week or >1 time/day on any day	
	0–4	>1 time each day		
Nighttime awakenings	≥12	≤2 times/month	1–3 times/week	≥4 times/week
	5–11	≤1 time/month	≥2 times/month	≥2 times/week
	0–4		>1 time/month	>1 time/week
Interference with normal activity	All ages	None	Some limitations	Extremely limited
Short-acting β ₂ -agonist use for symptom control ^a	All ages	≤2 days/week	>2 days/week	Several times a day
FEV ₁ or peak flow	≥12	>80% of predicted/ personal best	60%–80% of predicted/ personal best	<60% of predicted/ personal best
	5–11			
	0–4	N/A	N/A	N/A
Questionnaires ATAQ ACQ ACT	≥12 (N/A if <12)	0 ≤0.75 ≥20	1 or 2 ≥1.5 16–19	3 or 4 N/A ≤15
	≥12	0 or 1/year	≥2/year	≥2/year
	5–11			
0–4	2 or 3 times/year		>3 times/year	
Recommended action for treatment	All ages	Maintain current step; regular follow-up every 1–6 months; consider step-down if well controlled ≥3 months	Step-up one step Reevaluate in 2–6 weeks	Consider short course of oral steroids Step-up one or two steps Reevaluate in 2 weeks

^aDoes not include β₂-agonist used to prevent exercise-induced asthma.

ACQ = Asthma Control Questionnaire (Juniper EF, O'Byrne PM, Guyatt GH, et al. Eur Respir J 1999;14:902-7); ACT = Asthma Control Test (Nathan RA, Sorkness CA, Kosinski M, et al. J Allergy Clin Immunol 2004;113:59-65); ATAQ = Asthma Therapy Assessment Questionnaire (Vollmer WM, Markson LE, O'Connor E, et al. Am J Respir Crit Care Med 1999;160(5 pt 1):1647-52); FEV₁ = forced expiratory volume in 1 second; N/A = not applicable.

Adapted from NIH Asthma Guidelines. National Institutes of Health National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program (NAEPP) Guidelines. NAEPP Expert Panel Report 3. NIH Publication 08-5846. Available at www.nhlbi.nih.gov/guidelines/index.htm. Accessed September 12, 2014.

D. Treatment Goals

1. Reducing impairment

- a. Minimal or no chronic symptoms day or night.
- b. Minimal or no exacerbations.
- c. No limitations on activities; no school/work missed.
- d. Maintain (near) normal pulmonary function.
- e. Minimal use of SABA four times or less per week (not including exercise induced bronchospasm).

2. Reducing risk
 - a. Minimal need for emergency department visits or hospitalizations.
 - b. Prevent progressive loss of function.
 - c. Minimal or no adverse effects from medications.

E. Treatment Guidelines

Table 4. Treatment Guidelines

Step	Age Group, (years)	Long-term Control	Quick Relief
1	All ages	No controller needed	Use SABA prn
2	≥12	Preferred: Low-dose ICS Alternatives: LTRA, theophylline, or cromolyn ^a	SABA >2 times/week (excluding pre-exercise doses) indicates inadequate control and need to step-up treatment Consider step-down if well controlled ≥3 months
	5–11	Preferred: Low-dose ICS Alternatives: Montelukast or cromolyn ^a	
	0–4	Preferred: Low-dose ICS plus LABA OR medium-dose ICS alone Alternative: Low-dose ICS plus LTRA or theophylline	
3	≥12	Preferred: Low-dose ICS plus LABA, LTRA, or theophylline OR medium-dose ICS alone (medium-dose ICS preferred as initial therapy)	
	5–11	Medium-dose ICS	
	0–4	Preferred: Medium-dose ICS plus LABA Alternative: Medium-dose ICS plus LTRA or theophylline	
4	≥12	Preferred: Medium-dose ICS plus LABA or montelukast	
	5–11	Preferred: High-dose ICS plus LABA AND consider omalizumab for patients with allergic asthma	
	0–4	Preferred: High-dose ICS plus LABA Alternative: High-dose ICS plus LTRA or theophylline	
5	≥12	High-dose ICS plus LABA plus systemic corticosteroids AND consider omalizumab for patients with allergic asthma	
	5–11	Preferred: High-dose ICS plus LABA plus systemic corticosteroids Alternative: High-dose ICS plus LTRA or theophylline plus systemic corticosteroids	
	0–4	High-dose ICS plus LABA or montelukast plus systemic corticosteroids	
6	≥12	Preferred: High-dose ICS plus LABA plus systemic corticosteroids Alternative: High-dose ICS plus LTRA or theophylline plus systemic corticosteroids	
	5–11	High-dose ICS plus LABA or montelukast plus systemic corticosteroids	
	0–4	High-dose ICS plus LABA plus systemic corticosteroids	

^aCromolyn and nedocromil are included in the NAEPP guidelines. Cromolyn and nedocromil inhalers have been discontinued by the manufacturer; only generic cromolyn nebulizer solution is still available.

ICS = inhaled corticosteroid; LABA = long-acting β₂-agonist; LTRA = leukotriene receptor antagonist; NAEPP = National Asthma Education and Prevention Program; prn = as needed; SABA = short-acting β₂-agonist.

Adapted from NIH Asthma Guidelines. National Institutes of Health National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program (NAEPP) Guidelines. NAEPP Expert Panel Report 3. NIH Publication 08-5846. Available at www.nhlbi.nih.gov/guidelines/index.htm. Accessed September 12, 2014.

F. Pharmacologic Therapy for Asthma

Table 5. Pharmacologic Agent Use for Asthma and COPD^a

Generic	Brand	Dose	Adverse Effects	Comments
Corticosteroid inhalers				
Beclomethasone MDI 40 mcg/puff 80 mcg/puff	QVAR (HFA)	See ICS dosing table	Oral candidiasis Hoarseness May slow bone growth in children, but small reduction in adult height with persistent asthma	ICSs are first line for persistent asthma Use HOLDING CHAMBERS only if needed for technique; not well studied with HFA inhalers; holding chambers are only for MDIs – cannot be used for DPIs; holding chambers with a mask can be used for young children Rinse mouth with water after inhalations Use corticosteroid inhaler as SCHEDULED, not as needed Onset of improvement is 5–7 days; additional benefit may be seen throughout several weeks Pulmicort Respules only nebulized steroid available Asmanex and Arnuity Ellipta only steroids indicated as once-daily dosing for asthma
Budesonide DPI 90 mcg/dose 80 mcg/dose 0.25-, 0.5-, and 1-mg/2-mL nebs	Pulmicort Flexhaler and Respules			
Ciclesonide MDI 80 mcg/puff 160 mcg/puff	Alvesco (HFA)			
Flunisolide MDI 80 mcg/puff	Aerospan HFA			
Fluticasone propionate MDI 44 mcg/puff 110 mcg/puff 220 mcg/puff	Flovent HFA Flovent Diskus			
Fluticasone propionate DPI 50 mcg/puff 100 mcg/puff 250 mcg/puff	Arnuity Ellipta			
Fluticasone furoate DPI 100 mcg/puff 250 mcg/puff				
Mometasone DPI 110 mcg/puff 220 mcg/puff	Asmanex Twisthaler			

Table 5. Pharmacologic Agent Use for Asthma and COPD^a (*continued*)

Generic	Brand	Dose	Adverse Effects	Comments
Anticholinergics				
Ipratropium MDI 17 mcg/puff (short acting)	Atrovent HFA	2–4 puffs tid–qid (up to 12 puffs/ 24 hours)	Headache Flushed skin Blurred vision Tachycardia Palpitations	Used mainly for COPD or for acute asthma exacerbations requiring emergency treatment Duration: 2–8 hours Also available as a solution for nebulization
Tiotropium DPI 18 mcg (long acting)	Spiriva	Inhale 1 capsule once daily		Used for COPD; not currently recommended for asthma Long acting; not for rapid relief Duration: >24 hours Must insert powder-filled capsules with each dose
Aclidinium bromide DPI 400 mcg/puff	Tudorza Pressair	1 puff bid		Long-acting anticholinergic DPI with counter; does not involve putting capsules into inhaler at each dose
-Agonists (short acting) – SABA				
Albuterol MDI 90 mcg/puff 0.5 or 2.5 mL/vial	Proventil HFA Ventolin HFA ProAir HFA	2 puffs every 4–6 hours prn	Tremor Tachycardia Hypokalemia Hypomagnesemia Hyperglycemia Tachyphylaxis	Used for acute bronchospasm; regular use indicates poor control Also available as a solution for nebulization Duration of effect (MDI): 3–4 hours (up to 6 hours)
Levalbuterol MDI 45 mcg/puff 0.5 or 3 mL/vial	Xopenex HFA	2 puffs every 4–6 hours prn		<i>R</i> -enantiomer of albuterol Also available as a solution for nebulization Duration (MDI): 3–4 hours (up to 6 hours)
β₂-Agonists (long acting) – LABA				
Salmeterol DPI 50 mcg/puff	Serevent Diskus	Inhale 1 blister/puff bid	Tremor Tachycardia Electrolyte effects (rare)	Not for acute symptoms Should NOT be used as monotherapy for asthma Duration: 8–12 hours

Table 5. Pharmacologic Agent Use for Asthma and COPD^a (*continued*)

Generic	Brand	Dose	Adverse Effects	Comments
Formoterol DPI 12-mcg capsule	Foradil Aerolizer	Inhale 1 capsule bid		Onset of action 1–3 minutes, but not acute therapy Should NOT be used as monotherapy for asthma Duration of MDI: 8–12 hours
Formoterol 20 mcg/2 mL vial	Perforomist	20 mcg bid		Formoterol Aerolizer is indicated to prevent exercise-induced bronchospasm; should be used at least 15 minutes before exercise
Arformoterol 15 mcg/2 mL vial	Brovana	15 mcg bid		Arformoterol is the <i>R,R</i> -isomer of racemic formoterol
Indacaterol inhalation powder 75-mcg capsule	Arcapta Neohaler	Inhale 1 capsule once daily		Indacaterol is only indicated for COPD NOT indicated for use in asthma Duration of action: 24 hours
Combination inhalers				
Albuterol 100 mcg/ puff plus ipratropium 20 mcg/puff	Combivent Respimat	1 puff qid (Respimat) Max dose 6 puffs/day		Primarily used for COPD Combivent Respimat (propellant-free mist inhaler) replaced the MDI, which is no longer available Combination solution for nebulization is also available as DuoNeb or generic
Fluticasone/ salmeterol DPI 100/50, 250/50, 500/50 mcg/puff	Advair Diskus	1 puff bid		Combination of ICS and LABA Breo Ellipta is only approved for COPD and once daily combination treatment
Fluticasone/ salmeterol MDI 45/21, 115/21, 230/21 mcg/puff	Advair HFA	2 puffs bid		
Fluticasone furoate/vilanterol DPI 100/25 mcg/puff	Breo Ellipta	1 puff daily		
Budesonide/ formoterol MDI 80/4.5, 160/4.5 mcg/puff	Symbicort (HFA)	2 puffs bid		
Mometasone/ formoterol MDI 100/5, 200/5 mcg/puff	Dulera (HFA)	2 puffs bid		

Table 5. Pharmacologic Agent Use for Asthma and COPD^a (*continued*)

Generic	Brand	Dose	Adverse Effects	Comments
Leukotriene receptor antagonist (Note: *FDA caution)				
Zafirlukast 10-mg tablet 20-mg tablet	Accolate	10–20 mg bid	Hepatotoxicity (zileuton and zafirlukast); Zileuton: Monitor LFTs (baseline, every month × 3 months, every 2–3 months for remainder of first year); zafirlukast: Monitor symptoms, regular LFT monitoring not required; could be considered Headache GI upset	Drug interactions: Warfarin, erythromycin, theophylline For ≥5 years Bioavailability decreases with food; take 1 hour before or 2 hours after meals
Montelukast Oral 10-mg tablet Chewable 4- and 5-mg tablets Oral granules 4 mg/packet	Singulair	Dose in the evening Adults and children ≥15 years: 10 mg/day Children age 1 to <6 years: 4 mg/day Children age 6 to <15 years: 5 mg/day	*FDA caution: Risk of neuropsychiatric events (behavior and mood changes: Aggression, agitation, anxiousness, dream abnormalities, hallucinations, depression, insomnia, irritability, restlessness, suicidal thinking and behavior, and tremor)	Also indicated for exercise-induced bronchospasm and seasonal and perennial allergic rhinitis Drug interactions: Phenobarbital FDA approved for use in ≥1-year-olds; used in those 6 months and older Churg-Strauss syndrome associated with tapering doses of steroids
Zileuton 600-mg CR tablet	Zyflo CR	1200 mg bid		Drug interactions: Warfarin and theophylline Only for those 12 years and older

Table 5. Pharmacologic Agent Use for Asthma and COPD^a (*continued*)

Generic	Brand	Dose	Adverse Effects	Comments
Methylxanthine				
Theophylline Extended-release 24-hour capsules 100, 200, 300, 400 mg Extended-release 24-hour tablets 400, 600 mg Oral elixir Oral solution Extended-release 12-hour tablets 100, 200, 300, 450 mg	Elixophyllin Lufyllin Theo-24 Theo-Dur Theochron Uniphyll	<u>Adults</u> 300 mg/day initial dose – Divided according to formulation Adjust according to concentration Usual dose 400–600 mg/day <u>Children</u> Start at 10 mg/kg/day Adjust according to concentration Smokers may need higher doses at more frequent intervals	<u>At toxic concentrations</u> Nausea Vomiting CNS stimulation Headache Tachycardia, SVT Seizures Hematemesis Hyperglycemia Hypokalemia <u>At therapeutic concentrations</u> Insomnia GI upset Increased hyperactivity in some children Difficult urination in BPH	Achieve concentrations of 5–15 mcg/mL Beneficial for night symptoms Not for acute relief Duration: Variable; up to 24 hours
Monoclonal antibody/IgE binding inhibitor				
Omalizumab	Xolair	150–375 mg SC every 2–4 weeks Dose and frequency based on baseline IgE and weight in kilograms Do not inject >150 mg per injection site	Injection site reactions Urticaria Thrombocytopenia (transient) Anaphylaxis (rare) Malignancy Slight risk of TIA/MI	Used in severe persistent allergy-related asthma Use in ≥12 years Half-life: 26 days Second-line therapy High cost

^aThe following MDIs have recently been discontinued by the manufacturers and are no longer available: Maxair (pirbuterol) (December 2013), Combivent MDI (albuterol/ipratropium) (December 2013), and AeroBid (flunisolide) MDI (June 2011). They are not included in this table. OTC Primatene Mist has also been discontinued, and it was no longer available as of December 31, 2011.

bid = twice daily; BPH = benign prostatic hyperplasia; CNS = central nervous system; COPD = chronic obstructive pulmonary disease; CR = controlled release; DPI = dry powder inhaler; FDA = U.S. Food and Drug Administration; GERD = gastroesophageal reflux disease; GI = gastrointestinal; HFA = hydrofluoroalkane; ICS = inhaled corticosteroid; IgE = immunoglobulin E; LABA = long-acting β_2 -agonist; LFT = liver function test; max = maximum; MDI = metered dose inhaler; MI = myocardial infarction; neb = nebulizer; prn = as needed; qid = four times daily; SABA, short-acting β_2 -agonist; SC = subcutaneously; SVT = supraventricular tachycardia; TIA = transient ischemic attack; tid = three times daily.

Table 6. ICS Daily Dosing in Children and Adults^a

ICS	Low Dose, mcg/day Steps 2–3			Medium Dose, mcg/day Steps 3–4			High Dose, mcg/day Steps 5–6		
	0–4	5–11	≥12	0–4	5–11	≥12	0–4	5–11	≥12
Beclomethasone QVAR HFA 40, 80	N/A	80-160	80-240	N/A	>160-320	>240-480	N/A	>320	>480
Budesonide Pulmicort DPI 90, 180	N/A	180-360	180-540	N/A	>360-720	>540-1080	N/A	>720	>1080
Budesonide suspension for nebulization	0.25-0.5 mg	0.5 mg	N/A	>0.5–1 mg	1 mg	N/A	>1 mg	2 mg	N/A
Ciclesonide ^b Alvesco HFA 80, 160	N/A	80-160	160-320	N/A	>160-320	>320-640	N/A	>320	>640
Fluticasone propionate Flovent HFA 44, 110, 220 Flovent DPI 50, 100, 250	176 N/A	88-176 100-200	88-264 100-300	>176-352 N/A	>176-352 >200-400	>264-440 >300-500	>352 N/A	>352 >400	>440 >500
Mometasone Asmanex DPI 110, 220: Delivers 100 and 200 mcg/puff	100 ^a (age 4 years only)	110	110-220	100 ^a (age 4 only)	100 ^a (age 4 years only)	220-440	100 ^a (age 4 years only)	>440	>440

^aThe guidelines state the delivered dose of mometasone, not the actual dose; indicated in those 4–11 years of age after guidelines published; doses are estimated from package insert for children 0–4 and 5–11 years of age.

^bCiclesonide was unavailable when the NAEPP guidelines were published. The dose ranges are estimated from the package insert.

DPI = dry powder inhaler; HFA = hydrofluoroalkane; ICS = inhaled corticosteroid; N/A = not applicable; NAEPP = National Asthma Education and Prevention Program.

Adapted from Asthma Care Quick Reference. National Institutes of Health National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program (NAEPP) Guidelines. NAEPP Expert Panel Report 3. Available at http://www.nhlbi.nih.gov/files/docs/guidelines/asthma_qrg.pdf. Accessed March 2, 2015.

Patient Cases

Questions 1–3 pertain to the following case.

A 23-year-old woman has been coughing and wheezing about twice weekly, and she wakes up at night about three times per month. She has never been given a diagnosis of asthma, and she has not been to a physician “in years.” She uses her boyfriend’s albuterol inhaler, but he recently ran out of refills, so she is seeking care. Her activities are not limited by her symptoms. Spirometry is done today, and her FEV₁ is 82% of predicted.

1. From the current National Asthma Education and Prevention Program (NAEPP) guidelines, which is the best classification of her asthma?
 - A. Intermittent.
 - B. Mild persistent.
 - C. Moderate persistent.
 - D. Severe persistent.

2. Which medication is best to recommend for her, in addition to albuterol MDI 1 or 2 puffs every 4-6 hours as needed?
 - A. No additional therapy needed.
 - B. Montelukast orally 10 mg daily.
 - C. Mometasone DPI 220 mcg/puff 1 puff daily.
 - D. Budesonide/formoterol 80/4.5 mcg/puff 2 puffs twice daily.

3. At first, her symptoms were well controlled on your recommended therapy. However, when winter arrived, she started having symptoms and using her albuterol 3–4 days per week during the day. Which is the preferred treatment change?
 - A. No change in therapy needed.
 - B. Switch to budesonide/formoterol MDI 160/4.5 mcg/puff 2 puffs twice daily.
 - C. Add montelukast orally 10 mg daily.
 - D. Increase mometasone DPI to 220 mcg/puff 2 puffs daily.

4. An 8-year-old boy has been having daytime asthma symptoms once or twice weekly and is awakened twice weekly during the night with coughing. In addition to albuterol MDI 1 or 2 puffs every 4–6 hours as needed, which is the best initial therapy for him?
 - A. Fluticasone 44 mcg/puff 1 puff twice daily.
 - B. Montelukast 10 mg daily.
 - C. Fluticasone/salmeterol 100/50 mcg 1 puff twice daily.
 - D. Fluticasone 110 mcg/puff 1 puff twice daily.

-
- G. Long-acting β_2 -Agonists (LABAs): The U.S. Food and Drug Administration (FDA) issued a safety announcement because of safety concerns with LABAs. This is largely because of the results from the SMART (Salmeterol Multicenter Asthma Research Trial) trial (Chest 2006;129:15-26).
1. Use of a LABA alone without another long-term asthma control medication such as an inhaled corticosteroid (ICS) is contraindicated.
 2. LABAs should not be used for patients whose asthma is adequately controlled with low-or medium-dose ICSs.
 3. LABAs should only be used as additional therapy for patients who are currently taking, but whose condition is not adequately controlled with, a long-term asthma control medication (e.g., an ICS).
 4. Once asthma control is achieved and maintained, patients' condition should be assessed at regular intervals and treatment stepped-down (e.g., discontinue LABA), if possible, and the patient should continue to be treated with a long-term asthma control medication (e.g., an ICS).
 - a. Regular follow-up every 1–6 months.
 - b. Consider step-down if well controlled for 3 months or more.
 5. Pediatric and adolescent patients who require a LABA and an ICS should use a combination product to ensure adherence to both medications.
- H. Exercise-Induced Bronchospasm: Prevention and Treatment of Symptoms
1. Long-term control therapy, if otherwise appropriate (initiate or step-up).
 2. Pretreatment with a SABA before exercise.
 3. Leukotriene receptor antagonists (LTRAs) can attenuate symptoms in 50% of patients.
- I. Monitoring
1. Peak Flow Monitoring
 - a. Symptom-based and peak flow–based monitoring have similar benefits; either is appropriate for most patients. Symptom-based monitoring is more convenient.
 - b. Consider daily home peak flow monitoring for moderate-severe persistent asthma if history of severe exacerbations or if poor perception of worsening asthma symptoms.
 - c. Personal best peak expiratory flow rate (PEFR) should be determined if using peak flow–based asthma action plan, not predicted PEFR.
 - i. Personal best PEFR is the highest number obtained after daily monitoring for 2 weeks twice daily when asthma is under good control.
 - ii. Predicted PEFR is based on population norms using sex, height, and age.
 2. Spirometry (if 5 years of age or older)
 - a. At initial assessment or after treatment has started and symptoms have stabilized.
 - b. If prolonged or progressive loss of asthma control.
 - c. At least annually or more often, depending on response to therapy.
- J. Asthma Action Plan
1. Usually symptom based home treatment of an asthma exacerbation.
 2. Equal benefits of symptom-based or peak flow–based monitoring.

Table 7. Asthma Action Plan

Zone	Signs/Symptoms	Treatment^a
Green	Doing well; no/minimal symptoms of coughing, wheezing, and/or dyspnea PEFR 80%–100% of personal best	Take long-term asthma control agent only (if one is prescribed) Use 2 puffs of SABA 5–15 minutes before exercise with exercise-induced asthma and before known triggers
Yellow	Getting worse; increased frequency of symptoms of coughing, wheezing, and/or dyspnea PEFR 50%–79% of personal best	Use SABA: 2–4 puffs by MDI (up to 6 puffs if needed) or 1 nebulizer treatment; may repeat in 20 minutes if needed Reassess 1 hour after initial treatment a. If complete response at 1 hour, contact clinician for follow-up instructions and consider OCS burst ^b b. If incomplete response in 1 hour (still some coughing, wheezing, and/or dyspnea), repeat SABA and add OCS burst ^b ; contact clinician that day for further instructions c. If poor response in 1 hour (marked coughing, wheezing, and/or dyspnea), repeat SABA immediately; add OCS burst ^b ; contact clinician immediately; and go to the ED if the distress is severe and unresponsive to treatment; consider calling 911 May continue to use SABA every 3–4 hours regularly for 24–48 hours
Red	Medical alert; marked coughing, wheezing, and/or dyspnea; inability to speak more than short phrases; use of accessory respiratory muscles; drowsiness PEFR < 50% of personal best	Begin treatment and consult clinician immediately Use SABA: 2–6 puffs by MDI (higher dose of 4–6 puffs usually recommended) or 1 nebulizer treatment; repeat every 20 minutes up to three times; add OCS burst ^b If still in the red zone after 15 minutes and have not reached the doctor, go to the ED or call 911 Call 911 or go to the ED immediately if lips or fingernails are blue or gray or if there is trouble walking or talking because of shortness of breath

^aAfter initial treatment, immediate medical attention is required if patient is at high risk of a fatal attack. Risk factors: Asthma related (history of severe attack [previous intubation or intensive care unit admission for asthma], two or more asthma hospitalizations for asthma in past year, three or more ED visits for asthma in past year, hospitalization or ED visit for asthma in past month, using more than two canisters of SABA a month, difficulty perceiving asthma symptoms), social (low socioeconomic status or inner-city residence, illicit drug use, major psychosocial problems), and comorbidities (cardiovascular disease, other chronic lung disease, chronic psychiatric disease).

^bOCS burst: Prednisone (or equivalent); 40–60 mg/day for 5–10 days (adults) or 1–2 mg/kg/day (maximum 60 mg/day) for 3–10 days (children). ED = emergency department; MDI = metered-dose inhaler; OCS = oral corticosteroid; PEFR = peak expiratory flow rate; SABA = short-acting β -agonist.

Patient Cases

5. An asthma action plan is being developed for a 22-year-old man using Advair (fluticasone/salmeterol) 250/50 mcg/puff 1 puff twice daily and albuterol HFA 1 or 2 puffs every 4–6 hours as needed. His personal best peak flow is 500 L/minute. Which set of asthma action plan instructions is best for when he is doing well with no asthma symptoms (peak flow readings 400–500 L/minute)?
 - A. Hold fluticasone/salmeterol when asthma is under good control.
 - B. Use fluticasone/salmeterol regularly; may use albuterol HFA 1 or 2 puffs every 4–6 hours if needed before exercise.
 - C. Albuterol HFA 2 puffs; repeat in 20 minutes if needed; then reassess.
 - D. Albuterol HFA 6 puffs; repeat in 20 minutes; start prednisone 50 mg once daily for 5 days; then reassess.

6. Which, in addition to using his fluticasone/salmeterol regularly, is the best set of asthma action plan instructions for home treatment when he has some worsening symptoms of wheezing and dyspnea (mild exacerbation) with peak flow readings of 250–399 L/minute?
 - A. May use albuterol HFA 1 or 2 puffs every 4–6 hours if needed.
 - B. Albuterol HFA 2 puffs; repeat in 20 minutes if needed; then reassess; consider prednisone 50 mg once daily for 5 days.
 - C. Albuterol HFA 8 puffs; repeat in 20 minutes; start prednisone 50 mg once daily for 5 days; then reassess.
 - D. Albuterol HFA 10 puffs; repeat every 20 minutes for 4 hours; start prednisone 50 mg once daily for 5 days; then reassess.

7. Which, in addition to his using fluticasone/salmeterol regularly, is the best set of asthma action plan instructions for initial home treatment of a more severe exacerbation, with marked wheezing and dyspnea (with peak flow readings less than 250 L/minute)?
 - A. May use albuterol HFA 1 or 2 puffs every 4–6 hours if needed.
 - B. Albuterol HFA 2 puffs; repeat in 20 minutes if needed; then reassess.
 - C. Albuterol HFA 6 puffs; repeat in 20 minutes; start prednisone 50 mg once daily for 5 days; then reassess.
 - D. Albuterol HFA 10 puffs; repeat every 20 minutes for 4 hours; start prednisone 50 mg once daily for 5 days; then reassess.

K. Asthma Education for Patients

1. Control: Patients need to know what it means for their asthma not to be well controlled.
2. Medications
 - a. Controllers versus rescue medications.
 - b. How to use medication delivery devices (revisit often).
3. Self-management/asthma action plan.
4. The need for continuous ongoing interaction with the clinician to step-up and step-down therapy.
5. Triggers/environmental changes
 - a. Dust mite interventions.
 - i. Impermeable encasings for pillows/mattresses.
 - ii. Wash linens in hot water.
 - iii. High-efficiency particulate air (HEPA) filtration.

- b. Animal allergens.
 - i. Keep outside/out of bedroom.
 - ii. HEPA filtration.
 - c. Roach control.
 - i. Integrated pest management.
 - ii. Clean up food, spills, trash, and leaks.
 - d. Mold and mildew interventions.
 - i. Air conditioning
 - ii. Avoid humidifiers.
 - iii. Repair pipes and leaks.
 - e. Air pollution (includes secondhand smoke).
 - f. Exercise (pre-exercise SABA).
- L. Metered Dose Inhalers (pertinent for both asthma and COPD).
1. Education on proper technique with MDIs and DPIs is critically important.
 - a. Studies have shown MDI and DPI techniques to be poor.
 - b. Important to demonstrate correct technique to patient and to assess patient's technique with initial instruction and frequently thereafter.
 2. HFA inhalers: Smaller particle size, better lung deposition, less oropharyngeal deposition; holding chamber not necessary unless poor technique; not well studied with HFA MDIs.
 3. Important educational points for patients
 - a. All MDIs must be primed before first use.
 - i. First, shake the MDI (although Alvesco, QVAR, and Atrovent HFA do not need to be shaken, may be a confusing and an unnecessary teaching point).
 - ii. Spray into the air, away from the face.
 - iii. Priming: Number of sprays before first use varies; range two to four times.
 - iv. Shake in between each spray.
 - v. Must be reprimed after dropping inhaler or if not used for a certain number of days (range 3–28 days).
 - b. How to tell when an MDI is empty.
 - i. Most inhalers have a counter on the device; Proventil does not have a counter.
 - ii. For other MDIs, best way is to use tally marks to count puffs used. Recommend a product with a counter, whenever possible, but this may be limited because of insurance coverage.
 - c. Cleaning MDIs.
 - i. Clean once weekly.
 - ii. Remove canister and cap; rinse plastic case/mouthpiece under lukewarm water and let air-dry.
 - iii. For Advair HFA and Flovent HFA:
 - (a) Do not run under water.
 - (b) Open cap and swab small opening with a Q-tip where medicine sprays out (dry for Advair and wet for Flovent).
 - (c) Wipe mouthpiece with wet tissue and let air-dry.
 4. Valved holding chambers (e.g., AeroChamber, OptiChamber).
 - a. Holding chambers reduce oropharyngeal deposition and improve lung deposition with chlorofluorocarbon MDIs (almost 2-fold); not well studied with HFA MDIs.
 - b. Technique same as with MDIs, but can inhale up to 5 seconds after actuation.
 - c. One puff into chamber per inhalation.
 - d. For face mask: Five inhalations/exhalations per puff.

5. Children
 - a. In general, children 5 years and older are possible candidates for MDI with holding chamber or MDI alone. Must first assess their ability. Some younger children may be able to adequately use an MDI with holding chamber.
 - b. Most children younger than 5 years (and many children 5 years and older) require a holding chamber with face mask when an MDI is used. Nebulizers are also very appropriate options, especially for ICSs; however, a more portable option of MDI plus holding chamber/face mask for SABA is a good idea.
 - c. Children should always be educated on inhaler technique, and they should demonstrate proper use before MDIs are prescribed, with or without holding chambers and face masks.

Table 8. Educating Patients About How to Use a Metered Dose Inhaler

Getting ready	<ol style="list-style-type: none"> 1. Take off the cap and inspect for loose objects in the mouthpiece 2. Shake the inhaler 3. Breathe out all the way 4. Either put your inhaler mouthpiece in your mouth or use a holding chamber
Breathe in slowly	<ol style="list-style-type: none"> 5. Press down on the inhaler once as you start breathing in slowly through your mouth; be sure not to breathe in through your nose (if you use a holding chamber, first press down on the inhaler; within 5 seconds, begin to breathe in slowly) 6. Keep breathing in slowly, as deeply as you can, for about 3–5 seconds
Hold your breath	<ol style="list-style-type: none"> 7. Hold your breath as you count to 10 slowly, if you can 8. Wait about 30 seconds between puffs 9. Exhale

Table 9. Educating Patients About How to Use DPIs

<p><u>Dry Powder Inhalers</u></p> <ul style="list-style-type: none"> • Contain a small amount of powder; do not contain aerosol • Will feel different from an MDI; will not feel a “spray”; may not feel/taste anything • Do not shake before inhalation • Only budesonide (Pulmicort Flexhaler) has to be primed once; others are not primed • DPIs that come in foil pouches have expiration dates once opened (mometasone [Asmanex]: 45 days, fluticasone/salmeterol [Advair]: 1 month) • Protect DPIs from moisture • Each specific DPI has slightly different instructions for getting the inhaler ready for a dose • Once the dose is “prepped,” breathe out fully, away from the mouthpiece • Close lips around the mouthpiece and inhale quickly, forcefully, and deeply; this is different from the method used with an MDI (which is a slow, deep inhalation) • Hold breath for 5–10 seconds; then exhale
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DPI = dry powder inhaler; MDI = metered dose inhaler.

Table 10. Educating Patients About How to Use Peak Flow Meters

- Move the indicator to the bottom of the numbered scale
- Stand up; take a deep breath, filling your lungs completely
- Place the mouthpiece in your mouth and close your lips around it; keep your tongue out of the way
- Blow out as hard and fast as you can in a single blow
- Write down the number you get; but if you cough or make a mistake, do not write down the number; do it again
- Repeat steps 1–5 twice more, and write down the best of the three blows in your asthma diary

M. Vaccines: Adults With Asthma (19–64 years of age) should receive the following:

1. Pneumococcal
 - a. 23-valent pneumococcal polysaccharide vaccine (PPSV23 or Pneumovax) once and then revaccination with pneumococcal vaccine at age 65 years (or older if 5 years or more after the first vaccination). Both pneumococcal conjugate vaccine 13-valent (PCV13) and PPSV23 should be administered to adults older than 65 years.
 - i. Sixty-five years and older and pneumococcal vaccine-naïve (or unknown history) should receive PCV13 followed by PPSV23 6–12 months after PCV13 (do not administer the two vaccines at the same time and should be a minimum of 8 weeks apart).
 - ii. Sixty-five years and older and previous pneumococcal vaccination with at least one dose of PPSV23, should receive a PCV13 dose; at least 1 year after most recent PPSV23 dose; those needing an additional dose of PPSV23, give 6–12 months after PCV13 and at least 5 years after most recent PPSV23 dose.
 - b. PCV13 is not indicated for adults with asthma unless patient has received chronic systemic corticosteroid therapy.
2. Influenza Vaccination: Every fall/winter.

II. CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Guidelines

Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for Diagnosis, Management and Prevention of COPD. 2014 Update. Available at www.goldcopd.org/. Accessed September 26, 2014.

Qaseem A, Wilt TJ, Weinberger SE, et al. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society (ACP/ACCP/ATS/ERS Guidelines). *Ann Intern Med* 2011;155:179-91.

- A. Definition: COPD is a syndrome of chronic limitation in expiratory airflow, encompassing emphysema or chronic bronchitis. Airflow obstruction may be accompanied by airway hyperresponsiveness and may not be fully reversible.
 1. Chronic bronchitis consists of persistent cough plus sputum production for most days of 3 months in at least 2 consecutive years.
 2. Emphysema is abnormal permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls without obvious fibrosis.

B. Diagnosis and Assessment

1. The diagnosis of COPD is based on a history of exposure to risk factors and the presence of airflow limitation that is not fully reversible, with or without the presence of symptoms.
 - a. Symptoms: Dyspnea (described by patients as “increased effort to breathe,” “heaviness,” “air hunger,” or “gasping”), poor exercise tolerance, chronic cough, sputum production, wheezing.
 - b. Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines: Perform spirometry and consider COPD if an individual is older than 40 years and has any of the following:
 - i. Dyspnea that is progressive (worsens over time), persistent (present every day), and worse on exercise.
 - ii. Chronic cough that is present intermittently or every day; often present through the day; seldom only nocturnal. May be nonproductive.
 - iii. Chronic sputum production in any pattern.
 - iv. History of exposure to risk factors, especially tobacco smoke (most common risk factor), occupational dusts and chemicals, and smoke from home cooking and heating fuels.
 - c. American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society (ACP/ACCP/ATS/ERS) guidelines: The single best predictor of airflow obstruction is the presence of all three of the following:
 - i. Smoking history of more than 55 pack-years.
 - ii. Wheezing on auscultation.
 - iii. Patient self-reported wheezing.
2. For the diagnosis and assessment of COPD, spirometry is the gold standard.
 - a. Spirometry showing an FEV_1/FVC less than 70% of predicted is the hallmark of COPD. Bronchodilator reversibility testing is no longer recommended.
 - b. Measuring arterial blood gas tension should be considered for all patients with an FEV_1 less than 50% of predicted or with clinical signs suggestive of respiratory failure or right-sided heart failure.
3. Validated symptom scales/questionnaires.
 - a. Modified British Medical Research Council (mMRC) breathlessness scale for assessing severity of breathlessness (Thorax 1999;54:581-6).
 - b. The COPD Assessment Test (CAT) score measures health status impairment in COPD (www.catestonline.org).
 - c. Clinical COPD Questionnaire (CCQ) is a self-administered questionnaire that measures clinical control in patients with COPD (www.ccq.nl).

C. Factors Determining COPD Severity

1. Severity of symptoms.
2. Severity of airflow limitation (FEV_1).
3. Frequency of exacerbations.
4. Presence of comorbidities that may restrict activity (e.g., heart failure, heart disease, musculoskeletal disorders).

D. Therapy Goals

1. Relieve symptoms.
2. Reduce the frequency and severity of exacerbations.
3. Improve exercise tolerance.
4. Improve health status.
5. Minimize adverse effects from treatment.

E. Management of Stable COPD

1. Description of levels of evidence/grades of recommendations.
 - a. GOLD guidelines.
 - i. A: Randomized clinical trials, rich body of data.
 - ii. B: Randomized clinical trials, limited body of data.
 - iii. C: Nonrandomized trials, observational studies.
 - iv. D: Panel judgment consensus.
 - b. ACP/ACCP/ATS/ERS guidelines.
 - i. Recommendation grade:
 - (a) Strong (S): Benefits clearly outweigh risks and burden, or risks and burden clearly outweigh benefits.
 - (b) Weak (W): Benefits finely balanced with risks and burden.
 - ii. Quality of evidence:
 - (a) High (H)
 - (b) Moderate (M)
 - (c) Low (L)
2. Existing medications for COPD have not been shown to modify the long-term decline in lung function, the hallmark of this disease (Evidence A). Therefore, pharmacotherapy for COPD is used to decrease symptoms, complications, or both.
3. Smoking cessation is a critical component of COPD management.
4. Bronchodilator medications are central to the symptomatic management of COPD (Evidence A).
 - a. They are given on an as-needed or regular basis to prevent or reduce symptoms.
 - b. The principal bronchodilator treatments are β_2 -agonists, anticholinergics, or a combination of these drugs (Evidence A). Theophylline is also a bronchodilator but it is not recommended unless other long-term bronchodilators are unavailable or unaffordable.
 - c. Inhaled therapy is preferred.
 - d. The choice between a LABA, an anticholinergic, theophylline, and combination therapy depends on availability and individual response in symptom relief and adverse effects.
 - e. Regular treatment with a long-acting (LA) bronchodilator is more effective and convenient than regular treatment with a SABA (Evidence A).
 - f. Combining bronchodilators from different pharmacologic classes may improve efficacy with the same or fewer adverse effects, compared with increasing the dose of a single bronchodilator (Evidence A).
 - g. Adding tiotropium to LABA/ICS (triple therapy) improves lung function and health-related quality of life and reduces the number of exacerbations (Evidence B); retrospective data show decreased mortality, fewer hospital admissions, and fewer oral corticosteroid (OCS) bursts.
 - h. All bronchodilators improve symptoms and exercise capacity.
 - i. Treatment with an LA anticholinergic delays the first exacerbation, reduces the overall number of COPD exacerbations and related hospitalizations, improves health status (Evidence A), and improves the effectiveness of pulmonary rehabilitation (Evidence B). Anticholinergics may not significantly improve FEV₁.
 - (a) Conflicting differences found between tiotropium Respimat Soft Mist inhaler versus the dry-powder inhaler on mortality rates. Most recent study shows no difference (N Engl J Med 2013;369(16):1491-501).
 - (b) Aclidinium, glycopyrronium, and tiotropium have similar effects on breathlessness and lung function.

- ii. LABAs improve health status, quality of life, and FEV₁ and decrease COPD exacerbation rate (Evidence A). Salmeterol reduces hospitalization rate (Evidence B). Indacaterol significantly improves breathlessness, health status, and exacerbation rate (Evidence B). Indacaterol is a LABA with significantly greater bronchodilator effect than formoterol and salmeterol, and similar to tiotropium (Evidence A).
 - iii. LA anticholinergic versus LABAs:
 - (a) Tiotropium versus salmeterol for COPD: POET-COPD study (N Engl J Med 2011;364:1093-103).
 - (1) A total of 736 patients with moderate-severe COPD and one or more exacerbations in the past year; 1-year randomized, double-blind, parallel-group trial.
 - (2) Primary end point: Time to first exacerbation.
 - (A) Moderate exacerbation: Treated with an OCS, antibiotics, or both.
 - (B) Severe exacerbation: Hospitalized.
 - (3) Results: Tiotropium (vs. salmeterol) significantly:
 - (A) Increased time to first exacerbation (187 days vs. 145 days [42-day difference]) (HR 0.83; 95% CI 0.77–0.9; p<0.001); was significant for both moderate and severe exacerbations.
 - (B) Reduced annual number of exacerbations (RR] 0.89; 95% CI 0.83–0.96; p=0.002); rate for both moderate and severe exacerbations was significant.
 - (C) Benefit was consistent in all major subgroups and for more than one year.
 - (D) Significantly fewer patients taking tiotropium withdrew early (15.8% vs. 17.7%; HR 0.88; 95% CI 0.78–0.98; p=0.02).
 - (4) Conclusion: Tiotropium is more effective than a LABA as initial LA bronchodilator therapy in moderate to very severe COPD with respect to time to first exacerbation and annual number of exacerbations.
 - (b) Cochrane review (Cochrane Database Syst Rev 2012;9:CD009157) concluded as follows:
 - (1) Tiotropium is more effective than LABAs in the prevention of COPD exacerbations and COPD-related hospitalization, but not in overall hospitalization or mortality.
 - (2) Symptom and lung function improvement are similar. However, there are only a few studies. There were fewer serious adverse events and withdrawals from studies with tiotropium than with LABAs.
5. ICSs in stable COPD.
- a. ICSs improve symptoms, lung function, and quality of life and decrease the frequency of exacerbations in patients with FEV₁ less than 60% of predicted; they do not modify the progressive decline in FEV₁ or decrease mortality (Evidence A).
 - b. The dose-response with ICS in COPD is unknown (in contrast to asthma treatment). Moderate-high doses have been used in COPD clinical trials.
 - c. An ICS combined with a LABA is more effective than the individual components alone (Evidence A). An ICS-LABA combination reduces the rate of decline in FEV₁ and reduces the exacerbation rate; the reduction in mortality compared with placebo falls just short of statistical significance (relative risk reduction, 17.5%; absolute risk reduction, 2.6%; adjusted p=0.052) (TORCH study) (N Engl J Med 2007;356:775-89). A subsequent meta-analysis showed that ICS-LABA may reduce mortality (number needed to treat (NNT) = 36) (Evidence B) (Cochrane Database Syst Rev 2007;4:CD003794).
 - d. ICS use is associated with an increased incidence of pneumonia in COPD (Am J Respir Crit Care Med 2007;176:162-6; Arch Intern Med 2009;169:219-29).
 - e. Monotherapy with ICS is not recommended; in combination may not provide much benefit in patients with frequent exacerbations in severe COPD (WISDOM trial) (N Engl J Med 2014;Vol:371:1285-1294).

- f. Chronic treatment with OCSs should be avoided because of an unfavorable benefit-risk ratio (Evidence A).
- g. ICSs should not be used outside their indications in long-term treatment because of the risk of pneumonia and the possible increased risk of fractures after long-term exposure.
- 6. Patient assessment and selection of therapy.
 - a. Previous GOLD guidelines categorized COPD severity and recommended treatment of COPD by postbronchodilator FEV₁ alone. Staging is no longer based on FEV₁ alone. New GOLD guidelines combine symptoms (based on symptom scores), airflow limitation (based on postbronchodilator FEV₁), and frequency of exacerbations to determine patient risk group and recommended treatment.
 - b. ACP/ACCP/ATS/ERS guidelines simplify treatment even further on the basis of FEV₁ in patients with COPD with symptoms. They do not provide detailed treatment guidelines.

Table 11. GOLD Guidelines: Assessment of COPD Severity/Risk

Patient Group	Characteristic	Spirometric GOLD Classification ^a	Exacerbations per Year ^a	Symptom Score ^b
A	Low risk Less symptoms	GOLD 1: Mild (FEV ₁ ≥ 80% of pred) <i>or</i> GOLD 2: Moderate (50% ≤ FEV ₁ < 80% of pred)	≤1	mMRC 0–1 CAT < 10 CCQ 0–1
B	Low risk More symptoms	GOLD 1: Mild (FEV ₁ ≥ 80% of pred) <i>or</i> GOLD 2: Moderate (50% ≤ FEV ₁ < 80% of pred)	≤1	mMRC ≥ 2 CAT ≥ 10 CCQ > 1
C	High risk Less symptoms	GOLD 3: Severe (30% ≤ FEV ₁ < 50% of pred) <i>or</i> GOLD 4: Very severe (FEV ₁ < 30% of pred)	≥2	mMRC 0–1 CAT < 10 CCQ 0–1
D	High risk More symptoms	GOLD 3: Severe (30% ≤ FEV ₁ < 50% of pred) <i>or</i> GOLD 4: Very severe (FEV ₁ < 30% of pred)	≥2	mMRC ≥ 2 CAT ≥ 10 CCQ > 1

^aTo determine the risk of exacerbation, either the spirometric GOLD classification or the number of exacerbations per year can be used. If they are both used and the patient’s condition would fall into two different categories, always assign patient condition to the category with the highest risk/symptoms.

^bCAT score is preferred, but any may be used.

CAT = COPD Assessment Test (validated questionnaire); CCQ = Clinical COPD Questionnaire (validated questionnaire); COPD = chronic obstructive pulmonary disease; FEV₁ = forced expiratory volume in 1 second; GOLD = Global Initiative for Chronic Obstructive Lung Disease; mMRC = modified Medical Research Council breathlessness scale (validated questionnaire); pred = predicted.

Adapted from: Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for Diagnosis, Management and Prevention of COPD. Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2014 Update. Available at www.goldcopd.org/. Accessed September 26, 2014.

Table 12. GOLD Guidelines: Pharmacotherapy for Stable COPD^a

Patient Group	Recommended First Choice	Alternative Choice	Other Possible Treatments^b
A	SA anticholinergic prn <i>or</i> SABA prn	LA anticholinergic <i>or</i> LABA <i>or</i> SABA + SA anticholinergic	Theophylline ^c
B	LA anticholinergic <i>or</i> LABA	LA anticholinergic + LABA	SABA <i>and/or</i> SA anticholinergic Theophylline ^c
C	ICS + LABA <i>or</i> LA anticholinergic	LA anticholinergic + LABA <i>or</i> LA anticholinergic + PDE-4 inhibitor ^d <i>or</i> LABA + PDE-4 inhibitor ^d	SABA <i>and/or</i> SA anticholinergic Theophylline ^c
D	ICS + LABA <i>and/or</i> LA anticholinergic	ICS + LABA + LA anticholinergic <i>or</i> ICS + LABA + PDE-4 inhibitor ^d <i>or</i> LA anticholinergic + LABA <i>or</i> LA anticholinergic + PDE-4 inhibitor ^d	Carbocysteine N-acetylcysteine SABA <i>and/or</i> SA anticholinergic Theophylline ^c

^aNote: All medication choices are listed in alphabetic order and are not necessarily in order of preference.

^bMedications in third column (other possible treatments) can be used alone or in combination with first- and alternative-choice columns.

^cTheophylline is not recommended unless other long-term bronchodilators are unavailable or unaffordable.

^dIf patient has chronic bronchitis.

COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICS = inhaled corticosteroid; LA = long acting; LABA = long-acting β_2 -agonist; PDE-4 = phosphodiesterase 4 inhibitor; prn = as needed; SA = short-acting; SABA = short-acting β_2 -agonist.

Adapted from: Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for Diagnosis, Management and Prevention of COPD. Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2014 Update. Available at www.goldcopd.org/. Accessed September 26, 2014.

Table 13. ACP/ACCP/ATS/ERS Guidelines: Treatment Recommendations for Stable COPD

- For patients with respiratory symptoms and FEV₁ between 60% and 80% of predicted, treatment with long-acting inhaled bronchodilators is suggested (Grade: W, Evidence: L)
- For patients with respiratory symptoms and FEV₁ < 60% of predicted, treatment with long-acting inhaled bronchodilators is recommended (Grade: S, Evidence: M)
- Monotherapy using either long-acting inhaled anticholinergics or LABAs is recommended for symptomatic patients with FEV₁ < 60% of predicted; the choice of specific monotherapy should be based on patient preference, cost, and adverse effect profile (Grade: S, Evidence: M)
- Combination inhaled therapies (long-acting inhaled anticholinergics, LABAs, or ICS) may be used for symptomatic patients with FEV₁ < 60% of predicted (Grade: W, Evidence: M)

ACP/ACCP/ATS/ERS = American College of Physicians/American College of Chest Physicians/American Thoracic Society/European Respiratory Society; COPD = chronic obstructive pulmonary disease; FEV₁ = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; LABAs = long-acting β_2 -agonists.

Qaseem A, Wilt TJ, Weinberger SE, et al. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society (ACP/ACCP/ATS/ERS guidelines). *Ann Intern Med* 2011;155:179-91.

7. Other pharmacologic treatments.

a. Phosphodiesterase-4 inhibitor: Roflumilast (Daliresp).

- i. Indication: Indicated as a daily treatment to reduce the risk of COPD exacerbations in patients with severe COPD (FEV₁ less than 50% of predicted) associated with chronic bronchitis and a history of frequent exacerbations. In these patients, studies show a reduction in exacerbations and a reduction in the composite end point of moderate exacerbations treated with oral or systemic corticosteroids or severe exacerbations requiring hospitalization or causing death (Evidence B). These effects are also seen when roflumilast is added to LA bronchodilators (Evidence B). No trials have assessed the effects of roflumilast on COPD exacerbations when added to ICS/LA bronchodilator combination. No comparison of adding roflumilast versus ICS to LA bronchodilators.
- ii. Mechanism: Reduces inflammation through inhibition of the breakdown of intracellular cyclic adenosine monophosphate; no direct bronchodilator activity.
- iii. Dose: 500 mcg orally once daily.
- iv. Contraindications: Moderate to severe liver impairment; use in nursing mothers.
- v. Precautions: Weight loss (monitor), psychiatric events including suicidality (monitor; weigh risks vs. benefits in patients with preexisting psychiatric illness); 20% of patients studied had weight loss of 5%–10% of body weight compared with 7% with placebo; average weight loss is 2 kg.
- vi. Adverse reactions: Diarrhea, weight loss/decreased appetite, nausea, headache, back pain, influenza, insomnia, and dizziness.
- vii. Drug interactions: Use with strong cytochrome P450 (CYP) enzyme inducers is not recommended (e.g., rifampin, phenobarbital, carbamazepine, phenytoin); use with CYP3A4 inhibitors or dual inhibitors of CYP 3A4 and 1A2 (e.g., erythromycin, ketoconazole, fluvoxamine, enoxacin, cimetidine) increases roflumilast exposure and adverse effects (risk vs. benefit must be weighed).

- b. Smoking cessation (essential for all patient groups A–D).
- c. Influenza vaccine annually (essential for all patient groups A–D).
- d. Pneumococcal vaccine (essential for all patient groups A–D).
- e. α_1 -Antitrypsin augmentation therapy (Evidence C).
 - i. For young patients with severe hereditary α_1 -antitrypsin deficiency and established emphysema; however, it is expensive.
 - ii. Characteristics of patients with α_1 -antitrypsin deficiency are as follows: white race, development of COPD at a young age (younger than 45 years), and strong family history of COPD. It may be worthwhile to screen such patients.

Patient Cases

Questions 8 and 9 pertain to the following case.

A 62-year-old man was recently given a diagnosis of COPD. Spirometry shows FEV₁/FVC 60%; prebronchodilator FEV₁ 70% of predicted; and postbronchodilator FEV₁ 72% of predicted. His symptoms are very bothersome, and he reports walking slower than others because of shortness of breath and having to stop to catch his breath every so often when walking on level ground (mMRC grade 2). He had one exacerbation in the past year.

8. Which is the most appropriate patient group classification for him, according to the GOLD guidelines?
 - A. Patient group A.
 - B. Patient group B.
 - C. Patient group C.
 - D. Patient group D.

9. In addition to albuterol HFA 2 puffs every 4–6 hours as needed, which pharmacotherapy option is most appropriate to initiate?
 - A. No additional therapy needed.
 - B. Formoterol: Inhale contents of 1 capsule twice daily.
 - C. Salmeterol/fluticasone 50/500 1 puff twice daily.
 - D. Salmeterol/fluticasone 50/500 1 puff twice daily plus roflumilast 500 mcg orally once daily.

10. A 52-year-old woman with COPD reports a gradual worsening in shortness of breath during the past few years. Spirometry shows FEV₁/FVC 55% and FEV₁ 63% of predicted. Her CAT score is 10. She has not had a COPD exacerbation or received systemic corticosteroids in the past 2 years. Her current COPD medications are tiotropium inhaler once daily and albuterol HFA as needed. According to the GOLD guidelines, which is the most appropriate course of action?
 - A. Add salmeterol 50 mcg 1 inhalation twice daily.
 - B. Add long-term azithromycin 250 mg once daily.
 - C. Add fluticasone 110 mcg 2 puffs twice daily.
 - D. Discontinue tiotropium and start salmeterol/fluticasone 250/50 1 puff twice daily.

8. Nonpharmacologic therapy.
 - a. Home oxygen therapy.
 - i. Recommended for patients with a PaO₂ of 55 mm Hg or less (or 55–60 mm Hg if pulmonary HTN, peripheral edema, or polycythemia – Evidence D) or Sao₂ of 88% or less, with or without hypercapnia, confirmed twice during a 3-week period (Evidence B).
 - ii. Long-term (more than 15 hours a day) use in patients with chronic respiratory failure improves survival.

- b. Pulmonary rehabilitation (essential for patient groups B–D; Evidence A).
 - i. Includes exercise training, nutrition counseling, and education.
 - ii. Improves many outcomes in COPD, including quality of life and survival.
- 9. Newer data on COPD.
 - a. Chronic azithromycin therapy for prevention of COPD exacerbations (N Engl J Med 2011;365:689-98)
 - i. A total of 1577 subjects at increased risk of exacerbations (stage II—Moderate or worse COPD either with continuous O₂ or after receiving systemic corticosteroids in past year), and history of a COPD exacerbation requiring ED visit or hospitalization; no history of hearing impairment.
 - ii. Subjects randomly assigned to receive daily azithromycin 250 mg or placebo for 1 year.
 - iii. Results:
 - (a) Median time to exacerbation: 266 days (azithromycin group) versus 174 days (placebo) (p<0.001).
 - (b) Rate of acute exacerbation: 1.48 versus 1.83 for azithromycin versus placebo (p=0.01).
 - (c) Number needed to treat to prevent one acute exacerbation of COPD: 2.86.
 - (d) Quality of life improved more with azithromycin than with placebo (based on St. George's Respiratory Questionnaire; p=0.03).
 - (e) However, hearing decrements (by audiometry) were more common with azithromycin versus placebo (25% vs. 20%, p=0.04) (number needed to harm = 20), and in azithromycin group, there was an increased incidence of colonization with macrolide-resistant organisms (81% vs. 41%, p<0.001).
 - iv. Conclusion: Daily azithromycin lengthens time to first exacerbation, decreases rate of exacerbations, and improves quality of life for patients with COPD at increased risk of exacerbations, at the expense of risk of hearing decrements and increasing macrolide-resistant organism colonization. The GOLD guidelines still do not recommend treatment with antibiotics, except for when indicated during acute exacerbations.
 - b. β -Blockers.
 - i. Observational data suggest that long-term treatment with β -blockers reduces the risk of exacerbations and improves survival, even in patients without overt cardiovascular disease (CVD) (Arch Intern Med 2010;170:880-7).
 - ii. More than one-half of the patients in the study had cardiovascular (CV) risk factors or coronary artery disease. Mostly cardioselective β -blockers were used.
 - iii. Too early to recommend β -blockers for the treatment of COPD, but β -blockers should not be withheld in patients with COPD who also have heart disease, chronic heart failure, or other CV conditions in which β -blockers are beneficial. (Cochrane Database of Systematic Reviews 2005;4:CD003566).
 - iv. Mechanism for benefit in COPD is unknown, but β -blockers can up-regulate β_2 -receptors in the lungs and may improve the effectiveness of inhaled β -agonists.
- F. Management of Exacerbations of Chronic COPD.
 - 1. A COPD exacerbation is an acute worsening of a patient's baseline respiratory symptoms (dyspnea and/or cough and/or an increase in quantity or purulence of sputum) that is worse than normal day-to-day variation and results in a change in medication. Diagnosis is based purely on clinical presentation.
 - 2. Common precipitating factors include infection of tracheobronchial tree and viral upper respiratory tract infections (most common) and air pollution, but the cause of one-third of exacerbations cannot be determined (Evidence B).

3. Spirometry is not accurate during an exacerbation and is not recommended.
4. Pulse oximetry can be used to determine the need for supplemental oxygen, which should be given to those with severe exacerbations.
5. Inhaled bronchodilators (inhaled SABA with or without short-acting [SA] anticholinergics) are preferred treatment for COPD exacerbations (Evidence C).
 - a. Usual doses of albuterol are 2.5 mg by nebulizer every 1–4 hours as needed or 4–8 puffs by an MDI with holding chamber every 1–4 hours as needed.
 - b. SA anticholinergics (ipratropium) are generally added for acute exacerbations.
6. Systemic corticosteroids are effective and shorten recovery time, improve FEV₁, and improve hypoxemia (Evidence A). They may also lower the risk of treatment failure, early relapse, and length of hospital stay. Systemic corticosteroids should be used in most exacerbations; the GOLD guidelines no longer provide criteria for use.
 - a. Dose of OCSs for outpatient treatment: 40 mg of oral prednisone once daily for 5 days according to the GOLD guidelines (Evidence B).
 - b. Patients with a COPD exacerbation presenting to the hospital: A shorter course of systemic corticosteroids (5 days) was noninferior to a longer (14 days) course, with respect to re-exacerbation within 6 months (JAMA 2013;309:2223-31).
7. Antibiotic treatment should be initiated for exacerbations if criteria below are met. Most common pathogens in COPD exacerbations: *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. In patients with GOLD 3 and GOLD 4 severity, *Pseudomonas aeruginosa* becomes an important pathogen.
 - a. The three cardinal symptoms in COPD exacerbations are increased dyspnea, increased sputum volume, and increased sputum purulence.
 - i. Antibiotics should be given if all three cardinal symptoms are present (Evidence B).
 - ii. Antibiotics should be given if two of the three cardinal symptoms are present *and* if increased sputum purulence is one of the symptoms (Evidence C).
 - iii. Antibiotics should be given to patients with a severe exacerbation requiring mechanical ventilation (Evidence B).
 - b. Recommended duration of antibiotic treatment is usually 5–10 days (Evidence D).
 - c. Recommended antibiotics:
 - i. Optimal antibiotic therapy has not been determined and should be based on local resistance patterns.
 - ii. If recent (less than 3 months) use of antibiotics, use alternative class.
 - iii. Usual initial antibiotics for uncomplicated COPD: Azithromycin, clarithromycin, doxycycline, trimethoprim/sulfamethoxazole, or amoxicillin, with or without clavulanate
 - iv. In complicated COPD with risk factors: Amoxicillin/clavulanate, levofloxacin, moxifloxacin. Risk factors: Comorbid diseases, severe COPD (FEV₁ less than 50% of predicted), more than three exacerbations per year, antibiotic use in past 3 months.
 - v. If at risk of *Pseudomonas* infection: High-dose levofloxacin (750 mg) or ciprofloxacin; obtain sputum culture. Risk factors: Four or more courses of antibiotics in past year, recent hospitalization (past 90 days), isolation of *Pseudomonas* during past hospitalization, severe COPD (FEV₁ less than 50% of predicted).
 - vi. If exacerbation does not respond to initial antibiotic, then sputum culture and sensitivity test should be performed.

- G. Vaccinations: All patients with COPD should receive the influenza vaccine yearly and the polysaccharide pneumococcal vaccine once before age 65 years; then, a one-time revaccination with pneumococcal vaccine 5 years or more after the first vaccination.

Patient Case

11. A 64-year-old woman with COPD in GOLD patient group A presents for a clinic visit. In the past few days, she has had a worsening in shortness of breath and a productive cough with more “cloudy” and more copious sputum than usual. Pulse oximetry is 95% on room air. She has a nebulizer at home. In addition to regular use of albuterol plus ipratropium by nebulizer every 1–4 hours, which is the best course of action?
- A. No additional therapy is necessary.
 - B. Add oral prednisone 40 mg once daily for 5 days.
 - C. Add trimethoprim/sulfamethoxazole double strength one tablet twice daily for 7 days.
 - D. Add oral prednisone 40 mg once daily for 5 days and trimethoprim/sulfamethoxazole double strength one tablet twice daily for 7 days.

III. OBSTRUCTIVE SLEEP APNEA

Guidelines

Epstein LJ, Kristo D, Strollo PJ, et al.; Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep Medicine. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *J Clin Sleep Med* 2009;5:263-76.

Qaseem A, Holty JE, Owens DK, et al; Clinical Guidelines Committee of the American College of Physicians. Management of obstructive sleep apnea in adults: a clinical practice guideline from the American College of Physicians. *Ann Intern Med* 2013;159:471-83.

- A. Definition and Characteristics
 1. OSA is characterized by obstructive apneas and hypopneas caused by repetitive collapse of the upper airway, which occurs during sleep.
 2. Characterized by daytime sleepiness, loud snoring, breathing interruptions during sleep that are witnessed, or awakenings that are from choking or gasping (5 or more events per hour of sleep, or 15 or more events per hour of sleep in an asymptomatic patient).
 3. Untreated OSA can cause anxiety, depression, loss of interest in sex, poor performance at work or school; daytime sleepiness can increase risk of motor vehicle accidents or industrial accidents; may cause or worsen heart disease (heart arrhythmias, heart failure, hypertension, stroke).
 4. Affects 2%–4% of adult population; more common in men 18–60 years of age.
 5. Blood pressure may be elevated, especially in the morning; 50% of patients with OSA also have HTN.
 6. Hypothyroidism may cause or exacerbate OSA.
 7. Risk factors for OSA: Obesity, congestive heart failure (CHF), atrial fibrillation, HTN that is refractory to treatment, type 2 diabetes mellitus, stroke, nocturnal dysrhythmias, pulmonary HTN, high-risk drivers (e.g., commercial truck drivers), and patients being considered for bariatric surgery.
 8. Structural abnormalities may put a patient at risk of OSA, such as increased neck circumference, tonsillar hypertrophy, enlarged/elongated uvula, and nasal and palate abnormalities.

B. Diagnosis and Assessment

1. Patients thought to have OSA should undergo sleep testing.
2. Diagnosis is established by either in-laboratory polysomnography (standard) or home testing with portable monitors (only if patient has high pretest likelihood of moderate to severe OSA; not for patients with comorbid conditions; polysomnography unavailable).
3. Home testing is done only in conjunction with a comprehensive sleep evaluation and must be supervised by a practitioner.

C. Treatment

1. Positive airway pressure (PAP) is the treatment of choice to improve sleep symptoms.
 - a. PAP is recommended for all patients with mild, moderate, and severe OSA.
 - b. The most commonly used type of PAP is continuous PAP (CPAP). Limited or insufficient data to support one type of CPAP over another (e.g. Bilevel, fixed, C-flex, auto).
 - c. Preferred application of PAP is nasal, oral, or oronasal; used during sleep.
 - d. Not shown to improve cardiovascular mortality or other significant clinical outcomes.
2. Outcome variables to monitor:
 - a. Resolution of sleepiness (using Epworth Sleepiness Scale or Multiple Sleep Latency Test, or Maintenance of Wakefulness Test if sleepiness persists).
 - b. OSA-specific quality-of-life measures.
 - c. Patient and spousal satisfaction.
 - d. Adherence to PAP.
 - e. Obtaining an adequate amount of sleep.
 - f. Use of good sleep hygiene.
 - g. Weight loss if overweight/obese.
 - h. Avoidance of factors that worsen OSA.
3. Treatment of underlying conditions: Hypothyroidism or acromegaly.
4. Behavioral treatment.
 - a. Weight loss (ideally to a body mass index [BMI] of 25 kg/m² or less).
 - b. Exercise.
 - c. Positional therapy.
 - d. Avoidance of alcohol and sedatives before bedtime.
5. Other therapies.
 - a. Oral appliances such as mandibular repositioning appliances and tongue-retaining devices.
 - b. Bariatric surgery (to achieve weight loss).
 - c. Use topical nasal corticosteroids if concurrent rhinitis (adjunctive treatment).
 - d. Modafinil is recommended (in conjunction with PAP) for patients who still have excessive daytime sleepiness, despite PAP. However, before using modafinil, other causes of sleepiness must first be ruled out, such as suboptimal adherence to PAP, poorly fitting PAP masks, and insufficient sleep.
 - e. Therapies that have insufficient evidence to support use: Oral decongestants, selective serotonin reuptake inhibitors, mirtazapine, fluticasone, pantoprazole, protriptyline, theophylline, estrogen.
 - f. Oxygen supplementation is not recommended for primary treatment; may be used as an adjunct therapy if hypoxemia present.
 - g. Surgery: Upper airway reconstructive or bypass procedures.

Patient Case

12. A 50-year-old man with OSA and a BMI of 33 kg/m² has been using nasal CPAP nightly, titrated to the optimal PAP level. He is adherent to use of his CPAP machine nightly, his PAP mask fits well, and he is getting sufficient sleep, but he still reports excessive daytime sleepiness, which is interfering with his job as an accountant. He has even started an exercise and weight management program, and he has lost 6.8 kilograms in the past 2 months. Which is the most appropriate adjunctive treatment for his OSA?
- A. Bariatric surgery.
 - B. Pseudoephedrine.
 - C. Oxygen.
 - D. Modafinil.

IV. SMOKING CESSATION

Guidelines

U.S. Preventive Services Task Force. Counseling and interventions to prevent tobacco use and tobacco-caused disease in adults and pregnant women: U.S. Preventive Services Task Force reaffirmation recommendation statement. *Ann Intern Med* 2009;150:551-5.

U.S. Public Health Service. Treating Tobacco Use and Dependence. Clinical Practice Guideline [monograph on the Internet]. Rockville, MD: U.S. Department of Health and Human Services, 2008. Available at www.ncbi.nlm.nih.gov/books/NBK63952/. Accessed September 26, 2014.

- A. Smoking Statistics
 1. Forty-six million adult Americans smoke (20.6% of all adults).
 2. Smoking is the No. 1 cause of preventable deaths in the United States.
 3. Medical costs for smokers are more than \$50 billion a year.
 4. 4000 substances in cigarette smoke; more than 60 are known carcinogens
 5. Seventy percent of smokers want to quit.
 6. Thirty-five percent quit for at least 1 day a year.
 7. About 50% of people who have ever smoked have quit.
 8. Most quitters need several attempts at quitting (five or six) before they are successful.

- B. Health Consequences Linked to Smoking
 1. Aortic aneurysm, early abdominal aortic atherosclerosis in young adults.
 2. Asthma
 3. Cancer: Acute myelocytic leukemia, bladder, cervical, colorectal, esophageal, gastric, kidney, laryngeal, liver, oral cavity, pancreatic, pharyngeal.
 4. Chronic obstructive pulmonary disease.
 5. Coronary heart disease.
 6. Diabetes.
 7. Ectopic pregnancy.
 8. Erectile dysfunction (male).
 9. Hip fractures.
 10. Increased risk of pneumonia and other respiratory infections.
 11. Ocular: Blindness, cataracts, age-related macular degeneration.

12. Osteoporosis.
 13. Reduced fertility.
 14. Rheumatoid arthritis.
 15. Stroke.
 16. Adverse pregnancy outcomes: Smoking during pregnancy results in the death of 1000 infants annually and increases the risk of premature birth and intrauterine growth retardation.
 17. Mortality:
 - a. More than 430,000 smoking-related deaths in the United States each year.
 - b. One in every five deaths in the United States is attributable to smoking.
 - c. Rate of death from any cause in smokers is three times that of never-smokers.
 - d. Life expectancy is shortened by more than 10 years in current smokers compared with never-smokers.
 - e. Environmental tobacco smoke (secondhand smoke) contributes to the death of 38,000 people a year.
- C. Benefits of Quitting Smoking
1. The chance of surviving to age 80 years is twice as great for never-smokers compared with current smokers.
 2. Quitting smoking before age 40 years lowers the risk of death by 90% compared with continuing smoking.
 3. Smokers who quit:
 - a. At age 25–34 years, gain 10 years of life
 - b. At age 35–44 years, gain 9 years of life.
 - c. At age 45–54 years, gain 6 years of life. (N Engl J Med 2013;368:341-50)
 4. After 1 year of abstinence, 50% lower risk of heart disease
 5. After 3–5 years of abstinence:
 - a. Fifty percent lower risk of bladder cancer.
 - b. Fifty percent lower risk of oral and esophageal cancer.
 6. After 10 years of abstinence, 50% lower risk of lung cancer.
 7. After 15 years of abstinence, risk of heart disease is the same as in people who never smoked.
 8. After 5–15 years of abstinence, risk of stroke is the same as in people who never smoked.
 9. After 11–15 years of abstinence, risk of dying is almost the same as in people who never smoked.
- D. Nicotine Addiction and Withdrawal
1. Physical and psychological addiction.
 2. Symptoms of withdrawal: Depressed mood, insomnia, irritability, frustration, anger, anxiety, difficulty concentrating, restlessness, impatience, decreased heart rate, increased appetite, weight gain.
 3. Symptoms of withdrawal may start within 24 hours and last 1–2 weeks.
- E. Patient Assessment and Education (“The 5 A’s”: Ask, Advise, Assess, Assist, and Arrange)
1. Ask
 - a. At every visit, ask about tobacco use and document it in the patient’s chart.
 - b. Consider making “tobacco use” a vital sign.
 2. Advise
 - a. Even a few strong statements show you care and may help a patient decide that he or she wants to quit.
 - b. Advice should be clear, strong, and personalized to patient situation (e.g., concurrent conditions, risks to children).
 - c. Brief behavioral counseling (less than 10 minutes) significantly increases cessation rates.

- d. Shorter interventions (less than 3 minutes) are less effective, but they still increase quit rates.
 - i. “Quitting smoking is the single most important thing you can do for your health.”
 - ii. “I think it is important for you to quit smoking now, and I will help you.”
 - iii. “Continuing to smoke makes your asthma worse.”
- 3. **Assess**
 - a. Assess tobacco use; identify tobacco users willing to quit.
 - b. Addiction level:
 - i. Heavy: More than 25 cigarettes per day.
 - ii. Moderate: 11–24 cigarettes per day.
 - iii. Light: 1–10 cigarettes per day.
 - c. Assess patient’s readiness to quit/stage of smoking cessation and belief that he or she can quit.
 - i. “How badly do you want to quit now (1–10)?”
 - ii. “Do you think you can successfully quit with help?”
 - d. Self-efficacy (motivation plus confidence plus effort plus believing he or she can quit).
 - e. If the patient does not want to quit (precontemplative or contemplative):
 - i. Discuss why he or she should quit (in a supportive manner).
 - ii. Discuss his or her personal barriers to quitting.
 - iii. “Why do you smoke?” and “What scares you about quitting?”
 - iv. Build a patient’s confidence about quitting.
 - v. Use motivational interviewing strategies (see Table 14).
 - vi. Discuss the five “R’s” (shown to enhance future quit attempts):
 - (a) **Relevance** (why quitting is personally relevant for them).
 - (b) **Risks** (health risks of smoking).
 - (c) **Rewards** (potential benefits of quitting tobacco; tailor to individual patients; examples listed are from U.S. Public Health Service [PHS] guidelines).
 - (1) Improved health (specific for patient situation).
 - (2) Food tastes better.
 - (3) Improved sense of smell.
 - (4) Saving money.
 - (5) Feeling better about oneself.
 - (6) Home, car, clothing, and breath will smell better.
 - (7) Setting a good example for children and decreasing the likelihood they will smoke.
 - (8) Having healthier babies and children.
 - (9) Feeling better physically.
 - (10) Performing better in physical activities.
 - (11) Improved appearance, including reduced wrinkling/aging of skin and whiter teeth.
 - (d) **Roadblocks** (ask patients to identify barriers; why they are reluctant to quit or what scares them about quitting).
 - (e) **Repetition** (motivational intervention should be repeated at each clinic visit).

Table 14. Using Motivational Interviewing Strategies with Patients Unwilling to Quit

Express empathy	<ul style="list-style-type: none"> • Use open-ended questions to explore the following: <ul style="list-style-type: none"> – The importance of addressing smoking or other tobacco use (e.g., “How important do you think it is for you to quit smoking?”) – Concerns and benefits of quitting (e.g., “What might happen if you quit?” “What would be the best part of being a nonsmoker?”) • Use reflective listening to seek shared understanding <ul style="list-style-type: none"> – Reflect words or meaning (e.g., “So it sounds like smoking helps you to maintain your weight”) without adding your own information or assessment – Summarize what you heard the patient say • Normalize feelings and concerns (e.g., “Many people worry about managing without cigarettes”) • Support the patient’s autonomy and right to choose or reject change (e.g., “I hear you saying you are not ready to quit smoking right now; I’m here to help you when you are ready”)
Develop discrepancy	<ul style="list-style-type: none"> • Highlight the discrepancy between the patient’s present behavior and expressed priorities, values, and goals (e.g., “It sounds like you are very devoted to your family; how do you think your smoking is affecting your children?”) • Reinforce and support “change talk” and “commitment” language <ul style="list-style-type: none"> – “It’s great that you are going to quit when you get through this busy time at work” • Build and deepen commitment to change <ul style="list-style-type: none"> – “We would like to help you avoid a stroke like the one your father had”
Roll with resistance	<ul style="list-style-type: none"> • Back off and use reflection when the patient expresses resistance <ul style="list-style-type: none"> – “Sounds like you are feeling pressured about your smoking” • Express empathy <ul style="list-style-type: none"> – “You are worried about how you would manage withdrawal symptoms” • Ask permission to provide information
Support self-efficacy	<ul style="list-style-type: none"> • Help the patient to identify and build on past successes • Offer options for achievable small steps toward change <ul style="list-style-type: none"> – Call the quitline (1-800-QUIT-NOW) for advice and information – Read about quitting benefits and strategies – Change smoking patterns (e.g., no smoking in the home) – Ask the patient to share his or her ideas about quitting strategies

From U.S. Public Health Service. Treating Tobacco Use and Dependence. Clinical Practice Guideline [monograph on the Internet]. Rockville, MD: U.S. Department of Health and Human Services, 2008. Available at www.surgeongeneral.gov/tobacco/treating_tobacco_use08.pdf. Accessed September 26, 2014.

4. Assist

- a. Once the patient has decided to quit (is in planning stage), help him or her.
- b. If time is an issue, can schedule visit just for tobacco cessation (but do not miss an opportunity).
- c. Combination of drugs and counseling is more effective than either drugs or counseling alone (Evidence A), and longer counseling sessions improve quit rates (U.S. Preventive Services Task Force). Quit rates plateau after 90 minutes of total counseling contact time.
- d. Assess their smoking history, quit attempt history, smoking/tobacco habits, motivators for quitting, barriers to quitting, and triggers.

Table 15. Fagerström Test for Assessment of Nicotine Dependence^a

- | |
|--|
| <p>1) How soon after you awaken do you smoke your first cigarette?
 >1 hour (0), ½–1 hour (1), 6–30 minutes (2), ≤5 minutes (3)</p> <p>2) Do you find it difficult to refrain from smoking in places where it is forbidden?
 No (0), Yes (1)</p> <p>3) Which cigarette would you hate to give up the most?
 Any other than first in the morning (0), first in the morning (1)</p> <p>4) How many cigarettes per day do you smoke?
 <10 (0), 11–20 (1), 21–30 (2), >31 (3)</p> <p>5) Do you smoke the most in the first hours of the morning?
 No (0), Yes (1)</p> <p>6) If you are so ill that you are in bed most of the day, do you still smoke?
 No (0), Yes (1)</p> |
|--|

^aA score of 7 or greater indicates greater nicotine dependence and the possibility of more severe withdrawal symptoms.

- e. Help patient with a quit plan (“STAR”).
 - i. Set a quit date.
 - (a) This is a vital step to do with the patient.
 - (b) Within 2 weeks is ideal.
 - (c) Do not do it on a stressful, difficult day.
 - (d) Consider having a “contract.”
 - ii. Tell family, friends, coworkers.
 - iii. Anticipate challenges (including withdrawal).
 - iv. Remove tobacco products/paraphernalia from environment; clean home and car.
- f. Help patient get ready for the quit date.
- g. Help patient recognize danger signs: Stress, being around other smokers, alcohol, after meals, other triggers.
- h. Help patient develop coping skills.
 - i. Identify triggers.
 - (a) Anticipate and avoid triggers, if possible.
 - (b) Plan ahead: Learn cognitive and behavioral activities to cope with triggers.
 - ii. Alcohol use: Alcohol use is related to relapse. Drinkers should limit/abstain from alcohol while attempting to quit smoking.
 - iii. Caffeine: Cut back when discontinuing tobacco because the metabolism of caffeine decreases with tobacco cessation. Increased caffeine worsens irritability during withdrawal.
- i. Support system: Have patients identify people in their lives whom they can count on for support, and have patients call these people when difficult times arise.
- j. Reward system.
 - i. Average cost of pack of cigarettes (2014): \$5.98 (cost varies per state, from \$4.23 in North Dakota to \$10.11 in New York)
 - ii. If smoke 1 pack/day
 - (a) Money saved in 1 year: \$2,182.70/year for 1 pack/day
 - (b) Money saved in 5 years: \$10,913.50
 - (c) Money saved in 10 years: \$21,827.00

- k. Do not slip.
 - i. This is a lifetime commitment.
 - ii. Total abstinence is essential. Cannot even have “just one puff”; just say NOPE (Not One Puff Ever).
 - iii. If a slip occurs, renew commitment and do not use tobacco again.
- 5. Arrange
 - a. Arrange a follow-up contact.
 - i. Call or visit within the first week of quit date, if possible.
 - ii. Second follow-up contact in first month.
 - b. A follow-up contact is important because of the risk of relapse.
 - i. Sixty-five percent of self-quitters relapse during the first week.
 - ii. Most smokers who relapse do not return to the precontemplation stage; 85% of relapsers cycle to the contemplation or preparation stage.
 - iii. After 1 year of abstinence, 40% relapse.
 - iv. After 4–5 years of abstinence, only 7% relapse.
 - v. After 5 years of abstinence, most quit for good.

Patient Case

13. A 39-year-old woman with obesity, type 2 diabetes mellitus, and HTN smokes 2 packs of cigarettes per day but is uninterested in quitting. Which is the best intervention currently?
- A. Do nothing currently because she is uninterested in quitting.
 - B. Provide individualized messages for a minimum of 10 minutes on how quitting smoking will improve her specific diseases.
 - C. Use motivational interviewing strategies to discuss her concerns and the benefits of tobacco cessation.
 - D. Explore her various medication options and help her set a quit date.

- F. Pharmacologic Treatment for Tobacco Cessation
- 1. General approach to pharmacotherapy.
 - a. Assess the patient’s tobacco use (e.g., chain smoking, smokes when nervous).
 - b. Assess past attempts: What worked and did not work; how did they use the medication; involve patient in the decision of what therapy to use.
 - c. Previous success with a drug may be helpful in a subsequent quit attempt.
 - d. For previous failure with a drug, it is unclear whether the drug should be retried for future quit attempts; data are conflicting on this issue; discuss with the patient.
 - e. No accepted algorithm to guide selection of therapy.
 - f. Pregnancy: The U.S. Preventive Services Task Force concluded that evidence is inadequate to evaluate the safety or efficacy of smoking cessation pharmacotherapy during pregnancy.
 - 2. First-line treatments for smoking cessation (according to the U.S. Department of Health and Human Services [DHHS]; PHS): All smokers trying to quit should be offered medication unless medications are contraindicated or for certain populations in which there is not enough evidence of effectiveness (e.g., pregnant women, breastfeeding, smokeless tobacco users, light smokers, adolescents).
 - a. Medications more effective than the nicotine patch alone:
 - i. Varenicline.
 - ii. Combination of nicotine patch and ad libitum SA nicotine replacement therapy (NRT).
 - b. These should be considered first, if possible, and/or if not contraindicated (DHHS; PHS).

Table 16. Medications for Smoking Cessation

Medications and 6-Month Abstinence Rate	Dose and Mechanism of Action	Duration	Precautions/ Cautions/ AEs	Patient Education
Nicotine patch (OTC ^a) 23.4%–26.5%	21 mg/24 hours ^b 14 mg/24 hours 7 mg/24 hours	4 weeks ^b ; then 2 weeks; then 2 weeks	AEs: Local skin reaction, insomnia, vivid dreams Caution: If CV event in past 2 weeks, serious arrhythmias, unstable angina	<ul style="list-style-type: none"> • Start on quit date • Apply to clean, dry, hairless area between neck and waist; rotate sites; no lotion; do not smoke when using patches • If sleep disruption occurs, remove at night
Nicotine gum (OTC) 2 and 4 mg 19% (6–14 weeks' use) 26.1% (>14 weeks' use)	1–24 cigarettes per day: 2-mg gum (1-mg gum = 1-mg nicotine) 25+ cigarettes per day: 4-mg gum (up to 24 pieces/day) • Initially, chew on a fixed schedule (1 piece of gum every 1–2 hours) for 6 weeks; then use ad libitum	Up to 12 weeks (longer-term use as needed up to 6 months may be helpful if needed)	AEs: Mouth soreness, dyspepsia Caution: If CV event in past 2 weeks, serious arrhythmias, unstable angina	<ul style="list-style-type: none"> • Start on quit date • Do not eat or drink anything except for water 15 minutes before and while gum is in mouth • Directions: Chew until “peppery” taste emerges and then “park” between gum and cheek; re-chew every few minutes and “park” again on other side; chew each piece for 30 minutes • 4-mg strength delays weight gain
Nicotine lozenge (OTC) 2 and 4 mg 23.6% (2 mg) 24.2% (4 mg)	Use 2 mg if first morning cigarette ≥30 minutes after waking; use 4 mg if first morning cigarette <30 minutes after waking • Initially, use on a fixed schedule for 6 weeks (1 every 1–2 hours; at least 9 lozenges – Maximum 20 per day); then 1 every 2–4 hours on weeks 7–9; then 1 every 4–8 hours during weeks 10–12	Up to 12 weeks (longer-term use as needed up to 6 months may be helpful if needed)	AEs: Throat irritation, hiccups, indigestion/ heartburn, nausea Caution: If CV event in past 2 weeks, serious arrhythmias, unstable angina	<ul style="list-style-type: none"> • Start on quit date • Do not eat or drink anything except for water 15 minutes before and while lozenge is in mouth • Directions: Suck on and move from side to side in the mouth; suck each piece until it dissolves; do not chew • 4-mg strength delays weight gain

Table 16. Medications for Smoking Cessation (*continued*)

Medications and 6-Month Abstinence Rate	Dose and Mechanism of Action	Duration	Precautions/ Cautions/ AEs	Patient Education
Nicotine inhaler (Nicotrol; no generic) (Rx) 24.8%	Each cartridge = 4 mg of nicotine (80 puffs); almost matches the milligrams of nicotine smoked to daily dose (more if needed); use 6–16 cartridges a day; can use partial amount of cartridge and then put away until needed again	Up to 6 months	AE: Local irritation of mouth and throat Caution: If CV event in past 2 weeks, serious arrhythmias, unstable angina	<ul style="list-style-type: none"> • Start on quit date • No special inhalation technique; use as if smoking a cigarette • Do not eat or drink anything except for water 15 minutes before and during use • Delivery decrease if <40°F in winter, keep in warm area or coat pocket (not in car)
Nicotine nasal spray (Nicotrol NS; no generic) (Rx) 26.7%	8–40 doses/day 0.5 mg/spray; one in each nostril (1 mg per dose)	3–6 months	AEs: Nasal irritation (94% get moderate-severe nasal irritation) Caution: If CV event in past 2 weeks, serious arrhythmia, unstable angina Avoid use in severe reactive airway disease	<ul style="list-style-type: none"> • Start on quit date • Tilt head slightly back; do not sniff, inhale through nose, or swallow while spraying
Varenicline (Chantix; no generic) (Rx) 33.2% (2 mg daily) 25.4% (1 mg daily)	0.5 qd for 3 days; then 0.5 mg bid for 4 days; then 1 mg bid starting on quit date (start 1 week before quit date) ^b ; decrease dose in CKD - Binds to neuronal nicotine receptors ($\alpha 4\beta 2$ subtype); agonist/antagonist	3 months; maintenance up to 6 months	AEs: Nausea, insomnia, vivid dreams Caution: Monitor for changes in mood, behavior, psychiatric/ depression symptoms, and suicidal ideation	<ul style="list-style-type: none"> • Take evening dose at suppertime instead of at bedtime if insomnia occurs • Report any depression symptoms • Patients may experience impaired ability to drive or operate machinery • Take with food to reduce nausea

Table 16. Medications for Smoking Cessation (*continued*)

Medications and 6-Month Abstinence Rate	Dose and Mechanism of Action	Duration	Precautions/ Cautions/ AEs	Patient Education
Bupropion SR (Rx) 24.2%	150 mg every morning for 3 days; then bid (start 1–2 weeks before quit date) - Mechanism in smoking cessation unclear; blocks dopamine and/ or norepinephrine reuptake	7–12 weeks; maintenance up to 6 months	AEs: Dry mouth, insomnia Contraindications: History of seizure, eating disorder; use of MAO inhibitors in past 14 days; abrupt discontinuation of alcohol, benzodiazepines, barbiturates, or antiepileptic drugs	<ul style="list-style-type: none"> • Take evening dose at supertime instead of at bedtime if insomnia occurs (doses should be ≥ 8 hours apart) • Delays weight gain

^aDose and duration are for smokers smoking 1 pack/day; if smoking ½ pack/day, start with 14-mg patch.

^b“Preloading” for 4 weeks before quit date significantly increased abstinence rates, especially in those who reduced nicotine use before quit date (Hajek P, McRobbie HJ, Myers KE, et al. Use of varenicline for 4 weeks before quitting smoking. Arch Intern Med 2011;171:770-7).

AE = adverse effect; bid = twice daily; CKD = chronic kidney disease; CV = cardiovascular; MAO = monoamine oxidase; NS = nasal spray; OTC = over the counter; qd = once daily; Rx = prescription; SR = sustained release.

3. Second-line treatments for tobacco cessation.
 - a. Clonidine.
 - b. Nortriptyline.
4. Heavier smokers/more dependent/history of more severe withdrawal.
 - a. Use higher-dose preparations of NRT.
 - b. Evidence that combination NRT therapy is effective (e.g., nicotine patch plus as-needed nicotine gum).
 - c. Can use two 21-mg patches initially for heavy smokers (more than 2 packs/day) (off-label).
5. Light smokers (fewer than 10 cigarettes per day):
 - a. Cessation medications have not been shown helpful, but can still be used.
 - b. Use lower doses of NRT; doses for varenicline or bupropion are the same.
6. For patients concerned about weight gain: Bupropion, 4-mg nicotine gum, and 4-mg lozenge delay (but do not prevent) weight gain.
7. Patients with CVD: NRT need not be avoided; caution in first 2 weeks after an event.
8. Combinations shown to be effective (6-month abstinence rate).
 - a. Patch and gum (36.5%).
 - b. Patch and nasal spray (36.5%).
 - c. Patch and inhaler (25.8%).
 - d. Patch and bupropion sustained release (28.9%).
 - e. Patch and varenicline (65.1%) (JAMA.2014;312(2):155-61).
 - f. The only combination recommended as first-line therapy is as follows: Nicotine patch plus ad libitum SA NRT (DHHS; PHS).

9. Psychiatric risk: The FDA issued public health advisories on psychiatric risks. Initially, the advisory was only for varenicline (February 2008); then, bupropion was added to the public health advisory (July 2009). The FDA required the manufacturers to include boxed warnings and develop medication guides. Then, in October 2011, the FDA reviewed two epidemiologic studies and found no difference in neuropsychiatric risk resulting in hospitalization with varenicline and NRT, but there were no changes in their recommendations. The FDA still believed that “the drug’s benefits outweigh the risks” and that the “current warnings are appropriate.” A subsequent independent analysis of reports submitted to the FDA showed an increase in suicide-related events that may not have resulted in hospitalization (reports for varenicline, bupropion, and NRT for completed suicide were 272, 19, and 4, respectively; for suicidal ideation, 1135, 73, and 40, respectively; and for suicide attempt, 323, 56, and 2, respectively) (JAMA 2012;307:129-30). No changes to the FDA recommendations (below) were made.
- Depressed mood, changes in behavior, hostility, agitation, suicidal thoughts and behavior, and attempted suicide have been reported in patients using varenicline and bupropion for smoking cessation, some with no history of psychiatric disease, and have worsened in patients with psychiatric illness. The FDA also states that some of these cases may have been confounded by typical nicotine withdrawal symptoms.
 - Clinicians should obtain information regarding patients’ psychiatric histories and monitor patients for changes in mood and/or behavior.
 - Patients should be instructed to discontinue the drug if they experience any symptoms of depressed mood, agitation, or behavior changes that do not seem to be from nicotine withdrawal or if they experience suicidal thoughts. Family members and caregivers should also be educated about symptoms to watch for.
 - The FDA is clear that varenicline and bupropion are effective smoking cessation aids and that these risks should be discussed in the context of the benefits of quitting smoking.
10. CV risk: Newer FDA Drug Safety Communication 2012 for varenicline.
- Update on December 12, 2012.
 - Meta-analysis (CMAJ 2011;183:1359-66).
 - Fourteen trials; 8216 subjects; all except for one trial, which excluded subjects with a history of heart disease.
 - Significantly increased risk of serious CV events (ischemia, arrhythmia, heart failure, sudden death, CV-related death); 1.06% versus 0.82%; Peto odds ratio 1.72 (95% CI, 1.09–2.71).

Patient Cases

14. A 50-year-old woman presents for smoking cessation. She currently smokes 1½ packs/day and has smoked 1–2 packs/day for 24 years. She has COPD, eating disorder, depression, and anxiety (her depression and anxiety are both well controlled with medications; no history of suicidal ideation). She has tried nicotine patches, inhalers, and lozenges, none of which helped her quit. She would like to try something different. In addition to instructing the patient, family members, and caregivers to discontinue pharmacotherapy if they experience any symptoms of depressed mood, agitation, or behavior changes, which would be the most appropriate pharmacotherapy recommendation?
- Bupropion sustained release 150 mg once daily for 3 days; then twice daily.
 - Varenicline 0.5 mg once daily for 3 days; then twice daily for 4 days; then 1 mg twice daily.
 - Nicotine gum 2 mg; one piece every 1–2 hours for 6 weeks; then ad libitum.
 - Nicotine patch 14 mg; one patch every day for 2 weeks; then decrease to 7 mg daily for 2 weeks.

Patient Cases *(continued)*

15. A 27-year-old woman wants to quit smoking and is interested only in NRT for smoking cessation. She does not want to take any “pills.” She smokes 1 pack/day. Her first cigarette is 1 hour after waking up. She has tried quitting “cold turkey” about four times in the past, but for a few days, she was unsuccessful. She is now more serious, given that her son’s asthma is getting worse because of her smoking. Which is the most appropriate first-line therapy for her?
- A. Nicotine patch: 21 mg daily for 4 weeks; then 14 mg daily for 2 weeks; then 7 mg daily for 2 weeks.
 - B. Nicotine inhaler: 6 cartridges a day; use regularly for 6 weeks; then use ad libitum.
 - C. Nicotine gum 4 mg: Use regularly for 6 weeks; then use ad libitum (maximum 10 pieces a day).
 - D. Nicotine patch: 21 mg daily for 4 weeks; then 14 mg daily for 2 weeks; then 7 mg daily for 2 weeks plus nicotine gum 2 mg (use ad libitum).

G. Electronic Cigarettes (e-cigarettes)

1. Highly advertised battery-operated devices.
2. Deliver a vapor that typically contains nicotine and/or other chemicals, including propylene glycol, carcinogens, and diethylene glycol (antifreeze).
3. Not FDA approved; types and quantities of other chemicals contained in e-cigarettes are unknown; amount of nicotine inhaled is unknown; safety unknown; no warning labels required.
4. Not sold or regulated as drugs, but rather as tobacco products. No age restrictions and are available in flavors such as chocolate and mint, which could appeal to young people and increase risk of addiction in children. Risk of nicotine toxicity if the cartridge malfunctions.
5. Refill cartridges are a risk if used improperly. Amount of nicotine may vary from cartridge to cartridge. Cartridges have been found to contain unapproved drugs in liquid form for inhalation through e-cigarettes, such as tadalafil and rimonabant.
6. The FDA has warned consumers about potential health risks associated with e-cigarettes. Intends to develop regulations for e-cigarettes.
7. Pharmacists should recommend against using e-cigarettes.

H. Complementary and Alternative Medicine: Guidelines state that there is insufficient evidence to support the use of acupuncture or hypnosis for tobacco use treatment (DHHS).

I. Vaccinations: All smokers 19–64 years of age should receive the polysaccharide pneumococcal vaccine once and then a one-time revaccination 5 years or more after the first vaccination, in addition to the influenza vaccine every fall.

V. PUBLIC HEALTH

Table 17. Agencies/Associations Specific to Asthma, COPD, and/or Smoking Cessation with Resources/Educational Programs for the Public

Agency/ Association	Web Site/ Telephone Numbers	Programs/Resources
American Lung Association (ALA)	www.lungusa.org/	Information on management of asthma, COPD, and smoking cessation Can enter zip code and search for local associations Many local programs available Better Breathers Club (COPD), Breathe Well/Live Well Self-Management Program (asthma), Freedom From Smoking Online program Lung helpline 1-800-LUNGUSA to help with any questions on asthma, COPD, smoking cessation Can also do an online chat
Asthma and Allergy Association of America (AAFA)	www.aafa.org/	Educational programs (online, classroom), resources, materials, tools (e.g., asthma action plans/cards), publications, and educational materials Local educational support groups, including parent support groups
Allergy and Asthma Network; Mothers of Asthmatics (AANMA)	www.aanma.org/	“Ask a Nurse” patient support center, educational tools and materials, and asthma and allergy topics in the news Help for parents dealing with children with asthma and allergies
National Heart, Lung, and Blood Institute (NHLBI)	www.nhlbi.gov	Area for public; includes information on asthma, COPD, and smoking cessation National Asthma Control Initiative Publications, fact sheets Demonstration projects around the country addressing guideline implementation and dealing with asthma disparities
COPD Council	www.copdcouncil.org/	National and international organizations Programs in many different states/areas Local Better Breathers clubs List of speakers available
Smokefree.gov	www.smokefree.gov 1-800-QUITNOW (connects to state quitlines)	From the NCI (Tobacco Control Research Branch) Online step-by-step research guide Local and state telephone quitlines NCI national telephone quitline NCI instant messaging service Publications; resources such as a craving journal, discovering reasons for quitting

Table 17. Agencies/Associations Specific to Asthma, COPD, and/or Smoking Cessation with Resources/Educational Programs for the Public (*continued*)

Agency/ Association	Web Site/ Telephone Numbers	Programs/Resources
CDC Office on Smoking and Health (OSH)	www.cdc.gov/tobacco	Patient educational materials Data and statistics Links to state and community resources
Nicotine Anonymous	www.nicotine-anonymous.org	12-step program offering support to those who want to quit smoking; similar to AA Links to local support groups and meetings; information on telephone meetings
American Academy of Sleep Medicine	www.aasmnet.org www.sleepeducation.com	“Sleep Education” provides online patient education

AA = Alcoholics Anonymous; CDC = Centers for Disease Control and Prevention; COPD = chronic obstructive pulmonary disease; NCI = National Cancer Institute.

VI. PRACTICE MANAGEMENT

A. Certification

1. Certified Asthma Educator (AE-C).
 - a. National Asthma Educator Certification Board (www.naecb.org/).
 - b. National examination based on a detailed content outline: Pathophysiology, contributing factors, obtainment of history from a patient with asthma, physical signs, objective measures, educational needs, asthma management (medications, delivery devices), behavioral and environmental modifications, asthma education plan, organizational issues (needs assessment, program development, implementation, evaluation), referral, and professional networking.
 - c. Many local associations offer review classes.
 - d. Two clinical pharmacists are on the board.
2. Tobacco Treatment Specialist (TTS).
 - a. The Council for Tobacco Treatment Training Programs (<http://www.attudaccred.org/>).
 - b. The council is the accrediting body for TTS Training Programs; an independent panel carefully reviews the training program and determines that it meets the core competencies; TTSs have demonstrated a high-level of proficiency in the treatment of tobacco dependence by completing coursework, documenting experience, and passing an examination.

VII. PATIENT ADVOCACY

- A. For Asthma and COPD: All inhalers are brand name and are not available generically. Cost may be an issue for many patients.

- B. Patient Assistance Programs: Available from Manufacturers
 - 1. Examples: www.rxassist.org and www.needymeds.com
 - 2. Can search by name of drug to find criteria and instructions on enrolling patients in the program.
 - 3. Discounts are available for certain medications by using www.needymeds.com

- C. Ventolin HFA: Available in a smaller canister on the \$4 programs of some retail pharmacies.
 - 1. Cost: \$8 per canister (60 puffs per canister instead of 200).
 - 2. Generic albuterol and ipratropium nebulizer solutions are also available for \$4 a month.

- D. Some Manufacturers Offer Coupons on Their Web Sites.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: B

The patient's symptom frequency of twice weekly, her FEV₁ more than 80% of predicted (normal), and the lack of interference with her activities are consistent with intermittent asthma. However, her nighttime awakenings for asthma symptoms occur three times a month, which is consistent with mild persistent asthma. In addition, mild persistent asthma still has normal spirometry values. The specific level of persistent asthma is based on the most severe category met, so even though only one of her signs/symptoms falls under mild persistent and the rest under intermittent, her asthma severity would be categorized as mild persistent.

2. Answer: C

Because she has mild persistent asthma, step 2 is recommended for initial treatment. In addition to an inhaled SABA as needed, she would need to use a low-dose inhaled corticosteroid (preferred treatment); mometasone 220 mcg once daily is a low-dose ICS. Montelukast is alternative therapy (not first line) for step 2. Budesonide/formoterol, in the dose listed, is a low-dose ICS plus a LABA, which is a step 3 therapy.

3. Answer: D

Her asthma falls in the "not well-controlled" category because the frequency of her daytime symptoms and albuterol use is more than 2 days a week. The recommended action for treatment is to go up one step to step 3: A low-dose ICS plus a LABA or a medium-dose ICS alone. Budesonide/formoterol MDI is incorrect because it is a medium-dose ICS plus a LABA (a step 4 treatment). Adding montelukast to a low-dose ICS is an alternative therapy.

4. Answer: D

This patient has moderate persistent asthma because of his nighttime symptoms twice weekly and requires step 3 therapy. A medium-dose ICS alone is preferred as initial therapy in this age group (5–11 years). Fluticasone 44 mcg 1 puff twice daily is a low-dose ICS for this age group. Montelukast is not recommended for moderate persistent asthma in this age group as monotherapy; montelukast is recommended only in combination with a low-dose ICS. Fluticasone/salmeterol 100/50 mcg twice daily is a medium-dose ICS plus a LABA, which is step 4 in this age group.

5. Answer: B

In an asthma action plan, this would be the green zone instructions (doing well, no symptoms, peak flow meter [PFM] of 80% or greater of personal best). Instructions should be to take the controller agent only (and the patient may use albuterol HFA 1 or 2 puffs every 4–6 hours only if needed for periodic symptoms). In this case, the controller is fluticasone/salmeterol (Advair) 250/50 mcg/puff 1 puff twice daily.

6. Answer: B

In an asthma action plan, this would be the yellow zone instructions (some symptoms; getting worse; PFM 50%–79% of personal best). Instructions should be to use albuterol HFA 2–6 puffs; repeat in 20 minutes if needed; and then reassess. For a milder yellow zone exacerbation, 2 puffs should be sufficient, but for a moderate exacerbation, 4–6 puffs could be used. In addition, the patient should contact the clinician for follow-up instructions and could continue the SABA every 3–4 hours regularly for 24–48 hours. An OCS burst could be considered, but this is usually not necessary for a mild exacerbation.

7. Answer: C

In an asthma action plan, this would be the red zone instructions (marked wheezing and dyspnea; more severe exacerbation; PFM less than 50% of personal best). Instructions should be to use albuterol HFA 2–6 puffs; repeat in 20 minutes; start an OCS burst; and then reassess. For red zone exacerbations, the higher dose (e.g., 6 puffs) is usually recommended. If the response is incomplete or poor, repeat a high dose of SABA. If there is no response, go to the ED or call 911. Of importance, the patient should call 911 immediately if he or she cannot walk or talk because of shortness of breath or if lips or fingernails are blue. The treatment can begin while waiting for the ambulance to arrive. In addition, the patient should go to the hospital if there is no improvement after 15 minutes of taking a high-dose SABA.

8. Answer: B

According to GOLD guidelines, he is in patient group B because his postbronchodilator FEV₁ is between 50% and 80%, he has had one or no exacerbations in the past year, and his mMRC score is 2 or more. If the CAT were being used, the score would be 10 or greater.

9. Answer: B

According to the GOLD guidelines, the recommended treatment for patient group B is regular treatment with an LA bronchodilator (either a LABA or LA anticholinergic), in addition to an SA bronchodilator as needed. Inhaled corticosteroids are recommended only in groups C and D. Roflumilast is recommended only if FEV₁ is less than 50% of predicted with chronic bronchitis and a history of frequent exacerbations.

10. Answer: A

This patient is in GOLD risk group B, according to spirometry and CAT score, and is receiving the first-choice therapy. Because of worsening control of COPD, she should receive the second-choice therapy, for which combined LA bronchodilators can be used. Inhaled corticosteroids are only recommended in risk groups C and D. Although a recent study showed benefits with chronic azithromycin, the guidelines do not recommend regular treatment with long-term antibiotics. In addition, the study showing the benefits of azithromycin included only patients at a higher risk of exacerbations (receiving continuous oxygen therapy or using systemic corticosteroids, plus a history of exacerbation requiring an ED visit or hospitalization). She does not meet these criteria.

11. Answer: D

According to the latest GOLD guidelines, OCSs are indicated in most exacerbations. The recommended dose is oral prednisolone (or equivalent) 30–40 mg daily for 5 days. Prednisolone has a dose equivalent to prednisone. Antibiotic treatment is also indicated because the patient has all three cardinal symptoms of airway infection: (1) increased sputum purulence, (2) increased sputum volume, and (3) increased dyspnea. Trimethoprim/sulfamethoxazole is one of the recommended antibiotics.

12. Answer: D

Modafinil is recommended as an adjunct to PAP in patients with excessive daytime sleepiness despite adequate PAP. Bariatric surgery is indicated only if BMI is 40 kg/m² or greater or 35 kg/m² or greater if important comorbidities are present. Oral decongestants are not recommended because of a lack of evidence. Oxygen is recommended only if concomitant hypoxemia is present.

13. Answer: C

This patient does not want to quit smoking right now. The steps to take when individuals are not ready to quit include using motivational interviewing strategies, discussing reasons they should quit (in a supportive manner), discussing their personal barriers to quitting, and discussing the five “R’s” (relevance, risks, rewards, roadblocks, and repetition). Less than 10 minutes is effective in increasing quit rates; even 3 minutes of strong, clear, and personalized statements can increase quit rates. If the patient does not want to quit, it is too early to set a quit date with him or her or to prescribe medication.

14. Answer: B

Varenicline is more effective than the nicotine patch alone, and the PHS recommends it to be one of the therapies that should be considered first line, if possible and/or not contraindicated. Although the patient has depression, it is well controlled, so varenicline may still be used. The patient should be monitored for any worsening depression. She should be instructed to discontinue the agent if she experiences any symptoms of depressed mood, agitation, or behavior changes that do not seem to be from nicotine withdrawal or if she experiences suicidal thoughts. Family members and caregivers should also be educated about symptoms to watch for. Bupropion is contraindicated because of her eating disorder. Nicotine gum 2 mg would not be an appropriate dose for her; she would need to use the 4-mg dose because she smokes more than 25 cigarettes a day. Nicotine patch was not a preference by the patient and would not be an appropriate dose.

15. Answer: D

The combination of a nicotine patch and an ad libitum SA NRT is more effective than the nicotine patch alone. In addition, the PHS recommends this combination as first-line therapy (or varenicline, which the patient does not want). Although the nicotine patch or inhaler alone might be sufficient, the PHS recommends combination therapy. Because she smokes 20 cigarettes per day, the 2-mg, not 4-mg, gum is recommended.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS**1. Answer: D**

That the patient uses her inhaler four times daily, every day, and twice weekly at night indicates she has symptoms throughout the day. In the severe persistent asthma category, the frequency of symptoms is throughout the day; nighttime symptoms are often seven times weekly. Her nighttime symptoms are not in the severe persistent category, but a patient's condition should be classified by the most severe category in any given area.

2. Answer: D

Initial treatment of the severe persistent asthma class is step 4 or 5. Step 4 preferred treatment is an inhaled steroid (medium dose) plus a LABA. An alternative is an inhaled steroid (medium dose) plus either an LTRA or sustained-release theophylline or zileuton. Step 5 preferred treatment is an inhaled steroid (high dose) plus a LABA. Monotherapy with a LABA (salmeterol) is not recommended.

3. Answer: A

Hydrofluoroalkane inhalers have a smaller particle size with better lung deposition. A holding chamber should not be used unless patients have difficulty with the MDI technique. Hydrofluoroalkane inhalers have not been well studied with holding chambers. Most HFA inhalers now have counters. Most HFA cases should be washed in water once weekly to ensure accurate dosage. Hydrofluoroalkane inhalers do need to be primed, but not with each use.

4. Answer: B

The inhaler technique with DPIs is very different from that with MDIs. The inhalation must be quick, forceful, and deep, rather than slow and deep. When using a DPI, the "puff" feels different from that of the MDIs; no aerosol puff is felt; the patient may not feel anything. Dry powder inhalers should not be shaken or be used with a holding chamber.

5. Answer: A

The patient is in GOLD patient group B. A single LA bronchodilator is first choice for medication treatment. Initiating therapy with tiotropium (an LA anticholinergic) would be appropriate for this patient. A LABA would also be appropriate, but it was not one of the choices. Montelukast is recommended for asthma, not COPD. An ICS is recommended only in patient group C or D.

6. Answer: C

For all acute exacerbations of chronic COPD, albuterol with or without ipratropium by nebulization should be given. For most exacerbations, a burst of OCSs should be given. Antibiotics are only recommended if all three cardinal symptoms of COPD exacerbations (increased dyspnea, increased sputum volume, and increased sputum purulence) are present or if two cardinal symptoms are present and increased sputum purulence is one of the symptoms. This patient does not meet these criteria, so antibiotics are not indicated. He has only two of the cardinal symptoms (increased dyspnea and volume), and increased sputum purulence is not one of his symptoms.

7. Answer: B

Hypothyroidism may cause or exacerbate OSA, and because this patient just received a diagnosis of OSA and just began treatment, hypothyroidism is a risk factor for his OSA. Hypertension and smoking are risk factors for OSA. Gastroesophageal reflux disease is not a risk factor.

8. Answer: B

Bupropion, 4-mg nicotine gum, and 4-mg lozenge delay (but do not prevent) the weight gain associated with smoking cessation.

9. Answer: A

A combination of behavioral counseling and drugs is more effective than either behavioral counseling or drugs alone. Longer counseling sessions are more effective than shorter ones, with efficacy plateauing at 90 minutes. Setting a quit date is recommended. Varenicline can be used for 6 months and has additional mental health concerns compared with nicotine replacement therapy.