Overview of smoking cessation management in adults

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INTRODUCTION — Pharmacotherapy for smoking cessation aims to reduce the symptoms of nicotine withdrawal, thereby making it easier for a smoker to stop the use of cigarettes. The main medications that have demonstrated efficacy as smoking cessation aids include nicotine replacement, varenicline, and bupropion [1]. Smokers who wish to quit should be managed with a combination of behavioral therapy and pharmacotherapy, as the combination of counseling and pharmacologic therapies produces higher quit rates than either one alone [2].

Pharmacologic options to help patients stop smoking are reviewed here. An overview of smoking cessation management and behavioral therapies for smoking cessation are discussed separately. (See "Overview of smoking cessation management in adults" and "Behavioral approaches to smoking cessation".)

FIRST-LINE MEDICATIONS — Smoking cessation clinical guidelines from the US Public Health Service (2008) and the US Preventive Services Task Force (2015) consider the following drugs to be first-line agents for tobacco cessation: nicotine replacement therapy (NRT; transdermal nicotine patch, nicotine gum, lozenge, inhaler, and/or nasal spray), varenicline, and bupropion (table 1) [3-5]. Other medications have been evaluated for smoking cessation but have less established efficacy than first-line agents. (See 'Other medications' below.)

With a few exceptions, choice of first-line medication is generally based on patient preference after discussion with a clinician. (See 'Initiating therapy' below.)

Combination nicotine replacement therapy — The goal of NRT is to provide nicotine to a smoker without using tobacco, thereby relieving nicotine withdrawal symptoms as the smoker breaks the behavior of cigarette smoking. Three NRT products are available in the United States without a prescription (patch, lozenge, and gum). Two (nasal spray and oral inhaler) are available by prescription only. A nicotine mouth spray and sublingual tablet are available in some countries, but are not licensed for sale in the United States.

Differences in the bioavailability of nicotine replacement products provide a rationale for combining NRT products to increase efficacy [2]. The long-acting, slow-onset nicotine patch is the primary NRT to control baseline nicotine withdrawal symptoms [6]. Adding a short-acting form of NRT (lozenge, gum, inhaler, or nasal spray) helps

to control cravings and withdrawal symptoms during the day on an as-needed basis. The choice of a short-acting agent depends on patient preference and comorbidities.

Efficacy — In randomized trials, individual NRT products were found to be superior to placebo, increasing quit rates approximately twofold (table 1) [2,3,7,8]. Few trials have directly compared one product with another. One randomized trial found no difference in efficacy between the patch, gum, inhaler, and nasal spray [9]. In some but not all trials, NRT benefits men more than women [10,11].

For those wishing to use NRT, we recommend the combined use of a long- and short-acting NRT as initial therapy. Combination NRT is more effective than single-product therapies [12-15]. In a 2013 meta-analysis of nine randomized trials, the combination of nicotine patch with a short-acting NRT product (gum, spray, or inhaler) was more effective than a single type of NRT alone (relative risk [RR] 1.34, 95% CI 1.18 to 1.51) [14]. However, a subsequent randomized trial including 1086 smokers compared 12 weeks of varenicline, nicotine patch, and nicotine patch plus nicotine lozenge therapy [16]. The trial found no differences in biochemically confirmed rates of smoking abstinence among the three groups.

The initial dosing of most NRT products is based on the number of cigarettes smoked daily as discussed below. The dose of NRT is gradually tapered as nicotine withdrawal symptoms subside. In general, NRT use is recommended for two to three months after smoking cessation, though use for a longer period of time is acceptable in patients with a high risk of smoking relapse. NRT products can also be used while the smoker is still smoking [17].

Transdermal nicotine patch — The nicotine patch is the simplest NRT product for a smoker to use and provides the most continuous nicotine delivery of all NRT products. The patch has a long-acting, slow-onset pattern of nicotine delivery, producing relatively constant withdrawal relief over 24 hours, but requiring several hours to reach peak levels. Compliance with the patch is high; however, the user has no control of the nicotine dose to respond to nicotine cravings and withdrawal symptoms. The patch is available over the counter in the United States.

Starting on the quit day, patients who smoke >10 cigarettes/day (one-half pack) use the highest dose of the nicotine patch (21 mg/day) for six weeks, followed by 14 mg/day for two weeks, and finish with 7 mg/day for two weeks. Smokers who weigh less than 45 kg or smoke ≤10 cigarettes per day are advised to begin with the 14 mg/day strength for six weeks, followed by 7 mg/day for two weeks.

To use the nicotine patch, the smoker applies one patch each morning to any non-hairy skin site. It is removed and replaced with a new patch the next morning. The patch site should be rotated daily to avoid skin irritation, which is the most common side effect.

Insomnia and vivid dreams are frequently reported when the patch is left on overnight. These can be minimized by removing the patch at bedtime. Smoking cessation rates are similar whether the patch is left on for 24 hours or taken off at night [18]. If the patch is removed at night, substantial plasma levels of nicotine are reached 30 minutes to three hours after a new patch is applied in the morning [19].

Patients who remove the patch at night and experience morning cravings for nicotine can use a short-acting form of NRT (eg, gum, lozenge) while waiting for the nicotine patch to take effect.

Longer duration (more than 8 to 10 weeks) of treatment with the nicotine patch may lead to improved smoking cessation rates. For example, a randomized trial of 568 smokers found that compared with standard (8 weeks) nicotine patch therapy, extended (24 weeks) therapy was associated with higher rates of seven-day point-prevalence abstinence at 24 weeks (odds ratio [OR] 1.81, 95% CI 1.23-2.66) [20]. This study excluded patients with significant medical comorbidities and may not be representative of the general smoking population. Another randomized trial in 525 smokers found that compared with standard therapy (8 weeks), extended (24 weeks) and maintenance (52 weeks) of nicotine patch therapy was associated with higher seven-day point-prevalence of abstinence at 24 weeks (OR 1.7, 95% CI 1.03-2.81) [21]. However, there were no differences in abstinence rates at 52 weeks. All smokers also received 12 smoking cessation behavioral counseling sessions.

Adjunctive short-acting agents — Short-acting NRT are used in combination with the transdermal nicotine patch to control cravings and withdrawal symptoms. The short-acting forms require repeated use throughout the day, lead to more variable nicotine levels, and require more instruction for correct use. Smokers are instructed to use the product when they have a craving, but this generally leads them to underuse the products. An alternative approach is to have the smoker use the product every hour while awake at minimum and as needed in addition.

Options include nicotine gum, lozenge, inhaler, and nasal spray. Nicotine gum and lozenges are available over the counter in the United States. A nicotine mouth spray and sublingual tablet are available is some countries but not licensed for sale in the United States.

Nicotine gum — Nicotine gum is one of the most commonly used short-acting NRT. Chewing the gum releases nicotine that is absorbed through the oral mucosa, resulting in a peak of blood nicotine levels 20 minutes after starting to chew. Nicotine gum is available in several flavors that most users find preferable to the original flavor.

The 4 mg dose of gum is recommended for smokers who smoke 25 or more cigarettes per day, whereas the 2 mg dose is recommended for lighter smokers [3]. Smokers are instructed to chew the gum whenever they have an urge to smoke. They can chew one piece of gum every one to two hours for six weeks, with a gradual reduction over a second six weeks, for a total duration of three months. Acidic beverages (eg, coffee, carbonated drinks) should be avoided before and during gum use, as acidic beverages lowers oral pH, causing nicotine to ionize and reducing nicotine absorption.

A "chew and park" pattern of gum use is recommended. A piece of gum is chewed until the nicotine taste appears, then "parked" in the buccal mucosa until the taste disappears. At this point, the gum is chewed a few more times to release more nicotine. This cycle is repeated for 30 minutes, at which point the gum is discarded because all of the nicotine in the gum has been released.

Proper chewing of gum is important for optimal results. If the gum is chewed too rapidly, nicotine is released faster than it can be absorbed by the buccal mucosa and the nicotine is swallowed. Nicotine absorbed from the gastrointestinal tract is largely metabolized by the liver and is therefore relatively ineffective. Swallowed nicotine can also cause gastric and esophageal irritation. Side effects are mostly a consequence of excess nicotine release with overly vigorous chewing and consist of nausea, vomiting, abdominal pain, constipation, hiccups, headache, excess salivation, a sore jaw, and mouth irritation or ulcers.

Chewing gum may exacerbate temporomandibular joint disease and can damage or adhere to dental appliances. Smokers with temporomandibular joint disease, poor dentition, or those who use dental appliances may do better with an alternative short-acting form of NRT such as the lozenge or inhaler.

Nicotine lozenge — The lozenge is another commonly used short-acting form of NRT and has a pharmacokinetic profile similar to nicotine gum. It is easier to use correctly than nicotine gum and is also sold in different flavors. A smaller mini-lozenge that resembles a "Tic Tac" is also on the US market. It dissolves more rapidly and delivers nicotine more rapidly than the original lozenge.

The 4 mg dose is recommended for smokers who smoke within 30 minutes of awakening (a measure of greater nicotine dependence); the 2 mg dose is recommended for all other smokers. The dosing schedule is similar to that of the gum: one lozenge every one to two hours for six weeks, with a gradual reduction in the number of lozenges used per day over a second six weeks. The maximum dose is 5 lozenges every six hours or 20 lozenges per day.

The lozenge is placed in the mouth and allowed to dissolve for 30 minutes. In contrast to nicotine gum, the lozenge does not need to be chewed. The lozenge can be used in smokers with temporomandibular joint disease, poor dentition, or dentures.

Adverse effects of the nicotine lozenge include mouth irritation or ulcers, in addition to nicotine-related side effects of abdominal pain, nausea, vomiting, diarrhea, headache, and palpitations.

Nicotine inhaler — The nicotine inhaler consists of a mouthpiece and a plastic, nicotine-containing cartridge. The inhaler addresses not only physical dependence, but also the behavioral and sensory aspects of smoking (ie, having a cigarette between one's fingers and inhaling from the cigarette). The pharmacokinetics of the inhaler resemble those of nicotine gum. The ad lib use of the nicotine inhaler produces plasma nicotine levels that are roughly one-third of those that occur with cigarette smoking.

The recommended dose of the nicotine inhaler is 6 to 16 cartridges per day for the first 6 to 12 weeks, followed by gradual reduction of dose over the next 6 to 12 weeks. When the smoker inhales through the device, nicotine vapor (not smoke) is released and deposited primarily in the oropharynx and absorbed through the oral mucosa. Nicotine vapor does not reach the lungs to an appreciable extent.

Localized irritation of the mouth or throat is common, particularly during the early stages of use. Because inhaled nicotine may cause bronchospasm, it may be less appropriate for smokers with a history of severe airway reactivity.

Nicotine nasal spray — The nicotine nasal spray delivers an aqueous solution of nicotine to the nasal mucosa. The nicotine nasal spray produces a more rapid rise in plasma nicotine concentration than orally absorbed nicotine replacement products (gum, inhaler, lozenge), producing a peak of nicotine 10 minutes after use. Although the nasal spray more closely mimics changes seen with smoking, it does not deliver nicotine nearly as fast as smoking a cigarette [22].

One or two sprays per hour are recommended for about three months. The maximum dose is 10 sprays per hour or 80 total sprays per day.

In clinical practice, nicotine nasal spray use is limited by the side effects of nasal and throat irritation, rhinitis, sneezing, and tearing. Nasal irritation is extremely common, occurring in 94 percent of patients during the first two days of use, and continuing in 81 percent of patients after three weeks of therapy [23].

Other short-acting agents — The nicotine mouth spray and sublingual tablets are available in some countries but not in the United States.

●**Nicotine mouth spray** – A nicotine mouth spray delivers 1 mg nicotine per spray. Typical use is one or two sprays when cravings occur, with up to four sprays per hour [24]. Frequent side effects with the oral spray include hiccups (occurring in more than 55 percent of those treated in one trial [25]), throat irritation, and nausea.

●**Nicotine sublingual tablets** – A typical dose is one 2 mg tablet allowed to dissolve sublingually (typically over 30 minutes) every one to two hours; patients who are heavily nicotine-addicted can use two tablets sublingually (4 mg total) for each dose [26]. Common side effects include sore mouth or throat and dryness or burning in the mouth [27].

Safety — NRT products used in combination are safe, as each agent produces lower blood nicotine levels than that produced by the average smoker who smokes a pack of cigarettes daily. Smokers may worry that they will remain dependent on nicotine if they use these products when stopping smoking. This rarely occurs [3].

The common side effects of NRT products include gastrointestinal symptoms (nausea, vomiting, abdominal pain, diarrhea), headache, and local irritation depending on the delivery method [28]. The side effect profile that is specific to each NRT is discussed above [3]. In contrast to bupropion and varenicline, smokers who experience side effects from NRT products can titrate use to minimize side effects or change products.

Nicotine replacement is safe to use in patients with known and stable cardiovascular disease (CVD). There is limited information regarding its use after acute coronary syndrome (ACS). (See "Cardiovascular effects of nicotine", section on 'Safety of nicotine replacement therapy'.)

Varenicline — Varenicline is effective for smoking cessation. Varenicline is a partial agonist at the alpha-4 beta-2 subunit of the nicotinic acetylcholine receptor, the receptor that appears to produce the reinforcing effects of nicotine and leads to nicotine dependence [29-31]. Varenicline is hypothesized to aid smoking cessation in two ways. As a partial agonist, it binds to and produces partial stimulation of the alpha-4 beta-2 nicotinic receptor, thereby reducing the symptoms of nicotine withdrawal. Secondly, since varenicline binds to the alpha-4 beta-2 receptor subunit with high affinity, it blocks the nicotine in tobacco smoke from binding to the receptor, thereby reducing the rewarding aspects of cigarette smoking [29].

Efficacy — The efficacy of varenicline for smoking cessation has been demonstrated in several randomized placebo-controlled trials conducted in the United States [32-36], Japan [37], and Taiwan [38]. A 2013 meta-analysis of randomized trials found that compared with placebo, varenicline was more effective for smoking cessation (RR 2.27, 95% CI 2.02-2.55) [14]. The meta-analysis result was confirmed subsequently in a randomized controlled trial that compared varenicline with a nicotine patch, bupropion, and placebo in over 8000 smokers [8]. At both three and six months' follow-up, varenicline produced a higher rate of continuous tobacco abstinence compared with the other three groups. The trial did not compare varenicline with combination nicotine therapy.

Administration — Smokers are instructed to quit one week after starting varenicline, by which time stable blood levels are achieved. The recommended dose of varenicline is 0.5 mg daily for three days, then 0.5 mg twice daily for four days, and then 1 mg twice daily for the remainder of a 12-week course. The risk of nausea is reduced if the dose of varenicline is titrated upward [39]. Nausea can also be minimized by taking varenicline with food and a full glass of water.

Because varenicline undergoes no liver metabolism, it has few interactions with other drugs. However, varenicline is excreted almost entirely by the kidney and requires a dose reduction in individuals with moderate renal insufficiency.

A longer preloading period prior to the quit date may be more effective in achieving abstinence. In one trial of 101 smokers, abstinence rates at 12 weeks were higher among those randomly assigned to varenicline for four weeks before the quit date compared with those assigned to three weeks of placebo followed by one week of varenicline (47 versus 21 percent) [40]. Larger trials with longer follow-up periods are needed to determine whether a longer preload period leads to improved abstinence rates.

Varenicline may also be helpful for patients who are less committed to quitting. A randomized trial in 1510 smokers who were not willing or able to make a quit attempt within the next month but were willing to reduce smoking and make a quit attempt within the next three months found that compared with placebo, patients on varenicline for 24 weeks had a higher continuous abstinence rate during weeks 21 through 24 (37.8 versus 12.5 percent) and weeks 21 through 52 (27 versus 9.9 percent) [41].

Patients who have successfully quit at 12 weeks can be continued on varenicline for an additional 12 weeks. A randomized trial in 1236 individuals who had quit smoking

after an initial 12-week course of varenicline compared an additional 12 weeks of varenicline with placebo [42]. Smokers treated with varenicline for an additional 12 weeks had higher rates of continuous abstinence during weeks 13 through 24 (71 versus 50 percent) as well as during weeks 13 through 52 (44 versus 37 percent).

Increasing the dose of varenicline has not been shown to improve smoking cessation rates. A placebo-controlled randomized trial in 200 smokers who did not respond to standard-dose varenicline (2 mg/day) compared continuing the standard dose with an increased dose (maximum of 5 mg/day) [43]. The study found no difference in smoking cessation rates between the two groups.

Safety — The two main safety concerns that have been raised with varenicline are neuropsychiatric and cardiovascular side effects.

Safety reports reinforce the importance of careful follow-up of smokers started on varenicline. A follow-up visit or telephone call within one week to monitor for adverse effects is advised. (See "Overview of smoking cessation management in adults", section on 'Arrange follow-up'.)

In 2009, the US Food and Drug Administration (FDA) required varenicline packaging to include a “black box” warning about potential neuropsychiatric side effects, but this warning was removed in 2016 [44] based on results of a randomized trial that found no difference in adverse neuropsychiatric events comparing varenicline with nicotine patch or placebo, in patients with or without a coexisting psychiatric disorder [8].

Neuropsychiatric effects — We recommend taking a careful psychiatric history prior to prescribing the drug, avoiding it in smokers with current unstable psychiatric status or a history of recent suicidal ideation. Other clinicians take a more conservative approach and do not offer the drug to patients with depression. Any patient started on varenicline who reports neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed mood, suicidal ideation, and suicide attempts should stop the medication.

Concerns of neuropsychiatric side effects from both varenicline and bupropion were first raised in review of post-marketing case reports [45]. A review of case reports from the FDA Adverse Event Reporting System from 1998 to 2010 identified 3249 case reports of suicidal/self-injurious behavior and/or depression in patients on treatment for smoking cessation. Varenicline was associated with 90 percent of these events, followed by bupropion (7 percent) and nicotine replacement (3 percent) [46]. Some of the reported neuropsychiatric symptoms overlap with those of nicotine withdrawal, but nicotine withdrawal could not explain all of the reported adverse events because some occurred in smokers who had not quit smoking. Case reports can call attention to a potential adverse drug effect but cannot prove an association. This requires stronger study designs.

Neuropsychiatric side effects were not reported in the randomized controlled trials that demonstrated the efficacy of varenicline. These trials excluded potentially vulnerable groups of smokers (eg, those with a history of major depression or other psychiatric disorders). However, a 2015 systematic review and meta-analysis of 39 randomized trials including over 10,000 participants and several trials enrolling

patients with psychiatric illness found that, compared with placebo, varenicline users did not have an increased risk of suicide or suicide attempts, suicidal ideation, depression, aggression, or death [47]. Varenicline was associated with an increased risk of sleep disorders (OR 1.62, 95% CI 1.29-2.07). A subsequent large randomized trial enrolled over 8000 smokers motivated to quit compared 12 weeks of varenicline, bupropion, and the nicotine patch with placebo [8]. Approximately half of the patients had stable psychiatric disorders (primarily major depressive, bipolar, or anxiety disorders). Varenicline, bupropion, nicotine patch, and placebo did not differ from one another in the proportion of smokers who reached a combined endpoint of moderate to severe neuropsychiatric adverse events. Adverse events were more common for all groups in smokers with current or past psychiatric diagnoses compared with smokers with no psychiatric history, but the rates were low for both groups. This trial's results were consistent with the findings of previous observational studies that analyzed data from health records and found no difference between varenicline, bupropion, and NRT in rates of serious neuropsychiatric symptoms [48-50]. After reviewing this trial, the FDA in December 2016 removed the black box warning that it had placed on varenicline and bupropion in 2009. Randomized trials in specific populations of psychiatric illness are discussed below. (See 'Other effects' below and 'Psychiatric illness' below.)

Cardiovascular effects — There is a small concern based on limited evidence that varenicline might increase the risk of adverse cardiovascular events. For low-risk patients, it appears unlikely that there is a clinically important increase. For patients at high risk for acute coronary events, this is less certain as trials have included relatively few such patients but it is safe to say that no large increase in risk has been observed. Any risk is likely to be far smaller than the risk of continuing to smoke cigarettes.

The 2011 FDA advisory that varenicline may increase the risk of cardiovascular events in patients with known CVD was based upon findings from a randomized trial in 714 smokers with stable CVD [51]. Compared with placebo, more patients treated with varenicline had non-fatal myocardial infarction (2 versus 0.9 percent) and need for coronary revascularization (2.3 versus 0.9 percent), although these differences were not significant [36]. Patients treated with varenicline appeared to have a lower rate of cardiovascular mortality (0.6 versus 1.4 percent); that difference was also not significant. The FDA suggested that the known benefits of varenicline for smoking cessation be weighed against potential harms in patients with CVD.

The available data from other randomized trials and meta-analyses do not clearly confirm or refute this association. Two large meta-analyses of randomized trials found no differences in the rates of cardiovascular events in patients treated with varenicline compared with placebo [52,53]. However, the overall rates of cardiovascular events in the trials was low, limiting the power of the analyses to detect a difference. An earlier meta-analysis excluded trials with no cardiovascular events and found an association between varenicline and cardiovascular events (OR 1.72, 95% CI 1.09-2.71); however, this methodology may have also introduced some bias [54,55]. In a subsequent cohort study (n = 35,852), there was no increase in the risk of major cardiovascular events in smokers who took varenicline versus bupropion (6.9 cases versus 7.1 cases per 1000 person years) [56]. In the study from general medical practices in England described above, cardiovascular events

were less common in patients prescribed varenicline than NRT (HR 0.86 and 0.58 for ischemic heart disease and stroke, respectively) [49].

Other effects — A review of adverse drug reports to the FDA by the Institute for Safe Medication Practices, a nonprofit medicine safety group, found an unusually high rate of accidental injuries from road accidents and falls in patients taking varenicline [57]. The FDA issued a public health advisory stating that patients taking varenicline may experience impairment of the ability to drive or operate heavy machinery [58]. The Federal Aviation Administration subsequently prohibited pilots and air traffic controllers from taking the drug [29]. However, in an observational study in Sweden, varenicline use was not associated with an increase in traffic crimes or transport accidents [50].

Other frequently reported adverse events included nausea, insomnia, abnormal dreams, visual disturbances, syncope, and moderate to severe skin reactions. A clinical trial demonstrated that the risk of nausea is reduced if the dose of varenicline is titrated upward [39]. Dreams that are troubling to the patient can be reduced by taking the evening dose of varenicline earlier in the day or by lowering the dose by skipping the evening dose.

Varenicline is safe for use among smokers with chronic obstructive pulmonary disease (COPD) [59].

Bupropion — Bupropion is effective for smoking cessation and is believed to act by enhancing central nervous system noradrenergic and dopaminergic release. A sustained-release formulation of the drug (Zyban) is licensed as an aid to smoking cessation; it is identical to the antidepressant Wellbutrin SR and generic sustained-release bupropion.

Efficacy — Randomized trials have demonstrated the efficacy of bupropion in smoking cessation. A 2014 meta-analysis of 44 randomized trials found that compared with placebo, bupropion monotherapy increases the likelihood of smoking cessation (RR 1.62, 95% CI 1.49-1.76) [60]. A representative multicenter, randomized trial of 615 smokers comparing sustained-release bupropion (150 mg twice daily) with placebo found that patients receiving bupropion had greater rates of point-prevalence abstinence at the end of a seven-week course (44 versus 19 percent) and one year (23 versus 12 percent) [61]. A subsequent randomized controlled trial that enrolled over 8000 smokers confirmed that bupropion was more effective than placebo in patients with and without psychiatric comorbidity [8]. In that study, varenicline produced higher quit rates than bupropion, while nicotine patch produced comparable cessation rates to bupropion.

Other studies have demonstrated the efficacy of bupropion in specific populations, including in African-American smokers, and in smokers who have stable CVD or COPD [62-64]. The use of bupropion in patients with CVD is discussed below. (See 'Cardiovascular disease' below.)

Administration — Since sustained-release bupropion takes five to seven days to reach steady-state blood levels, it is started one week before a smoker's target quit date. The recommended dose is 150 mg/day for three days, then 150 mg twice a

day thereafter [3]. A lower dose of 150 mg/day (rather than 300 mg/day) is an option for smokers who do not tolerate the full dose due to side effects. Two randomized trials found that the 150 mg/day dose was as effective as the 300 mg/day dose and associated with fewer side effects [61,65].

We recommend treating with bupropion for at least 12 weeks. Longer duration of treatment can be considered in individual cases, based on previous quit attempts and patient preference. However, if the rationale for longer treatment is improved mood, it is important to assess the change in depressive symptoms from the initiation of treatment and to make dosing adjustments accordingly. (See "Unipolar major depression in adults: Choosing initial treatment", section on 'Dose'.)

Longer-duration therapy may prevent relapse in successful quitters. A randomized trial of 461 smokers who successfully quit smoking after seven weeks of bupropion therapy compared active ongoing treatment with bupropion 300 mg per day with placebo for one year [66]. Patients receiving active therapy had a higher abstinence rate at one year (51 versus 42 percent) that persisted 16 weeks after discontinuation of therapy (47 versus 37 percent), a longer median time to relapse after cessation of therapy (156 days versus 65 days), and less weight gain at two years (4.1 versus 5.4 kg). However, the abstinence rate at two years was the same in both groups (41 versus 40 percent).

Safety — There are concerns about neuropsychiatric side effects with bupropion. In the review of post-marketing case reports discussed above, bupropion was associated with increased risks of suicidal/self-injurious behavior or depression that were smaller than those observed for varenicline but greater than seen in patients taking NRT [46]. However, a randomized trial comparing varenicline, bupropion, and the nicotine patch with placebo found no difference in adverse neuropsychiatric effects [8]. (See 'Neuropsychiatric effects' above.).

Based on this information, the FDA rescinded the black box warning about serious neuropsychiatric side effects associated with bupropion.

Bupropion reduces the seizure threshold and is contraindicated in patients with a seizure disorder or predisposition to seizure. In clinical trials of bupropion in smoking cessation, the risk of seizure was 0.1 percent. The risk of seizure with bupropion use is dose-dependent and is most often described in the setting of overdose and/or in patients with other risk factors for seizures.

The most common side effects of bupropion are insomnia, agitation, dry mouth, and headache. Bupropion is safe for use among smokers with stable CVD [63] and COPD [64]. While studies have not shown efficacy in smokers hospitalized for acute myocardial infarction, bupropion was found to be safe for use in those patients [67-69].

Bupropion may be a good choice for smokers who are especially concerned about post-cessation weight gain, which bupropion blunts temporarily [70]. (See "Obesity in adults: Drug therapy", section on 'Bupropion'.)

Other side effects of bupropion are discussed separately. (See "Atypical antidepressants: Pharmacology, administration, and side effects", section on 'Bupropion'.)

OTHER MEDICATIONS — A number of other pharmacologic agents have been evaluated as aids to smoking cessation, all of which have less or uncertain efficacy in comparison to the first-line agents [14].

●Nortriptyline – Nortriptyline may be considered a second-line therapy for smoking cessation. (See 'Patients who fail to quit' below.)

●**Cytisine** – Cytisine is a plant derivative that, like varenicline, is a partial agonist at the alpha-4 beta-2 nicotinic acetylcholine receptor [29]. It has been used for smoking cessation in Eastern Europe for decades but is not available in the United States or Western Europe [71,72]. Cytisine appears to be a reasonable option for smoking cessation where available and may offer a low-cost pharmacologic alternative to therapies such as varenicline.

A 2013 systematic review and meta-analysis of two high-quality trials concluded that cytisine is effective for smoking cessation with efficacy that appears to be comparable with other pharmacologic therapies; gastrointestinal side effects are more common with cytisine than with placebo [73]. A subsequent randomized trial in 1310 adult daily smokers found that compared with nicotine replacement therapy (NRT), self-reported continuous abstinence was higher with cytisine at one month (40 versus 31 percent) and six months (22 versus 15 percent) [74]. More adverse events were reported with cytisine; the most common adverse events were nausea and vomiting and sleep disorders.

●Clonidine – Despite promising initial studies, clonidine is now generally regarded as having limited efficacy for smoking cessation [75-77]. Although a meta-analysis suggested that clonidine was superior to placebo in facilitating smoking cessation, the majority of individual studies evaluating the drug have not demonstrated statistically significant efficacy [14]. Adverse effects, such as drowsiness, fatigue, and dry mouth, also limit the use of clonidine as a smoking cessation aid.

●**Selective serotonin reuptake inhibitors (SSRIs)/anxiolytics** - SSRIs and anxiolytic drugs generally have not been shown to be effective for smoking cessation [14,60,78].

●**Nicotine vaccine** – A novel experimental approach to treating tobacco dependence is a vaccine that causes the body to generate specific anti-nicotine antibodies [79]. The antibody binds to nicotine that reaches the bloodstream from smoking cigarettes. The resulting nicotine-antibody complex is too large to cross the blood-brain barrier. Thus, nicotine from tobacco smoke is unable to reach the central nervous system nicotinic receptors to produce the rewarding effects of smoking [80,81]. Theoretically, a decrease in the rewarding effects of nicotine will lead to smoking cessation. Several companies have taken candidate vaccines into clinical trials, but none has demonstrated efficacy versus placebo.

●**Electronic cigarettes** – Electronic cigarettes (e-cigarettes) use an electronic delivery system that aerosolizes nicotine. Many e-cigarette products are available that vary in their consistency and nicotine delivery. The role of e-cigarettes in smoking cessation treatment is unclear but trials are ongoing. (See "E-cigarettes".)

INITIATING THERAPY — With a few exceptions, choice of a first-line medication (combination nicotine replacement therapy [NRT], varenicline, or bupropion) is based on patient preference after discussion with a clinician (table 2). In the United States, the Affordable Care Act's provisions require health insurance plans to cover medications approved by the US Food and Drug Administration (FDA) for smoking cessation, although this has not yet been universally implemented [82,83].

Patients who fail to quit on initial therapy should be evaluated to be sure that they have used the medication correctly and for an adequate trial. Patients who fail to quit despite correct medication use with initial therapy may benefit from switching to a different medication or combination medication therapy. (See 'Patients who fail to quit' below.)

In addition to medication, all smokers should be offered behavioral counseling for smoking cessation. (See "Overview of smoking cessation management in adults", section on 'Treatment options' and "Behavioral approaches to smoking cessation".)

For any smoker attempting to quit, we recommend scheduling a follow-up contact (a visit or more likely, a telephone call) one to two weeks after starting any pharmacotherapy to monitor for adverse effects and provide reinforcement for smoking cessation. Close follow-up is particularly important in patients started on varenicline and bupropion due to concerns about neuropsychiatric side effects. (See "Overview of smoking cessation management in adults", section on 'Arrange follow-up' and 'Neuropsychiatric effects' above.)

Comparative efficacy and safety — When choosing between combination NRT, varenicline, or bupropion, we regard combination NRT or varenicline as roughly equivalent first-line choices (table 2) [14].

Bupropion or single-type NRT is a reasonable alternative based on cost, patient preferences, comorbid diseases (eg, depression), and side effect profiles. Bupropion may be attractive to smokers who are especially concerned about post-cessation weight gain, which bupropion blunts temporarily [70].

We recommend taking a psychiatric history prior to prescribing varenicline and avoiding it in smokers with current unstable psychiatric status or history of past-year suicidal ideation. Bupropion is contraindicated in patients with a seizure disorder or a predisposition to seizure. (See 'Psychiatric illness' below and 'Safety' above.)

Randomized trials have found varenicline to be superior to bupropion [8,32-34,47,84]. One randomized trial has directly compared the efficacy of varenicline with combination NRT. The trial included 1086 smokers and compared 12 weeks of varenicline, nicotine patch, and nicotine patch plus nicotine lozenge therapy [16]. The trial found no differences in biochemically confirmed rates of smoking abstinence among the three groups.

Studies also suggest that varenicline is superior to the nicotine patch. A 2016 meta-analysis including open-label randomized controlled trials found eight trials comparing varenicline with the nicotine patch [84]. More patients were likely to be abstinent at 24 weeks on varenicline (relative risk [RR] 1.25 (95% CI 1.14 to 1.37)).

Issues in specific populations — While choice of pharmacotherapy is generally based on patient preference, pharmacotherapy may need to be tailored for patients with comorbidities (eg, psychiatric illness) or patients in specific populations (eg, hospitalized smokers or light smokers).

Psychiatric illness — Evidence indicates that the same medications that are effective for smokers without psychiatric comorbidity also work for smokers with psychiatric illness [8]. A randomized trial that include 4116 smokers with current or a history of psychiatric diagnoses found that varenicline was more effective than bupropion or the nicotine patch, although the absolute quit rates were lower in smokers with psychiatric comorbidity and in those without. Varenicline, bupropion, and nicotine patch did not differ in the proportion of smokers who developed moderate to severe neuropsychiatric symptoms. We avoid using varenicline in patients with a current unstable psychiatric status or a history of suicidal ideation. Combination NRT is a good choice in individuals for whom the safety of varenicline is a concern. Bupropion may be helpful for smoking cessation in patients with depression and schizophrenia but can exacerbate illness in patients with bipolar disorder.

Care should be coordinated with their psychiatrist. (See 'Neuropsychiatric effects' above.)

●**Depression** – For patients with mild untreated depression, bupropion is theoretically an attractive first-line agent since it has the ability to treat both depression and smoking. However, there is no evidence demonstrating the superiority of bupropion over other agents in this group of patients [85]. In patients with more severe depression who are receiving multiple antidepressant agents, coordination of care with the patient's psychiatrist is essential before making pharmacotherapeutic recommendations.

While we consider varenicline a safe option in smokers with stable depression who do not have a history of suicidal ideation, there are limited data in this population. In a randomized trial comparing varenicline with placebo in 525 adult smokers with stable, treated current or past depression, there was no difference in rates of suicidal ideation and suicidal behavior, with neither group showing overall worsening of depression or anxiety [86]. However, the trial had a high rate of loss to follow-up (approximately one-third of patients in both groups).

●**Schizophrenia** – Bupropion or varenicline are is considered first-line therapies for smoking cessation in patients with schizophrenia. In a meta-analysis including seven randomized trials of patients with schizophrenia, smoking cessation rates at the end of treatment were higher with bupropion compared with placebo (RR 3.03, 95% 1.69-5.42) [87]. Smoking cessation rates were also higher compared with placebo in the two trials evaluating varenicline (RR 4.74, 95% CI 1.34-16.71). There was no difference in psychiatric symptoms; however, there were reports of suicidal ideation and behavior in two patients taking varenicline.

A randomized trial in 127 smokers with schizophrenia or schizoaffective disorder found that, compared with placebo, varenicline was associated with higher smoking cessation rates at 12 weeks (19 versus 4 percent on placebo) [88]. Varenicline was well-tolerated and did not exacerbate symptoms of schizophrenia. Another randomized trial studied 87 patients with schizophrenia or bipolar disorder who had achieved smoking cessation while receiving open-label varenicline and cognitive behavioral therapy [89]. Maintenance therapy with varenicline was associated with higher abstinence rates (60 versus 19 percent on placebo) at 52 weeks. There was no evidence that treatment with varenicline affected psychiatric symptoms or events.

●**Bipolar disorder** – Nicotine replacement may be a good first-line choice for patients with bipolar disorder. Antidepressant therapy may trigger mania in patients with bipolar disorder. For this reason, we avoid bupropion in smokers with bipolar disorder. While varenicline appeared to be safe in the study cited above, this was a small study in selected patients who were followed closely [89]. (See "Bipolar disorder in adults: Choosing maintenance treatment", section on 'Potentially problematic drugs'.)

Cardiovascular disease — In patients with stable cardiovascular disease (CVD), we suggest the same treatments as those in the general population. Both NRT and bupropion are safe in this population [63,90-95]. Concerns have been raised about varenicline in this population, but our interpretation of the data is that varenicline is safe in patients with stable CVD and of little, if any, risk in patients with unstable CVD. (See "Cardiovascular effects of nicotine", section on 'Safety of nicotine replacement therapy' and 'Cardiovascular effects' above.)

The initiation of NRT in patients after acute coronary syndrome (ACS) is discussed separately. It is likely that the benefits of smoking cessation outweigh any potential risks of NRT in most smokers with ACS. (See "Overview of the non-acute management of unstable angina and non-ST elevation myocardial infarction", section on 'Smoking cessation' and "Overview of the non-acute management of ST elevation myocardial infarction", section on 'Smoking cessation'.)

Bupropion is efficacious for smoking cessation in patients with stable CVD [63]. Several trials that started bupropion in hospital in patients with acute myocardial infarction did not find the drug to be efficacious compared with placebo for long-term smoking cessation [67-69]. In the largest trial, 393 patients post-myocardial infarction were randomized to bupropion or placebo for nine weeks and followed for one year [68]. At 12 months, point prevalence and continuous abstinence rates did not differ between the two groups. One likely reason for the discrepancy of findings of efficacy of bupropion in stable versus unstable CVD is the setting in which use is initiated. In the acute myocardial infarction setting, bupropion has been started in hospital. Hospitalized acute myocardial infarction patients are usually discharged home, with its many cues to smoke, before the five to seven days needed to achieve adequate blood levels of the drug.

Randomized trials have found that varenicline is safe and efficacious for smoking cessation in patients with CVD. A randomized trial in 714 smokers with stable CVD found that, compared with placebo, patients receiving 12 weeks of varenicline had a higher rate of continuous abstinence from weeks 9 to 52 (19.2 versus 7.2 percent)

[36]. There was no difference in cardiovascular events or mortality. Another randomized trial in 302 smokers with ACS initiated in-hospital placebo or varenicline for 12 weeks (in addition to low-intensity counseling) [96]. At 24 weeks, patients who received varenicline had higher rates of point abstinence (47.3 versus 32.5 percent) and continuous abstinence (35.8 versus 25.8 percent). Adverse events within 30 days of study drug discontinuation were similar between groups.

Hospitalized smokers — NRT is a reasonable option in hospitalized smokers, as NRT products immediately treat nicotine withdrawal symptoms while varenicline and bupropion take time to reach steady state.

A 2012 meta-analysis of randomized trials in hospitalized smokers found that pharmacotherapy with NRT (six trials) appeared to improve smoking cessation compared with intensive counseling alone (RR 1.54, CI 1.34-1.79); varenicline (two trials) showed a trend toward improved rates (RR 1.28, CI 0.95-1.74), while bupropion (three trials) did not show additive benefit (RR 1.04, CI 0.75-1.45) [97].

Patients who use NRT in hospital are more likely to continue to use it after discharge [98] and may be more likely to quit long-term. A randomized trial in 397 hospitalized smokers that allowed smokers a choice of medication as part of a post-discharge intervention found that most hospitalized smokers chose NRT products over bupropion or varenicline [99].

Pregnant women — Pharmacotherapy for smoking cessation in pregnant women is discussed in detail elsewhere. (See "Cigarette smoking: Impact on pregnancy and the neonate", section on 'Pharmacotherapy'.)

Adolescents — Pharmacotherapy for smoking cessation in adolescents is discussed in detail elsewhere. (See "Management of smoking cessation in adolescents", section on 'Pharmacotherapy'.)

Light smokers — While evidence regarding the efficacy of medications in light smokers is limited, it is reasonable to think they have similar efficacy in this population. NRT is an appropriate option because the dosage and frequency of use can be adjusted based on nicotine withdrawal symptoms and lower doses may be indicated. There is no theoretical reason to reduce the dose of varenicline or bupropion in this population.

Preoperative smokers — In the preoperative setting, there is often a special motivation to stop smoking in order to reduce associated postoperative complications. Pharmacotherapy in preoperative smokers has been found to increase smoking cessation rates and decrease postoperative complications.

NRT (combined with behavioral interventions) is effective in these patients [100]. The potential benefits of preoperative smoking cessation counseling and nicotine replacement were demonstrated in a prospective, randomized trial of 120 smokers awaiting major orthopedic surgery [101]. Patients who underwent counseling and nicotine replacement six to eight weeks prior to surgery had a lower rate of overall postoperative complications compared with patients in the control group (18 versus 52 percent).

Varenicline has also been shown to be effective in this population. A randomized trial in 286 smokers scheduled for elective noncardiac surgery compared varenicline with placebo and found that preoperative treatment with varenicline improved the abstinence rate at 12 months (36.4 versus 25.2 percent, RR 1.45, 95% CI: 1.01-2.07) [102]. All patients received counseling regarding smoking cessation.

PATIENTS WHO FAIL TO QUIT — Before changing medications, we recommend interviewing patients who fail to quit on a drug to ascertain that the drug was used correctly and for a sufficient period of time, as this is often not the case. It is important to distinguish between failure due to an incorrect use of the medication (eg, chewing nicotine gum too rapidly), failure of the medication to reduce nicotine withdrawal, or intolerance of medication side effects.

For patients who do not tolerate medication side effects, we suggest lowering the dose or switching to an alternate agent. Some nicotine replacement therapy (NRT) products and bupropion may be titrated down to lower doses. There is some evidence that the efficacy and side effects of pharmacotherapies may vary by a patient's nicotine metabolism [103]. (See 'Combination nicotine replacement therapy' above and 'Administration' above.)

Smokers who had severe withdrawal symptoms should have the medication dose increased if possible.

In patients who are unable to quit with an adequate trial of all acceptable first-line therapies, we suggest adding another of the first-line therapies or nortriptyline for combination pharmacologic therapy or consider the use of nortriptyline monotherapy. Combinations of drugs appear be more effective than monotherapy but can also lead to more side effects [3,12,13,104]. The following are options for second-line therapy:

●**Nicotine patch and** varenicline – In a randomized trial, 435 smokers were assigned to treatment with varenicline combined with either a nicotine or a placebo patch [105]. Nicotine or placebo patches were started two weeks before the quit day and varenicline was started one week before the quit day. Both patches and varenicline were continued for 12 weeks. Treatment with varenicline and the nicotine patch had a higher rate of continuous abstinence compared with varenicline and the placebo patch (49 versus 33 percent) at six months after the end of drug treatment.

●Bupropion **and** varenicline – A randomized trial in 506 smokers receiving 12 weeks of therapy comparing bupropion and varenicline with varenicline monotherapy found smokers treated with combination therapy had higher rates of prolonged abstinence at 12 and 26 weeks [106]. At 52 weeks, the rates of seven-day abstinence appeared to be higher with combination therapy, although the difference was not significant (37 versus 29 percent; odds ratio [OR] 1.40, 95% CI 0.96-2.05). The combination was well-tolerated.

●Bupropion **and NRT** – In a 2014 meta-analysis of 12 randomized trials, there was only a nonsignificant trend toward higher rates of abstinence with the combination of NRT and sustained-release bupropion than with NRT alone (relative risk [RR] 1.19, 95% CI 0.94-1.51) [60].

●Nortriptyline **and NRT** – In a 2014 meta-analysis, adding nortriptyline to NRT (four trials) showed a trend toward higher rates of abstinence compared with NRT alone (RR 1.21, CI 0.94-1.55); this result is similar to what was found with adding bupropion to NRT [60].

●Nortriptyline – Nortriptyline is a tricyclic antidepressant. Randomized trials have shown that it has efficacy in aiding smoking cessation [60,64,107-111]. A 2014 meta-analysis of six randomized trials found that nortriptyline increased the likelihood of abstinence (RR 2.03, 95% CI 1.48-2.78) [60]. Patients receiving nortriptyline were more likely to report side effects including dry mouth and sedation.

RELAPSE — For patients who successfully quit but experience subsequent relapse, we suggest that patients be restarted on a pharmacologic agent that previously worked for the patient. This strategy may be enhanced with more intensive behavioral support and/or intensifying pharmacotherapy by adding another medication. (See "Overview of smoking cessation management in adults", section on 'Relapse' and "Behavioral approaches to smoking cessation".)

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

●Basics topics (see "Patient education: Quitting smoking (The Basics)" and "Patient education: Cough in adults (The Basics)")

●Beyond the Basics topic (see "Patient education: Quitting smoking (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

●We recommend that smokers be managed with a combination of behavioral support and pharmacologic therapy (**Grade 1B**). The combination of counseling and pharmacologic treatment can produce higher quit rates than either one alone. (See "Overview of smoking cessation management in adults" and "Behavioral approaches to smoking cessation".)

●The first-line pharmacologic therapies for smoking cessation include nicotine replacement therapy (NRT), varenicline, and bupropion. (See 'First-line medications' above.)

●In the absence of specific safety concerns, the choice of pharmacotherapy should be based on patient preference after discussion with a clinician (table 2). We suggest either varenicline or combined nicotine replacement (a patch plus a short-acting form such as the gum or lozenge) as first-line pharmacologic therapy (**Grade 2B**).

Bupropion or single-type NRT are reasonable alternatives based on cost, patient preferences, comorbid diseases, and side effect profiles. Bupropion may be attractive to smokers who are especially concerned about post-cessation weight gain, which bupropion blunts temporarily. (See 'Comparative efficacy and safety' above.)

Combination NRT is a good choice in individuals for whom the safety of varenicline is a concern (eg, recent history of suicidal ideation). (See 'Psychiatric illness' above.)

●Pharmacotherapy for smoking cessation may need to be tailored for patients with comorbidities (eg, psychiatric illness) or patients in specific populations (eg, hospitalized smokers or light smokers). (See 'Issues in specific populations' above.)

●Patients who do not tolerate the side effects of one pharmacologic agent can have the dose lowered or be switched to an alternate agent. Before changing course, patients who fail to quit on a drug should be interviewed to determine that the drug was used correctly, as this is often not the case. (See 'Patients who fail to quit' above.)

●In patients who are unable to quit with first-line therapy, we suggest adding another of the first-line therapies or nortriptyline for combination pharmacologic therapy or considering the use of nortriptyline monotherapy as second-line options (**Grade 2C**). There is emerging evidence of benefit in combining varenicline with either nicotine replacement or bupropion, but the safety and efficacy of these combinations have not been well-established. (See 'Patients who fail to quit' above.)

●We suggest that patients who successfully quit but experience relapse be treated with the pharmacologic agent that previously worked for the patient (**Grade 2C**). This strategy may be enhanced with more intensive behavioral support or by combining therapy with another medication. (See 'Relapse' above.)

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