



**Department of Vermont Health Access**  
**Therapeutic Class Review**  
**Smoking Cessation Agents**

**Overview/Summary**

Smoking is the cause of multiple cancers, coronary heart disease, stroke, chronic obstructive pulmonary disease (COPD) and pregnancy complications.<sup>1</sup> Although smoking is an avoidable cause of these illnesses, over 20% of adults in the United States (U.S.) currently smoke.<sup>2</sup> Smoking causes almost 450,000 deaths, \$97 billion dollars in lost productivity and \$96 billion dollars in direct medical costs.<sup>3</sup> Smoking cessation reduces the risk of smoking related deaths with the risks of most diseases returning to the equivalent of a non-smoker by 15 years.<sup>1</sup> An estimated 70% of smokers report a desire to quit; however, very few are successful in their attempt, especially when tried on their own.<sup>4</sup>

Patients treated with smoking cessation agents have significantly higher abstinence rates when compared to placebo.<sup>5-7</sup> Varenicline tartrate has higher rates of abstinence compared to bupropion hydrochloride (HCl) sustained-release or nicotine replacement therapy.<sup>7</sup> Guidelines from the U.S. Public Health Service recommend bupropion HCl sustained-release, nicotine inhaler, nicotine nasal spray, nicotine polacrilex gum, nicotine polacrilex lozenge, nicotine transdermal patch and varenicline tartrate as first line agents for smoking cessation unless otherwise contraindicated.<sup>8</sup> The guidelines make no recommendation for the use of medications for smoking cessation in pregnancy due to lack of substantial safety and efficacy data. All of the first line agents are Food and Drug Administration (FDA) approved for smoking cessation and are included in this review. The nicotine replacement therapies substitute the nicotine product for smoking. The dose of the nicotine is tapered for 12 weeks or longer to reduce the withdrawal symptoms that patients experience when attempting to quit. Bupropion HCl sustained-release was the first non-nicotine treatment approved by the FDA for smoking cessation. Although the mechanism by which bupropion HCl sustained-release works to assist patients with smoking cessation is unknown, it may be related to its action as a weak inhibitor of norepinephrine and dopamine uptake.<sup>9</sup> Varenicline tartrate is a partial agonist of the  $\alpha 4\beta 2$  neuronal nicotinic acetylcholine receptors which stimulates receptor-mediated activity and blocks nicotine from activating the receptors.<sup>10</sup>

Nicotine inhaler, nicotine nasal spray and varenicline tartrate are available as brand name products only; all other agents included in this review are available generically. Bupropion HCl sustained-release, nicotine inhaler, nicotine nasal spray and varenicline tartrate are available by prescription only.

**Medications**

**Table 1. Medications Included Within Class Review**

| Generic Name (Trade name)  | Medication Class  | Generic Availability |
|--|-------------------|----------------------|
| Bupropion hydrochloride sustained-release (Zyban <sup>®</sup> )* | Smoking cessation | ✓                    |
| Nicotine inhaler (Nicotrol <sup>®</sup> )*                       | Smoking cessation | -                    |
| Nicotine nasal spray (Nicotrol <sup>®</sup> )*                   | Smoking cessation | -                    |
| Nicotine polacrilex gum (Nicorette <sup>®</sup> )                | Smoking cessation | ✓                    |
| Nicotine polacrilex lozenge (Commit <sup>®</sup> )               | Smoking cessation | ✓                    |
| Nicotine transdermal patch (NicoDerm CQ <sup>®</sup> )           | Smoking cessation | ✓                    |
| Varenicline tartrate (Chantix <sup>®</sup> )*                    | Smoking cessation | -                    |

\* Available by prescription only.

## Indications

**Table 2. Food and Drug Administration Approved Indications**<sup>9-13</sup>

| Generic Name                              | Smoking Cessation |
|---|-------------------|
| Bupropion hydrochloride sustained-release | ✓                 |
| Nicotine inhaler                          | ✓                 |
| Nicotine nasal spray                      | ✓                 |
| Nicotine polacrilex gum                   | ✓                 |
| Nicotine polacrilex lozenge               | ✓                 |
| Nicotine transdermal patch                | ✓                 |
| Varenicline tartrate                      | ✓                 |

## Pharmacokinetics

**Table 3. Pharmacokinetics**<sup>9-14</sup>

| Generic Name                              | Time to Peak Concentration (hours) | Protein Binding (%) | Renal Excretion (%) | Active Metabolites   | Half-Life (hours)  |
|---|------------------------------------|---------------------|---------------------|--|--------------------|
| Bupropion hydrochloride sustained-release | 3                                  | 84                  | 87                  | Hydroxybupropion, threohydrobupropion, erythrohydrobupropion | 21 (20, 33, 37*)   |
| Nicotine inhaler                          | 0.25                               | <5                  | 10                  | Cotinine, trans-3-hydroxycotinine                            | 1 to 2 (15 to 20*) |
| Nicotine nasal spray                      | 0.25                               | <5                  | 10                  | Cotinine, trans-3-hydroxycotinine                            | 1 to 2 (15 to 20*) |
| Nicotine polacrilex gum                   | 5 to 10                            | <5                  | 10                  | Cotinine   | 3 to 4             |
| Nicotine polacrilex lozenge               | Not reported                       | <5                  | 10                  | Cotinine   | Not reported       |
| Nicotine transdermal patch                | 2 to 12                            | <5                  | 10 to 20            | Cotinine   | 3 to 4             |
| Varenicline tartrate                      | 3 to 4                             | ≤20                 | 90                  | None   | 24                 |

\*Metabolites.

## Clinical Trials

A meta-analysis by Hughes et al evaluated the efficacy of bupropion hydrochloride (HCl) sustained-release compared to placebo, nicotine replacement therapy or varenicline tartrate. Abstinence rates with bupropion HCl sustained-release were significantly higher when compared to placebo ( $P<0.001$ ); however, bupropion HCl sustained-release had significantly lower abstinence rates compared to varenicline tartrate ( $P<0.001$ ).<sup>5</sup> In this meta-analysis as well as the Stead et al meta-analysis, the same double blind placebo-controlled study that compared bupropion HCl sustained-release and nicotine transdermal patch was included. Patients treated with bupropion HCl sustained-release had significantly higher abstinence rates than the nicotine transdermal patch group ( $P<0.008$ ). In addition, the meta-analysis by Stead et al found that all nicotine replacement therapies had significantly higher abstinence rates than placebo (all  $P<0.001$ ) and there were no significant differences between the different nicotine replacement therapies ( $P=0.35$ ).<sup>6</sup> Also included in this meta-analysis was a study by Wisborg et al that compared nicotine transdermal patch with placebo in pregnant smokers. There was no significant difference in the proportion of patients that were continuously abstinent in the nicotine transdermal patch group compared to placebo (21 vs 19%; 95% confidence interval [CI], 0.7 to 1.8;  $P$  value not reported). Additionally, the mean birth weight difference was 186 g higher in the nicotine group compared to placebo (95% CI, 35 to 336) and there was no significant difference in the rate of preterm labor.<sup>15</sup> In another study in pregnant smokers that was not included in the meta-analysis, nicotine gum was compared to placebo.

This study found no significant differences in abstinence between the groups; however, the nicotine treated patients had significantly higher birth weight compared to placebo ( $P < 0.001$ ).<sup>16</sup>

In a meta-analysis by Cahill et al, varenicline tartrate was compared to placebo, nicotine replacement therapy or bupropion HCl sustained-release. Results found that varenicline tartrate had significantly higher abstinence rates compared to placebo and bupropion HCl sustained-release (both  $P < 0.001$ ). In the one open-label study included in the review that compared varenicline tartrate to nicotine transdermal patch, varenicline tartrate had a significantly higher abstinence rate ( $P = 0.046$ ).<sup>7</sup>

**Table 4. Clinical Trials**

| Study and Drug Regimen  | Study Design and Demographics                             | Sample Size and Study Duration                          | End Points   | Results  |
|---|---|---|--|--|
| Hughes et al <sup>5</sup><br>Bupropion SR<br>vs<br>placebo<br>or<br>bupropion SR plus NRT<br>vs<br>NRT plus placebo<br>or<br>bupropion SR<br>vs<br>NRT<br>or<br>bupropion SR<br>vs<br>varenicline<br>or<br>bupropion SR | MA<br>Patients who are current smokers or recent quitters | N>20,000 (bupropion SR receiving patients)<br>≥6 months | Primary:<br>Abstinence from smoking or incidence of 50% reduction from baseline of cigarette consumption<br>Secondary:<br>Not reported | Primary:<br>The abstinence at six months or greater in the bupropion SR group was higher when compared to placebo (weighted average, 17 vs 9%; RR, 1.69; 95% CI, 1.53 to 1.85; $P<0.00001$ ). There was no significant difference in abstinence between bupropion SR 300 and 150 mg (RR, 1.08; 95% CI, 0.93 to 1.26; $P=0.31$ ). The use of bupropion SR for relapse prevention did not show significant benefit compared to the control group (RR, 1.17; 95% CI, 0.99 to 1.39; $P=0.067$ ).<br>There was no significant difference in abstinence comparing bupropion SR plus NRT to NRT alone (RR, 1.23; 95% CI, 0.67 to 2.26; $P=0.51$ ). In the one PC trial included, abstinence at six months or greater was significantly higher in the bupropion SR group compared to the nicotine transdermal patch group (RR, 1.88; 95% CI, 1.88 to 2.98; $P$ value not reported).<br>When compared to varenicline, bupropion SR had significantly lower abstinence rates (RR, 0.66; 95% CI, 0.53 to 0.82; $P=0.00016$ ).<br>Abstinence in the nortriptyline group was significantly higher compared to placebo (RR, 2.03; 95% CI, 1.48 to 2.78; $P<0.0001$ ). There was no significant difference comparing nortriptyline plus NRT to NRT alone (RR, 1.29; 95% CI, 0.97 to 2.78; $P=0.08$ ). There was no significant difference in abstinence when comparing bupropion SR to nortriptyline (RR, 1.30; 95% CI, 0.93 to 1.82; $P=0.13$ ).<br>When the other antidepressants were compared to placebo, there were no significant differences between the groups.<br>Secondary:<br>Not reported |

| Study and Drug Regimen   | Study Design and Demographics | Sample Size and Study Duration | End Points  | Results   |
|--|-------------------------------|--------------------------------|---|---|
| vs<br>nortriptyline<br>or<br>other antidepressants (fluoxetine, moclobemide*, nortriptyline, selegiline, sertraline or venlafaxine)<br>vs<br>placebo<br>or<br>other antidepressants (fluoxetine, nortriptyline, paroxetine or selegiline) plus NRT<br>vs<br>NRT plus placebo<br>Dosing utilized was in line with standard dosing regimens. |                               |                                |   |   |
| Stead et al <sup>6</sup><br>NRT<br>vs<br>placebo or no NRT control   | MA<br>Patients who smoked     | N>43,000<br>≥6 months          | Primary:<br>Smoking cessation<br>Secondary:<br>Not reported | Primary:<br>When compared to placebo or no NRT, there was a significantly higher smoking cessation in the NRT groups (RR, 1.58; 95% CI, 1.50 to 1.66; $P<0.00001$ ). In addition, the subgroup analysis by type of NRT showed significant benefit for all: nicotine gum (RR, 1.43; 95% CI, 1.33 to 1.53; $P<0.00001$ ), nicotine transdermal patch (RR, 1.66; 95% CI, 1.53 to 1.81; $P<0.00001$ ), nicotine inhaler (RR, 1.90; 95% CI, 1.36 to 2.67; $P<0.00001$ ), |

| Study and Drug Regimen  | Study Design and Demographics  | Sample Size and Study Duration | End Points   | Results  |
|---|--|--------------------------------|--|--|
| <p>or<br/>NRT<br/>vs<br/>bupropion SR</p> <p>Dosing utilized was in line with standard dosing regimens.</p>                                   |  |                                |  | <p>nicotine tablets/lozenges (RR, 2.00; 95% CI, 1.63 to 2.45; <math>P&lt;0.00001</math>), and nicotine nasal spray (RR, 2.02; 95% CI, 1.49 to 2.73; <math>P&lt;0.00001</math>).</p> <p>When comparing higher dose (4 mg) with lower dose nicotine gum (2 mg) in heavy smokers, there was a significant benefit with the higher dose (RR, 1.85; 95% CI, 1.36 to 2.50; <math>P&lt;0.000081</math>). However, there was no significant difference when comparing the dose in light smokers (RR, 0.77; 95% CI, 0.49 to 1.21; <math>P=0.25</math>).</p> <p>When comparing higher vs lower doses of nicotine transdermal patch, smoking cessation favored the higher dose (RR, 1.15; 95% CI, 1.01 to 1.30; <math>P=0.038</math>).</p> <p>There were no significant differences when the different types of NRT were compared (RR, 0.86; 95% CI, 0.62 to 1.18; <math>P=0.35</math>).</p> <p>One study included compared nicotine transdermal patch to bupropion SR. Smoking cessation was significantly lower in the nicotine transdermal patch treated patients than bupropion SR treated patients (RR, 0.55; 95% CI, 0.34 to 0.85; <math>P=0.0077</math>).</p> <p>Secondary:<br/>Not reported</p> |
| <p>Oncken at al<sup>16</sup></p> <p>Nicotine gum 2 mg to replace every cigarette usually smoked up to 20 pieces/day</p> <p>vs<br/>placebo</p> | <p>DB, MC, PC, PRO, RCT</p> <p>Pregnant patients <math>\geq 16</math> years of age who were <math>\leq 26</math> weeks gestation, currently smoking at least one cigarette/day, able to speak Spanish or English, intending to carry</p> | <p>N=194</p> <p>12 weeks</p>   | <p>Primary:<br/>Biochemically confirmed abstinence rates at 6 weeks of nicotine gum use and at the end of pregnancy</p> <p>Secondary:<br/>Birth weight</p> | <p>Primary:<br/>There were no significant differences between the nicotine gum group and the placebo group in abstinence at six weeks of treatment (13.0 vs 9.6%; <math>P=0.45</math>) and at 32 to 34 weeks gestation (18.0 vs 14.9%; <math>P=0.56</math>).</p> <p>Secondary:<br/>There were no significant differences in cigarettes/day in the nicotine gum group compared to placebo at six weeks after treatment (<math>P=0.16</math>) and at 32 to 34 weeks gestation (<math>P=0.077</math>).</p> <p>Birth weight was significantly higher in the nicotine gum treated patients compared to placebo (<math>P&lt;0.001</math>). Gestational age was also significantly greater in the nicotine gum group compared to placebo (<math>P=0.014</math>) with</p>  |

| Study and Drug Regimen   | Study Design and Demographics   | Sample Size and Study Duration | End Points  | Results   |
|--|---|--------------------------------|---|---|
|  | pregnancy to term and living in a stable residence  |                                | and measures of smoking reduction   | significantly more pre-term deliveries in the placebo group ( $P=0.027$ ).  |
| Fagerstrom et al <sup>17</sup><br>Varenicline 1 mg BID<br>vs<br>placebo<br><br>Participants were instructed to set a target quit date during 8 to 28 days after initiation of treatment. | DB, MC, PC, PG, RCT<br><br>Patients $\geq 18$ years of age using smokeless tobacco containing nicotine ( $\geq 8$ times a day during the previous year with no period of abstinence in the 3 months before screening) who are motivated to stop use of all tobacco products | N=432<br><br>12 weeks          | Primary:<br>Continuous abstinence rate<br><br>Secondary:<br>Evaluations of efficacy for an additional 14 weeks of follow-up after treatment, safety | Primary:<br>The continuous abstinence rate at the end of treatment (weeks nine to 12) was significantly higher in the varenicline group than in the placebo group (59 [125] vs 39% [85]; risk difference, 20%; NNT, 5).<br><br>Secondary:<br>Continuous abstinence rates were also significantly higher in the long term (weeks nine to 26) in the varenicline group than in the placebo group (45 [95] vs 34% [73]; risk difference, 11%; NNT, 9).<br><br>The most commonly reported adverse events were nausea (35 vs 6%), headache (10 vs 9%), fatigue (10 vs 7%) and sleep disorder (10 vs 7%). Concerning neuropsychiatric adverse events, only sleep disorder, abnormal dreams (8 vs 1%) and insomnia (6 vs 3%) were higher with varenicline than with placebo.   |
| Cahill et al <sup>1</sup><br>Varenicline<br>vs<br>placebo<br>or<br>varenicline<br>vs<br>bupropion SR<br>or   | MA<br><br>Adult smokers   | N>7,000<br><br>$\geq 6$ months | Primary:<br>Abstinence for $\geq 6$ months<br><br>Secondary:<br>Not reported  | Primary:<br>Varenicline had significantly higher abstinence at nine to 12 weeks compared to placebo (RR, 2.36; 95% CI, 2.08 to 2.67; $P<0.00001$ ). Continuous abstinence at 24 weeks or more was significantly higher in the varenicline group (RR, 2.33; 95% CI, 1.95 to 2.80; $P<0.00001$ ). In addition, there was a significantly higher point prevalence of abstinence in the varenicline group after 52 weeks in the one long-term safety trial (RR, 4.91; 95% CI, 2.56 to 9.42).<br><br>When evaluating varenicline for maintenance treatment, one study found a significantly higher continuous abstinence at 52 weeks in the varenicline group compared to placebo after 12 additional weeks of treatment (RR, 1.18; 95% CI, 1.03 to 1.36; $P=0.018$ ).<br><br>When compared to bupropion SR, varenicline had a significantly higher abstinence rate at 12 months (RR, 1.52; 95% CI, 1.22 to 1.88; $P<0.00001$ ). There was a higher abstinence rate in the varenicline group compared to the |

| Study and Drug Regimen   | Study Design and Demographics | Sample Size and Study Duration | End Points | Results  |
|--|-------------------------------|--------------------------------|------------|--|
| varenicline<br><br>vs<br><br>NRT<br><br>or<br><br>cytisine*<br><br>vs<br><br>placebo<br><br>Dosing utilized was in line with standard dosing regimens. |                               |                                |            | nicotine transdermal patch group in an OL, RCT (RR, 1.31; 95% CI, 1.01 to 1.71; $P=0.046$ ).<br><br>Patients treated with varenicline had significantly higher nausea (RR, 3.25; 95% CI, 2.73 to 3.86; $P<0.00001$ ), insomnia (RR, 1.45; 95% CI, 1.21 to 1.75; $P=0.000082$ ) and abnormal dreams (RR, 2.79; 95% CI, 2.09 to 3.72; $P<0.00001$ ) compared to placebo.<br><br>Secondary:<br>Not reported |

\*Agent not available in the United States.

Drug regimen abbreviations: BID=twice daily, SR=sustained-release

Study abbreviations: CI=confidence interval, DB=double-blind, MA=meta-analysis, MC=multicenter, NNT=number needed treat, OL=open-label, PC=placebo-controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk

Miscellaneous abbreviations: NRT=nicotine replacement therapy

**Table 5. Special Populations**<sup>9-12,14</sup>

| Generic Name                              | Population and Precaution   |   |   |                    |                         |
|---|---|---|---|--------------------|-------------------------|
|   | Elderly/<br>Children  | Renal Dysfunction   | Hepatic Dysfunction   | Pregnancy Category | Excreted in Breast Milk |
| Bupropion hydrochloride sustained-release | No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.<br><br>Safety and efficacy in children have not been established. | Renal dose adjustment is required; a reduced dose and/or frequency are recommended. | Hepatic dose adjustment is required; a maximum dose of 150 mg every other day is recommended. | C                  | Yes                     |
| Nicotine inhaler                          | Safety and efficacy in elderly patients have not been established.<br><br>Safety and efficacy in children have not been established.  | Not studied in renal dysfunction.   | Not studied in hepatic dysfunction.   | D                  | Yes                     |
| Nicotine nasal spray                      | Safety and efficacy in elderly patients have not been established.<br><br>Safety and efficacy in children have not been established.  | Not studied in renal dysfunction.   | Not studied in hepatic dysfunction.   | D                  | Yes                     |
| Nicotine polacrilex gum                   | Safety and efficacy in elderly patients have not been established.<br><br>Safety and efficacy in children have not been established.  | Not studied in renal dysfunction.   | Not studied in hepatic dysfunction.   | C                  | Yes                     |
| Nicotine polacrilex lozenge               | Safety and efficacy in elderly patients have not been established.<br><br>Safety and efficacy in children have not been established.  | Not studied in renal dysfunction.   | Not studied in hepatic dysfunction.   | C                  | Yes                     |
| Nicotine transdermal patch                | Safety and efficacy in elderly patients have not been established.<br><br>Safety and efficacy in children have not been established.  | Not studied in renal dysfunction.   | Not studied in hepatic dysfunction.   | D                  | Yes                     |
| Varenicline tartrate                      | No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.   | Renal dose adjustment is required; for creatinine clearances of <30 mL/minute, an   | No dosage adjustment required.  | C                  | Unknown                 |

| Generic Name | Population and Precaution                                  |   |                        |                       |                               |
|--------------|--|---|------------------------|-----------------------|-------------------------------|
|              | Elderly/<br>Children                                       | Renal Dysfunction   | Hepatic<br>Dysfunction | Pregnancy<br>Category | Excreted<br>in Breast<br>Milk |
|              | Safety and efficacy in children have not been established. | initial dose of 0.5 mg QD with dose titration to a maximum of 0.5 mg BID; and for end stage renal disease undergoing dialysis a maximum dose of 0.5 mg QD is recommended. |                        |                       |                               |

BID=twice daily, QD=once daily

### Adverse Drug Events

Adverse drug events reported in the package inserts for the prescription medications and Drug Facts and Comparisons for the over-the-counter medications are listed in Table 6.

**Table 6. Adverse Drug Events**<sup>9-13</sup>

| Adverse Event                        | Generic Name                    | Reported Frequency (%) |
|--------------------------------------|---------------------------------|------------------------|
| Abnormal dreams                      | Varenicline tartrate            | 9 to 13                |
| Constipation                         | Bupropion HCl sustained-release | 8                      |
|                                      | Varenicline tartrate            | 5 to 8                 |
| Depression                           | Varenicline tartrate            | ✓                      |
| Disturbed concentration              | Bupropion HCl sustained-release | 9                      |
| Dry mouth                            | Bupropion HCl sustained-release | 10 to 11               |
| Dyspepsia                            | Nicotine inhaler                | 18                     |
|                                      | Nicotine nasal spray            | ✓                      |
| Flatulence                           | Varenicline tartrate            | 6 to 9                 |
| Headache                             | Nicotine inhaler                | 26                     |
|                                      | Nicotine nasal spray            | 18                     |
|                                      | Varenicline tartrate            | 15 to 19               |
| Insomnia                             | Bupropion HCl sustained-release | 31 to 40               |
|                                      | Varenicline tartrate            | 18 to 19               |
| Local irritation in mouth and throat | Nicotine inhaler                | 40                     |
| Nasal irritation                     | Nicotine nasal spray            | 81 to 94               |
| Nausea                               | Bupropion HCl sustained-release | 9                      |
|                                      | Varenicline tartrate            | 16 to 40               |
| Pruritus                             | Bupropion HCl sustained-release | 3                      |
| Skin irritation                      | Nicotine transdermal patch      | ✓                      |
| Suicidal ideation                    | Varenicline tartrate            | ✓                      |
| Suicide attempt                      | Varenicline tartrate            | ✓                      |
| Suicide completed                    | Varenicline tartrate            | ✓                      |
| Tremor                               | Bupropion HCl sustained-release | 1 to 2                 |
| Withdrawal symptoms                  | Nicotine inhaler                | 3                      |
|                                      | Nicotine nasal spray            | ✓                      |
|                                      | Nicotine polacrilex gum         | ✓                      |
|                                      | Nicotine polacrilex lozenge     | ✓                      |
|                                      | Nicotine transdermal patch      | ✓                      |

HCl=hydrochloride.

✓ Percent not specified.

**Contraindications/Precautions**<sup>9-14</sup>

Bupropion hydrochloride (HCl) sustained-release is contraindicated in patients with seizure disorder, bulimia or anorexia, or taking other forms of bupropion due to an increased risk of seizures. Bupropion HCl sustained-release is also contraindicated in patients undergoing abrupt withdrawal of alcohol or benzodiazepines and in patients who are allergic to it. Bupropion HCl sustained-release is associated with psychosis, confusion and other neuropsychiatric symptoms such as delusion, hallucinations and paranoia (see Black Box Warning below). Bupropion HCl sustained-release is also associated with hypertension.

Nicotine inhaler, nicotine nasal spray, nicotine polacrilex gum, nicotine polacrilex lozenge and nicotine transdermal patch are contraindicated in patients with known hypersensitivity to it or any components of the product. Nicotine nasal spray has been associated with exacerbations of asthma, bronchospasm or reactive airway disease. Nicotine inhaler should be used in caution in patients with bronchospastic disease. Patients with cardiovascular disease should be evaluated carefully before initiating nicotine replacement therapy. Nicotine should be used with caution in patients with endocrine disorders. It can delay healing in peptic ulcer disease. Nicotine has been associated with tachycardia and an increased risk of hypertension.

Varenicline tartrate is contraindicated in patients with known hypersensitivity or skin reactions to the drug. Varenicline tartrate has been associated with angioedema, serious skin reactions and accidental injury. In addition, varenicline tartrate has a black box warning regarding neuropsychiatric side effects (see below).

**Black Box Warning for Bupropion Hydrochloride (HCl) Sustained-release**<sup>9,13,14</sup>

**WARNING**

Serious neuropsychiatric events, including but not limited to depression, suicidal ideation, suicide attempt, and completed suicide have been reported in patients taking bupropion hydrochloride (HCl) sustained-release for smoking cessation. Some cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking bupropion HCl sustained-release who continued to smoke.

All patients being treated with bupropion HCl sustained-release should be observed for neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed mood, and suicide-related events, including ideation, behavior, and attempted suicide. These symptoms, as well as worsening of pre-existing psychiatric illness and completed suicide have been reported in some patients attempting to quit smoking while taking bupropion HCl sustained-release in the postmarketing experience. When symptoms were reported, most were during treatment with bupropion HCl sustained-release, but some were following discontinuation of treatment with bupropion HCl sustained-release. These events have occurred in patients with and without pre-existing psychiatric disease; some have experienced worsening of their psychiatric illnesses. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the premarketing studies of bupropion HCl sustained-release.

Advise patients and caregivers that the patient should stop taking bupropion HCl sustained-release and contact a healthcare provider immediately if agitation, hostility, depressed mood, or changes in thinking or behavior that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. In many postmarketing cases, resolution of symptoms after discontinuation of bupropion HCl sustained-release was reported, although in some cases the symptoms persisted; therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.

The risks of bupropion HCl sustained-release should be weighed against the benefits of its use. Bupropion HCl sustained-release has been demonstrated to increase the likelihood of abstinence from smoking for as long as six months compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial.

Although bupropion HCl sustained-release (Zyban<sup>®</sup>) is not indicated for treatment of depression, it contains the same active ingredient as the antidepressant medications Wellbutrin<sup>®</sup> (bupropion HCl),

**WARNING**

Wellbutrin SR<sup>®</sup> (bupropion HCl sustained-release) and Wellbutrin XL<sup>®</sup> (bupropion HCl extended-release). Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder and other psychiatric disorders. Anyone considering the use of bupropion HCl sustained-release or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Bupropion HCl sustained-release is not approved for use in pediatric patients.

**Black Box Warning for Varenicline Tartrate**<sup>10,13,14</sup>

**WARNING**

Serious neuropsychiatric events including, but not limited to, depression, suicidal ideation, suicide attempt and completed suicide have been reported in patients taking Varenicline tartrate. Some reported cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking varenicline tartrate who continued to smoke.

All patients being treated with varenicline tartrate should be observed for neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed mood, and suicide-related events, including ideation, behavior, and attempted suicide. These symptoms, as well as worsening of pre-existing psychiatric illness and completed suicide, have been reported in some patients attempting to quit smoking while taking varenicline tartrate in the postmarketing experience. When symptoms were reported, most were during varenicline tartrate treatment, but some were following discontinuation of varenicline tartrate therapy.

These events have occurred in patients with and without preexisting psychiatric disease. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the premarketing studies of varenicline tartrate, and the safety and efficacy of varenicline tartrate in such patients has not been established.

Advise patients and caregivers that the patient should stop taking varenicline tartrate and contact a healthcare provider immediately if agitation, hostility, depressed mood, or changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. In many postmarketing cases, resolution of symptoms after discontinuation of varenicline tartrate was reported, although in some cases the symptoms persisted; therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.

The risks of varenicline tartrate should be weighed against the benefits of its use. Varenicline tartrate has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial.

**Drug Interactions**

**Table 7. Drug Interactions**<sup>9-14,18</sup>

| Generic Name                    | Interacting Medication or Disease | Potential Result  |
|---------------------------------|-----------------------------------|---|
| Bupropion HCl sustained-release | Amantadine, levodopa              | There is an increased incidence of adverse experience when patients receive bupropion HCl sustained-release and levodopa or |

| Generic Name   | Interacting Medication or Disease  | Potential Result   |
|--|--|--|
|  |  | amantadine concomitantly. Bupropion HCl sustained-release should be started at low doses with gradual dose increases.  |
| Bupropion HCl sustained-release  | CYP2B6 inducers (e.g., carbamazepine, phenobarbital, phenytoin)  | Bupropion HCl sustained-release serum levels may be reduced.   |
| Bupropion HCl sustained-release  | CYP2B6 (e.g., cimetidine)  | Bupropion HCl sustained-release serum levels may be increased.   |
| Bupropion HCl sustained-release  | CYP2D6 (e.g., antipsychotics, antiarrhythmics, $\beta$ -blockers, SSRIs, TCAs)                               | Coadministration should be done with caution.  |
| Bupropion HCl sustained-release  | Drugs that lower seizure threshold (e.g., antidepressants, antipsychotics, systemic steroids, theophylline.) | Extreme caution is recommended if use concomitantly. Bupropion HCl sustained-release should be started at low doses with gradual dose increase.  |
| Bupropion HCl sustained-release  | MAOIs  | Coadministration increases risk of acute bupropion HCl sustained-release toxicity and is contraindicated. At least 14 days should elapse between discontinuation of MAOI and starting bupropion HCl sustained-release. |
| Nicotine (inhaler, nasal spray, polacrilex gum, polacrilex lozenge, transdermal patch) | $\beta$ -blockers, imipramine, oxazepam, pentazocine, theophylline   | Nicotine is an enzyme inducer and can increase metabolism of these drugs.  |
| Nicotine (inhaler, nasal spray, polacrilex gum, polacrilex lozenge, transdermal patch) | Clozapine  | Nicotine may reduce plasma levels of clozapine.  |
| Nicotine (inhaler, nasal spray, transdermal patch)                                     | Memantine  | Coadministration may result in altered plasma levels of both drugs.  |
| Nicotine nasal spray   | Nasal vasoconstrictor (e.g., xylometazoline)   | Nasal vasoconstrictors can prolong the time to peak concentration.   |
| Varenicline tartrate   | Cimetidine   | Coadministration reduces renal clearance of varenicline tartrate and increases systemic exposure.  |
| Varenicline tartrate   | Nicotine replacement therapy   | Coadministration increases the incidence of adverse effects.   |

HCl=hydrochloride, MAOIs=monoamine oxidase inhibitors, SSRIs=selective serotonin reuptake inhibitors, TCAs=tricyclic antidepressants

## Dosage and Administration

**Table 8. Dosing and Administration**<sup>9-14</sup>

| Generic Name                              | Adult Dose  | Pediatric Dose   | Availability                      |
|---|---|--|-----------------------------------|
| Bupropion hydrochloride sustained-release | <u>Smoking cessation:</u><br>Tablet, sustained-release: initial, 150 mg QD for 3 days; maintenance, 150 mg BID for 7 to 12 weeks; maximum, 150 mg BID | Safety and efficacy in children have not been established. | Tablet, sustained-release: 150 mg |
| Nicotine inhaler                          | <u>Smoking cessation:</u><br>Inhaler: initial, 6 to 12 cartridges QD for up   | Safety and efficacy in                                     | Inhalation system, cartridge:     |

| Generic Name                | Adult Dose  | Pediatric Dose   | Availability                                       |
|-----------------------------|---|--|--|
|                             | to 12 weeks then gradual reduction of dose for 6 to 12 weeks  | children have not been established.                        | 10 mg (4 mg delivered)                             |
| Nicotine nasal spray        | <u>Smoking cessation:</u><br>Nasal spray: initial, 1 spray (0.5 mg) each nostril 1 or 2 times/hour; dose may be increased up to maximum, 80 sprays daily  | Safety and efficacy in children have not been established. | Nasal spray:<br>10 mg/mL                           |
| Nicotine polacrilex gum     | <u>Smoking cessation:</u><br>Gum: heavy smokers ( $\geq 25$ cigarettes/day), 4 mg; light smokers, 2 mg; weeks 1 to 6: 1 piece of gum every 1 to 2 hours; weeks 7 to 9: 1 piece of gum every 2 to 4 hours; weeks 10 to 12: 1 piece of gum every 4 to 8 hours                                       | Safety and efficacy in children have not been established. | Gum:<br>2 mg*<br>4 mg*                             |
| Nicotine polacrilex lozenge | <u>Smoking cessation:</u><br>Lozenge: heavy smokers ( $\geq 25$ cigarettes/day), 4 mg; light smokers, 2 mg; weeks 1 to 6: 1 lozenge every 1 to 2 hours; weeks 7 to 9: 1 lozenge every 2 to 4 hours; weeks 10 to 12: 1 lozenge every 4 to 8 hours; maximum, 5 lozenges/6 hours and 20 lozenges/day | Safety and efficacy in children have not been established. | Lozenge:<br>2 mg <sup>†</sup><br>4 mg <sup>†</sup> |
| Nicotine transdermal patch  | <u>Smoking cessation:</u><br>Transdermal patch: smokers of $\geq 10$ cigarettes/day: weeks 1 to 6, 21 mg patch QD; for weeks 7 to 8, 14 mg patch QD; for weeks 9 to 10, 7 mg patch QD; smokers of $< 10$ cigarettes/day: weeks 1 to 6, 14 mg patch QD; for weeks 7 to 8, 7 mg patch QD            | Safety and efficacy in children have not been established. | Transdermal patch:<br>7 mg<br>14 mg<br>21 mg       |
| Varenicline tartrate        | <u>Smoking cessation:</u><br>Tablet: week 1: days 1 to 3, 0.5 mg QD; days 4 to 7, 0.5 mg BID; weeks 2 to 12: 1 mg BID; re-treatment with an additional 12 weeks is recommended if successful cessation after first 12 weeks course  | Safety and efficacy in children have not been established. | Tablet:<br>0.5 mg<br>1 mg                          |

BID=twice daily, QD=once daily

\*Available in the following flavors: mint, cinnamon, fruit, and original.

†Available in the following flavors: mint, cherry, and original and as a "mini" lozenge.

## Clinical Guidelines

**Table 9. Clinical Guidelines**

| Clinical Guideline   | Recommendations   |
|--|---|
| United States Department of Health and Human Services-Public Health Services:<br><b>Treating Tobacco Use and Dependence: 2008 Update (2008)</b> <sup>8</sup> | <ul style="list-style-type: none"> <li>Although counseling and medication are effective when used by themselves, the combination is more effective than either alone.</li> <li>Unless contraindicated or for specific populations for which evidence of effectiveness is lacking (pregnant women, smokeless tobaccos users, light smokers and adolescents), all patients attempting to quit should be encouraged to use effective medications.</li> <li>First line agents for smoking cessation are: bupropion hydrochloride (HCl) sustained-release, nicotine inhaler, nicotine nasal spray, nicotine polacrilex gum, nicotine polacrilex lozenge, nicotine transdermal patch and varenicline tartrate.</li> <li>Second line medications include clonidine and nortriptyline and should be used if there is no success with first-line medications or first line medications are contraindicated.</li> </ul> |

| Clinical Guideline  | Recommendations   |
|---|---|
|   | <ul style="list-style-type: none"> <li>• Combinations of first line medications are effective and should be considered in patients willing to quit. Combinations that are recommended as first line include:               <ul style="list-style-type: none"> <li>○ Long-term (&gt;14 weeks) nicotine transdermal patch and other nicotine replacement therapy (nicotine polacrilex gum and nicotine nasal spray).</li> <li>○ Nicotine transdermal patch and nicotine inhaler.</li> <li>○ Nicotine transdermal patch and bupropion HCl sustained-release.</li> </ul> </li> <li>• When compared to nicotine transdermal patch alone, varenicline tartrate and the combination of long term nicotine transdermal patch and other nicotine replacement therapy (nicotine polacrilex gum or nicotine nasal spray) had a significantly greater likelihood of long-term abstinence.</li> <li>• The use of over-the-counter nicotine transdermal patch is effective and should be encouraged.</li> <li>• The tobacco dependence treatments are cost-effective relative to other treatments and should be provided to all smokers.</li> <li>• Providing tobacco dependence treatments as a covered benefit has increased the use of treatment and should be included as a covered service in public and private health benefit plans.</li> <li>• Pregnant smokers should be offered psychosocial interventions that exceed minimal advice to quit. Quitting anytime during pregnancy will yield benefits; however, abstinence early in pregnancy will yield the greatest benefits. Effective tobacco dependence interventions should be offered at the first prenatal visit and throughout the pregnancy. Due to insufficient data, there are no recommendations on the use of medications in pregnancy.</li> </ul>   |
| <p>National Institute for Health and Clinical Excellence:<br/> <b>Smoking Cessation Services in Primary Care, Pharmacies, Local Authorities and Workplaces, Particularly for Manual Working Groups, Pregnant Women and Hard to Reach Communities</b><sup>19</sup></p> | <ul style="list-style-type: none"> <li>• Behavioral counseling, group therapy, pharmacotherapy or a combination of treatments that have been proven effective should be offered.</li> <li>• Behavioral support should be tailored to the patient and offered by trained staff.</li> <li>• Pharmacotherapy (bupropion HCl sustained-release, nicotine replacement therapy, or varenicline tartrate) should be offered to people that are planning to quit smoking.</li> <li>• Pharmacotherapy should be given as part of an abstinence-contingent treatment that has a target stop date. The amount of pharmacotherapy should be sufficient to last until only two weeks after the target stop date, and subsequent prescriptions should only be given to people that have demonstrated that their quit attempt is continuing.</li> <li>• The risks and benefits of nicotine replacement therapy should be explained to people aged 12 to 17 years, pregnant or breastfeeding women and people with unstable cardiovascular disorders. People in these groups should be strongly encouraged to use behavioral support to maximize the benefits of nicotine replacement therapy in their quit attempt.</li> <li>• Bupropion HCl sustained-release and varenicline tartrate should not be offered to pregnant or breastfeeding women or people less than 18 years old; however, these treatments may be offered to patients with unstable cardiovascular disorders.</li> <li>• If a smoker's quit attempt is unsuccessful using pharmacotherapy, a repeat prescription should not be offered within six months unless there have been extenuating circumstances that hampered a person's attempt.</li> <li>• Nicotine replacement therapy, bupropion HCl sustained-release or varenicline tartrate should not be offered in any combination.</li> <li>• Combination therapy of nicotine patches plus another form of nicotine</li> </ul> |

| Clinical Guideline | Recommendations   |
|--------------------|---|
|                    | <p>replacement therapy (i.e., nicotine polacrilex gum, nicotine polacrilex lozenge, nicotine inhaler or nicotine nasal spray) may be offered to people with high levels of dependence or inadequate response to monotherapy in the past.</p> <ul style="list-style-type: none"> <li>The choice of pharmacotherapy should be made based on the intervention that seems most likely to succeed. The patient and physician should take into account contraindications, patient preference, availability of counseling and previous experience with smoking cessation.</li> </ul> |

**Conclusions**

Smoking is a significant public health problem that causes many preventable diseases including cancers, cardiovascular disease and complications during pregnancy. Smoking is also associated with substantial medical care costs. Various smoking cessation methods (or aids, or therapies or programs), including the use of medications, are effective in helping smokers quit. Bupropion hydrochloride (HCl) sustained-release, the nicotine replacement products and varenicline tartrate are all Food and drug Administration approved for smoking cessation and are recommended as first-line treatments. Bupropion HCl sustained-release and varenicline tartrate have been associated with neuropsychiatric symptoms when used for smoking cessation. In addition, bupropion HCl sustained-release and varenicline tartrate are not recommended for use in pregnant smokers and the use of nicotine replacement therapy should be weighed against the risk of continued smoking.<sup>19</sup>

**Appendix I: Utilization Within This Drug Class for DVHA: July 1, 2010 to December 31, 2010**

| Medication                      | Unique utilizers * | # of Rx's    | Market Share (%) | Plan Cost \$        | Avg \$/Rx      |
|---------------------------------|--------------------|--------------|------------------|---------------------|----------------|
| Nicoderm CQ                     | 1,329              | 1,839        | 44.60%           | \$126,538.22        | \$68.81        |
| Chantix                         | 898                | 1,389        | 33.69%           | \$177,973.38        | \$128.13       |
| Nicotrol Inhaler                | 263                | 284          | 6.89%            | \$55,925.54         | \$196.92       |
| Nicorette Starter Kit           | 163                | 203          | 4.92%            | \$10,022.20         | \$49.37        |
| Commit                          | 121                | 185          | 4.49%            | \$8,350.13          | \$45.14        |
| Nicorette                       | 124                | 137          | 3.32%            | \$7,030.35          | \$51.32        |
| Bupropion HCL SR                | 24                 | 29           | 0.70%            | \$1,361.63          | \$46.95        |
| Nicotine                        | 15                 | 21           | 0.51%            | \$955.73            | \$45.51        |
| Nicorette Mini                  | 3                  | 8            | 0.19%            | \$322.11            | \$40.26        |
| Buproban                        | 7                  | 7            | 0.17%            | \$500.13            | \$71.45        |
| Nicotine Transdermal System     | 5                  | 5            | 0.12%            | \$233.48            | \$46.70        |
| Nicotine Polacrilex             | 5                  | 5            | 0.12%            | \$178.91            | \$35.78        |
| SM Nicotine Polacrilex          | 2                  | 3            | 0.07%            | \$323.27            | \$107.76       |
| SM Nicotine                     | 3                  | 3            | 0.07%            | \$75.92             | \$25.31        |
| Nicotrol NS                     | 1                  | 2            | 0.05%            | \$741.04            | \$370.52       |
| Nicotine Polacrilex Starter Kit | 1                  | 1            | 0.02%            | \$29.33             | \$29.33        |
| Nicotine Polacrilex Refill      | 1                  | 1            | 0.02%            | \$35.61             | \$35.61        |
| Nicorelief                      | 1                  | 1            | 0.02%            | \$52.35             | \$52.35        |
| <b>Class Total:</b>             | <b>2,968</b>       | <b>4,123</b> | <b>100%</b>      | <b>\$390,649.33</b> | <b>\$94.75</b> |

### **Recommendations**

In recognition of the established safety and efficacy of the smoking cessation agents for the management of smoking cessation, recommendations from current clinical guidelines, and the availability of certain generics, it is recommended that no changes be made to the current Department of Vermont Health Access (DVHA) approval criteria:

#### **nicotine patch OTC/Rx, Nicotine System Kit**

- The patient has had a documented intolerance to Nicoderm CQ patch.

#### **nicotine gum**

- The patient has had a documented intolerance to Nicorette gum.

#### **nicotine lozenge**

- The patient has had a documented side effect or allergy to Nicorette lozenge or Commit lozenge.

#### **Nicotrol Inhaler**

- The patient has had a documented treatment failure with BOTH Nicoderm CQ patch and Nicorette gum.

#### **Nicotrol Nasal Spray**

- The prescriber must provide a clinically valid reason for the use of the requested medication.

#### **Zyban**

- The patient has had a documented side effect or allergy to bupropion SR.
- In addition, after approval criteria are met, the length of authorization is up to 16 weeks (2 x 8 weeks) for nicotine replacement or up to 24 weeks (2 x 12 weeks) for oral therapy (per rolling 365 days). A quantity limit of two tablets per day is in place for varenicline.

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