TABLE 1: EFFECTIVE MEDICATIONS FOR TREATING TOBACCO DEPENDENCE

Drug	Preparations	Usual, Daily Adult Maintenance Dose	Common Adverse Effects[A]	FDA Approved	PHS Recommended
COMBINATION MEDICATIONS					
3 or more medications[2,107-109,192,199,230]	See below under individual medications.	Dosages are the same per individual medication; see sections below.	No different than for individual medications, but such combinations usually provide better control of nicotine withdrawal symptoms, better tobacco-dependence treatment, and higher stop-smoking rates	Not Addressed	Not Addressed
Bupropion SR + a nicotine transdermal[1,2]	150-mg Bupropion SR + 15-mg nicotine/16 hr OR 21-mg nicotine/24 hr	Dosages are the same per individual medication; see above sections.	Bizarre dreams; insomnia; nausea; patch-site erythema or pruritus	Yes	Yes
Bupropion SR + a nicotine rescue medication[1,2]	See below under individual medications.	Dosages are the same per individual medication; see above sections.	Insomnia; xerostomia; side effects specific to the specific nicotine medication	Not Addressed	Yes
Nicotine transdermal + nicotine nasal spray[1,2]	See bellow under individual medications.	Dosages are the same per individual medication; see above sections.	Nasal irritation; pruritus and skin irritation at the patch site[B]	Not Addressed	Yes
Nicotine transdermal + nicotine oral inhaler[1,2]	See below under individual medications.	Dosages are the same per individual medication; see above sections.	Throat irritation and pruritus at the patch site[B]	Not Addressed	Yes
Nicotine transdermal + nicotine polacrilex gum[1,2]	See below under individual medications.	Dosages are the same per individual medication; see above sections.	Indigestion, nausea, flatulence, unpleasant taste, hiccups, sore mouth, sore throat, sore jaw; pruritus and skin irritation at the patch site[B]	Not Addressed	Yes
Nicotine transdermal + nicotine lozenge[194]	See below under individual medications.	Dosages are the same per individual medication; see above sections.	Indigestion, nausea, flatulence, unpleasant taste, hiccups, sore mouth, sore throat, sore jaw; pruritus and skin irritation at the patch site[B]	Not Addressed	Not Addressed
Varenicline + bupropion SR[192,193]	See below under individual medications.	Dosages are the same per individual medication; see above sections.	No serious side effects reported. No seizures or suicidal behavior reported.	Not Addressed	Not Addressed
FIRST-LINE CONTROLLER MEDICATIONS					
α_4-β_2 NICOTINIC RECEPTOR PARTIAL AGONISTS					
Varenicline (*Chantix*)	0.5- & 1.0-mg tablet	1 mg 2x/day	Nausea, vomiting, constipation, flatulence, abnormal dreams, headache, xerostomia, weight gain. See Note #2, below.	Yes	Yes
DOPAMINERGIC-NORADRENERGIC RE-UPTAKE INHIBITORS					
Bupropion HCl (immediate acting)	75- & 100-mg tablet	100 mg 3x/day	Insomnia, xerostomia, headache, all generally mild and transient. Seizure incidence in long-term, anti-depression, safety-surveillance studies was 0.4% for the immediate-acting formulation and 0.1% for the sustained-release formulation. Seizure has not occurred, even with daily usage of 300 mg up to 1 year, in the > 2,500 study participants double-blindly randomized to an active bupropion SR formulation in tobacco-dependence treatment trials. Exceeding rare incidence rate of Stevens-Johnson Syndrome, hyper-anxiety state, and elevated hepatic enzymes. ***General Caution:*** Bupropion should not be administered in conjunction with a MAO inhibitor. See Note #3, below.	Not Addressed	Yes
Bupropion SR (*Wellbutrin SR*, *Zyban*)	100-, 150-, & 200-mg sustained-release tablet	150 mg 2x/day		Not Addressed (*Wellbutrin SR*); Yes (*Zyban*)	Yes (*Wellbutrin SR*); Yes (*Zyban*)
Bupropion XL (*Wellbutrin XL*)	150- & 300-mg extended-release tablet	300 mg 1x/day in AM		Not Addressed	Not Stated
NICOTINIC-RECEPTOR AGONISTS					
Nicotine transdermal (*NicoDerm CQ*, *Nicotrol*)[C,D]	7, 14, & 21 mg/24 hr 5, 10, & 15 mg/16 hr	1 patch/day[E]	Pruritus at the patch site; insomnia; bizarre dreams; ~2.5% incidence of cutaneous hypersensitivity reaction caused by 24-hour wear cycle. Neither nicotine overdose nor cardiac events increase with use of transdermal nicotine in conjunction with cigarette smoking beyond that seen with cigarette smoking, alone.	Yes	Yes

FIRST-LINE RELIEVER (RESCUE) MEDICATIONS

NICOTINIC-RECEPTOR AGONISTS

Nicotine-β-cyclodextrin sublingual tablet[F]	2-mg tablet	2 mg 8–16x/day	Hiccups; nausea; dyspepsia	Not Available in United States	Not Stated
Nicotine nasal spray (*Nicotrol NS*)	0.5 mg/spray; 1 dose = 2 sprays	1 dose 8-40x/day	Minor burning and stinging of the nasal mucosa; minor throat irritation; cough; sneeze; increased lacrimation; rhinorrhea; nausea. (**NB**: All these side effects generally last only a few seconds.)	Yes	Yes
Nicotine oral inhaler (*Nicotrol Inhaler*)	4-mg cartridge	4–16 cartridges/day	Minor mouth irritation; throat irritation; cough	Yes	Yes
Nicotine polacrilex gum (*Nicorette*)[D]	2 & 4 mg/piece	8–24 pieces/day	Side effects generally result from improper chewing technique and include indigestion, nausea, flatulence, unpleasant taste, hiccups, sore mouth, sore throat, sore jaw	Yes	Yes
Nicotine polacrilex lozenge (*Commit*)[D]	2 & 4 mg/lozenge	8–20 lozenges/day	Heartburn, hiccup, and nausea, due to swallowed nicotine; headache	Yes	Yes

SECOND-LINE CONTROLLER MEDICATIONS (*Options if First-Line Medications Not Tolerated*)

ALPHA$_2$ ADRENERGIC AGONISTS

Clonidine HCl (*Catapres*)[G]	0.1- & 0.2-mg tablet	0.2 or 0.3 mg 2x/day	From tobacco-dependence trials: Dose-related – Decreased heart rate; decreased systolic blood pressure; decreased diastolic blood pressure; xerostomia; drowsiness; spacey feeling; dizziness; postural hypotension. Not necessarily dose-related – Nausea; vomiting. With transdermal only – Pruritus; erythema; edema; vesicles; blisters, all at the patch application site, only.	No	Yes
Clonidine transdermal (*Catapres-TTS*)[G]	0.1, 0.2, & 0.3 mg/day/1-week patch	1 patch/week delivering 0.2–0.3 mg/day		No	Yes

NORADRENERGIC-SEROTONERGIC RE-UPTAKE INHIBITORS

Nortriptyline HCl (*Aventyl, Pamelor*)	25- & 75-mg capsule	25 mg 3–4x/day	From tobacco-dependence trials: constipation; xerostomia; lightheadedness; tremor; blurred vision. From anti-depression trials: rash; weight gain; xerostomia; lightheadedness; tremor; constipation, blurred vision; impotence; decreased libido; urinary retention; tachycardia; pedal edema; chest pain; shortness of breath; headache; agitation; nausea; vomiting; dizziness; insomnia; hyperhidrosis. ***General Caution:*** Nortriptyline should not be administered in conjunction with a MAO inhibitor.	Not Addressed	Yes

UNCERTAIN PHARMACOLOGIC CLASS

Topiramate (*Topamax*)	25-, 50-, 100-, & 200-mg tablets	50 mg 2x/day	From migraine trials: dizziness, metabolic acidosis, somnolence, fatigue, nervousness, memory difficulty, ataxia, speech disturbance, nystagmus, anorexia, nausea, depression, confusion, diplopia, mood disturbances, insomnia, and anxiety, among others.	No	No

Notes:

1. The ACCP Tool Kit Committee is aware of the existence of the so-called electronic cigarette, but does not recommend it at this time because of the complete absence of any data or scientific information – toxicologic, safety, or efficacy.

2. On July 1, 2009 the FDA issued a "Black-Box Warning" to the varenicline label because of the possibility of, particularly, treatment-emergent suicidality. In published data, the FDA reported 37 individuals who demonstrated suicidal behavior, 19 of whom killed themselves while taking varenicline.[11] These data were not presented in a normalized fashion, as a function of total varenicline users. There have been 5.5 million varenicline users since product launch on 8/1/06 (Data provided by Pfizer, Inc.). This produces an annual suicide completion rate of 0.49 suicides/100,000 varenicline users/year. To put this in perspective, based on CDC data, the annual suicide rate of the U.S. population, overall, is 11.01 suicides/100,000 people in the U.S. population.[12] The suicide rate of varenicline users is significantly *less* than that of the U.S. population at large (P<0.0001). Additionally, the FDA-reported death rate of varenicline users is also significantly *lower* than the death rate caused each year by tobacco-caused diseases: 0.49 suicide deaths/100,000 varenicline users/year vs. 1,031.2 tobacco-caused deaths/100,000 cigarette smokers/year (P<0.0001). The ACCP Tool Kit Committee does not see an association between varenicline and suicide, much less a causal link and suggests that the FDA re-evaluate the recent Black Box Warning in light of this broader perspective. (NB: Data from the United Kingdom also fail to show such an association or causal link.[13]) (See also §1.7, Pharmacologic Treatment, sub-§ "Depression, Suicidality & Tobacco Dependence" & sub-§ "Depression, Suicide, Cigarette Use, & Pharmacotherapy" for additional, pertinent information.)

3. On July 1, 2009 the FDA also issued a "Black-Box Warning" to the bupropion label because of the possibility of, particularly, treatment-emergent suicidality. In published data, the FDA reported 29 individuals who demonstrated suicidal behavior since bupropion launch for tobacco-dependence treatment in September 1997, 12 years ago.[11] Of the 29 bupropion users who made suicide attempts, 10 killed themselves while taking bupropion.[11] Were the ACCP Tool Kit Committee to have the time to determine the total number of bupropion users for tobacco-dependence treatment, only, from 9/1997 through 2009, that total would certainly be larger than the varenicline total, producing an even smaller suicide rate per year for bupropion than for varenicline. (See Note #2, above and §1.7, Pharmacologic Treatment, sub-§ "Depression, Suicidality & Tobacco Dependence" & sub-§ "Depression, Suicide, Cigarette Use, & Pharmacotherapy".)

[A] Adverse effects listed are those reported in tobacco-dependence treatment trials, unless otherwise indicated, since some side effects frequently associated with a given drug (e.g., impotence with nortriptyline) did not occur significantly more often for active drug than placebo drug condition.
[B] No additive or synergistic side effects; side effects similar in incidence and severity to those seen with individual medications.
[C] See specific label for details regarding dose up-titration.
[D] Available without prescription, over-the-counter (OTC)
[E] Wearing the 24-hr patch for 16 hrs yields the same dosage as a 16-hr patch, 15-mg nicotine.
[F] Available in some European countries.
[G] Efficacy data are much less convincing for clonidine than for any of the First-Line medications or for nortriptyline.

TABLE 2: INEFFECTIVE MEDICATIONS FOR TOBACCO DEPENDENCE

Drug	FDA Approved	PHS Recommended
ANXIOLYTICS/BENZODIAZEPINES/BETA-BLOCKERS		
Buspirone (anxiolytic; *BuSpar*)	No	No
Diazepam (anxiolytic; *Valium*)	No	No
Propranolol (beta-blocker: *Inderal*)	No	No
NICOTINIC RECEPTOR ANTAGONISTS		
Mecamylamine (*Inversine*)	No	No
OPIOID PARTIAL AGONISTS/ANTAGONISTS		
Buprenorphine (opioid partial agonist: *Buprenex*)	No	No
Naltrexone (*Revia, Vivitrol*)	No	No
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)		
Fluoxetine *(Prozac)*	No	No
Paroxetine *(Paxil)*	No	No
Sertraline *(Zoloft)*	No	No
Venlafaxine *(Effexor)*	No	No
OTHER		
Lobeline (Nicotine Analog)	No	No
Silver Acetate	No	No

All of the above medications have been studied in clinical trials and found to be ineffective.[8]

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