Smoking Cessation; 2015 Update

Para 2017

TABLE 50-1 Health Consequences of Smoking

Cancer

Acute myeloid leukemia
Bladder
Cervical
Esophageal
Gastric
Kidney
Laryngeal
Lung
Oral cavity and pharyngeal
Pancreatic

Cardiovascular Diseases

Abdominal aortic aneurysm
Coronary heart disease (angina pectoris, ischemic heart disease, myocardial infarction)
Cerebrovascular disease (transient ischemic attacks, stroke)
Peripheral arterial disease

Pulmonary Diseases

Acute respiratory illnesses
- Upper respiratory tract (rhinitis, sinusitis, laryngitis, pharyngitis)
- Lower respiratory tract (bronchitis, pneumonia)

Chronic respiratory illnesses
- Chronic obstructive pulmonary disease
- Respiratory symptoms
- Poor asthma control
- Reduced lung function

Reproductive Effects

Reduced fertility in women
Pregnancy and pregnancy outcomes
- Preterm, premature rupture of membranes
- Placenta previa
- Placental abruption
- Preterm delivery
- Low infant birth weight

Infant mortality
- Sudden infant death syndrome (SIDS)

Other Effects

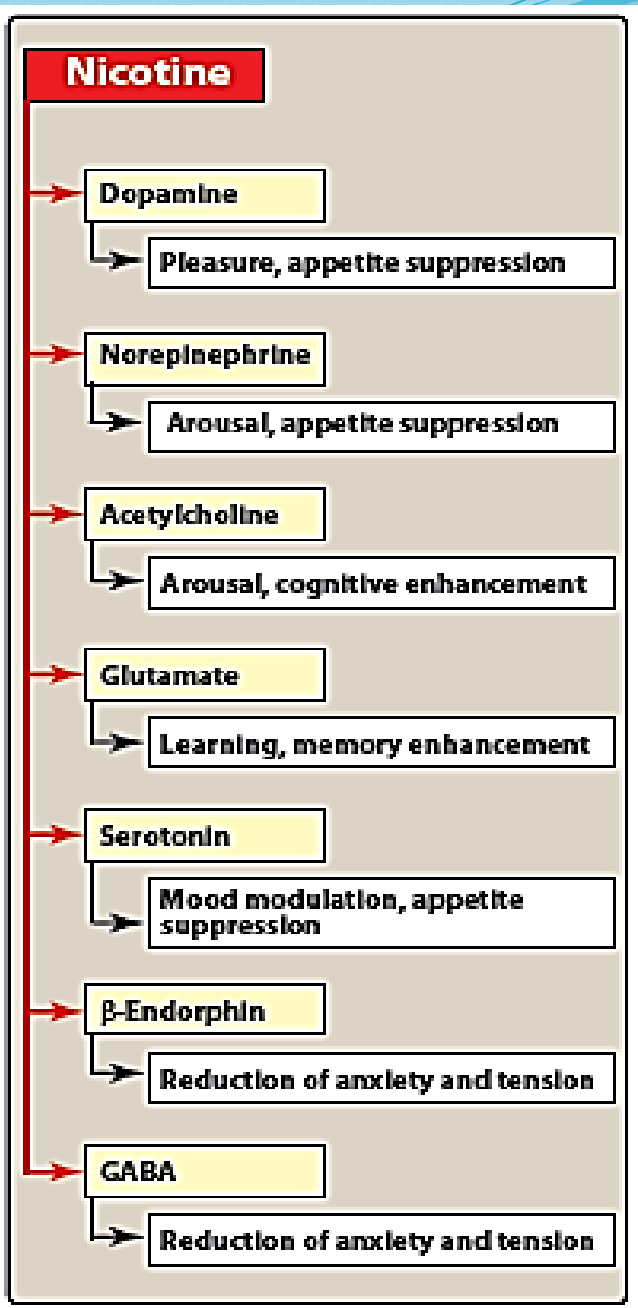
Cataract
Osteoporosis (reduced bone density in postmenopausal women, increased risk of hip fracture)
Periodontitis
Peptic ulcer disease (in patients infected with *Helicobacter pylori*)
Surgical outcomes
- Poor wound healing
- Respiratory complications

Nicotine

A component of cigarette smoke, *nicotine* is a poison with many undesirable actions. It is without therapeutic benefit and is deleterious to health. ***Depending on the dose, nicotine depolarizes autonomic ganglia, resulting first in stimulation and then in paralysis of all ganglia.***

The stimulatory effects are complex and result from increased release of neurotransmitter , due to effects on both sympathetic and parasympathetic ganglia. For example, enhanced release of dopamine and norepinephrine may be associated with pleasure as well as appetite suppression, the latter of which may contribute to lower body weight.

The overall response of a physiological system is a summation of the stimulatory and inhibitory effects of *nicotine*. *These include increased blood pressure and cardiac rate (due to release of transmitter from adrenergic terminals and from the adrenal medulla) and increased peristalsis and secretions. At higher doses, the blood pressure falls because of ganglionic blockade, and activity in both the GI tract and bladder musculature ceases.*



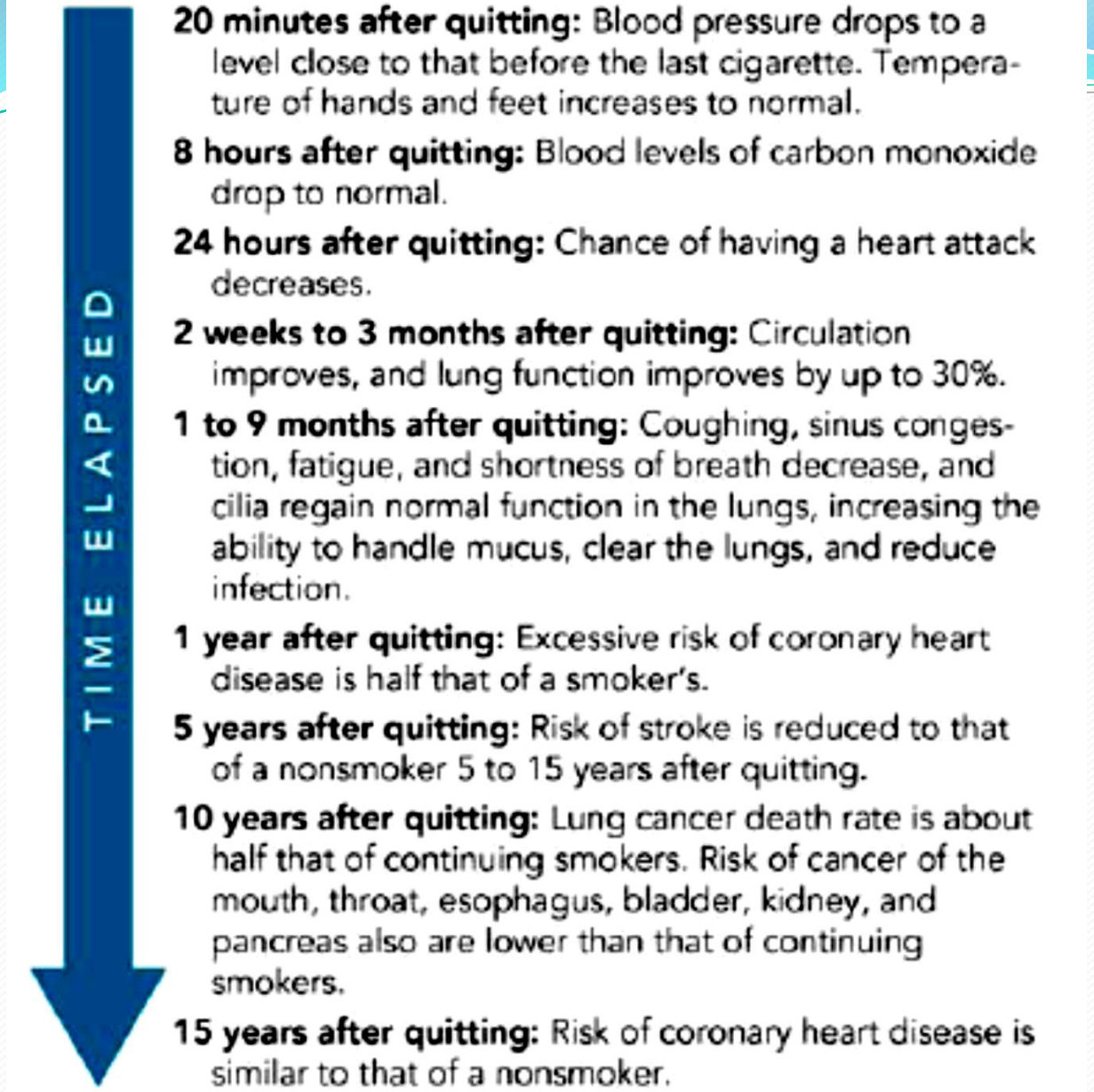


FIGURE 50-1 Health benefits of smoking cessation.

Recommendation:

Clinicians should encourage all patients attempting to quit to use effective medications for tobacco dependence treatment, except where contraindicated or for specific populations for which there is insufficient evidence of effectiveness (i.e., pregnant women, smokeless tobacco users, light smokers, and adolescents). (Strength of Evidence = A)

Each year more than 70% of smokers want to quit and about 40% try, but only about 3% to 5% of them are successful without formal help.

Tobacco dependence treatments are both clinically effective and cost-effective relative to other medical and disease prevention interventions

- *About 50% to 60% of initially successful quitters relapse within a year*.

- Intensive smoking cessation therapies including both counseling and pharmacotherapy should be recommended for smokers attempting to quit unless there are contraindications.

- **A recent study suggests that genetic makeup may influence an individual's response to specific smoking cessation medications.**

- **Therefore, it is reasonable to try another smoking cessation agent when an individual fails the initial agent.**

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: **seven first-line (FDA-approved) medications (bupropion SR, nicotine gum, nicotine inhaler, nicotine lozenge, nicotine nasal spray, nicotine patch, and varenicline)** and **two second-line (non-FDA-approved for tobacco use treatment) medications (clonidine and nortriptyline)** as being effective for treating smokers.

Each has been documented to increase significantly rates of long-term smoking abstinence. These results are consistent with other independent reviews.

No other medication treatments were consistently supported by the available scientific evidence.

Nicotine Replacement Therapy

- *Nicotine replacement therapy (NRT) medications deliver nicotine with the intent to replace, at least partially, the nicotine obtained from cigarettes and to reduce the severity of nicotine withdrawal symptoms.*

- Nicotine replacement products are effective in reducing the severity of withdrawal symptoms and cravings, and for reducing the reinforcing effects of tobacco-delivered nicotine.

- The meta-analysis results in the current smoking cessation guidelines show the **abstinence rates of nicotine therapies at six months range from 19% to 26.7%**. However, *a recent Cochrane review showed that nicotine replacement therapies increase the rate of quitting by 50% to 70%.*
- **Currently there is no scientific basis for recommending one form of nicotine replacement over others.**
- **The combination of a nicotine patch with a self-administered form of nicotine replacement therapy (e.g., gum, nasal spray, or lozenge) is more efficacious than a single form of nicotine replacement. However, *there is relatively little safety data on the combined use of nicotine replacement therapies, and nicotine combination therapy may increase the risk of nicotine overdose***

اسم الدواء	التركيز	التعبئة	بلد الشركة الصانعة	بلد الشركة المالكة	سعر الجمهور مع الضريبة
Clear Assiquit 10mg/16hr Patches	10 mg/16hr	7	الأردن	الأردن	**9.58**
Clear Assiquit 15mg/16hr Patches	15 mg/16hr	7	الأردن	الأردن	**9.58**
Clear Assiquit 5mg/16 hr Patches	5 mg/16hr	7	الأردن	الأردن	**9.58**
Nicorette Chew Gum	4 mg	105	السويد	السويد	**15.5**
Nicorette Chew Gum	2 mg	105	السويد	السويد	**12.24**
Nicorette Chew Gum	4 mg	30	السويد	السويد	**6.1**
Nicorette Chew Gum	2 mg	30	السويد	السويد	**4.24**
Nicorette Fresh Fruit	4 mg	30 Gum	السويد	السويد	**6.1**
Nicorette Fresh Fruit	2 mg	30 Gum	السويد	السويد	**4.24**
Nicorette Freshmint	2 mg	30 Gum	السويد	السويد	**4.24**

- Current guidelines *encourage patients to use nicotine combination therapy if they are unable to quit using a single agent.*
- Nicotine replacement therapy should be used with *caution in patients within two weeks following a myocardial infarction, in those with serious arrhythmias, or in those with serious or worsening angina pectoris*.

- *Of the nicotine products, the nicotine patch (e.g., NicoDerm, etc) has the highest compliance rate and lowest dependence rate, but it doesn't treat acute cravings*

Current guidelines recommend nicotine replacement therapy as a first-line smoking cessation therapy [Evidence level A, high quality meta-analysis].

In some smokers, use of nicotine patch longer than 12 weeks may be beneficial

Nicotine transdermal patch

- Apply the patch to a clean, dry, hairless area of skin on the upper chest, upper arm, or hip as directed by the package directions.
- Avoid areas of irritated, oily, scarred, or broken skin.
- Remove the patch from the package, peel off the protective strip, and immediately apply the patch to your skin.
- With the sticky side touching the skin, press the patch in place with the palm of your hand for about 10 seconds.
- Be sure the patch is held firmly in place, especially around the edges. Wash your hands with water alone after applying the patch. If the patch falls off or loosens, replace it with a new one.

Nicotine transdermal patch

Dosing

- 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.
- *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 .
- 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
- 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.

Nicotine transdermal patch

- ***You should wear the patch continuously for 16 to 24 hours***, depending on the specific directions inside your nicotine patch package. ***The patch may be worn even while showering or bathing***. Remove the patch carefully, and dispose of it by folding it in half with the sticky sides touching.
- **After removing the used patch, apply the next patch to a different skin area to prevent skin irritation. Never wear two patches at once.**
- A switch to a lower strength patch may be considered after the first 2 weeks on the medication.
- A gradual reduction to lower strength patches is recommended to reduce nicotine withdrawal symptoms

Usual Duration of Therapies

Medication	Coding	Meaning
Nicotine Patch	Usual duration	6–14 weeks
	Long duration	> 14 weeks
	Usual dose/day	15 mg/16 hours/day 21 mg/24 hours/day
	High dose	> 25 mg/day
Nicotine Gum	Usual duration	6–14 weeks
	Long duration	> 14 weeks
Nicotine Inhaler and Nasal Spray	Usual duration	Up to 6 months
	Long duration	> 6 months
Bupropion SR	Usual duration	Up to 14 weeks
	Usual dose/day	150 mg once daily or twice daily
Varenicline	Usual duration	Up to 14 weeks
	Usual dose/day	1 mg daily or 1 mg twice daily (analyzed separately)

Nicotine Gum.

Recommendation:
Nicotine gum is an effective smoking cessation treatment that patients should be encouraged to use.
(Strength of Evidence = A)

Recommendation:
Clinicians should offer 4 mg rather than 2 mg nicotine gum to highly dependent smokers.
(Strength of Evidence = B)

Nicotine Gum.

- **How should this medicine be used**
- If you smoke your first cigarette more than 30 minutes after waking up, use the 2-mg gum. People who smoke their first cigarette within 30 minutes of waking up should use the 4-mg gum.
- Nicotine gum may be used regularly by chewing one piece of gum every 1 to 2 hours for the first 6 weeks, followed by one piece every 2 to 4 hours for 3 weeks, and then one piece every 4 to 8 hours for 3 weeks.
- If you have strong or frequent cravings, you may chew a second piece within one hour. *To improve your chances of quitting smoking, chew at least 9 pieces of nicotine gum each day for the first 6 weeks.*
- Chew nicotine gum slowly until you can taste the nicotine or feel a slight tingling in your mouth. Then stop chewing and place (park) the chewing gum between your cheek and gum. When the tingling is almost gone (about 1 minute), start chewing again; repeat this procedure for about 30 minutes.
- *Avoid eating and drinking for 15 minutes before and during chewing of nicotine gum.*
- ***Do not chew nicotine gum too fast, do not chew more than one piece of gum at a time, and do not chew one piece too soon after another***.
- Chewing one piece of gum after another continuously may cause hiccups, heartburn, nausea, or other side effects.
- **Do not chew more than 24 pieces a day.**
- You should stop using nicotine gum after 12 weeks of use. If you still feel the need to use nicotine gum after 12 weeks, talk to your doctor.

Nicotine Gum.

- 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.

Nicotine Lozenge

- **Recommendation:**

The nicotine lozenge is an effective smoking cessation treatment that patients should be encouraged to use. (Strength of Evidence = B).

- *Nicotine lozenges release nicotine slowly as they dissolve in the mouth. They are convenient and effective.*

Nicotine lozenges

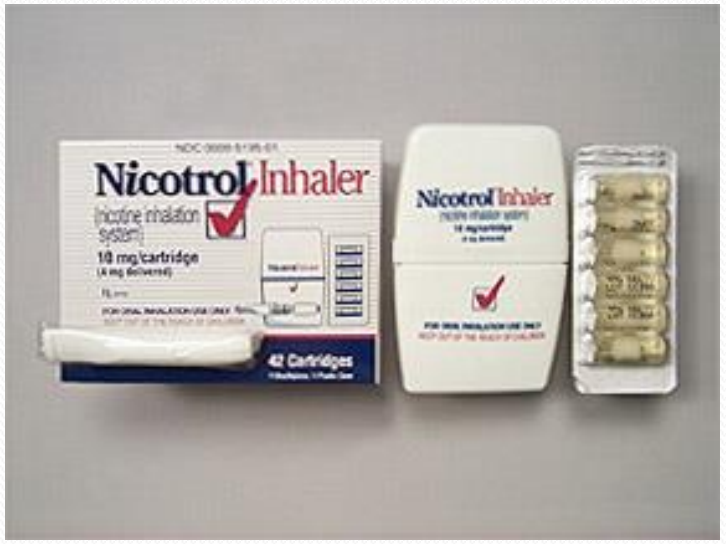
- If you smoke your first cigarette within 30 minutes of waking up in the morning, you should use 4-mg nicotine lozenges. If you smoke your first cigarette more than 30 minutes after waking up in the morning, you should use 2 mg-nicotine lozenges.
- For Weeks 1 to 6 of treatment, you should use one lozenge every 1 to 2 hours.
- **Using at least nine lozenges per day will increase your chance of quitting**.
- **For Weeks 7 to 9, you should use one lozenge every 2 to 4 hours. For Weeks 10 to 12, you should use one lozenge every 4 to 8 hours.**
- *Do not use more than five lozenges in 6 hours or more than 20 lozenges per day*.
- Do not use more than one lozenge at a time or use one lozenge right after another. Using too many lozenges at a time or one after another can cause side effects such as hiccups, heartburn, and nausea.
- To use the lozenge, *place it in your mouth and allow it to slowly dissolve. Do not chew or swallow lozenges. Once in a while, use your tongue to move the lozenge from one side of your mouth to the other. It should take 20 to 30 minutes to dissolve*. Do not eat while the lozenge is in your mouth.

Nicotine Inhaler.

- **Recommendation: The nicotine inhaler is an effective smoking cessation treatment that patients should be encouraged to use. (Strength of Evidence = A).**

- Nicotine nasal spray provides fast nicotine delivery, but it is associated with poor compliance rate and potential for dependence.

- *Nicotine inhaler replaces the hand-to-mouth action of cigarette smoking, but it is associated with only moderate compliance*



Nicotine Inhaler.

- 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.

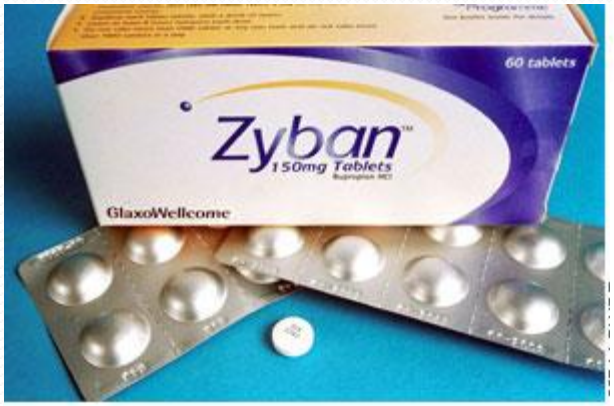
nicotine nasal spray

- 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
- 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

- **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

Bupropion Sustained Release

- Bupropion SR (*Zyban*) was the first non-nicotine medication approved for smoking cessation.
- It works by blocking neural re-uptake of dopamine (relieves cravings) and/or norepinephrine (relieves nicotine withdrawal).



- A Cochrane review of 40 bupropion trials found that ***it doubles the chances of smoking cessation compared with placebo.*** Bupropion has also been shown to decrease nicotine withdrawal symptoms and cravings.

- ***Pooled analyses of studies with bupropion generally showed similar quit rates as nicotine replacement therapy.***

- The most commonly reported **side effects with bupropion are insomnia (35% to 40%) and dry mouth (10%).** Taking the second dose of the day earlier in the afternoon (at least eight hours after the first dose) may help reduce insomnia side effects.

- Bupropion is contraindicated in individuals with a history of seizure disorder or a history of an eating disorder. There are also reports of bupropion-induced mania in patients with bipolar-disorder; therefore, bupropion should be used with caution in this patient population.

- **Bupropion is recommended as first-line therapy for smoking cessation according to current guidelines [Evidence level A, high quality meta-analysis].**

- **Bupropion may be especially useful in smokers who also suffer depression.**

- **Bupropion can delay weight gain during therapy; therefore, it may be appropriate for those who are concerned with weight gain.**

- **Unlike nicotine replacement therapy, bupropion should be started one to two weeks before the set quit date.**

Bupropion Sustained Release

- 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
- A lower dose of 150 mg/day(rather than 300 mg/day) may be an option for smokers who do not tolerate the full dose due to side effects

- **Bupropion can be used in combination with nicotine replacement therapies. Combination therapy may be useful when managing smokers who have high levels of nicotine dependence and in those with a history of psychiatric problems.**

- However, a significant benefit with nicotine replacement therapy plus bupropion combination is yet to be confirmed. In one study, the combination of bupropion and nicotine patch significantly increased the quit rate over placebo or patch alone, but not over bupropion alone.

- In another study, the quit rates of nicotine lozenge alone, bupropion alone, and bupropion plus nicotine lozenge combination appear to be comparable. A study of triple combination therapy with bupropion sustained release, nicotine patch, and nicotine oral inhaler showed that the abstinence rate with this combination and the time to relapse rate was significantly higher than nicotine replacement alone.

- Insomnia and anxiety occurred more frequently in the triple combination group. Blood pressure monitoring is recommended as hypertension has been associated with nicotine replacement and bupropion combination therapy.

Varenicline

- **Recommendation: Varenicline is an effective smoking cessation treatment that patients should be encouraged to use. (Strength of Evidence = A)**

- Varenicline (*Chantix*, *Champix* [Canada]) is the first *partial alpha-4-beta-2 nicotinic acetylcholine receptor agonist* indicated as an aid to smoking cessation.
- 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
  - **The partial stimulation of the nicotinic receptor helps reduce the severity of the smoker's craving and withdrawal symptoms.**
- In addition, *if a person smokes a cigarette while receiving varenicline, the sense of satisfaction associated with smoking may potentially be decreased.*

اسم الدواء	التركيز	التعبئة	بلد الشركة الصانعة	بلد الشركة المالكة	سعر الجمهور مع الضريبة
Champix 0.5	**0.5 mg**	56	ألمانيا	بريطانيا	**44.74**
Champix 0.5mg & 1.0mg	**1, 0.5 mg**	11 tab * 0.5mg & 14 tab * 1.0mg	ألمانيا	بريطانيا	**43.05**
Champix 1mg	**1 mg**	56	ألمانيا	بريطانيا	**75.83**
Champix 1mg Tablet	**1 mg**	28	ألمانيا	بريطانيا	**43.08**

- Varenicline was shown to be effective in reducing the urge to smoke and patients treated with varenicline were more likely to maintain abstinence throughout the follow-up period compared to placebo.

- Patients who received varenicline reported a significantly greater decrease in craving and withdrawal symptoms compared to those who received placebo.

- **In addition, patients who received varenicline also reported a significant decrease in smoking satisfaction and psychological reward from smoking compared to those who received placebo.**

Varnecline

- **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*
- **Nausea can also be minimized by taking varenicline with food and a full glass of water.**

- **Meta-analyses have shown varenicline to be more effective than bupropion or nicotine patch.** Smokers treated with varenicline are 1.5 times more likely to have quit at one year (RR 1.52, 95% CI 1.22 to 1.88) than those treated with bupropion.

- Varenicline appears to offer a modest benefit over nicotine patches in an open label trial (1.3 times more likely to quit at one year; RR 1.31, 95% CI 1.01 to 1.71).

- Results from a recently published randomized trial in patients with established heart disease indicate that varenicline significantly improved smoking cessation rates vs placebo and the cardiovascular outcomes were similar between varenicline and placebo groups.

- However, a definitive conclusion about varenicline safety in patients with established cardiovascular disease can't be made due to the limited number of patients studied (n=714) and short duration (52 week follow up)

- The most common adverse events associated with the target dose of 1 mg twice daily in 12-week studies were *nausea (30%), insomnia (18%), headaches (15%), abnormal dreams (13%), constipation (8%), flatulence (6%), vomiting (5%), and change in taste perception (5%).*

- Psychiatric side effects that occurred "frequently" (in >1% to <10% of patients, but not more than 0.5% incidence of placebo group) included anxiety, depression, emotional disorders, irritability, and restlessness.
- Nausea and vomiting can sometimes be reduced by slower dosage titration or by taking varenicline after a meal with fluids.

- 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

Neuropsychiatric effects of varnecline

- Varenicline may have serious neuropsychiatric side effects in some patients, but the nature and magnitude of this risk is not well-defined.
- It is recommended to take a careful psychiatric history prior to prescribing the drug, avoiding it in smokers with current unstable psychiatric status or a history of suicidal ideation.
- Other clinicians take a more conservative approach and do not offer the drug to patients with depression.
- Any patient started on varenicline should be monitored for neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed mood, suicidal ideation, and suicide attempts

Neuropsychiatric effects of varnecline

- Evidence regarding the neuropsychiatric side effects of varenicline is mixed.
- Neuropsychiatric side effects were not reported in randomized trials 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.
- **Varenicline was associated with an increased risk of sleep disorders (OR 1.62, 95% CI 1.29-2.07).**

Neuropsychiatric effects of varnecline

- Concerns of neuropsychiatric side effects from both varenicline and bupropion were raised in review of post-marketing case reports
- These were reported even in individuals with no history of psychiatric disease and without concomitant psychiatric medications. 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)
- *While some of the reported neuropsychiatric symptoms overlap with those of nicotine withdrawal, they were disproportionately reported in patients on varenicline. Nicotine withdrawal does not explain all of the reported adverse events because some occurred in smokers on varenicline who had not quit smoking.*
- **Also, it is possible that adverse events due to varenicline were over-reported due to extensive media coverage of the drug.**

- 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

Cardiovascular effects of VARNECLINE

- There is concern based on limited evidence that varenicline may increase 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.*
- *While varenicline is not contraindicated in smokers with stable cardiovascular disease (CVD), patients should be counseled to self-monitor for cardiovascular signs and symptoms that are new or worsening, and to get prompt medical care if needed.*

Cardiovascular effects of VARNECLINE

- 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
- 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
- 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*

Cardiovascular effects of VARNECLINE

- 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*
- 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
- 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)

- **It is important to keep in mind that adverse event reports only indicate that there is a suspected relationship between the adverse events and varenicline and do not establish a causal relationship.**

- Also note that *most people were taking multiple medications; therefore, there is possibility that these adverse events may be related to other drug use. Further investigation is needed to confirm a causal relationship.*

- **At this time, it is not clear whether varenicline itself is harmful or if nicotine withdrawal or tobacco use plays a role.** Smoking increases risk of heart disease, stroke, and diabetes.
- **Nicotine withdrawal can lead to depression, insomnia, irritability, anxiety, difficulty concentrating, restlessness, and an exacerbation of underlying psychiatric disorders**.

Current evidence indicates that varenicline is well-tolerated for periods up to a year and that extended treatment may be useful in reducing the likelihood of relapse. Current U.S. smoking cessation guidelines recommend varenicline as a first-line smoking cessation agent along with nicotine replacement products and bupropion.

[Evidence level A, high quality meta analyses].

The combination of varenicline plus nicotine replacement therapy appears to be safe and effective; however, the incidence of nausea, headache, vomiting, dizziness, dyspepsia, and fatigue was greater for combination therapy than for nicotine replacement therapy alone.

At this time, **there is not enough data to support the use of varenicline in combination with either bupropion sustained release or nicotine replacement therapy.**

Other Agents

- Several other non-nicotine therapies have been shown to be effective as an aid to smoking cessation.

- ***Nortriptyline or clonidine may be considered as second-line agents if a patient does not respond to any of the first-line agents [Evidence level A, high quality meta-analysis].***

- ***These agents are considered second line because they are not approved for smoking cessation and are associated with more adverse effects than the first-line agents.***

- **Another promising smoking cessation agent is the nicotine vaccine. The nicotine vaccine (*NicVAX* by Nabi Biopharmaceuticals) is currently under phase III clinical trials.**
- **The nicotine vaccine generates antibodies that bind to nicotine molecules and prevents them from binding to the nicotine receptors in the brain. Preliminary data show that the nicotine vaccine impairs the pleasure sensation induced by nicotine**

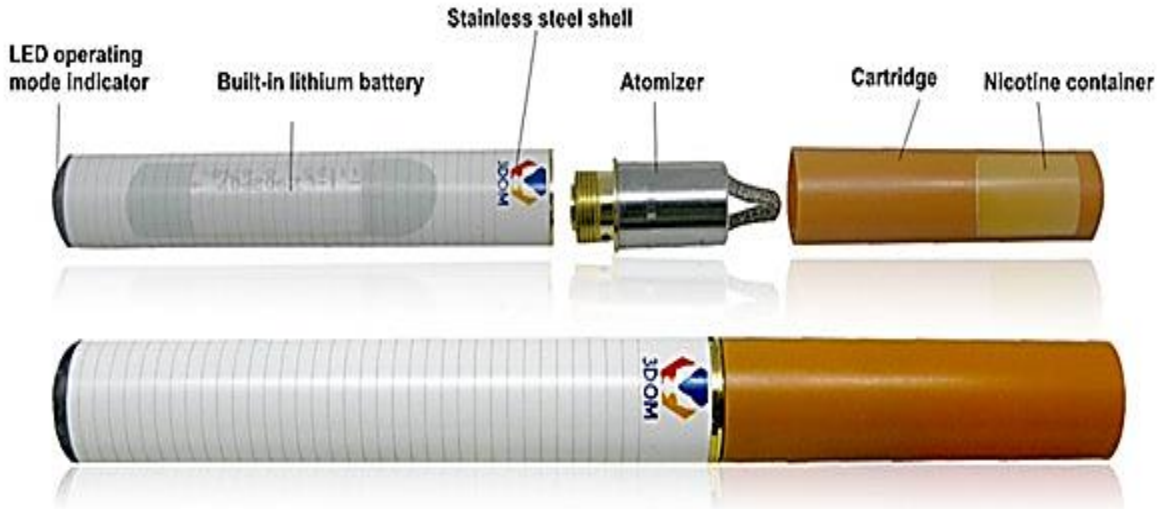
Other Agents

- Nabi Biopharmaceuticals conducted two Phase III trials of the drug. The first started in November 2009 and the second in March 2010. Nabi issued press releases announcing the start of these trials.
- In July 2011 it was announced that the first of two planned phase III trials for NicVAX failed, sending the market capitalization of NABI Biopharmaceuticals to below the value of its cash holdings.
- In November 2011, NABI announced that NicVAX had failed the second phase III clinical trial, performing no better than a placebo.

The practice of using smokeless tobacco as a smoking cessation aid is discouraged and smokeless tobacco users should be counseled to quit. At this time, there is insufficient evidence to support the use of pharmacotherapy to help patients quit their smokeless tobacco habit.

Also advise against using electronic cigarettes.

Electronic cigarettes deliver nicotine vapor using a battery powered device. There is no data to support their use as a smoking cessation aid and they may contain harmful chemicals.



Smoking Cessation in Pregnant Women

- Smoking during pregnancy is associated with adverse neonatal outcomes, ***placental abruption, spontaneous abortion, stillbirth, fetal growth restriction, preterm delivery, low birth weight, and sudden infant death syndrome.***

- While nicotine replacement therapies are well documented effective smoking cessation aids in non-pregnant smokers, their effectiveness in pregnant smokers is inconclusive. However, most recent data suggest that in pregnancy, using nicotine replacement therapy is no more harmful and is probably safer than continuing to smoke.

- **Cigarette smoke contains over 4,000 toxic substances, many of which are teratogenic or carcinogenic. In contrast, nicotine replacement therapy delivers pure nicotine, and therefore poses less risk to a pregnant women and her fetus.**

A few pharmacokinetic studies reported no higher plasma nicotine or nicotine levels with use of nicotine replacement therapy than with smoking ten or more cigarettes per day.

One of the reasons why nicotine may not be effective in pregnancy might be related to increased metabolism of nicotine during late pregnancy, making conventional doses of nicotine replacement therapy insufficient for pregnant women. Standard doses of nicotine replacement therapy may not be sufficient for a beneficial effect in late pregnancy.

Women who smoke five cigarettes or fewer per day should be advised to quit smoking by using behavioral support. For moderately or highly addicted pregnant smokers who cannot quit smoking with behavioral intervention alone, nicotine replacement therapy may be considered [Evidence level C, expert opinion].

College of Obstetricians and Gynecologists (ACOG), **bupropion may be considered during pregnancy and lactation when nonpharmacologic therapies fail** [Evidence level C, expert opinion].

Varenicline's safety in pregnancy is unknown and it is not recommended for use in this population.

Smoking Cessation in Adolescents

- The Institute for Clinical Systems Improvement (ICSI) recommends aggressive intervention for smoking cessation in adolescents 16 years and older, including community interventions, formal tobacco cessation programs, and pharmacotherapy.

- Most studies on smoking cessation have been conducted in adults. **The nicotine patch, nicotine gum, and bupropion are the only therapies that have been evaluated in adolescents.** Most studies in adolescents have shown significant reductions in the number of cigarettes smoked daily, but low overall abstinence rates. *The combination of bupropion plus nicotine patch is not more effective than nicotine patch alone in adolescent smokers.*

- A Cochrane review concludes that neither nicotine replacement therapy nor bupropion are effective for adolescent smokers and these agents should not be routinely recommended for this patient population [Evidence level A, high quality metaanalysis].

- **There is no data on varenicline use in adolescents.**

Educational Aids for Healthcare Professionals and Patients

Numerous useful smoking cessation resources are available on the internet for healthcare professionals and patients. Links to some of these useful websites are provided:

U.S.

- U.S. Department of Health and Human Services. http://www.surgeongeneral.gov/tobacco/ (educational material for both healthcare professionals and consumers)
- American Lung Association. http://www.lungusa.org/stop-smoking/ (educational material and quit smoking action plan for consumers)
- Centers for Disease Control and Prevention. http://www.cdc.gov/tobacco/quit_smoking/ (educational material for consumers)
- Smoking Cessation. http://www.smoking-cessation.org/ (educational material for consumers)
- Quitnet. http://www.quitnet.com/ (educational material and online peer support for consumers)

Canada

- Quitnow.ca British Columbia. http://bc.quitnet.com/ (educational material and online peer support for consumers)
- Canadian Cancer Society. http://www.cancer.ca/ccs/internet/standard/0,3182,3172_12971_langId-en,00.html (educational material for consumers)
- Canadian Council for Tobacco Control. http://www.cctc.ca/ (educational materials for healthcare professionals)

Questions		Points
How soon after you wake in the morning do you smoke your first cigarette?	Within 5 minutes 6-30 minutes 31-60 minutes After 60 minutes	3 2 1 0
Do you find it difficult to refrain from smoking in places where it is forbidden, e.g. in church, in the library, in cinema, etc.?	Yes No	1 0
Which cigarettes would you hate most to give up?	The first one in the morning All others	1 0
How many cigarettes do you smoke a day?	10 or less 11-20 21-30 31 or more	0 1 2 3
Do you smoke more frequently during the first hours after waking than during the rest of the day?	Yes No	1 0
Do you smoke even if you are so ill that you are in bed most of the day?	Yes No	1 0

Note: The higher the score, the more severe the addiction.

From: Heatherton, T.F., Kozlowski, L.T., Frecker, R.C., & Fagerstrom, K.O. (1991). The Fagerstrom test for nicotine dependence: a revision of the Fagerstrom tolerance questionnaire. *British Journal of Addiction, 86*, 1119-1127.

First line medications used to treat tobacco dependence in adults

Drug	OTC? (US)	Dosing	Administration †	Common adverse effects	Advantages	Disadvantages and precautions	Other notes
Nicotine patch	Yes	21 mg for >10 cigarettes/day 14 mg for ≤10 cigarettes/day 7 mg used when tapering	Apply 1 new patch daily May start patch before quit date Rotate application site	Skin irritation, insomnia, vivid dreams	Provides steady nicotine level Easiest nicotine product to use	User cannot alter nicotine level in case of craving	If removed before bedtime, takes 0.5 to 3 hrs after reapplication to reach effective levels
Nicotine gum	Yes	2 mg for <25 cigarettes/day 4 mg for ≥25 cigarettes/day	1 piece every hr Maximum: ≤24 pieces/day No food or drink for 30 min before and during use	Mouth irritation, jaw soreness, or heartburn, hiccups, nausea (gastrointestinal side effects usually due to overly vigorous chewing)	User controls nicotine dose Oral substitute for cigarettes	Unpleasant taste Can damage dental work Difficult for denture wearers to use	Proper chewing technique required (chew and park)

Nicotine lozenge	Yes	2 mg if first cigarette ≥30 min after waking 4 mg if first cigarette <30 min after waking	1 piece every 1 to 2 hrs Maximum: 5 lozenges/6 hrs 20 lozenges/day No food or drink for 30 min before and during use	Mouth irritation, hiccups, heartburn, or nausea	User controls nicotine dose Oral substitute for cigarettes Can be used by smokers with poor dentition or dentures	Unpleasant taste	
Nicotine inhaler	No	10 mg per cartridge	Inhale as needed (eg, every 1 to 2 hrs) Maximum: 16 cartridges/day	Mouth and throat irritation	User controls nicotine dose Oral substitute for cigarettes	Device visible when being used Use caution in reactive airway disease	Frequent puffing required
Nicotine nasal spray	No	0.5 mg per spray (10 mg/mL)	Apply one spray to each nostril every 1 to 2 hrs Maximum: 10 sprays/hr 80 sprays/day	Nasal and throat irritation, rhinitis, sneezing, cough, or teary eyes	User controls nicotine dose Most rapid delivery of nicotine among nicotine replacement products	Local irritation to nasal mucosa is difficult for many to tolerate	

Varenicline	No	0.5 mg pill	0.5 mg/day for 3 days, then 0.5 mg twice a day for 4 days, then 1 mg twice a day Start 1 to 2 weeks before quit date May be started up to 4 weeks prior to quit date	Nausea, insomnia, abnormal dreams, headache, skin rash (≤3%)	Dual action: relieves nicotine withdrawal and blocks reward from smoking Oral agent (pill)	Reduced dose in severe renal insufficiency Avoid in patients with unstable psychiatric status or history of suicidal ideation Monitor for neuropsychiatric symptoms*	
Bupropion sustained release	No	150 mg pill	150 mg/day for 3 days, then 150 mg twice a day Start 1 to 2 weeks before quit date	Insomnia, agitation, dry mouth, headache	Blunts postcessation weight gain while being used Oral agent (pill)	Monitor for neuropsychiatric symptoms* Contraindicated in patients with seizure disorder or predisposition	A lower dose of 150 mg per day is an option for patients who do not tolerate the full dose