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An Update In Cardiology

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2018 Guideline Update on the Management of Blood Cholesterol

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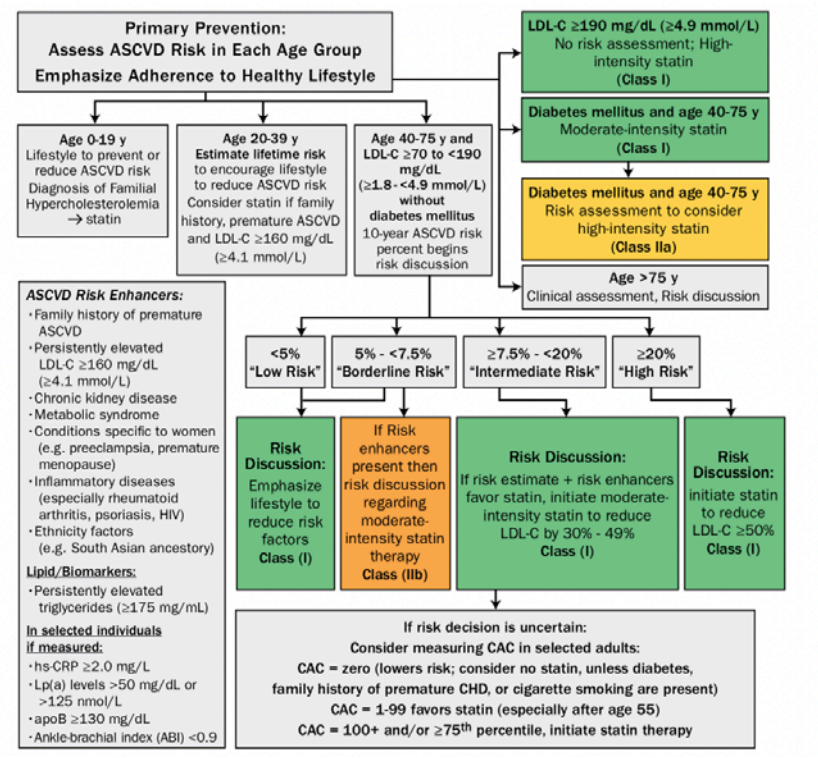
Background information

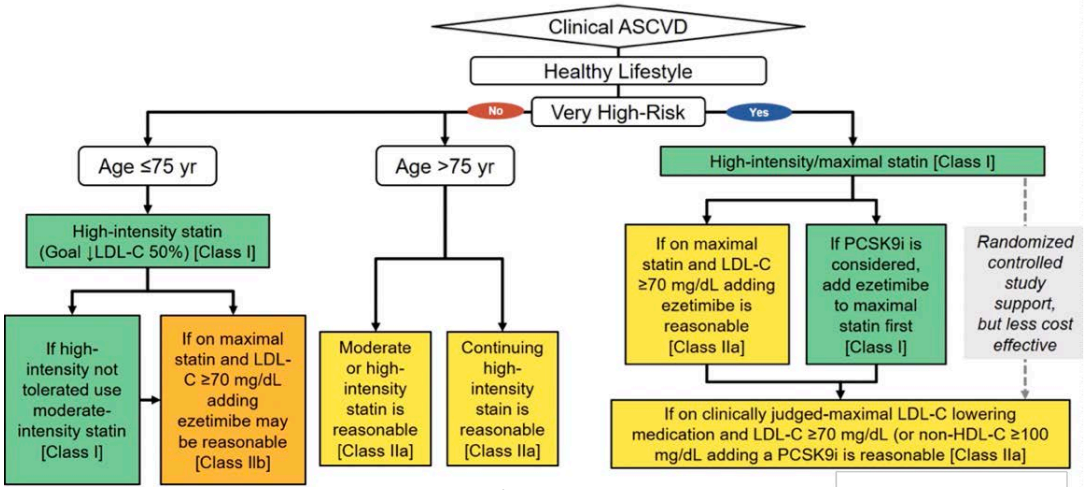
An update to guidelines on recommendations in the management of blood cholesterol was published in 2018 with the intent to address the practical management of patients with high blood cholesterol and related diagnoses. The authors noted that since the most recent publication in 2013, several new cholesterol-lowering agents have been brought to market and increased evidence is available regarding these agents. This 2018 publication focused on patient-provider discussion on risks and benefits of therapy and introduced new literature and recommendations regarding newer cholesterol-lowering medications, specifically PCSK9 inhibitors. Treatment algorithms outlining recommendations for both primary and secondary hypercholesterolemia are listed below.

Primary Prevention



2018 Guideline on Management of Blood Cholesterol; Available at www.acc.org

Secondary Prevention



2018 Guideline on Management of Blood Cholesterol; Available at www.acc.org

2018 Guideline Changes and Updates

The 2018 update supports previous recommendations including the treatment of "four statin benefit groups" found within the algorithms above. Changes to the updated recommendations include further discussion of patients in whom statin therapy benefit may seem unclear as well as additional definitions for describing patient risk factors. Major changes made in the 2018 guideline update are listed below:

1. Definitions

   The 2018 guidelines provided a more in-depth approach to defining patients at high risk of developing ASCVD. Apart from the traditional ASCVD definition, the update now classifies some patients with "Major ASCVD" and also considers particular comorbid conditions to be either "high risk" or "very high risk".

ASCVD	Major ASCVD
Acute coronary syndrome	Recent ACS (in past 12 months)
History of Myocardial Infarction	History of Myocardial Infarction
Stable or unstable angina	History of ischemic stroke
Coronary revascularization	Symptomatic PAD
Arterial revascularization	Previous revascularization
Stroke	Previous amputation
Transient ischemic attack	
Peripheral artery disease (PAD)	

High risk conditions	Very high risk conditions
Age ≥ 65	History of multiple major ASCVD events
History CABG or PCI	
Hypertension	
Diabetes	**OR**
Current Smoker	
Chronic Kidney Disease	One major ASCVD event
History of heart failure	**PLUS**
Heterozygous FH	Multiple high-risk conditions
Elevated LDL (≥ 100) despite max statin + ezetimibe	

2. Considering the "borderline" patient

   While the guidelines continue to recommend treatment for the traditional "four statin benefit groups", the 2018 update has expanded recommendations on the treatment of patients who may be at "borderline" risk of ASCVD. One consideration for providers who may need clarification on patient risk is the list of ASCVD risk enhancing factors provided in the guidelines:

ASCVD Risk Enhancers

- Family history of premature ASCVD
- Persistently elevated LDL ≥160
- Chronic kidney disease
- Metabolic syndrome
- Conditions specific to women (preeclampsia, premature menopause)
- Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
- Ethnicity factors (i.e. south Asian ancestry)

Of the risk factors listed, premature menopause is a new condition not referred to in previous guideline publications that now warrants consideration in the risk-benefit discussion.

Coronary Artery Calcium Scoring

In addition to consideration of risk enhancing factors, the 2018 guidelines recommend the use of Coronary Artery Calcium (CAC) Scoring when treatment benefit is unclear after ASCVD risk assessment, including the use of listed ASCVD risk enhancing factors. CAC scoring involves a non-invasive CT scan of the patient's heart that measures the amount of calcified plaque in the coronary arteries. The test provides a score that places patients into a risk category that represents their risk of developing coronary artery disease.

Guideline recommendations give suggestions to providers in terms of patients who may benefit from CAC testing, specifically those patients who may benefit from knowing their CAC score is zero:

- Patients reluctant to initiate statin therapy
- Patients wishing to understand their risk/benefit more precisely
- Patients concerned to reinitiate statin therapy after experiencing statin-associated muscle pain
- Older patients with a low burden of risk factors in which therapeutic benefit is uncertain
- Patients (40-55) with a 10-year ASCVD risk 5-7.4% + other factors that increase risk

3. LDL Targets

Although not a change since the 2013 publication, there was excitement surrounding the topic of LDL goals prior to the 2018 publication. Since 2013, guidelines have not recommended that patient have specific LDL "goals", but rather, mentioned at what LDL levels providers should begin treatment, and with what treatment we should expect particular LDL reductions. The 2018 guidelines continue this previous recommendation, but do mention treating patients until LDL < 70 and that LDL > 190 is considered "severely elevated LDL".

4. Pitavastatin

The update states Pitavastatin has been moved from the low-intensity statin classification to a moderate intensity statin group, now considered to provide LDL lowering between 30-49%.

5. Clarification on use of ezetimibe and PCSk9 inhibitors

The 2018 update provides a reference for consideration of PCSK9 inhibitor therapy, focusing on when the benefits of these novel agents begin to outweigh risks of therapy. The guideline recommends consideration of an addition cholesterol-lowering agent when patients continue to have an LDL ≥ 70mg/dL even after a maximally tolerated statin. In this instance, additional agents include a choice between ezetimibe therapy or a PCSK9 inhibitor. The guidelines recommend the addition of ezetimibe therapy first, before addition of a PCSK9 inhibitor for several reasons, the first being the cost associated with these newer agents. Aside from cost, the guidelines also mention that efficacy has not been proven beyond three years of use with PCSK9 inhibitors due to their newer status on the market. If a patient continues to experience LDL levels ≥ 70mg/dL after initiation of maximally tolerated statin in combination with ezetimibe therapy, a PCSK9 inhibitor may then be appropriately considered.

6. Aging out of statin therapy

The 2018 guidelines provide specific clarification to providers regarding statin benefit regarding patient age groups, specifically older patient populations. Previous guidelines did not explicitly state the role of statin therapy in patients > 75 years of age, leaving many with the assumption that treatment may not be beneficial in this population. The update clarifies this assumption by stating that risk-benefit is still an important discussion to have

with patients >75. More importantly, these guidelines state that patients do not "age out" of statin therapy. If a patient is controlled on a high intensity statin and not experiencing any adverse events, there is no reason to decrease the dose or discontinue a statin after the patient turns 75.

Summary

In all, the 2018 guideline update to the treatment of blood cholesterol solidified many previously stated guideline recommendations, including the "four statin benefit groups" and the absence of LDL goals. The update also acknowledged novel drug therapies as well as their place in treatment, including recommendations surrounding additional cholesterol-lowering therapies for patients who remain uncontrolled on a maximally tolerated statin. Additional recommendations of the update include further guidance on the treatment of patients in whom ASCVD risk is unclear, additional definitions outlining "very high risk" patients, as well as patients who may benefit from coronary artery calcium scoring. The 2018 update provides a useful tool for clinicians in the assessment and treatment of patients with elevated blood cholesterol and additional diagnoses.

Anticoagulant Antidotes: Understanding the Current Implications of Andexanet Alfa for Pharmacists

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The Direct Oral Anticoagulants (DOACs), including factor Xa inhibitors and direct thrombin inhibitors (Table 1), have grown into widespread use for both the treatment of venous thromboembolism (VTE) as well as the prevention of VTE in atrial fibrillation since the release of dabigatran (Pradaxa) in October 2010. These agents have shown similar or superior efficacy and safety as compared to the standard of care warfarin (Coumadin) along with reduced drug/food interaction profiles and reduced need for additional monitoring, particularly with the factor Xa inhibitors. However, these agents are not entirely free of risk as serious bleeding events remain a possibility, particularly in the setting of improper prescribing or dose adjustments for age, weight, renal function, or interacting medications.[1-8]

Table 1:

Generic Name	Trade Name	Drug Class	Reversal Agent
Dabigatran	Pradaxa	Direct Thrombin Inhibitor	Idarucizumab (Praxbind)
Apixaban	Eliquis	Factor Xa Inhibitor	Andexanet alfa (Andexxa)
Rivaroxaban	Xarelto		
Edoxaban	Savaysa		None FDA approved
Betrixaban	Bevyxxa		

In October of 2015, idarucizumab (Praxbind) was approved by the FDA for the reversal of dabigatran. However, the factor Xa inhibitors have lacked a direct reversal agent until recently. In the setting of acute bleeding or other indication for acute reversal of anti-Xa activity, off-label products such as 3-factor (Profilnine, Bebulin) and 4-factor concentrate (KCentra, Breiplex, Octaplex) have been utilized, but definitive evidence of efficacy is lacking.[8-10]

In May 2018, andexanet alfa (Andexxa) was approved for the reversal of anticoagulation with apixaban (Eliquis) and rivaroxaban (Xarelto). Andexanet alfa is a decoy protein that mimics factor Xa and binds to factor Xa inhibitors to prevent their anticoagulant activity. Dosing strategy is based on timing and dose of the last receipt of a factor Xa inhibitor by the patient (Figure 1). Phase 2 studies demonstrated an anti-factor Xa activity reduction of 94% with apixaban and 92% with rivaroxaban within 5 minutes following an andexanet alfa bolus. These reductions were sustained throughout a two-hour infusion following the bolus dose.[8,11]

Figure 1:

Andexanet alfa (Andexxa) Dose Based on Apixaban or Rivaroxaban Dose				
FXa Inhibitor	**Trade Name**	**FXa Inhibitor Last Dose**	**Timing of FXa Inhibitor Last Dose Before Andexanet alfa Initiation**	
			<8 Hours or Unknown	**≥8 Hours**
Apixaban	**Eliquis**	≤5 mg	Low dose	Low dose
		>5 mg or unknown	High dose	
Rivaroxaban	**Xarelto**	≤10 mg	Low dose	
		>10 mg or unknown	High dose	

Adapted from: Andexanet alfa. In: Lexicomp. Wolters-Kluwer. Updated 2019 Apr 1. Accessed 2019 Apr 18. Available from: https://online.lexi.com/

In September 2016, the initial findings were released for the Phase 3 portion of the ANNEXA-4 study evaluating the use of andexanet alfa for reversal of anti-factor Xa activity in acute major bleed. These interim findings in the efficacy population (n = 47) demonstrated consistency with the Phase 2 study showing a reduction in anti-factor Xa activity immediately following initial bolus for apixaban (93%) and rivaroxaban (89%) with sustained effect throughout the 2-hour infusion. An update on the progress of the now Phase 4 ANNEXA-4 study was presented to the American College of Cardiology in March 2018. In the efficacy population (now n = 137), the reduction in anti-Xa activity following initial bolus remains consistent at 91% reduction in the apixaban group and 88% reduction in the rivaroxaban group from baseline. These reductions are also consistent following the 2-hour infusion at 91% and 87% with anti-Xa activity 4 hours after infusion showing a rebound to a 36% and 42% reduction from pre-bolus baseline for apixaban and rivaroxaban, respectively. For the 132 patients able to be evaluated for hemostatic efficacy, 83% were found to have excellent or good hemostasis 12 hours after andexanet alfa infusion.[11-13]

A small sample of patients who were reversed with andexanet alfa following enoxaparin therapy were also evaluated showing a 75% reduction in anti-Xa activity from baseline following initial bolus that was sustained to 73% at the end of the 2-hour infusion. A similar 4-hour post-infusion increase in anti-Xa activity to 44% below pre-bolus baseline was noted as with the factor Xa inhibitor patients. Of the 10 patients evaluated for hemostatic efficacy, 8 were found to have excellent or good hemostatic efficacy at 12 hours after the infusion.[13]

Although andexanet alfa has been shown to be efficacious in rapidly inducing large reductions in anti-Xa activity, the direct correlation of these reductions to clinical efficacy cannot be definitively extrapolated due to the single-cohort design of the study and lack of a comparator arm. As it stands, no comparison of hemostatic efficacy can be made to patients not receiving the study treatment or any specific comparator. A post-marketing study evaluating andexanet alfa versus standard of care is expected to begin sometime in 2019 with estimated completion in 2022.[14-15]

Pharmacists should be mindful of the patient population evaluated in the ANNEXA-4 study. The study included patients having received a factor Xa inhibitor or enoxaparin within 18 hours who have an acute major bleed constituting hemodynamic compromise, acute anemia (decreased Hgb/Hct), and/or bleed in a critical area or organ such as retroperitoneal or intracranial hemorrhage. The study excluded the most critical patients including those with an expected survival <1 month as well as those having an intracranial hemorrhage and Glasgow coma score (GCS) <7 or hematoma volume >60 cc. The study also excluded those expected to undergo surgery other than minimally invasive procedures or those expected to receive blood products within 12 hours which ruled out many of those expected to undergo certain acute interventions. Other excluded patient populations were those with sepsis/septic shock, pregnant patients, and patients who recently received blood products or non-study anticoagulants. Finally, the study targeted patients who received the factor Xa inhibitor edoxaban as well as the low molecular weight heparin enoxaparin, but the currently low or no inclusion of patients with these therapies may be insufficient to fully represent the expectations of use. These key excluded populations will need to be the focus of future evaluations in order to determine the applicability of current knowledge to the use of andexanet alfa in these settings.[12-13]

Another area of emphasis lies within the current safety findings of andexanet alfa and the rate of thromboembolism following treatment. The phase 2 ANNEXA-A and ANNEXA-R studies found that endogenous thrombin generation increased above the lower limit of normal within 2-10 minutes following initial bolus in 100% and 96% of patients receiving andexanet alfa following apixaban and rivaroxaban, respectively. This is beneficial for targeting clot formation and hemostatic efficacy, but introduces added concern for negative thromboembolic events.[11]

In the updated phase 4 findings for ANNEXA-4, 24 patients (11%) in the safety population (n = 227) were noted as having a thromboembolic event within 30 days, with six patients (2.6%) having an event within 3 days after treatment. This rate of thromboembolic events is somewhat lower than the 18% first reported in the 2016 phase 3 findings. Twenty-seven deaths (12%) occurred within 30 days with eleven due to cardiovascular causes in the phase 4 update; only slightly lower than the 15% mortality rate in the phase 3 findings. These findings are paired with anticoagulation being resumed in 18 patients (27%) within 30 days in the phase 3 findings which has increased to 129 patients (57%) in the phase 4 update. Only nine patients with a thromboembolic event had resumed anticoagulant therapy.[12-13]

The decrease in thromboembolic events paired with increased rates of resuming anticoagulation highlights an important intervention for pharmacists providing care for andexanet alfa patients. To summarize key points for pharmacists:

- In the ANNEXA-4 study, investigators were encouraged to restart anticoagulation when clinically indicated, but no further guidance was provided.
- Additionally, ¼ of study patients experiencing a thromboembolic event experienced the event within 3 days of andexanet alfa treatment while the rest occurred after day 3 up to 30 days.
- Pharmacists should be mindful of the persistence or resolution of objective findings
    - Hgb/Hct, platelets, and other coagulation studies
    - Repeat imaging (ex. CT, MRI)
    - Removal of any instigating or contributing factors such as drug interactions.
- Note: Although the mechanism of action for andexanet alfa should be compatible pharmacologically with all factor Xa inhibitors, including edoxaban and betrixaban, its use with these other agents has not been studied and its efficacy and safety with these agents cannot be stated.

While the exact timing of anticoagulation resumption is not defined and left up to clinical judgement, it is important for pharmacists to maintain a dialogue with prescribers about addressing a patient's original anticoagulation indication prior to the need for reversal.[12-13]

Smoking Cessation

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Why smoking is an unhealthy habit:[9,12,13]

- Smoking contributes to almost 1 in 5 deaths with the top three causes being from smoking-related cardiovascular disease, lung cancer, and chronic obstructive pulmonary disease (COPD). Around 540,000 people die from smoking in the United States each year and it has been found to be the leading preventable cause of death in the United States.
- Smokers are 4 times more likely to develop coronary artery disease or have a stroke and 25 times more likely to develop lung cancer than non-smokers.
- Smoking damages blood vessels which can lead to increased blood pressure and risk of clots.
- Nicotine is addicting: smokers confuse the relief of withdrawal with the feeling of relaxation.

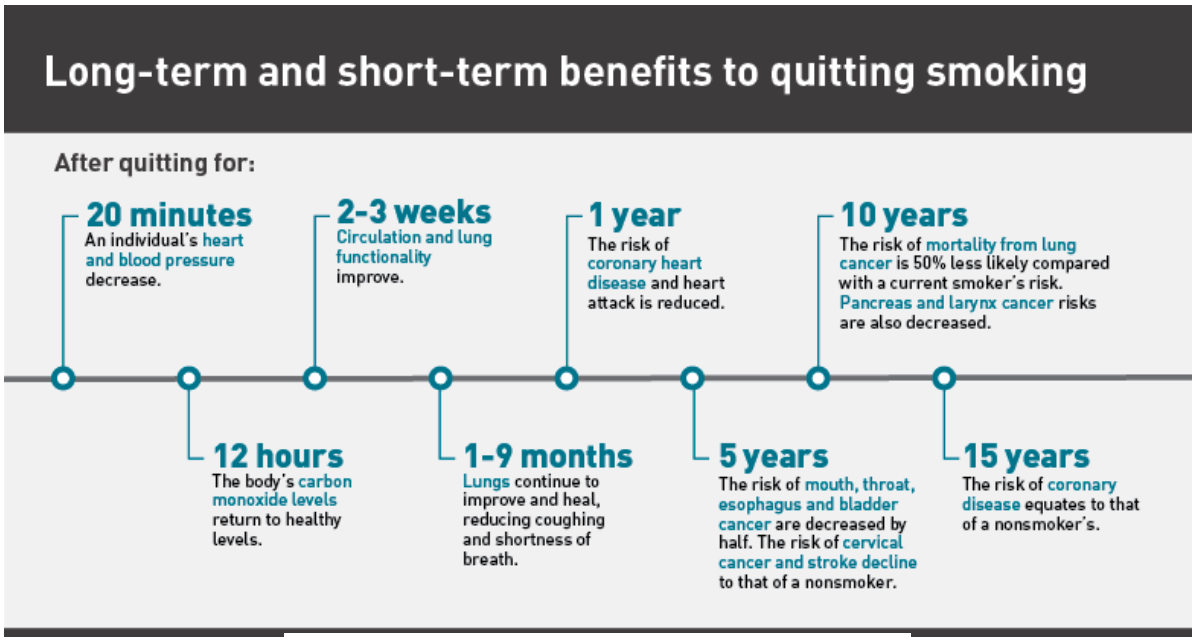

Image: https://www.cdc.gov/mmwr/volumes/67/wr/mm6745a5.htm

Secondhand smoke:[3]

- A mixture of exhaled smoke and smoke released from the burn of a cigarette/pipe/cigar that is involuntarily inhaled by nonsmokers or persons nearby.
- The surgeon general estimated that premature death occurred in about 41,000 adults and more than 400 infants each year.
- Classified as a group A carcinogen (known to cause cancer in humans and animals).
    - Secondhand smoke contains arsenic, lead, polonium-210, formaldehyde, benzene, and more, all of which are known carcinogens.

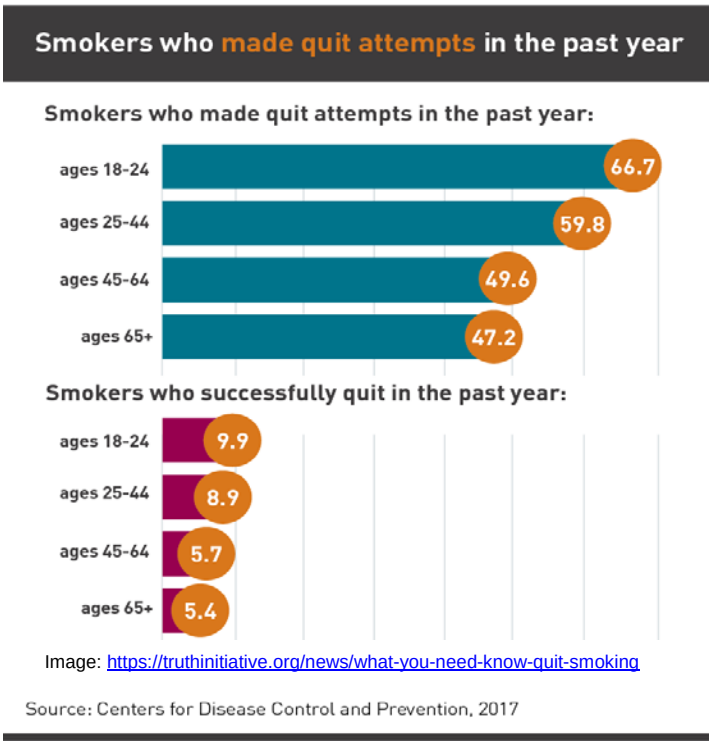

Image: https://truthinitiative.org/news/what-you-need-know-quit-smoking

How to approach patient counseling:[10]

1.Determine patient readiness to quit:
Ask: inquire about smoking habits to identify the patient's tobacco use
Advise: advise the patient to quit in a clear, strong, personalized manner
Assess: determine willingness to quit (see #3 – can also use a scale of 1-10)
Assist: help develop a personalized quit plan with a quit date and offer treatment options
Arrange: arrange follow-up with the patient within the first weeks of the quit date

2.If a patient is not ready to quit, review:
Relevance: help the patient identify why quitting tobacco is relevant to them
Risk: encourage the patient to verbalize potential consequences of tobacco use
Rewards: help identify potential benefits of quitting
Roadblocks: help identify potential obstacles to quitting
Repetition: review the 5 A's at every visit, one intervention may not be enough

3. **Remember the stages of change:**
    - **Precontemplation:** not planning on quitting within the next 6 months
    - **Contemplation:** considering quitting within the next 6 months without an attempt
    - **Preparation:** made quit attempts in the last year and are planning to quit within 30 days
    - **Action:** not currently smoking and stopped within the past 6 months
    - **Maintenance:** stopped spoking greater than 6 months but less than 5 years ago

Non-pharmacologic treatment options:

- Counseling (in-person, telephone, web-based), group programs, massage therapy, etc.

Pharmacologic treatment options:[11]

- **Nicotine Replacement Therapy**
    - **Patch**:
        - Long-acting, slow-onset = relatively constant relief from withdrawal over 24 hours
        - Dosing:
            - > 10 cigarettes/day and weight >45kg: 21 mg/day x6 weeks then 14 mg/day x2 weeks then 7 mg/day x2 weeks
            - ≤ 10 cigarettes/day or weight <45kg: 14 mg/day x6 weeks then 7 mg/day x2 weeks
        - Apply one patch each morning to any non-hairy skin site, rotate site daily
    - **Gum**:
        - Short-acting, nicotine absorbed through oral mucosa, peak in ~20 minutes
        - Dosing:
            - ≥ 25 cigarettes/day: 4 mg
            - < 25 cigarettes/day: 2 mg
        - Chew at least one piece of gum every two hours and whenever there is an urge to smoke
        - Use up to 24 pieces of gum per day for six weeks
        - Gradually reduce use over a second six weeks for a total duration of three months
        - Proper chewing: “chew and park” – chew the gum until the nicotine taste appears (peppery taste) then “park” the gum between the teeth and gum until the taste disappears, then chew a few more times until more nicotine is released and repeat for 30 minutes.
        - Acidic beverages such as coffee and soda will reduce the nicotine absorption
        - Avoid vigorous chewing
    - **Lozenge**:
        - Short-acting, similar to gum
        - Dosing:
            - Smoke within 30 minutes of awakening: 4 mg
            - Wait more than 30 minutes to smoke after awakening: 2 mg
        - Use one lozenge every one to two hours for six weeks
        - Maximum five lozenges every six hours or 20 per day
        - Place lozenge in mouth and allow it to dissolve for 30 minutes – do not chew
    - **Inhaler**:
        - Will help with physical and behavioral aspect of smoking (hand to mouth)
        - Dosing:
            - Use 6-16 cartridges per day for 6-12 weeks
            - Gradually reduce dose over next 6-12 weeks

- **Nasal spray**:
  - Fast-acting, nasal mucosa absorption, peak levels at 10 minutes
  - Dosing:
    - 1-2 sprays per hour
    - Use for three months
    - Max dose is 10 sprays per hour – do not exceed 80 sprays per day

- **Varenicline**
  - Reduces the symptoms of nicotine withdrawal by blocking nicotine from binding to receptors that lead to dependence – this reduces the rewarding aspects of smoking
  - Possible suicide or suicidal ideation has been observed with this product
  - 12-week course
  - Patients should quit smoking one week after starting varenicline and then titrate dose.
- **Bupropion**
  - Enhances central nervous system dopamine release
  - Contraindicated in patients with a seizure disorder
  - Patients should quit smoking one week after starting bupropion; continue for at least 12 weeks

E-cigarettes "vape pens" "e-cigs" "tank systems" "mods":

- Entry nicotine product that can lead to using traditional cigarettes and other nicotine products.
- Originally designed to help traditional cigarette users quit smoking
- **JUUL®**: A thin and sleek e-cigarette that claims to be "simple, clean, and satisfying". Originally created to help wean users off traditional cigarettes, this vaping device has gained popularity with teenagers due to its sleek design, USB charging capability, and variety of flavor pods.[4]
  - Contains more nicotine than any other e-cigarette with a nicotine strength of 5%, which equates to around 20 cigarettes worth of nicotine per pod.
  - The majority of JUUL users between 15 and 24 years of age are not aware of the nicotine content in JUUL pods – many users believe they are vaping flavor only.[5]

Risks

- The brain continues to develop until the age of 25. E-cigarette use in youth and young adults can increase the risk of long-term effects such as addiction, mood disorders, permanent lowering of impulse control, decreased attention control and ability to learn.[7]
- **Popcorn lung:**[14]
  - The chemical diacetyl is found in many flavoring agents.
  - Workers in a popcorn factory became ill by breathing in diacetyl from the production of the butter flavoring for popcorn. This caused many deaths and cases of "bronchiolitis obliterans" or "popcorn lung" which is an irreversible lung condition that scars the alveoli causing coughing, wheezing, and shortness of breath.
  - Diacetyl is found in many e-cigarette flavors, which means that many e-cigarette users are directly inhaling diacetyl.

Helpful resources: truthinitiative.org

- smokefree.gov
- Free text-message program:
  - Text "QUIT" to 202-804-9884
  - Anonymous, tailored by age group[6]
- Quit Now hotline: 1-800-784-8669

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2018 Guideline Update on the Management of Blood Cholesterol

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Anticoagulant Antidotes: Understanding the Current Implications of Andexanet Alfa for Pharmacists

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Smoking Cessation

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The last "dose" …

"A merry heart doeth good like a medicine."
--Proverbs 17:22

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