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Drugs for Smoking Cessation

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Smoking tobacco remains the primary preventable cause of death in the US. Smoking cessation often requires both pharmacotherapy and behavioral support.[1,2]

NICOTINE REPLACEMENT — All FDA-approved nicotine replacement therapies (NRTs) deliver nicotine to nicotinic acetylcholine receptors in the central nervous system (CNS) in a lower dose and at a substantially slower rate than tobacco cigarettes and electronic nicotine delivery systems. Nicotine undergoes extensive first-pass metabolism, which limits its effectiveness in oral formulations. Nicotine gum, lozenges, and patches are available over the counter in the US for persons ≥18 years old; they appear to be as effective as nicotine products that require a prescription (oral inhaler and nasal spray).

Transdermal – Nicotine **patches** deliver nicotine continuously, but they require 6-8 hours to achieve peak serum concentrations and deliver nicotine to the CNS more slowly than any other NRT.

Rapid Onset – Nicotine from a **gum, lozenge, or oral inhaler** is absorbed through the buccal mucosa. Serum concentrations peak in 20-60 minutes. If nicotine is swallowed, first-pass metabolism reduces its bioavailability.

Nicotine **nasal spray** is the fastest-acting of all NRTs (but still much slower than cigarettes); serum concentrations peak in 4-15 minutes. Patients report that relief of nicotine withdrawal symptoms is faster with the nasal spray than with other NRT formulations.

When used as monotherapy, rapid-onset NRT should be taken on a regular schedule to prevent nicotine withdrawal symptoms.

Summary: Drugs for Smoking Cessation

- Smoking cessation can be safely and effectively achieved with pharmacotherapy and behavioral support.
- All nicotine replacement therapies (NRTs) appear to be about equally effective; combining a patch and a rapid-onset formulation is more effective than either one alone.
- Bupropion SR is as effective as single NRT.
- Varenicline is the most effective monotherapy and is as effective as combination NRT.
- The optimal duration of treatment is not clear; most patients should receive at least 3-6 months of effective therapy.
- The efficacy and safety of using electronic cigarettes for smoking cessation have not been established.

Efficacy – All NRTs increase smoking cessation rates by 50-60%. In the short term, they may also decrease weight gain associated with smoking cessation.[3,4] The combination of a patch and a rapid-onset formulation is more effective than either one alone.[5]

Adverse Effects – The nicotine **transdermal patch** is generally well tolerated, but pruritus at the application site, insomnia, and vivid dreams can occur. Removing the patch at bedtime can minimize or eliminate vivid dreams and other sleep disturbances. Nicotine **gum** can cause flatulence, indigestion, nausea, unpleasant taste, hiccups, and a sore mouth, throat, and jaw. Nicotine **lozenges** can cause mouth irritation, heartburn, hiccups, and nausea. The nicotine **oral inhaler** can cause mild mouth and throat irritation and cough; tolerance to the irritating effects usually develops within one or two days. Nicotine **nasal spray** can cause transient burning and stinging of the nasal mucosa, throat irritation, flushing, coughing, sneezing, lacrimation, rhinorrhea, and nausea; these adverse effects are a common cause of discontinuation.

Drug Interactions – Nicotine does not induce or inhibit CYP450 enzymes to a clinically significant extent. Tobacco smoke, not nicotine itself, induces CYP1A2, CYP2E1, and some uridine diphosphate-glucuronosyltransferases (UGTs); it may increase the metabolism and decrease the efficacy of drugs that are substrates

Table 1. Some Drugs for Smoking Cessation

Drug	Some Formulations	Usual Adult Dosage[1,2]	Cost[3]
Nicotine Replacement Therapies (NRTs)			
Nicotine transdermal patch[4] – generic	7, 14, 21 mg/24 hr patches	1 patch/day[5]	$44.20[6]
NicoDerm CQ (GSK)			63.30[6]
Nicotine polacrilex gum[4] – generic	2, 4 mg/pieces	8-24 pieces/day[5,7,8]	60.00
Nicorette Gum (GSK)			101.30
Nicotine polacrilex lozenge[4,9] – generic	2, 4 mg/lozenges	8-20 lozenges/day[5,7,10]	89.60
Nicorette Lozenge (GSK)			99.60
Nicotine oral inhaler – *Nicotrol* (Pfizer)	10 mg cartridges	4-16 cartridges/day[5]	416.60[11]
Nicotine nasal spray – *Nicotrol NS* (Pfizer)	200 sprays/10 mL bottles (0.5 mg/spray)	2 sprays 8-40x/day (max 10 sprays/hr)[4]	328.00[12]
Dopaminergic-Noradrenergic Reuptake Inhibitor			
Bupropion SR – generic	100, 150, 200 mg SR tabs[13]	150 mg PO once/day x 3 days, then 150 mg PO bid	21.00
Wellbutrin SR (GSK)[14]			445.30
Zyban (GSK)	150 mg SR tabs		247.80
Nicotinic Receptor Partial Agonist			
Varenicline tartrate – *Chantix* (Pfizer)	0.5, 1 mg tabs	0.5 mg PO once/day x 3 days, then 0.5 mg bid on days 4-7, then 1 mg bid	451.40

SR = sustained-release
1. Dosage reductions may be needed for hepatic or renal impairment.
2. Patients should receive a minimum of 3-6 months of effective therapy. In general, the dosage of NRTs can be tapered at the end of treatment; bupropion SR and varenicline can usually be stopped without a gradual dosage reduction, but some clinicians recommend a taper.
3. Approximate WAC for 30 days' treatment at the lowest usual dosage. WAC = wholesaler acquisition cost, or manufacturer's published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. June 5, 2019. Reprinted with permission by First Databank, Inc. All rights reserved. ©2019. www.fdbhealth.com/policies/drug-pricing-policy.
4. Available over the counter (OTC) for persons ≥18 years old.
5. See expanded table for dosage titration instructions, available at: medicalletter.org/TML-article-1576c.
6. Cost of 28 transdermal patches.
7. Eating or drinking within 15 minutes of using a gum or lozenge should be avoided.
8. A second piece of gum can be used within one hour. Continuously chewing one piece after another is not recommended.
9. Also available in a mini-lozenge.
10. Maximum of 5 lozenges in 6 hours or 20 lozenges/day. Use of more than one lozenge at a time or continuously using one after another is not recommended.
11. Cost of 168 10-mg cartridges; each cartridge delivers 4 mg of nicotine.
12. Cost of 3 10-mL bottles.
13. Only the generic 150-mg SR tablets are FDA-approved as a smoking cessation aid.
14. Not FDA-approved as a smoking cessation aid.

of these enzymes, such as clozapine (*Clozaril,* and others), olanzapine (*Zyprexa,* and generics), and propranolol (*Inderal*, and others).[6-8] The dosages of these drugs may need to be reduced when patients stop smoking.

BUPROPION — Bupropion, which is used mainly for treatment of depression, has some nicotinic-receptor-blocking activity and may also aid smoking cessation by inhibiting dopamine reuptake. A sustained-release (SR) formulation of bupropion *(Zyban)* is FDA-approved as a smoking cessation aid. Bupropion SR should be started 7-14 days before the target quit date to allow serum concentrations to reach steady state.

Efficacy – Bupropion SR has doubled smoking cessation rates compared to placebo in short-term trials. It has been as effective as single NRT in increasing long-term (≥6 months) smoking cessation rates and decreasing weight gain.[9]

Adverse Effects – Bupropion is generally well tolerated. The most common adverse effects in clinical trials were insomnia and dry mouth. Headache, nausea, and anxiety can also occur.[10] Bupropion SR has been associated with a dose-related increase in the risk of seizures; patients with a history of seizure, stroke, brain tumor, severe head injury, anorexia nervosa, or bulimia should not take bupropion.

Drug Interactions – Bupropion is primarily metabolized by CYP2B6 to hydroxybupropion, its most active metabolite. Drugs that are inhibitors or inducers of CYP2B6 may alter serum concentrations of hydroxybupropion, resulting in decreased efficacy or toxicity. Bupropion and hydroxybupropion inhibit CYP2D6; many antidepressants, antipsychotics, beta blockers, and class 1C antiarrhythmics are CYP2D6 substrates and should be used with caution in patients taking bupropion.[6] Use of bupropion with a monoamine oxidase (MAO) inhibitor or within 2 weeks of stopping one is contraindicated. Drugs that lower the seizure threshold, such as tricyclic antidepressants or theophylline, should be used with caution.

VARENICLINE — Varenicline tartrate *(Chantix)*, a nicotinic receptor partial agonist, is FDA-approved as a smoking cessation aid.[11] It selectively binds to $\alpha_4\beta_2$ neuronal nicotinic acetylcholine receptors, which mediate release of dopamine in the brain,

relieving cravings and withdrawal symptoms during abstinence. Varenicline has greater affinity for the $\alpha_4\beta_2$ receptor than nicotine, reducing the reward of smoking. Varenicline should be started 7 days before the target quit date to allow serum concentrations to reach steady state.

Efficacy – In randomized controlled trials, including both short-term trials and some lasting for up to one year, varenicline was more effective than single NRT or bupropion and as effective as combination NRT (nicotine patch plus a rapid-onset NRT) in increasing smoking cessation rates.[12,13] In one open-label trial in 1086 smokers, smoking cessation rates were similar with varenicline, combination NRT, and a nicotine patch alone at 26 and 52 weeks; the level of nicotine dependence among smokers at enrollment in the trial was relatively low.[14]

In an unpublished study, summarized in the package insert, 312 smokers 12-19 years old were randomized to receive weight-based varenicline or placebo for 12 weeks, followed by 40 weeks of no treatment; all patients received counseling during the study. No improvement in smoking abstinence rates was observed at weeks 9-12, compared to placebo. Varenicline is not recommended for use in patients ≤16 years old.

Adverse Effects – Varenicline is generally well tolerated. The most common adverse effects in clinical trials were nausea, sleep disturbances, abnormal dreams, headache, constipation, vomiting, and flatulence. In observational studies, use of varenicline has been associated with neuropsychiatric symptoms, exacerbations of pre-existing psychiatric disorders, suicidal behavior, and an increased rate of cardiovascular events.[15] However, in a retrospective cohort study in about 165,000 patients, varenicline was not associated with an increased risk of any cardiovascular or neuropsychiatric event, compared to NRT or bupropion.[16] Recent analyses of clinical trials have found no increase in suicidal behavior in patients treated with varenicline, compared to those treated with NRT, bupropion, or placebo.[17] Varenicline has increased smoking cessation rates in patients with psychiatric disorders without causing significant neuropsychiatric adverse effects.[18,19]

Drug Interactions – Varenicline has no clinically significant drug interactions.

A COMPARATIVE CLINICAL TRIAL — In a double-blind postmarketing trial (EAGLES), 8144 motivated-to-quit smokers with or without a diagnosed psychiatric disorder were randomized to receive varenicline 1 mg twice daily, bupropion SR 150 mg twice daily, a transdermal nicotine patch 21 mg daily with taper, or placebo for 12 weeks, followed by 12 weeks of no treatment. Continuous abstinence rates were significantly higher with all active treatments than with placebo (see Table 2). Varenicline was the most effective treatment; bupropion and the nicotine patch were similar in efficacy.

Patients without a psychiatric disorder who received active treatment had fewer neuropsychiatric events than those who received placebo. In patients with a psychiatric disorder, those who received active treatment had slightly higher rates of neuropsychiatric events than those who received placebo (6.5% with varenicline, 6.7% with bupropion SR, and 5.2% with the nicotine patch, vs 4.9% with placebo). Most events were transient and had no serious consequences.[20] Based on the outcomes of the EAGLES trial, the FDA approved removal of the boxed warning about serious neuropsychiatric events from the labels of varenicline and bupropion.

COMBINATION THERAPY — Combined use of NRTs, especially a patch with a rapid-acting formulation, has generally been more effective than single NRT for smoking cessation.[5] NRT in combination with other drugs has also been beneficial.

Table 2. EAGLES Trial Efficacy Results[1]

	Varenicline	Bupropion SR	Nicotine Patch	Placebo
All Patients	**(n=2037)**	**(n=2034)**	**(n=2038)**	**(n=2035)**
Continuous abstinence, week 9-12	33.5%*	22.6%†	23.4%†	12.5%
Continuous abstinence, week 9-24	21.8%*	16.2%†	15.7%†	9.4%
Psychiatric Cohort	**(n=1032)**	**(n=1033)**	**(n=1025)**	**(n=1026)**
Continuous abstinence, week 9-12	29.2%*	19.3%†	20.4%†	11.4%
Continuous abstinence, week 9-24	18.3%*	13.7%†	13.0%†	8.3%
Non-Psychiatric Cohort	**(n=1005)**	**(n=1001)**	**(n=1013)**	**(n=1009)**
Continuous abstinence, week 9-12	38.0%*	26.1%†	26.4%†	13.7%
Continuous abstinence, week 9-24	25.5%*	18.8%†	18.5%†	10.5%

* statistically significant difference vs all other treatments; † statistically significant difference vs placebo only

1. RM Anthenelli et al. Lancet 2016; 387:2507.

In a randomized trial in 127 smokers with comorbid conditions, smoking abstinence rates at 26 weeks were significantly higher with a **nicotine patch combined with a nicotine oral inhaler ad libitum and bupropion SR** than with a standard 10-week tapering regimen with the patch alone (35% vs 19%).[21]

In a randomized trial in 446 smokers that included a 12-week treatment period and a 12-week follow-up, continuous abstinence rates with **varenicline plus a nicotine patch** were significantly higher than with varenicline alone at 12 weeks (55.4% vs 40.9%) and 24 weeks (49.0% vs 32.6%).[22]

In a randomized trial in 506 smokers, prolonged abstinence rates were higher with **varenicline plus bupropion SR** than with varenicline alone at 12 weeks (53.0% vs 43.2%), 26 weeks (36.6% vs 27.6%), and 52 weeks (30.9% vs 24.5%), but the differences were only statistically significant at 12 and 26 weeks.[23]

In a prospective, placebo-controlled trial in 122 male smokers who had not achieved a >50% reduction in smoking with the nicotine patch (nonresponders), there was no significant difference in continuous abstinence rates at weeks 8-11 between those who received **varenicline plus bupropion SR** and those who received varenicline alone (32.1% vs 45.6%). Combination treatment was, however, significantly more effective than monotherapy in a subgroup of nonresponders who were highly nicotine dependent at baseline (66.7% vs 36.4%).[24]

DURATION OF TREATMENT — Longer-duration pharmacotherapy may improve smoking cessation rates.[25] Most patients should receive a minimum of 3-6 months of effective therapy. In one randomized trial in 525 treatment-seeking smokers, use of the nicotine patch for up to 1 year was safe, but was not more effective than 24 weeks of treatment.[26] In general, the dosage of NRTs can be tapered at the end of treatment; bupropion SR and varenicline can usually be stopped without a gradual dosage reduction, but some clinicians recommend a taper.

SMOKING CESSATION STRATEGIES – The standard practice is to advise patients that abrupt smoking cessation is more effective than gradual withdrawal, but studies comparing the 2 strategies have produced mixed results.[27]

A meta-analysis of 10 trials found that reducing cigarette consumption before the target quit date and quitting abruptly produced comparable smoking abstinence rates.[28]

In a randomized noninferiority trial in 697 adult smokers who received NRT, abrupt cessation was more likely than gradual withdrawal (75% reduction in baseline smoking over 2 weeks before a planned quit date) to result in abstinence at 4 weeks (49.0% vs 39.2%) and 6 months (22.0% vs 15.5%) after the target quit date.[29]

Other strategies that were found to have minimal to moderate success in stopping or reducing smoking include mailing free nicotine patches to willing-to-quit smokers, providing financial incentives to quit smoking, and using cigarettes with reduced nicotine content.[30-33]

ELECTRONIC NICOTINE DELIVERY SYSTEMS — Electronic cigarettes, also called e-cigarettes, are advertised as a safer, more convenient, and socially acceptable alternative to tobacco cigarettes. They are not approved by the FDA as smoking cessation aids. E-cigarettes are battery-operated devices that typically contain a heating element (atomizer) and a reservoir of liquid (usually nicotine dissolved in propylene glycol and/or glycerin). When the user inhales or activates the device with a button, the liquid nicotine is vaporized into a visible mist.

Clinical Studies – In a randomized trial in 657 tobacco cigarette smokers who wanted to quit, abstinence rates at 6 months were not significantly higher with a 16-mg nicotine e-cigarette (7.3%) than with a 21-mg nicotine patch (5.8%) or placebo e-cigarette device (4.1%).[34]

In a randomized trial in 886 smokers that compared use of the participant's choice of NRT, including combinations, with use of e-cigarettes for smoking cessation, the abstinence rate at 52 weeks was significantly higher in the e-cigarette group than in the NRT group (18.0% vs 9.9%). Among patients who reported abstinence at 52 weeks, significantly more of those in the e-cigarette group were still using their assigned product at 52 weeks (80% vs 9% in the NRT group). Patients using an e-cigarette had greater declines from baseline in cough and phlegm production at 52 weeks than those using NRT.[35]

In a meta-analysis of 38 trials in tobacco cigarette smokers, including some who wanted to quit, those who used e-cigarettes were 28% less likely to quit smoking tobacco cigarettes than those who did not use e-cigarettes.[36]

Adverse Effects – The long-term safety of e-cigarettes is unknown.[37,38] The most common adverse effects reported during clinical trials were mouth and throat irritation and dry cough. Daily e-cigarette use, adjusted for use of tobacco cigarettes, has been associated with myocardial infarction.[39] Lipoid pneumonia has

been reported.[40] In nonsmokers, repeated exposure to nicotine in e-cigarettes could lead to nicotine dependence. Use of e-cigarettes by adolescents has been increasing and is particularly concerning because it could lead to subsequent use of tobacco cigarettes.[41]

Toxic Substances – In a biomarker study in a total of 5105 subjects who provided urine samples, measurable levels of tobacco-related toxicants, including polycyclic aromatic hydrocarbons, tobacco-specific nitrosamines, and volatile organic compounds, were present in subjects who used e-cigarettes exclusively, but the levels were lower than those found in tobacco cigarette users. The highest levels of toxicants were found in dual e-cigarette and tobacco cigarette users.[42]

In a chemical analysis of e-cigarette emissions, potentially carcinogenic toxicants such as propylene oxide and glycidol were found in e-liquids and vapors; toxicant levels were highest with use of devices that reached higher temperatures (e.g., single-coil vs double-coil vaporizers) and devices that had residue buildup.[43] The vapor from e-cigarettes has also been found to contain potentially toxic and carcinogenic substances at levels lower than those found in cigarette smoke, but higher than those in ambient air.[44-46]

In 2 studies that performed bronchoscopies and collected induced sputum samples, changes in epithelial cells and defense proteins were detected more frequently in the lungs of e-cigarette users compared to nonsmokers.[47,48] In an *in vitro* study, endothelial cells exposed to e-cigarette vapors showed significantly decreased cell viability, increased levels of reactive oxygen species, and other markers of endothelial cell dysfunction.[49]

PREGNANCY — Counseling is the preferred treatment for pregnant women who smoke. Nicotine is known to cause adverse maternal and fetal effects, but NRT may be less harmful to the fetus than smoking, which has been associated with an increased incidence of low birth weight deliveries and peri- and post-natal complications. NRT can increase smoking cessation rates in late pregnancy by about 40% and, in one trial that followed infants after birth, it was associated with better developmental outcomes.[50]

Available human data on bupropion and varenicline use during pregnancy do not indicate an increased risk of major birth defects. Fetal toxicity was observed in animals given doses higher than maximum recommended human doses. ■

Additional Content Available Online

Expanded Table: Some Drugs for Smoking Cessation
http://medicalletter.org/TML-article-1576c

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Benzhydrocodone/Acetaminophen (*Apadaz*) for Pain

The FDA has approved *Apadaz* (KemPharm), a short-acting, fixed-dose combination of benzhydrocodone and acetaminophen, for short-term management (≤14 days) of acute pain severe enough to require an opioid and for which alternative treatment options are inadequate. Benzhydrocodone is a prodrug of hydrocodone. Fixed-dose combinations of short-acting hydrocodone and acetaminophen or ibuprofen have been available for years and are the most abused opioid products in the US.[1] *Apadaz* was developed under the presumption that inclusion of the inactive prodrug would reduce the potential for abuse of the combination by non-oral routes such as smoking, snorting, or injection, but the FDA did not approve *Apadaz* as an abuse-deterrent formulation.[2]

Pronunciation Key

Apadaz: ap' ah daz

OPIOIDS FOR ACUTE PAIN — For treatment of moderate to severe acute pain, a nonsteroidal anti-inflammatory drug (NSAID) plus acetaminophen may be as effective as an opioid plus acetaminophen.[3] For acute pain that is severe enough to require treatment with an opioid, short-acting formulations of full opioid agonists are generally used. Use of extended-release or long-acting opioid formulations for >1 week has been associated with an increased risk of unintended long-term use.[4,5]

Summary: Benzhydrocodone/Acetaminophen (*Apadaz*)

- Fixed-dose oral combination of benzhydrocodone, a prodrug of hydrocodone, and acetaminophen.
- FDA-approved for short-term management (≤14 days) of acute pain severe enough to require an opioid and for which alternative treatment options are inadequate.
- Available as the brand-name *Apadaz* and as an authorized generic made by the same manufacturer.
- A 6.12/325-mg dose is bioequivalent to a 7.5/325-mg dose of hydrocodone bitartrate/acetaminophen (*Norco*, and generics).
- Adverse effects and drug interactions are similar to those with hydrocodone/acetaminophen; overdose can result in serious, potentially fatal respiratory depression.
- Did not demonstrate potential to deter abuse and was not approved by the FDA as an abuse-deterrent formulation.
- Offers no advantage over short-acting formulations of hydrocodone/acetaminophen.

Table 1. Pharmacology

	Benzhydrocodone	Acetaminophen
Tmax (hrs)	1.25 fasted/2.5 fed*	1.0 fasted/1.5 fed
Metabolism	Converted to hydrocodone by GI esterases, then demethylation primarily by CYP3A4 and partly by CYP2D6	Primarily in the liver via glucuronidation and sulfonation, and via CYP2E1, 1A2, and 3A4
Elimination	Primarily in urine*	Primarily in urine as metabolites
Half-life (hrs)	4.33 fasted/4.53 fed*	4.78 fasted/5.64 fed

* Refers to hydrocodone; benzhydrocodone is not detected in plasma after oral administration

BIOEQUIVALENCE — In pharmacokinetic studies in healthy subjects, summarized in the package insert, tablets containing benzhydrocodone 6.12 mg and acetaminophen 325 mg met the criteria for bioequivalence to the hydrocodone and acetaminophen components in 3 other short-acting combination products: hydrocodone bitartrate 7.5 mg/ibuprofen 200 mg (*Vicoprofen*, and generics), tramadol 37.5 mg/acetaminophen 325 mg (*Ultracet*, and generics), and hydrocodone bitartrate 7.5 mg/acetaminophen 325 mg (*Norco*, and generics). No new clinical efficacy trials were required for FDA approval of benzhydrocodone/acetaminophen.

POTENTIAL FOR ABUSE — Some opioid products are recognized by the FDA as abuse-deterrent, but they are expensive, and whether they reduce overall opioid abuse remains to be determined.[6,7]

In vitro studies evaluating physical manipulation and extraction of benzhydrocodone from *Apadaz* tablets, summarized in the package insert, found no advantage for *Apadaz* over hydrocodone/acetaminophen tablets in deterring abuse by intravenous injection or smoking. Two abuse-potential studies in recreational opioid users, one published and the other summarized in the package insert, compared benzhydrocodone/acetaminophen 6.12/325-mg tablets with short-acting hydrocodone/acetaminophen 4.54/325-mg tablets. After oral administration of 4, 8, or 12 tablets, hydrocodone exposure and peak effects of drug liking were similar with the 2 combinations. After intranasal administration of 2 crushed tablets, hydrocodone exposure and scores for drug liking were lower for benzhydrocodone/acetaminophen for up to 2 hours after a dose, but overall hydrocodone exposure and peak effects of drug liking in the two groups were not significantly different.[8]

ADVERSE EFFECTS — In safety studies in healthy adults, the most common adverse effects of benzhydrocodone/acetaminophen were nausea, somnolence, vomiting, constipation, pruritus, dizziness, and headache. Respiratory depression is the most serious adverse effect of opioids.

DRUG INTERACTIONS — Hydrocodone is metabolized primarily by CYP3A4 and partly by CYP2D6. Coadministration of benzhydrocodone and a CYP3A4 or CYP2D6 inhibitor can increase plasma concentrations of hydrocodone and the risk of toxicity. Taking the drug with a CYP3A4 inducer may decrease the efficacy of hydrocodone and could precipitate withdrawal symptoms.[9]

Coadministration of opioids and serotonergic drugs or monoamine oxidase (MAO) inhibitors can result in serotonin syndrome. Use of benzhydrocodone/acetaminophen within 14 days of a MAO inhibitor is not recommended.

Taking benzhydrocodone/acetaminophen with other CNS depressants such as alcohol, sedatives, or other opioids can increase the risk of sedation, respiratory depression, coma, and death. Use with mixed agonist/antagonist opioid analgesics such as pentazocine *(Talwin)* or butorphanol (*Stadol*, and generics) could decrease the analgesic effect of hydrocodone and precipitate withdrawal symptoms. Urinary retention and severe constipation, possibly leading to paralytic ileus, could occur with concurrent use of an opioid and an anticholinergic drug.

PREGNANCY AND LACTATION — Opioid use during pregnancy has been associated with preterm delivery, poor fetal growth, stillbirth, and birth defects, including neural tube defects, congenital heart defects, and gastroschisis.[10] It can also lead to neonatal opioid withdrawal syndrome. Opioid withdrawal during pregnancy has been associated with spontaneous abortion and premature labor. Pregnant women who are physically dependent on opioids should receive opioid agonist maintenance therapy with buprenorphine or methadone.

Hydrocodone is secreted into human breast milk. Breastfed infants of mothers who are taking benzhydrocodone/acetaminophen should be monitored for respiratory depression. When the opioid is stopped or breastfeeding ceases, withdrawal symptoms can occur in the infant.

DOSAGE AND ADMINISTRATION — A 6.12/325-mg dose of benzhydrocodone/acetaminophen is bioequivalent to a 7.5/325-mg dose of hydrocodone bitartrate/

Table 2. Some Short-Acting Hydrocodone Combination Products

Drug	Some Formulations	Usual Adult Dosage	Cost[1]
Benzhydrocodone/acetaminophen — generic[2]	4.08/325, 6.12/325, 8.16/325 mg tabs[3]	1-2 tabs q4-6 hrs (max: 12 tabs/24 hrs)	$6.50
Apadaz (KemPharm)			12.90
Hydrocodone bitartrate/acetaminophen — generic	2.5/325, 5/300, 5/325, 7.5/300, 7.5/325, 10/325 mg tabs[4]	1-2 tabs q4-6 hrs (max: 8 tabs/day for hydrocodone 2.5 or 5 mg and 6 tabs/day for hydrocodone 7.5 or 10 mg)	11.60
Norco (Allergan)	5/325, 7.5/325, 10/325 mg tabs		59.20
Hydrocodone bitartrate/ibuprofen — generic	5/200, 7.5/200, 10/200 mg tabs	1 tab q4-6 hrs (max: 5 tabs/day)	57.10
Ibudone (Poly Pharm)	5/200, 10/200 mg tabs		16.70
Xylon 10 (AHP)	10/200 mg tabs		153.90

1. Approximate WAC for 5 days' treatment at the lowest available dosage. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. June 5, 2019. Reprinted with permission by First Databank, Inc. All rights reserved. ©2019. www.fdbhealth.com/policies/drug-pricing-policy.
2. An authorized generic, identical to the brand-name product and produced by the same manufacturer.
3. A 6.12/325-mg tablet is bioequivalent to a 7.5/325-mg hydrocodone/acetaminophen tablet.
4. Also available in oral solutions containing 7.5/300 and 10/300 mg hydrocodone/acetaminophen per 15 mL.

acetaminophen. The recommended dosage of *Apadaz* is 1-2 tablets every 4-6 hours as needed, not to exceed 12 tablets in a 24-hour period. The tablets can be taken with or without food. Treatment duration should not exceed 14 days.

REMS — Benzhydrocodone/acetaminophen is a schedule II controlled substance. As part of a Risk Evaluation and Mitigation Strategy (REMS) program, the FDA has required manufacturers of opioid analgesics to make educational programs on the proper use of these products available to practitioners.

CONCLUSION — The fixed-dose combination of benzhydrocodone and acetaminophen is bioequivalent to short-acting hydrocodone/acetaminophen (*Norco,* and generics). Although it was developed to provide deterrence against non-oral abuse, dedicated studies failed to demonstrate that *Apadaz* is less likely than short-acting hydrocodone/acetaminophen formulations to be abused, and it was not approved as an abuse-deterrent formulation by the FDA. *Apadaz* offers no advantage over other short-acting hydrocodone/acetaminophen combinations. ■

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Coming Soon

- Fluticasone Propionate *(Xhance)* for Nasal Polyps
- One-Time Gene Therapy for Spinal Muscular Atrophy
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Mark Abramowicz, M.D., President – The Medical Letter; no disclosure or potential conflict of interest to report.
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F. Peter Swanson, M.D., Consulting Editor – The Medical Letter; no disclosure or potential conflict of interest to report.

In addition to the Principal Faculty above, the following have also contributed to this activity:
Cynthia Covey has disclosed that her spouse is employed by a company that has pharmaceutical companies as clients and his work relates to the development of marketing materials for companies such as Merck, Pfizer and BMS.

MISSION:

The mission of The Medical Letter's Continuing Medical Education Program is to support the professional development of healthcare providers including physicians, nurse practitioners, pharmacists, and physician assistants by providing independent, unbiased drug information and prescribing recommendations that are free of industry influence. The program content includes current information and unbiased reviews of FDA-approved and off-label uses of drugs, their mechanisms of action, clinical trials, dosage and administration, adverse effects, and drug interactions. The Medical Letter delivers educational content in the form of self-study material.

The expected outcome of the CME program is to increase the participant's ability to know, or apply knowledge into practice after assimilating, information presented in materials contained in *The Medical Letter*.
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Through this program, The Medical Letter expects to provide the healthcare community with unbiased, reliable, and timely educational content that they will use to make independent and informed therapeutic choices in their practice.

LEARNING OBJECTIVES:

Activity participants will read and assimilate unbiased reviews of FDA-approved and off-label uses of drugs and other treatment modalities. Activity participants will be able to select and prescribe, or confirm the appropriateness of the prescribed usage of, the drugs and other therapeutic modalities discussed in *The Medical Letter* with specific attention to clinical trials, pathophysiology, dosage and administration, drug metabolism and interactions, and patient management. Activity participants will make independent and informed therapeutic choices in their practice.

Upon completion of this activity, the participant will be able to:

1. Discuss the pharmacologic options available for smoking cessation and compare them based on their efficacy, dosage and administration, and potential adverse effects.
2. Determine the most appropriate therapy for smoking cessation given the clinical presentation of an individual patient.
3. Review the efficacy and safety of the fixed-dose, short-acting combination of benzhydrocodone and acetaminophen *(Apadaz)* for short-term treatment of acute pain.

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Issue 1576 Questions

(Correspond to questions #1-10 in Comprehensive Activity #81, available January 2020)

Drugs for Smoking Cessation

1. The fastest-acting nicotine replacement formulation is the:
   a. gum
   b. oral inhaler
   c. lozenge
   d. nasal spray

2. Which combination of nicotine replacement products has been shown to be more effective than nicotine monotherapy?
   a. gum and nasal spray
   b. transdermal patch and any rapid-acting formulation
   c. gum and oral inhaler
   d. lozenge and nasal spray

3. A 28-year-old man has been applying a 14-mg transdermal nicotine patch every morning for about a week. He hasn't been smoking, but he is having difficulty sleeping because of vivid dreams. To help improve his sleep, you should advise him to:
   a. increase to a 21-mg patch
   b. remove the patch at bedtime
   c. take zolpidem at bedtime
   d. apply the patch at bedtime

4. Bupropion SR has been associated with a dose-related increase in the risk of:
   a. seizures
   b. anaphylaxis
   c. aplastic anemia
   d. hemolytic anemia

5. Varenicline is more effective for smoking cessation than:
   a. placebo
   b. a rapid-onset nicotine replacement therapy
   c. bupropion
   d. all of the above

6. Effective smoking cessation pharmacotherapy should be continued for at least:
   a. 3-6 months
   b. 6-9 months
   c. 6-12 months
   d. 12 months

7. The EAGLES trial found that:
   a. varenicline causes serious neuropsychiatric effects in patients with and without a psychiatric disorder
   b. varenicline causes serious neuropsychiatric effects in patients with a psychiatric disorder, but not in patients without one
   c. bupropion causes serious neuropsychiatric effects in patients with a psychiatric disorder, but not in patients without one
   d. neither varenicline nor bupropion causes serious neuropsychiatric effects

8. E-cigarettes:
   a. have been approved by the FDA for use as smoking cessation aids
   b. have produced mixed results in clinical trials for smoking cessation
   c. are significantly more effective than varenicline for smoking cessation
   d. have not been associated with adverse effects

9. Used in pregnancy, nicotine replacement therapy to aid smoking cessation:
   a. has been shown to increase smoking cessation rates
   b. was associated with better developmental outcomes in one trial
   c. may be less harmful to the fetus than smoking
   d. all of the above

Benzhydrocodone/Acetaminophen *(Apadaz)* for Pain

10. The results of abuse-deterrence studies comparing benzhydrocodone/acetaminophen *(Apadaz)* with hydrocodone/acetaminophen led the FDA to conclude that:
    a. there was no overall advantage with benzhydrocodone in deterring extraction of the drug by physical manipulation
    b. overall hydrocodone exposure was not significantly different with the new combination
    c. peak effects of drug liking were not significantly different with the new combination
    d. all of the above

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