Tobacco Treatment Guideline Team

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Initial Release
September, 1998
Most Recent Major Update
March, 2012

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Tobacco Treatment

Patient population: Adult and adolescent tobacco users.

Objectives: Provide a framework for care providers to assist patients in quitting tobacco use:
1) Assess and document tobacco use status of every patient.
2) Provide quitting intervention to all tobacco users.
3) Treat behavioral/psychological aspects of cigarette addiction with advice and counseling.
4) Treat biologic aspects of cigarette addiction with pharmacological therapies.

Key Points

Tobacco use is a chronic disease that needs ongoing monitoring and treatment. Monitor and treat all forms of tobacco use (e.g., smoking, spit tobacco, hookah, electronic cigarettes).

ASK all patients about tobacco use and assess user's readiness to quit. Tobacco use status should be documented in the medical record *[I A*]*.

ADVISE all tobacco users to seriously consider making a quit attempt using a clear and personalized message. Advice as brief as 3 minutes is effective *[I A*]*.

ASSESS all tobacco users' willingness to make a quit attempt. If not yet ready to quit, offer motivational intervention using the 5 "R's" - relevance, risks, rewards, roadblocks, repetition *[I A*]*.

REFER patients interested in quitting within 30 days to a Tobacco Treatment Specialist or other appropriate tobacco treatment program *[I A*]*. Alternatively, health care providers can directly provide the following treatment.

Treatment options

- **ASSIST** those ready to make a quit attempt *[I A*]*:
  - Set a quit date. Quit date abstinence is a strong predictor of long term success.
  - Give advice on quitting and provide supplementary materials.
  - Prescribe pharmacologic therapy as appropriate. Nicotine replacement therapies, bupropion hydrochloride, and varenicline have been proven effective.
- **ARRANGE** follow-up either with phone call or office visit *[I A*]*.
  - Prevent relapse by congratulating successes and reinforcing reasons for quitting.
  - Assess any difficulties with pharmacologic therapy.

*** Strength of recommendation:**
I = generally should be performed; II = may be reasonable to perform; III = generally should not be performed.
Levels of evidence reflect the best available literature in support of an intervention or test:
A=randomized controlled trials; B=controlled trials, no randomization; C=observational trials; D=opinion of expert panel.

Clinical Background

Clinical Problem

Deaths related to tobacco use account for a fourth of all deaths in this country. Estimated annual cost of medical care related to tobacco use is $75 billion. Approximately 25% of American men and women continue to smoke. Of these, approximately 70% see a physician each year. A great majority of tobacco users report a desire to quit and cite physician advice as an important motivator for making a quit attempt *[C*]*.

While rates of tobacco use among students are at their lowest levels in the past decade, currently 5.2% of middle school students and 17.2% of high school students in the U.S. are cigarette smokers. For all forms of tobacco use, rates are 8.2% and 23.9% respectively. Among adults who have ever smoked daily, more than 80% first tried cigarette sand 53% smoked daily before age 18 years.

According to recent estimates, almost one half of current adolescent smokers who continue to smoke regularly will die from a smoking-related disease. Although cessation is less common among adolescents than adults, interest in quitting is strong: nearly three fourths of adolescent smokers have seriously thought about quitting, 64% report having made a quit attempt, and 40% of daily smokers report having tried to quit at least once and failed. On the other hand, evidence is limited regarding the efficacy of brief clinician interventions in treating tobacco use in adolescence. Expert opinion rather than empirical data is often used to guide clinical interventions for young tobacco users.

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Figure 1. Clinician's Actions to Help Patients Quit Tobacco Use

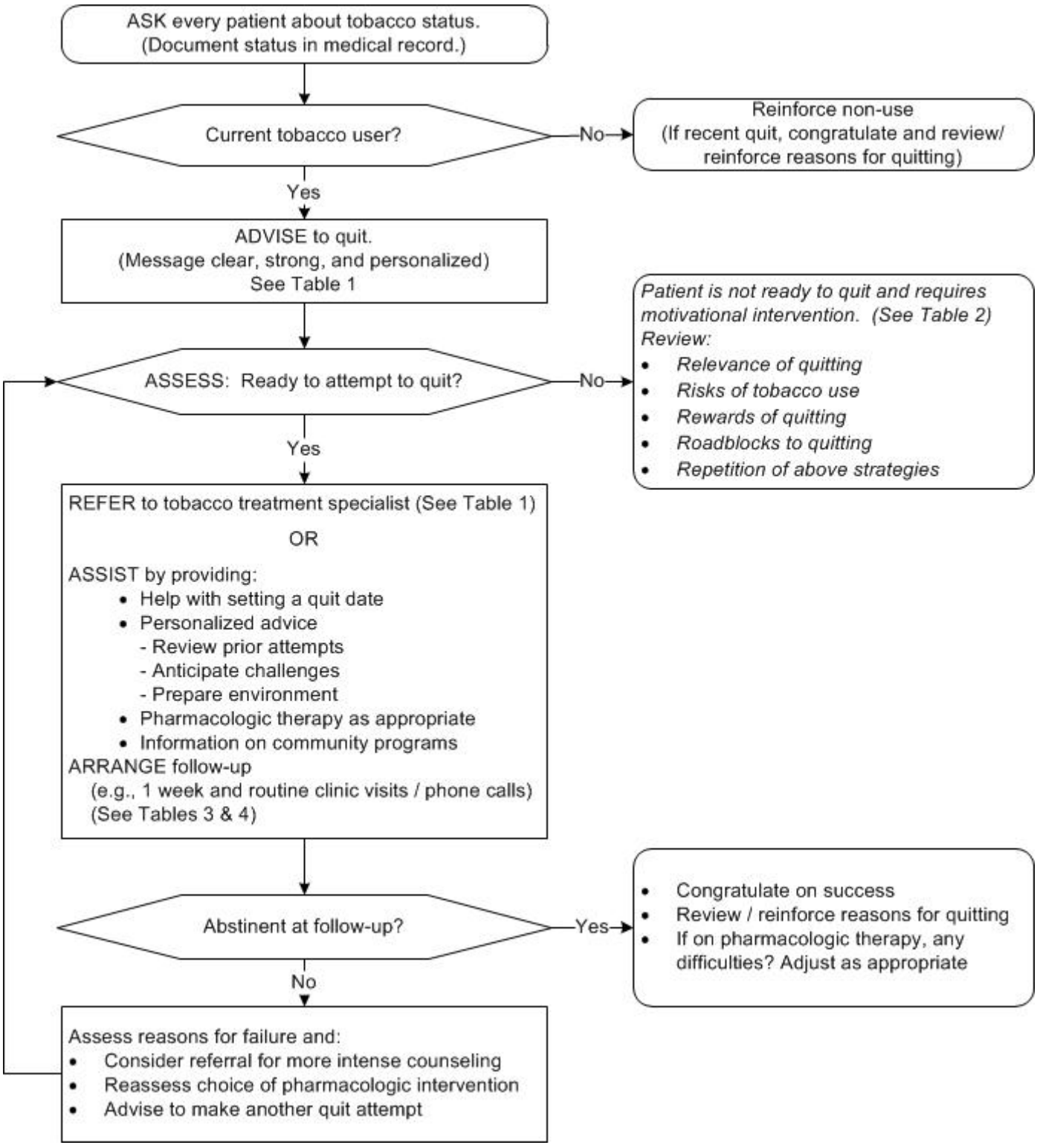

Table 1. Initial Interventions for Treating Tobacco Use

ADVISE Advise the patient.	ASSESS Determine the patient's willingness to make a quit attempt.	REFER Refer patients to tobacco treatment specialist.
Brief clinician intervention Advice should be: • **Clear -** "I think it is important for you to quit using tobacco now, and I will help you." • **Strong -** "As your clinician, I need you to know that quitting tobacco use is the most important thing you can do to protect your current and future health." • **Personalized -** Tie tobacco use to current health/illness, and/or social and economic costs of tobacco, and/or impact on children or others in household. "The frequency of your child's ear infections is certainly related to your tobacco use."	**Brief clinician intervention** "Are you ready to make a quit attempt within the next 30 days? • If the patient is willing: "Most patients who are thinking about quitting do much better if they talk with a tobacco treatment specialist. I would like to make that referral for you." • If the patient is unwilling to make a quit attempt: Provide a motivational intervention (5R's - Relevance, Risks, Rewards, Roadblocks, Repetition – see table 2). • If the patient is in a special population (e.g., pregnant or breastfeeding tobacco user), consider providing additional information.	**Referral** • Refer to tobacco treatment specialist affiliated with your practice or region. (For example, at UMHS, refer to the Tobacco Consultation Service: fax 734-998-2191 or online at http://www.hr.umich.edu/mhealthy/programs/tobacco/) • Refer to tobacco quit program in your area (e.g., American Cancer Society or American Lung Association). Listings of programs are often available from state or local public health departments. • Refer to a quit line (e.g., in the State of Michigan, Michigan Quitline: 800-480-7848) • Internet-based counseling web-sites.

Table 2. "5 R's" of Motivational Intervention
For Patients Not Yet Ready to Make a Quit Attempt

Relevance

Tie tobacco use to any or all of the following:

- Current health/illness
- Social and economic costs
- Motivation level/readiness to quit
- Impact of tobacco use on children and others in the household.

For example, "Smoking is making your upper respiratory infections worse. It would be in your child's best interest for you to set a quit date in the near future."

Risks

Ask patient to identify potential negative consequences of tobacco use:

- Acute risks - shortness of breath, exacerbation of asthma, impotence, infertility
- Long term risks - heart attacks, strokes, lung and other cancers, COPD
- Environmental risks - increased risk of lung cancer in spouse and children; higher rates of tobacco use by children; increased risk for SIDS, asthma, middle ear disease and respiratory infection in children

Rewards

Ask patient to identify

- any positive benefits they currently derive from tobacco use. Discuss alternative methods for filling the potential void after cessation.
- the potential rewards of quitting tobacco use including improved health, improved taste, money saved, healthier children, freedom from addiction, and satisfaction with accomplishing a difficult personal goal.

Roadblocks

Ask patient to identify barriers to quitting tobacco use (e.g., partner or co-worker who uses tobacco, fears about quitting tobacco use, weight gain, etc.).

Repetition

Repeat above strategies every time an unmotivated patient has a visit.

Table 3. Treatment Interventions for Tobacco Use

ASSIST Aid the patient in quitting.	**ARRANGE** Arrange follow-up at the same visit patient sets quit date.
1. Help the patient with a quit plan. • Set a quit date and record this on patient's chart. Ask the patient to mark this on his/her calendar. Abstinence on quit date is a strong predictor of long-term success *[C*]*. • Patient should inform family, friends, co-workers of quit plan and request support. • Have patient remove cigarettes from home, car and workplace environments. • Review previous quit attempts. • Anticipate challenges, particularly during the first critical few weeks, i.e., nicotine withdrawal symptoms. **2. Consider referral to intensive counseling (multi-session, group or individual).** Referral considerations include: • Multiple, unsuccessful quit attempts initiated by brief intervention. • Increased need for skill building (coping strategies/problem solving), social support and relapse prevention. • Psychiatric co-factor, such as depression, eating disorder, anxiety disorder, attention deficit disorder, or alcohol abuse. **3. Encourage pharmacologic therapies as appropriate. See Pharmacologic Therapies section and Table 4.** **4. Give key advice on successful quitting.** • **Abstinence.** Total abstinence is essential *[D*]*, not even a single puff after quit date. • **Alcohol.** Drinking alcohol is strongly associated with relapse*[C*]*. • **Other tobacco users in the household.** The presence of other tobacco users in the household, particularly a spouse, is associated with lower success rates *[C*]*. Patient should consider quitting with significant other, or develop specific plan to stay quit in a household where others still use tobacco. **5. Provide supplementary educational materials** • UMHS Patient Education materials: - "How to use your nicotine product" - "Tips for quitting tobacco use" - Tobacco Consultation Service booklet – "Living Free from Tobacco: It's your choice" • National Cancer Institute pamphlet - "Clearing the Air"	**1. Schedule follow-up.** Contact either in person or by telephone. If the patient is scheduled to return for a clinic appointment, follow-up cessation counseling should be done at that time. Other follow-up may be done over the telephone. (See in the text: "Organizing a Healthcare Site to Support Quitting Tobacco Use.") **2. Timing.** Follow-up contact should occur soon after the quit date, preferably during the first week *[C*]*. Extending treatment contacts over a number of weeks appears to increase cessation rates *[D*]*. **3. Actions during follow-up:** • **If abstinent:** – Congratulate success and stress importance of remaining abstinent. – Review benefits to be derived from quitting. – Inquire regarding problems encountered and offer possible solutions to maintaining abstinence. • **If using tobacco:** – Review circumstances and elicit re-commitment to total abstinence. – Remind patients that a lapse can be used as a learning experience. – Identify problems, suggest alternative behaviors and anticipate challenges in the immediate future. – Re-assess choice of pharmacologic intervention as needed. – Consider referral to a more intense or specialized program.

Table 4. Dosing and Administration of Medications for Tobacco Cessation

Agent	Available Dosages/Cost	Dosing	Duration	Instructions	Side Effects
Transdermal nicotine patch Continuous delivery of nicotine provides constant blood levels. Requires 2-3 days to achieve maximal serum levels.	**Over-the-Counter** Nicoderm CQ 21, 14, 7 mg/ 24 hr All: $80 / 28 patches Other Generic Nicotine Transdermal Patches 21, 14, 7 mg - $54 / 28 patches	>10 cigs per day, start with highest dose of given brand. 5 - 10 cigs per day, use mid-range dose *[D*]*.	8 weeks. No increase in long-term (52 weeks) cessation with longer duration. Suggest: • Weeks 1-4: highest dose of given brand • Weeks 4-6: next lowest dose of brand • Weeks 6-8: lowest dose Taper recommended for psychological reasons, but does not increase efficacy.	No tobacco use while on patch, rotate to new hairless skin site each day, remove before bed if insomnia. May consider supplement with 2 mg gum in first 48 hours while plasma levels building. May continue supplementation for 8 weeks or longer if effective	Skin reactions including pruritus, edema, rash; sleep disturbance.
Nicotine Lozenge Maximum nicotine levels achieved within 20-30 minutes of use.	**Over-the-Counter** Commit Lozenge 2, 4 mg $40 / 72-count packs	9 lozenges/daily during initial 6 weeks of therapy. 4 mg if first cigarette within 30 min of awakening; 2 mg if more than 30 min after awakening. 1 lozenge q 1-2 hrs for 6 wks, then q 4-8 hrs for last 3 wks. Maximum - 20/day	12 weeks	Place the lozenge in mouth between cheek and gum and allow to dissolve slowly over 20-30 mins. Do not chew, bite, or swallow lozenge. Avoid eating or drinking acidic beverages (i.e., orange juice, coffee) 15 min prior to, during, or after using a lozenge.	Headache, diarrhea, flatulence, heartburn, hiccups, nausea, coughing, sore throat, and upper respiratory infection (occurring in > 5% of patients).
Nicotine Gum (polacrilex): Maximum nicotine levels achieved within 20-30 minutes of use.	**Over-the-Counter** Nicorette - 2 and 4 mg sticks 2 mg - $40 / 100 sticks 4 mg - $40 / 100 sticks Generic nicotine polacrilex (various) 2 mg - $26 / 110 sticks 4 mg - $26 / 110 sticks	≥ 20 cigs per day, use 4 mg stick q one hour *[A*]*. < 20 cigs per day, use 2 mg stick q one hour. Maximum - 24/day	2-3 months	Chew until spicy flavor begins, then "park" between cheek and gum for absorption. Remove after 1/2 hour. Acidic beverages decrease absorption.	Jaw fatigue, hiccups, belching, nausea.

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Table 4. Dosing and Administration of Medications for Tobacco Cessation, continued

Agent	Available Dosages/Cost	Dosing	Duration	Instructions	Side Effects
Nicotine Nasal Spray Maximum levels of nicotine reached within 5 -10 minutes. Levels begin to fall within 30 minutes of dose. Most closely mimics nicotine delivery pattern of cigarette.	**Prescription** Nicotrol NS 1 mg = 1 spray each nostril = 1 dose 1-10 ml spray - $193 (no generic)	Spray q 30-60 minutes prn craving. Maximum 40 doses/day.	2-3 months	Careful instruction on spray technique (see patient education handout).	Nasal irritation / rhinorrhea (98% of pts), sneeze, cough. Decreased severity of effects after first week.
Nicotine Inhaler Nicotine absorbed through mouth and throat (not lungs) when smoker "puffs" on cylinder delivering nicotine and menthol. Peak nicotine levels in 20 minutes.	**Prescription** Each inhaler cartridge with 10 mg nicotine Nicotrol inhaler: 42 cartridge / 1 mouthpiece - $194 / 168 spray cartridge (no generic)	80 puffs =1mg Requires 3-4 puffs /minute for 20-30 minutes. Use prn or q 1 hour. Each cartridge good for approx. 20 minutes of continuous puffing.	2-3 months	Must puff more frequently than cigarettes. Careful instruction on spray technique is essential in patients with reactive airway disease to avoid inducing bronchospasm. Air temperature must be > 40º F.	Cough, mouth and throat irritation. Use with caution in patients with reactive airway disease
Bupropion hydrochloride SR (Zyban®)	**Prescription** 150 mg SR $202 / full 7-week course (brand) $ 32 / full 7-week course (generic)	150 mg/day for 3 days, then 150 mg daily or BID	7-12 weeks	Start 1 week before quit date Staff should monitor for mood changes including suicidality	Insomnia, dry mouth, nausea, and seizures (1 in 1000). **Contraindications:** Seizure disorder, major head trauma, eating disorder, or on Wellbutrin® or MAO inhibitors.
Varenicline ** (Chantix®)	**Prescription** 0.5, 1 mg $450 12-week course	Start with 0.5 mg daily for three days, then 0.5 mg BID for four days, then 1 mg BID	12 weeks, with option to continue for another 12 weeks	Start one week before quit date. Take after eating, with a full glass of water	Caution with poor renal function. Adjust dose with CrCl < 30. Nausea, insomnia, and unusual dreams. Neuropsychiatric symptoms: behavior changes, agitation, depressed mood, suicidal ideation, and attempted and completed suicide.

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Table 4. Dosing and Administration of Medications for Tobacco Cessation, continued

Agent	Available Dosages/Cost	Dosing	Duration	Instructions	Side Effects
Nortriptyline* (Pamelor®) ***[Second line]***	**Prescription** 10, 25, 50 mg $100 12-week course $22 12-week course (generic)	Titrate from 25 mg QHS slowly to 75-100 mg daily	12 weeks		Dry mouth, sedation, shaky hands constipation, urinary retention. Use with caution in patients over 65. **Contraindications:** Do not use in conjunction with MAOI and during recovery from Acute MI
Clonidine* ***[Second line]***	**Prescription** Oral: 0.1 mg $14 for 4 week course Transdermal: 0.1, 0.2 mg/day (7-day patch) $146 for 4 week course (box of 4)	Initial dosing: 0.1 mg po bid 0.1 transdermal Can be titrated up to: 0.2 mg po bid 0.2 mg transdermal	3–10 weeks	Start on or up to 3 days before quit date Place transdermal patch on hairless location between neck and waist. Change weekly. Discontinue use gradually over 2–4 days.	Dry mouth, sedation, dizziness, constipation **Contraindications:** Avoid transdermal if on anti-coagulation therapy, severe cardiovascular disease, or hemodynamically unstable

* Not FDA-approved for this use.

** The FDA issued alerts regarding serious neuropsychiatric symptoms occurring in patients taking varenicline, lower seizure threshold in patients with history of seizures, and increased intoxicating effects of alcohol.

AWP = Average Wholesale Price. For brand drugs, Average Wholesale Price minus 10%. AWP from Amerisource Bergen Wholesale Catalog, 8/16/2011. For generic drugs, Maximum Allowable Cost plus $3 from BCBS of Michigan MAC List, 8/16/2011.

Exposure of nonsmokers to environmental tobacco smoke (ETS) is another preventable cause of morbidity and mortality associated with tobacco use. Exposure to ETS is recognized as a cause of heart disease, and accounts for around 3000 lung cancer deaths per year in adults.

In infants and children, exposure to ETS causes middle ear infections and effusions, exacerbates 400,000 to 1 million cases of asthma annually, and causes 150,000 to 300,000 cases of lower respiratory tract infections each year.

Lack of time, lack of knowledge about counseling, and lack of familiarity with current pharmacologic therapies may all contribute to inadequate intervention being done by clinicians. Clinicians with access to tobacco treatment training are more likely to provide more frequent and effective interventions with their patients. Therefore, every clinician should become comfortable and knowledgeable with an approach to assist patients with quitting tobacco use.

Rationale for Recommendations

An updated brief clinic intervention is known as the "3-A's and Refer" model: **A**sk, **A**dvise, **A**ssess and **R**efer. The key component of the initial assessment is to consistently and accurately identify all tobacco users. Once it is established that a patient uses tobacco, clinician advice as brief as 3 minutes can be effective in quitting tobacco use *[A*]*. The clinician then assesses patient readiness to quit. If the patient is willing to make a quit attempt, it is recommended that he or she be referred to a Tobacco Treatment Specialist.

Prevention of Tobacco Use

Physician recommendation is one of the most powerful tools to prevent initiation of tobacco use. Patients should be asked at each visit about tobacco use status. Recommendation to encourage patients to designate a tobacco free home can reduce initiation of tobacco use and delay onset of tobacco use in adolescents.

Ask/Advise/Assess

All patients should be asked about their tobacco use and assessed for their willingness to quit (Table 1).

If a "never" tobacco user, reinforce avoidance of initiation of tobacco use, and encourage patients to designate a tobacco free home which leads to decreased initiation of tobacco use and delayed onset in adolescents *[B*]*.

If a former tobacco user, acknowledge and reinforce continued abstinence and offer support to do so.

If a patient uses tobacco, this should be documented in the medical record so that intervention can be offered. Techniques to remind physician of a patient's tobacco use status include tobacco status stickers, listing tobacco use on active problem list, or including tobacco status as part of the vital signs. Brief clinician advice should be offered to the patient, including a personalized message as to why it is important to quit using tobacco now. Patients should then be asked about their willingness to quit tobacco use in the next month.

Refer

If patients are willing to make a quit attempt, the clinician has two options. The first option is to refer the patient to a Tobacco Treatment Specialist (TTS) or other appropriate tobacco cessation program. A TTS is a trained health professional who specializes in the treatment of tobacco dependence as part of his or her professional role. Referral to a TTS has been shown to increase quit rates *[A*]*. The TTS demonstrates the knowledge and skills to provide effective and evidence-based treatment for tobacco dependence. The TTS also serves as a resource and consultant to other healthcare professionals. The TTS can also provide the most effective and appropriate treatment to special populations (e.g. patients with a variety of co-morbidities, chemical dependency, or pregnancy). Many health care organizations have a TTS on staff. Local tobacco treatment specialists can be identified by state tobacco control agencies or through the Association for Treatment of Tobacco Use and Dependence (www.attud.org). Many national organizations such as the American Cancer Society and American Lung Association offer tobacco cessation programs. Listings of local programs can often be obtained through state and local health departments.

The second option is to treat the patient (see Treatment, below) *[A*]*. Several factors make health care settings ideal for delivery of interventions to quit tobacco use. As stated above, at least 70% of tobacco users see a physician each year. As many as 70% of these users report a desire to quit and have made at least one serious quit attempt. Tobacco users also report that advice from a clinician is an important motivator to quit.

Treatment - Counseling

Results of the Public Health Service guideline panel meta-analysis showed that brief intervention increases long-term quit rates. In addition, a strong dose response relationship exists between the intensity of person-to-person contact and successful outcomes *[A*]*.

When providing counseling, health care providers should be aware that barriers to quitting tobacco use include, but are not limited to:

- Severe withdrawal during previous quit attempts
- Presence of other tobacco users in home or workplace
- Heavier tobacco use
- Low socioeconomic status
- Menthol cigarette
- Stressful life circumstances

- Psychiatric co- morbidities (i.e. depression, alcoholism)
- Multiple quit attempts
- Low motivation

Identifying these barriers during initial assessment will help to provide a tailored approach during counseling. In addition to clinician counseling in the office, intensive counseling (frequently defined as a minimum of weekly meetings for the first 4 - 7 weeks of cessation) significantly enhances quit rates. However, participation in intensive counseling is based largely on patients' motivation to quit *[C*]*. In some locations, if physicians formally refer patients to a tobacco cessation program, a third party may cover the fee with patients paying a reduced or no fee.

Evidence is mixed regarding the effectiveness of telephone counseling. However for a motivated patient without access to group or individual counseling programs, a telephone counseling program may provide enough structure and support for a successful quit attempt.

Typically, only a minority of tobacco users are willing to quit at any point in time, and many clinicians will spend more time promoting the motivation to quit than assisting in quit attempts. See Table 2 for the 5 R's of Motivational Intervention.

There is mixed evidence to support counseling to reduce environmental tobacco smoke (ETS) exposure in the home. In a systematic review of 18 studies, 12 of the 18 studies documented reduction of ETS exposure for children in both intervention and comparison groups. However, in only four of the 18 studies was there a statistically significant intervention effect. Three of these successful studies utilized intensive counseling interventions targeted to smoking parents. There is little difference between the well infant, child respiratory illness, and other child illness settings as contexts for parental smoking cessation interventions *[B*]*.

Treatment - Pharmacologic Therapies

Nicotine replacement therapy (NRT), bupropion hydrochloride SR (Zyban®), varenicline (Chantix®), nortriptyline, and clonidine have been shown to significantly improve cessation rates *[A*]*. Therefore, pharmacologic therapy should be recommended to all patients except in the presence of specific contraindications. Bupropion SR and varenicline are the two non-nicotine products with FDA approval for quitting tobacco use. Non-FDA approved agents with potential benefit in quitting tobacco use include nortriptyline and clonidine.

The following sections discuss choosing among the various forms of NRT, bupropion, varenicline, and other agents. A comparison of abstinence rates for various medications and combinations of medications is presented in the Appendix.

Nicotine replacement therapies (NRT). NRT has been used for many years, but alternative methods of delivery continue to be developed and new combinations are being tried.

Pharmacologic properties of nicotine. A smoker absorbs 1-3 mg of nicotine per cigarette regardless of nicotine-yield ratings on the box. Nicotine results in increased release of catecholamines, vasopressin, endorphins, cortisol, and ACTH. These biochemical changes lead to addiction as tobacco users experience pleasure, increased arousal, decreased anxiety, and decreased hunger with increased metabolic rate. Within hours of cessation of tobacco use, individuals begin to experience the nicotine withdrawal syndrome that peaks at 48 hours. Symptoms of nicotine withdrawal include: craving, anxiety, restlessness, irritability, depressed mood, increased appetite, and difficulty concentrating.

Demonstration of efficacy. The various nicotine replacement therapies (NRT) significantly decrease symptoms of the withdrawal syndrome as tobacco use abruptly stops *[A*]*. The different formulations of NRT provide alternate methods for delivery and have slightly different onset of action and duration. In meta-analyses, cessation rates with transdermal nicotine range from 15-31 per hundred with a trend toward decreased efficacy in the most highly dependent tobacco users (≥ 32 cigarettes / day or Fagerstrom nicotine dependence score > 6) *[A*]*. Nicotine gum studies demonstrate a similar range of cessation rates with greatest efficacy seen with the 4mg gum in highly dependent tobacco users *[A*]*. Nasal spray cessation rates range from 26-28 per hundred, also with greatest efficacy in the most dependent users *[A*]*. Inhaler studies report cessation rates similar to that of the nasal spray *[A*]*.

The efficacy of all forms of NRT is improved with concomitant counseling, but there is evidence for the effectiveness of NRT, even in the absence of counseling.

Level of dependence and dosing. In very highly dependent tobacco users, 4 mg gum is superior to 2 mg and most effective with counseling *[A*]*. High dose patch therapy (i.e., > 25mg/24 hours) is safe and decreases withdrawal symptoms in highly dependent tobacco users, and may increase long term cessation rates *[A*]*. Those smoking 5 or fewer cigarettes per day have been shown to have few symptoms of nicotine withdrawal when they quit *[C*]* and may not require nicotine replacement therapy *[D*]*.

For those using nicotine gum, lozenge, spray or inhaler, it is important that they are instructed in technique and dosing frequency so that under-dosing or over-dosing does not occur. See Table 4 for dosing and administration recommendations. The patient should also be provided with the educational handout, "How to Use Your Nicotine Product."

Choosing among various nicotine replacement therapies**.** A single randomized study comparing the 4 nicotine replacement therapies showed similar abstinence rates at 12

weeks, despite the fact that the nasal spray and inhaler groups had lower compliance with prescribed methods of use. Therefore, choice of NRT may be tailored to patients' preferences, side effects, and previous attempts. The transdermal patch offers convenience, minimal instruction, and minimal side effects. The continuous transdermal release of nicotine from the patch does not produce the peaks and troughs that are similar to cigarette smoking. Alternatively, gum, spray, lozenge or inhaler therapy may allow for a "quick fix" when cravings occur; this more closely simulates the nicotine peaks of actual cigarette smoking. The reinforcing effects of a bolus of nicotine may contribute to the habitual use of nicotine. Eight to 25% of gum users, 10-43% of spray users, and 16% of inhaler users who quit smoking were still using the nicotine replacement therapy beyond 6 months *[A*]*.

Combining nicotine replacement therapies. At least 3 randomized, controlled trials have examined the efficacy of combining either patch plus gum, patch plus inhaler, patch plus lozenge or patch plus nasal spray. While all show significantly improved early (6 week) abstinence rates, in one study the patch plus spray showed improved effectiveness over the patch alone at one year (27 per 100 versus 11 per 100.) One-third of those abstainers at one year were still using the nasal spray *[A*]*. In another study, the patch plus lozenge had higher quit rates at 6 months compared to patch alone (40% v 34%) *[A*]*. Given the additional cost of dual therapies and limited benefit, this approach is best reserved for highly addicted tobacco users with several previous failed quit attempts *[D*]*.

Combining bupropion with patch and inhaler. In one study, treatment with nicotine patch and inhaler with bupropion for up to 6 months with symptom based medication dosing was more effective than nicotine patch monotherapy, standard 10-week tapering course. At 26 weeks, the quit rate was 35% in the combined group compared to 19% in the patch group. However, significantly more side effects occurred in the combination group, with approximately 25% of patients reporting fatigue, insomnia or anxiety *[A*]*.

Gradual cessation vs abrupt cessation. In multiple studies, gradual cessation of tobacco prior to the quit date has no proven benefit compared to abrupt cessation at the time of the quit date. In one study, those with the gradual quit strategy were more likely to delay their quit date.

Patients with cardiovascular disease. The patch and nasal spray have demonstrated safety in patients with stable coronary artery disease *[A]*. These agents have not been evaluated in patients with unstable angina, recent myocardial infarction, uncontrolled congestive heart failure, or unstable arrhythmia. While patients should be reminded not to use tobacco while using these products, studies have shown no increase in cardiac event rates when patients use tobacco while wearing the patch *[C*]*. Nicotine gum and inhaler have not been specifically studied in this population.

Bupropion hydrochloride (Zyban®, Wellbutrin®). Bupropion was initially developed and marketed as an anti-depressant medication (Wellbutrin®). It has both dopaminergic and adrenergic actions, and also appears to be an antagonist at the nicotinic acetylcholinergic receptor. Bupropion appears to aid quitting tobacco use by blocking nicotine effects and relieving withdrawal. In a meta-analysis of 24 controlled trials, bupropion doubled smoking quit rates compared to placebo (OR=2.06, 95% CI 1.70-4.09) *[A*]*. Generic bupropion (SR or regular) is a substantial cost savings over brand. Generic bupropion SR now costs the same as bupropion, with bupropion SR preferred because it is FDA approved for tobacco treatment.

Dosing and administration. The manufacturer recommends initiation of drug therapy 1 week prior to the quit date. The recommended dosage schedule includes a starting dose of 150 mg per day for three days, then increasing to twice per day. While there was less weight gain with this dose of bupropion, there were no significant differences in smoking cessation rates among patients receiving total daily doses of 150 or 300 mg at 6 or 12 months *[A*]*. Therefore, patients who cannot afford or tolerate 300 mg/day may achieve successful results on 150 mg/day. The appropriate total duration of bupropion has not been studied.

Contraindications. Bupropion hydrochloride (Zyban®) is contraindicated in patients with seizure disorder, past or present eating disorder, and in patients being treated with Wellbutrin® or MAO inhibitors. To reduce seizure risk, the manufacturer recommends not exceeding maximum daily dose of 300 mg or single dose of 150 mg. Doses should be taken at least 8 hours apart. It should be used with caution in patients with predisposition to seizure (i.e., head trauma, alcohol withdrawal, concomitant use with other medications that lower seizure threshold: antipsychotics, antidepressants, theophylline.)

In 2008, the FDA reviewed post-marketing data and concluded that an association may exist between suicidal events and bupropion.

Choosing between bupropion hydrochloride or nicotine replacement. A single trial sponsored by the manufacturer of Zyban, compared bupropion, bupropion/nicotine patch combination, nicotine patch and placebo *[A*]*. At 1 year, bupropion and combination therapy had higher rates of smoking cessation than either the patch alone or placebo. (30 per hundred smokers with bupropion; 16 per hundred smokers with the nicotine patch.) There was no significant benefit of combination therapy over bupropion alone. The study suffered from an intervention discontinuation rate of 35%.

A more recent study compared nicotine lozenge, nicotine patch, bupropion, bupropion plus lozenge and patch plus lozenge. Bupropion plus lozenge was no more effective than nicotine replacement monotherapy or bupropion monotherapy.

A recent Cochrane Review concluded that bupropion added to nicotine replacement therapy was no more effective than nicotine replacement alone. Given the data, it remains reasonable to consider patient preferences, previous quit attempt experiences and cost when choosing among pharmacologic therapies *[D*]*.

For tobacco users who have previously been unsuccessful, one randomized study showed higher smoking quit rates for both bupropion alone or in combination with the nicotine patch, compared to nicotine patch alone *[A*]*.

Varenicline (Chantix®). Varenicline is a partial agonist for $\alpha_4\beta_2$ nicotinic acetylcholine receptor subtypes. As such, it provides a low-to-moderate level of dopamine stimulation to reduce nicotine craving and withdrawal symptoms. In two short term studies, varenicline resulted in substantially higher quit rates compared to placebo at 12 weeks (OR=3.85, 95% CI 2.70-5.50, number needed to treat=4) *[A*]*. Differences in abstinence remained significant even at 1 year. In both studies, varenicline was also superior to bupropion (OR=1.93, 95% CI, 1.40-2.68, number needed to treat=6) *[A*]*.

Dosing and administration. The manufacturer recommends initiation of drug therapy 1 week prior to the quit date. The recommended dosage schedule includes a starting dose of 0.5 mg per day for three days, then increasing to twice per day for the next four days, followed by 1 mg twice a day, beginning on the quit date. The appropriate total duration of varenicline has not been studied, but ranged from 12-24 weeks in published studies. In addition, since varenicline is a nicotine agonist, it should NOT be used in conjunction with NRT products. For patients with poor renal function, creatinine clearance <30 ml/min requires decreased dosing.

The FDA has issued alerts about varenicline causing neuropsychiatric symptoms:

- Changes in behavior, agitation, depressed mood, suicidal ideation, and attempted and completed suicide
- Lower seizure threshold in patients with history of seizures,
- Increased intoxicating effects of alcohol.

Use of varenicline may increase the risks of cardiovascular events. A recent meta-analysis of 14 double-blind randomized controlled trials involving over 8000 patients showed that varenicline was associated with a significantly increased risk of serious adverse cardiovascular events compared with placebo, with an OR of 1.72 [1.09 - 2.71].

Varenicline 0.5mg bid has been shown to be effective in smoking cessation as well. If patients are experiencing mild side effects such as nausea or insomnia, reducing the dose to 0.5mg bid may decrease side effects and still be effective.

Other pharmacologic therapies. A meta-analysis of 6 placebo-controlled trials of clonidine revealed a pooled odds ratio for benefit over placebo of 1.89 (CI 1.30-2.74). In only one of the 6 trials did clonidine show a statistically significant effect. Dry mouth and sedation were common side effects. Placebo-controlled studies of nortriptyline have documented a pooled odds ratio for benefit over placebo of 2.79 (CI 1.70-4.59). Dry mouth was also a common side effect of nortriptyline. Based on 3 studies no evidence supports nortriptyline as an addition to nicotine replacement therapy. Selective serotonin reuptake inhibitors do not increase quit rates.

To date, neither nortriptyline nor clonidine has FDA approval as an aid in smoking cessation. These drugs may best be used as second-line agents when patients cannot take or do not wish to take either NRT, bupropion, or varenicline *[D*]*.

Effect of quitting tobacco use on other drugs. Properties of smoke other than nicotine (benzopyrenes) increase metabolism of other drugs. In particular, theophylline half-life will increase within one week after smoking cessation. Quitting tobacco use can increase plasma caffeine concentrations greatly. Patients should be made aware that baseline caffeine intake may have greater physiologic effect and may be misinterpreted as nicotine withdrawal.

Weight Gain

Most smokers who quit will gain weight, but the majority will gain less than 10 pounds *[C*]*. The clinician should acknowledge this and encourage patients to adopt a healthy lifestyle that includes moderate exercise and healthy diet. However, very restrictive dieting at the same time may be counterproductive *[C*]*. A reminder to the patient to work on one issue at a time and that you will assist the patient with any weight gain issues as needed may be helpful *[D*]*.

Although bupropion at a dose of 300mg/day had a lower percentage weight gain after 7 weeks of therapy as compared to placebo, this effect was not sustained at 6 months and therefore is not likely to be any better than NRT for prevention of post-cessation weight gain *[A*]*. Nicotine gum may delay post-cessation weight gain, but the weight is usually gained once gum use ceases *[C*]*.

Special Populations

Pregnant patients. Intensive counseling interventions increase quit rates during pregnancy *[A*]*. If intensive counseling is not possible, brief in-office counseling still has a beneficial effect and should be offered. Several studies have addressed the safety of nicotine replacement therapy or bupropion in pregnancy directly; however, studies show that less nicotine and fewer metabolites cross the placenta with the use of NRT than with smoking itself. Studies have not demonstrated the efficacy of pharmacotherapy in pregnancy. FDA pregnancy risk categories are: bupropion - category C, nicotine transdermal, spray and inhaler - category D, nicotine gum - category C, varenicline – category C. Therefore, cautious

use of NRT (especially nicotine gum) in addition to counseling may be considered for refractory cases after reviewing risks and benefits with the patient.

Breastfeeding women. Smoking leads to a significant reduction in breast milk volume and increases the likelihood of early discontinuation *[A*]*. Data support the use of bupropion plus NRT in nursing mothers, with increased cessation rates. The safety profile is favorable, as less nicotine and fewer metabolites are found in breast milk with NRT, compared to smoking more than ½ pack per day. Additionally, eliminating environmental exposure to the infant is a favorable outcome. It is not known whether varenicline is excreted in human milk.

Racial and Ethnic Minorities. Tobacco treatment has been shown to be effective across both racial and ethnic minorities *[A*]*. Little research has examined intervention specifically designed for a particular ethnic or racial group; however, it is recommended that, when possible, tobacco treatment should be tailored to the specific ethnic or racial population with which they are used *[C*]*. It is essential that counseling or self-help materials be conveyed in a language understood by the tobacco user.

Psychiatric co-factors. If presence of psychiatric co-factors, such as depression, eating disorder, anxiety disorder, attention deficit disorder, or alcohol abuse, strongly consider referral to intensive counseling *[B*]*. Treatment of co-factors must be undertaken in preparation for quitting tobacco use.

Non-cigarette tobacco users. Spit tobacco users should be identified and strongly urged to quit tobacco use, using the same counseling interventions recommended for smokers *[A*]*. The clinicians should provide a clear message that the use of spit tobacco is not a safe alternative to smoking. However, several studies have found that use of nicotine gum and nicotine patch have not increased the abstinence rates in spit tobacco users.

Users of cigars, pipes, and other non-cigarette combustible forms of tobacco should be identified, strongly urged to quit, and offered the same counseling interventions recommended for smokers *[C*]*.

Gender concerns. Treatments to quit tobacco use benefit both women and men *[B*]*. Two studies suggest that some treatments are less efficacious in women than in men. Women may face different stressors and barriers to quitting (e.g., greater likelihood of depression, greater weight control concerns, and hormonal cycles). This research suggests cessation programs that address these issues would be more effective in treating women *[D*]*. Few studies have examined programs targeted to one gender.

Older tobacco users. Treatments to quit tobacco use are effective for older adults and should be provided, as cessation improves pulmonary function and cerebral circulation *[A*]*. Several studies have found cessation rates among motivated older adults similar to those for younger adults; however, supportive counseling and social support may be of more value to prevent relapse than education or skills training *[A*]*.

Pre-operative tobacco users. Patients should also be encouraged to quit tobacco use prior to any surgical procedure. Quitting close to surgery has no evidence of detrimental effect on clinical outcomes. In fact, limited evidence indicates that quitting may help improve outcomes *[B*]*.

Hospitalized tobacco users. Providing hospitalized patients with high-intensity behavioral counseling and follow-up of at least 30 days has been shown to increase cessation rates *[A*]*. NRT supplementation can also be useful in this population. Briefer interventions (<20 minutes, delivered only during the hospitalization) have not yet been shown to be helpful. Additional treatment can include self-help brochures or audio/video tapes, chart prompts reminding physicians to advise for cessation, pharmacological therapy, hospital counseling, and post-discharge counseling telephone calls. Hospitalization should be used as a springboard to promote quitting tobacco use.

Adolescent tobacco users. The evidence for the effectiveness of counseling in adolescent tobacco users is less robust. However, some studies do demonstrate that smoking cessation counseling in the primary care setting can improve adolescent smokers' quit rates *[A*]*.

The utility of pharmacologic therapy for adolescents has been examined in a number of small studies. While the evidence indicates that these therapies are safe, they seem to be more effective when coupled with counseling. Additional, larger trials are ongoing to evaluate this issue. In the meantime, nicotine replacement therapy or bupropion may be considered for second line use in adolescent smokers *[D*]*.

Controversial Areas

Electronic cigarettes (e-cig). Little research exists on the safety and effectiveness of the e-cig. The electronic cigarette is considered a tobacco product under the FD&C Act. For tobacco cessation, recommend the nicotine inhaler or other nicotine substitutes *[D*]*.

Web- and computer-based programs for quitting tobacco use. A Cochrane Review and a recent meta-analysis of 22 RCT's of Web-or computer-based smoking cessation programs found that some of these may be beneficial, particularly if the information is tailored to the user and is combined with follow-up contact *[A*]*.

Other cessation aids. There is good evidence to recommend against the use of additional modalities such as hypnosis, laser, acupuncture, and acupressure as aids to smoking cessation *[A]*. None of these modalities have been

shown to be superior to placebo in a number of meta-analysis.

Information the Patient Needs to Know

Supplementary materials. The UMHS produces two useful patient education handouts:

- "How to use your nicotine product"
- "Tips for quitting smoking"

Additionally, the National Cancer institute produces the pamphlet, "Clearing the Air" (NIH Pub. 03-1647). You may obtain 20 free copies at a time by calling 1 800-4-CANCER (1-800-422-6237). It is also available online at http://www.smokefree.gov/pubs/clearing_the_air.pdf

Preparation and effects. Review with patients the following additional information about preparing for quitting and related factors.

- **Review handout(s)**. The handout(s) provide many useful tips to help you with your quit attempt. Read these and make plans before your quit attempt.
- **NRT/bupropion/varenicline.** Nicotine replacement therapies, bupropion, and varenicline are most effective when used correctly. If you have any uncertainties about proper use, this should be clarified.
- **Caffeine.** You are likely to perceive greater effects from your usual caffeine consumption after you quit tobacco use and may need to decrease your intake.
- **Theophylline**. If you take theophylline, levels should be checked approximately 2 weeks after you quit tobacco use.

Organizing a Health Care Site to Support Quitting Tobacco Use

Successful intervention programs require coordinated efforts at a health care site. Several clinic personnel may be involved in the operational steps of "Asking, Advising, Assessing, and Referring". Clinicians should help their clinics develop a coordinated plan of tasks and who will perform them. Some specific areas for planning include:

- **Record tobacco use status.** Institute an office system to identify all tobacco users:
  - Identify where tobacco status will be recorded. Options include making tobacco status part of vital signs, placing tobacco status stickers on charts, or including tobacco status on a section of the Problem Summary List.
  - Determine who will routinely ask and record the information.
  - Instruct staff regarding their roles in documentation.
  - Reinforce the value of the documentation.
- **Follow-up for quitting tobacco use.** Develop a system and assigned role(s) at the health care site to:
  - Ensure the availability of patient education materials on quitting tobacco use.
  - Establish procedures for clinicians to provide a designated follow-up person with information on patients who are setting quit dates. Coordinate follow-up phone calls in conjunction with quit dates.
  - Patients prescribed bupropion or varenicline should be contacted 2 weeks after starting medications to assess for neuropsychiatric or other side effects.
  - Provide follow-up cessation counseling as needed at subsequent clinic visits.
  - Refer patients to more intensive counseling programs for quitting tobacco use, as needed.

Strategy for Literature Search

The update of literature beyond the search performed for the initial UMHS Smoking Cessation Guideline began with the literature search performed to produce "Treating Tobacco Use and Dependence 2008 Update," US Public Health service, May 2008 (see complete reference below). The guideline team then updated the PHS literature search through a Medline search of literature June 2007 – February 2011. This search used the major keywords of: smoking [prevention, cessation, & control], tobacco use [prevention treatment, control, & rehabilitation]. The search was restricted to literature that was also referenced: as guidelines, controlled trials, or cohort studies; as studies of humans; and as published in English. Specific searches were performed for the topics: counseling (includes assessment, transtheoretical model); pharmacologic treatment; other therapies (including complementary/alternative); electronic cigarette (e-cigarette); pregnancy; adolescents; older adults; racial/ethnic minority differences; gender differences; prevention (includes physician interactions with children and adolescents, counseling about having a smoke free home, and avoiding environmental tobacco smoke including residue); and other smoking cessation guidelines, controlled trials, or cohort studies not included above.

The literature search for this project was conducted prospectively. The search was conducted in components each keyed to a specific causal link in a formal problem structure (available upon request). The search was a single cycle. Conclusions were based on prospective randomized controlled trials (RCTs) if available, to the exclusion of other data. If RCTs were not available, observational studies were admitted to consideration. If no such data were available for a given link in the problem formulation, expert opinion was used to estimate effect size.

Related National Guidelines

Treating Tobacco Use and Dependence: 2008 Update. U.S. Public Health Service.

Measures of Clinical Performance

National programs that have clinical performance measures for tobacco treatment include the following.

Centers for Medicare & Medicaid Services:
- Clinical Quality Measures for financial incentives for Meaningful Use of certified Electronic Health Record technology (MU)
- Quality measures for Accountable Care Organizations (ACO)

National Committee for Quality Assurance: Healthcare Effectiveness Data and Information Set (HEDIS)

These programs have clinical performance measures for tobacco treatment addressed in this guideline. While specific measurement details vary (e.g., method of data collection, population inclusions and exclusions). The general measures are summarized below.

Tobacco use assessment. Percentage of patients aged 18 years or older who were queried about tobacco use one or more times within 24 months of the measurement end date. (MU, ACO)

Advising tobacco users to quit. The percentage of patients 18 years of age and older who were current smokers or tobacco users, who were seen by a provider during the measurement year, and who:
- received advice to quit smoking or using tobacco (MU)
- received cessation advice or were provided cessation methods during the measurement year. (HEDIS)

Advising tobacco users to how quit. The percentage of patients 18 years of age and older who were current smokers or tobacco users, who were seen by a provider during the measurement year, and:
- whose provider recommended or discussed smoking or tobacco use cessation medications, methods, or strategies. (MU, HEDIS)
- who have had tobacco use cessation counseling one or more times within 24 months of the measurement end date. (MU, ACO)

Disclosures

The University of Michigan Health System endorses the Guidelines of the Association of American Medical Colleges and the Standards of the Accreditation Council for Continuing Medical Education that the individuals who present educational activities disclose significant relationships with commercial companies whose products or services are discussed. Disclosure of a relationship is not intended to suggest bias in the information presented, but is made to provide readers with information that might be of potential importance to their evaluation of the information.

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Review and Endorsement

Drafts of this guideline were reviewed in clinical conferences and by distribution for comment within departments and divisions of the University of Michigan Medical School to which the content is most relevant: Family Medicine, General Internal Medicine, Pediatric Medical Surgical Joint Practice Committee, and Mott Executive Committee. The Executive Committee for Clinical Affairs of the University of Michigan Hospitals and Health Centers endorsed the final version.

Acknowledgments

The following individuals are acknowledged for their contributions to previous versions of this guideline.

2001 (May). Kym Orsetti, MD, General Medicine; Shon Dwyer, RN, MBA, Corporate Quality Improvement, Sharon Sheldon, MPH, UMH Health Promotion; and Mark Zamorski, MD, Family Medicine.

2006 (August). John G Frohna, MD, MPH, Internal Medicine and Pediatrics, R Van Harrison, PhD, Medical Education, David C Serlin, MD, Family Medicine, Linda A Thomas, MS LLP, UMHS Tobacco Consultation Service.

Annotated Reference

Treating Tobacco Use and Dependence: 2008 Update. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service. May 2008. Available at www.ahrq.gov/path/tobacco.htm (Accessed 6/3/11.)

This 257 page guideline is an updated version of the previous similar guidelines sponsored by the Agency for Healthcare Research and Quality [AHRQ]), U.S. Department of Health and Human Services. This Guideline contains strategies and recommendations designed to assist clinicians; tobacco dependence treatment specialists; and health care administrators, insurers, and purchasers in delivering and supporting effective treatments for tobacco use and dependence. The recommendations were made as a result of a systematic review and meta-analysis of 11 specific topics identified by the Panel (proactive quitlines; combining counseling and medication relative to either counseling or medication alone; varenicline; various

medication combinations; long-term medications; cessation interventions for individuals with low socioeconomic status/limited formal education; cessation interventions for adolescent smokers; cessation interventions for pregnant smokers; cessation interventions for individuals with psychiatric disorders, including substance use disorders; providing cessation interventions as a health benefit; and systems interventions, including provider training and the combination of training and systems interventions).

Appendix

Meta-analysis (2008): Effectiveness and Abstinence Rates for Various Medications and Medication Combinations Compared to Placebo at 6-Months Post-Quit (n = 86 studies)

Medication	Number of arms	Estimated odds ratio (95% C.I.)	Estimated abstinence rate (95% C.I.)
Placebo	80	1.0	13.8
Monotherapies			
Varenicline (2 mg/day)	5	3.1 (2.5, 3.8)	33.2 (28.9, 37.8)
Nicotine Nasal Spray	4	2.3 (1.7, 3.0)	26.7 (21.5, 32.7)
High Dose Nicotine Patch (> 25 mg) (These included both standard or long-term duration)	4	2.3 (1.7, 3.0)	26.5 (21.3, 32.5)
Long-Term Nicotine Gum (> 14 weeks)	6	2.2 (1.5, 3.2)	26.1 (19.7, 33.6)
Varenicline (1 mg/day)	3	2.1 (1.5, 3.0)	25.4 (19.6, 32.2)
Nicotine Inhaler	6	2.1 (1.5, 2.9)	24.8 (19.1, 31.6)
Clonidine	3	2.1 (1.2, 3.7)	25.0 (15.7, 37.3)
Bupropion SR	26	2.0 (1.8, 2.2)	24.2 (22.2, 26.4)
Nicotine Patch (6-14 weeks)	32	1.9 (1.7, 2.2)	23.4 (21.3, 25.8)
Long-Term Nicotine Patch (> 14 weeks)	10	1.9 (1.7, 2.3)	23.7 (21.0, 26.6)
Nortriptyline	5	1.8 (1.3, 2.6)	22.5 (16.8, 29.4)
Nicotine Gum (6-14 weeks)	15	1.5 (1.2, 1.7)	19.0 (16.5, 21.9)
Combination therapies			
Patch (long-term; > 14 weeks) + ad lib NRT (gum or spray)	3	3.6 (2.5, 5.2)	36.5 (28.6, 45.3)
Patch + Bupropion SR	3	2.5 (1.9, 3.4)	28.9 (23.5, 35.1)
Patch + Nortriptyline	2	2.3 (1.3, 4.2)	27.3 (17.2, 40.4)
Patch + Inhaler	2	2.2 (1.3, 3.6)	25.8 (17.4, 36.5)
Patch + Second generation antidepressants (paroxetine, venlafaxine)	3	2.0 (1.2, 3.4)	24.3 (16.1, 35.0)
Medications not shown to be effective			
Selective Serotonin Reuptake Inhibitors (SSRIs)	3	1.0 (0.7, 1.4)	13.7 (10.2, 18.0)
Naltrexone	2	0.5 (0.2, 1.2)	7.3 (3.1, 16.2)

Reproduced from Fiore MC, Jaén CR, Baker TB, et al. Treating Tobacco Use and Dependence: 2008 Update. Quick Reference Guide for Clinicians. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service. April 2009.