# 2021 WHO Expert Committee on the Selection and Use of Essential Medicines

## Application for the inclusion of bupropion hydrochloride on the WHO Model List of Essential Medicines (EML) for the treatment of nicotine dependence as an aid to stopping smoking and tobacco use.

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**1. Summary statement of the proposal for inclusion, change or deletion.**

Article 14 of the WHO Framework Convention on Tobacco Control*, "Demand reduction measures concerning tobacco dependence and cessation*", calls for collaboration to facilitate accessibility and affordability for treatment of tobacco dependence including pharmaceutical products (1). Nicotine replacement therapy (NRT), bupropion and varenicline are widely recommended smoking cessation therapies globally. Among 61 national tobacco cessation and treatment guidelines, 60 (98%) recommend NRT, 51 (84%) recommend bupropion and 50 (82%) recommend varenicline (2). Nicotine replacement therapy (gum and transdermal patches) has been included on the WHO Model List of Essential Medicines since 2009 and is currently the only treatment option for smoking cessation included on the Model List (3). The inclusion on the Model List of alternatives such as bupropion can serve to facilitate greater access and affordability to smoking cessation therapies. The availability of alternative smoking cessation therapies also provides choices for patients and prescribers.

This application therefore proposes the addition of bupropion hydrochloride to the core list of the WHO Model List of Essential Medicines as an pharmacological intervention for smoking cessation.

**2. Relevant WHO technical department and focal point (if applicable).**

WHO Department of Health Promotion, No Tobacco unit (TFI)
Dr Vinayak Prasad.

**3. Name of organization(s) consulted and/or supporting the application.**

N/A

**4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.**

INN: Bupropion
ATC code: N06AX12

**5. Dose forms(s) and strength(s) proposed for inclusion; including adult and age-appropriate paediatric dose forms/strengths (if appropriate).**

Bupropion is proposed for inclusion on the core list of the EML as:

| | |
|---|---|
| bupropion hydrochloride | Tablet, sustained-release: 150 mg |

Bupropion is not proposed for inclusion on the EMLc as the safety and effectiveness of bupropion for smoking cessation in the paediatric population have not been established.

**6. Whether listing is requested as an individual medicine or as representative of a pharmacological class.**

Listing for bupropion is proposed as an individual medicine in Section 24.5: Medicines for disorders due to psychoactive substance use.

## Treatment details, public health relevance and evidence appraisal and synthesis

### 7. Treatment details (requirements for diagnosis, treatment and monitoring).

Cessation medications are recommended for all adults who smoke daily where feasible and appropriate. The success of medications for quitting smoking is optimized when patients are prepared to quit and receive quit advice, counseling, and support from health care providers.

Patients who smoke tobacco should be encouraged to set a quit date. When using bupropion sustained-release (SR) to quit smoking, the patient should set a target quit date within the first 2 weeks of starting the medication (4). Treatment with bupropion SR should be initiated while the patient is still smoking, because approximately 1 week of treatment is required to achieve steady-state blood levels.

Bupropion SR should be taken orally and can be taken with or without food. The starting dose of bupropion SR is one 150-mg tablet each morning for the first 3 days. If the initial dose is tolerated, the dosage should be increased on day 4 to the recommended, maximum dosage of 300 mg/day, given as two 150-mg doses administered at least 8 hours apart (i.e., BID) (4). The dose is gradually increased to reduce seizure risk. Doses above 300 mg/day should not be used. Dose tapering on discontinuation is not necessary.

Bupropion SR can cause some increase in motor activity and agitation/excitement, often typical of central stimulant activity. Patients should avoid bedtime dosing to minimize insomnia.

For patients who experience side effects with the 300 mg/day bupropion SR regimen, a temporary or permanent dose reduction should be considered in consultation with their physician. Data suggest that 150 mg/day is better tolerated than 300 mg/day (i.e., 150 mg BID) and exhibits comparable long-term (>6 months) efficacy (5, 6).

The recommended duration of therapy is 7 to 12 weeks; however, some patients may benefit from extended treatment. According to the manufacturer, patients who successfully quit after 12 weeks of treatment but who do not feel ready to discontinue treatment should be considered for ongoing therapy and longer treatment should be guided by the relative benefits and risks for individual patients (4). A meta-analysis of seven trials that evaluated extended use of bupropion SR (25 to 52 weeks) found a slight benefit for relapse prevention relative to controls (7).

Bupropion SR may be used in combination with nicotine replacement therapy (NRT).

Patients who did not succeed in stopping smoking during prior bupropion SR therapy for reasons other than intolerability due to adverse events (AEs) or who relapsed after treatment, should be encouraged to make another quit attempt with bupropion SR once factors contributing to the failed attempt have been identified and addressed.

**Dosage in Special Populations**

<u>Patients with Impaired Renal Function</u>

For patients with renal impairment (Glomerular Filtration Rate: < 90 mL per min), consider reducing the dose and/or frequency of bupropion SR. Bupropion SR and its metabolites are cleared renally and may accumulate in such patients to a greater extent than usual. Monitor closely for adverse reactions that could indicate high bupropion SR or metabolite exposures.

Patients with Impaired Hepatic Function

For patients with mild hepatic impairment (Child-Pugh score: 5 to 6), consider reducing the dose and/or frequency of dosing. For patients with moderate to severe hepatic impairment (Child-Pugh score: 7 to 15), the maximum dose should not exceed 150 mg every other day.

**Pregnancy**

Regarding the use of bupropion SR in pregnancy, the product labelling differs by region. The European Medicines Agency (EMA) notes that the safety of bupropion SR for use in human pregnancy has not been established (8). Evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to the development of the embryo or fetus, the course of gestation and perinatal or postnatal development. Exposure in animals was, however, similar to the systemic exposure achieved in humans at the maximum recommended dose. The EMA concluded the potential risk of bupropion SR in human pregnancy is unknown; pregnant women should be encouraged to quit smoking without the use of pharmacotherapy; and bupropion SR should not be used in pregnancy (8). As bupropion SR and its metabolites are excreted in human breast milk, mothers should be advised not to breast feed while taking bupropion SR. In the US, bupropion SR is US FDA pregnancy category C: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. The US labelling recommends use of bupropion SR in pregnancy only if the benefit outweighs the potential risk to the fetus (4). In Australia, bupropion SR is AU TGA pregnancy category B2: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Health care providers should consult the local summary of product characteristics (SmPC) regarding the use of bupropion SR in pregnancy. Below is a summary of the available data on bupropion SR in pregnant and lactating women.

Risk Summary

Data from epidemiological studies of pregnant women exposed to bupropion SR in the first trimester indicate no increased risk of congenital malformations overall (see Human Data). All pregnancies, regardless of drug exposure, have a background rate of 2% to 4% for major malformations, and 15% to 20% for pregnancy loss. Smoking during pregnancy is associated with maternal, fetal, and neonatal risks (see Clinical Considerations). The estimated background risk of oral clefts is increased by approximately 30% in infants of women who smoke during pregnancy, compared to pregnant women who do not smoke. The background risk of other major birth defects and miscarriage are unknown. No clear evidence of teratogenic activity was found in reproductive developmental studies conducted in rats and rabbits; however, in rabbits, slightly increased incidences of fetal malformations and skeletal variations were observed at doses approximately 2 times the maximum recommended human dose (MRHD) and greater and decreased fetal weights were seen at doses three times the MRHD and greater (see Animal Data). Pregnant smokers should be encouraged to attempt cessation using educational and behavioural interventions before pharmacological approaches are used. The manufacturer recommends use of bupropion SR in pregnancy only if the benefit outweighs the potential risk to the fetus (4).

A systematic review and meta-analysis was conducted to assess the safety of bupropion SR in pregnancy for smoking cessation (9). Gestational safety outcomes with bupropion SR use were reported in 14 studies. The pooled estimate proportion of congenital malformations among live-

born infants was 1% (95% CI 0-3%, $I^2$=81%, 4 studies), the mean birthweight at delivery was 3306 (95% CI 3173-3439, $I^2$=78%, 5 studies), and the mean gestational age at delivery was 39.2 weeks (95% CI 38.8-39.6 weeks, $I^2$=70%, 5 studies). The authors concluded there was no strong evidence of major positive or negative outcomes associated with gestational use of bupropion.

Clinical Considerations

*Disease-Associated Maternal and/or Embryo/Fetal Risk*

Smoking during pregnancy causes increased risks of orofacial clefts, premature rupture of membranes, placenta previa, placental abruption, ectopic pregnancy, fetal growth restriction and low birth weight, stillbirth, preterm delivery and shortened gestation, neonatal death, sudden infant death syndrome and reduction of lung function in infants. It is not known whether quitting smoking with bupropion SR during pregnancy reduces these risks.

Data

*Human Data:* Data from the international bupropion SR Pregnancy Registry (675 first trimester exposures) and a retrospective cohort study using the United Healthcare database (1213 first trimester exposures) did not show an increased risk for malformations overall. No increased risk for cardiovascular malformations overall has been observed after bupropion SR exposure during the first trimester. The prospectively observed rate of cardiovascular malformations in pregnancies with exposure to bupropion SR in the first trimester from the international Pregnancy Registry was 1.3% (9 cardiovascular malformations/675 first trimester maternal bupropion SR exposures), similar to the background rate of cardiovascular malformations (approximately 1%). Data from the United Healthcare database and a case-control study (6853 infants with cardiovascular malformations and 5763 with non-cardiovascular malformations) from the National Birth Defects Prevention Study (NBDPS) did not show an increased risk for cardiovascular malformations overall after bupropion SR exposure during the first trimester.

Study findings on bupropion SR exposure during the first trimester and risk for left ventricular outflow tract obstruction (LVOTO) are inconsistent and do not allow conclusions regarding a possible association. The United Healthcare database lacked sufficient power to evaluate this association; the NBDPS found increased risk for LVOTO (n=10; adjusted OR=2.6; 95% CI: 1.2, 5.7), and the Slone Epidemiology case control study did not find increased risk for LVOTO.
Study findings on bupropion SR exposure during the first trimester and risk for ventricular septal defect (VSD) are inconsistent and do not allow conclusions regarding a possible association. The Slone Epidemiology Study found an increased risk for VSD following first trimester maternal bupropion SR exposure (n=17; adjusted OR=2.5; 95% CI: 1.3, 5.0) but did not find increased risk for any other cardiovascular malformations studied (including LVOTO as above). The NBDPS and United Healthcare database study did not find an association between first trimester maternal bupropion SR exposure and VSD. For the findings of LVOTO and VSD, the studies were limited by the small number of exposed cases, inconsistent findings among studies, and the potential for chance findings from multiple comparisons in case control studies.

*Animal Data:* In studies conducted in rats and rabbits, bupropion SR was administered orally during the period of organogenesis at doses of up to 450 and 150 mg per kg per day, respectively (approximately 15 and 10 times the MRHD respectively, on a mg/$m^2$ basis). No clear evidence of teratogenic activity was found in either species; however, in rabbits, slightly increased incidences of fetal malformations and skeletal variations were observed at the lowest dose tested (25 mg/kg per

day, approximately 2 times the MRHD on a mg/$m^2$ basis) and greater. Decreased fetal weights were observed at $\geq$ 50 mg/kg. When rats were administered bupropion SR at oral doses of up to 300 mg/kg per day (approximately 10 times the MRHD on a mg/$m^2$ basis) prior to mating and throughout pregnancy and lactation, there were no apparent adverse effects on offspring development.

**Lactation**

Bupropion SR and its metabolites are present in human milk. In a lactation study of 10 women, levels of orally dosed bupropion SR and its active metabolites were measured in expressed milk. The average daily infant exposure (assuming 150 mL/kg daily consumption) to bupropion SR and its active metabolites was 2% of the maternal weight-adjusted dose. Exercise caution when bupropion SR is administered to a nursing woman.

**Pediatric Use**

Safety and effectiveness of bupropion SR for smoking cessation in the pediatric population have not been established.

**Geriatric Use**

Of the approximately 6000 participants who participated in clinical trials with bupropion SR (depression and smoking cessation trials), 275 were aged ≥ 65 years and 47 were ≥ 75 years. In addition, several hundred participants aged ≥ 65 years participated in clinical trials using the immediate-release formulation of bupropion SR (depression trials). No overall differences in safety or effectiveness were observed between these participants and younger participants. Reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Bupropion SR is extensively metabolized in the liver to active metabolites, which are further metabolized and excreted by the kidneys. Risk of adverse reactions may be greater in those with impaired renal function. Elderly patients are more likely to have decreased renal function, so it may be necessary to consider this factor in dose selection and useful to monitor renal function.

No dosage adjustment is recommended for elderly patients.

**8. Information supporting the public health relevance.**

Tobacco smoking remains the leading cause of premature disability and death around the world (10). Cigarette smoke contains an estimated 7000 different chemical compounds of which at least 70 are proven or suspected human carcinogens including: arsenic, benzene, formaldehyde, lead, nitrosamines, and polonium 210. Tobacco smoke also contains poisonous gasses: carbon monoxide (CO), hydrogen cyanide, butane, toluene, and ammonia. More than half of all long-term smokers die from a tobacco-caused disease, with an average loss of at least 10 years of life (11). Smoking causes 87% of lung cancer deaths, 61% of pulmonary disease deaths (COPD, emphysema), and 1 in 3 cancer deaths. For every person who dies from smoking, at least 30 people live with serious smoking-related illnesses (11).

According to the World Health Organization (WHO) (12):

- The tobacco epidemic is one of the biggest public health threats the world has ever faced.

- Globally, 1.3 million people use tobacco; 80% live in low- and middle-income countries.
- Tobacco use contributes to poverty by diverting household spending from basic needs.
- Over 8 million people a year die from tobacco use
- The economic costs of tobacco use are substantial.

Estimates from 2012 are that the total global economic cost of smoking was $US 1436 billion, equivalent to 1.8% of the world's annual GDP, with about 40% of the total economic cost borne in developing countries (13).

The scale of human and economic harms that the tobacco industry imposes is astounding and preventable. In response, in 2003, WHO Member States unanimously adopted the WHO Framework Convention on Tobacco Control (WHO FCTC), currently endorsed by 182 Parties covering more than 90% of the world's population. To scale up implementation of the main demand reduction (i.e., tobacco control) provisions of the WHO FCTC, in 2007, the WHO introduced MPOWER, with "O" focused on offering treatment. The 6 MPOWER measures are:

- **M**onitor tobacco use and prevention policies
- **P**rotect people from tobacco use
- **O**ffer help to quit tobacco use
- **W**arn about the dangers of tobacco
- **E**nforce bans on tobacco advertising, promotion and sponsorship
- **R**aise taxes on tobacco.

Quitting smoking brings health benefits, and when smokers become aware of the dangers of tobacco, most want to quit. Yet, without medications or cessation support, only about 4% of attempts to quit tobacco will succeed. Professional support and proven cessation medications can more than double a tobacco user's chance of successfully quitting (13).

As stated in the 2019 WHO Report on the Global Tobacco Epidemic (14) "Every country has an obligation to protect the health of its people, and all parties to the WHO FCTC have made a specific commitment to implement strong tobacco control policies, including effective cessation services, as an important means of fulfilling their obligation to protect the health of their people."

Tobacco dependence is characterized as a physiological dependence (addiction to nicotine) and behavioral (or conditioned) habit of using tobacco. Hence, for maximal effectiveness, as recommended by clinical practice guidelines, tobacco dependence treatment engages a multi-pronged approach (15-17). Addiction can be treated with evidence-based cessation medications for smoking cessation, and the behavioral habit can be treated through counseling and behavior change programs. Either cessation medication or counseling alone has evidence, and the best outcomes are for the combination. Availability of interventions and their use is likely to vary. Having multiple cessation medication options available for clinicians and patients in the tobacco treatment toolbox is essential for addressing the significant global harms of tobacco use.

**9. Review of benefits: summary of evidence of comparative effectiveness.**

**Important Baseline Efficacy and Effectiveness Information**

Bupropion SR was first approved as an aid to smoking cessation treatment in adults in the United States (Brand name Zyban) in May 1997 (prescription only) and the generic form was approved in 2004. In the EU, bupropion SR was approved in 1999 and is sold under the trade names of Zyban, Quomem, Corzen, and Zyntabac. Bupropion SR is registered in all EU countries with the exception of Bulgaria.

Bupropion SR tablets are an oral antidepressant medication used as a non-nicotine aid to smoking cessation (4). The same chemical agent is marketed as Wellbutrin for use in treating depression. Bupropion SR is an atypical antidepressant thought to affect the levels of brain neurotransmitters (e.g., dopamine, norepinephrine). Bupropion SR does not inhibit monoamine oxidase. The purported mechanisms of action include blockade of neuronal re-uptake of dopamine and norepinephrine in the central nervous system and through antagonism of nicotinic acetylcholine receptors (15). Bupropion SR also has been shown to act as a competitive alpha-3-beta-4-nicotinic antagonist (18); which has been shown to interrupt addiction. These actions clinically result in reduced craving for nicotine and symptoms of withdrawal (15). The dopaminergic system is thought to play a role in self-reinforcing behaviour (reward pathways) and dependence, whereas noradrenergic effects are thought to prevent the symptoms of nicotine withdrawal.

**Clinical Efficacy**

The efficacy of bupropion SR as an aid to smoking cessation has been demonstrated in multiple placebo-controlled, double-blind trials. Where reported, 95% confidence intervals are presented.

The first three trials described were conducted by the manufacturer (GlaxoSmithKline, GSK) in nondepressed chronic cigarette smokers (N=1940, smoking $\geq$ 15 cigarettes per day) (4). In these trials, bupropion SR was used in conjunction with individual smoking cessation counseling. When tested at 300 mg per day, treatment with bupropion SR was initiated at 150 mg per day while the participant was still smoking then increased after 3 days to 300 mg per day given as 150 mg BID. Abstinence rates were determined by participant daily diaries and verified by CO levels in expired air and are the proportions of all participants initially enrolled (i.e., intent–to-treat analysis) who abstained through the specified week.

The first trial (N=615), conducted at three clinical centers, evaluated dose-response (6). Participants were treated for 7 weeks with 1 of 3 doses of bupropion SR (100, 150, or 300 mg per day) or placebo. Subjects set a target quit date after one week of medication (usually day 8). Table 1 presents CO-confirmed weekly point prevalence quit rates at week 6 (final week of study medication) and at months 3, 6, and 12. Treatment with bupropion SR (100, 150 or 300 mg per day) was more effective than placebo in helping participants achieve abstinence at week 6 and month 3. Treatment with bupropion at 150 or 300 mg per day were more effective than placebo in helping patients achieve abstinence at months 6 and 12. Rates of continuous abstinence from the target quit date through the end of treatment were 10.5% in the placebo group, 13.7% in the 100 mg group, 18.3% in the 150 mg group, and 24.4% in the 300 mg group. The rate of continuous abstinence was significantly better in the bupropion 300 mg group than in the placebo group ($p< 0.001$) and in the group that received 100 mg of bupropion ($p< 0.02$).

**Table 1. Dose-Response Trial: CO-Confirmed Weekly Point Prevalence Quit Rates**

| Treatment groups (7-weeks): | Wk 6* | 3 mo | 6 mo | 12 mo |
|---|---|---|---|---|
| Bupropion SR 300 mg/day, n=156 | 44.2%** | 29.5%** | 26.9%* | 23.1%* |
| Bupropion SR 150 mg/day, n=153 | 38.6%** | 26.1%* | 27.5%* | 22.9%* |
| Bupropion SR 100 mg/day, n=153 | 28.8%* | 24.2%* | 24.2% | 19.6% |
| Placebo, n=153 | 19.0% | 14.4% | 15.7% | 12.4% |

* Final week of study medication, Wk = Week, ** p<.001 and * p<.05 relative to placebo

The second, a comparator combination treatment trial (N=893), conducted at four clinical centers, evaluated 9-week treatments of: bupropion SR 300 mg, nicotine patch 21 mg per day, combination of bupropion SR 300 mg plus nicotine patch 21 mg per day, and placebo (19). Nicotine patch 21 mg

per day was added to treatment with bupropion SR after approximately 1 week when the participant reached the target quit date. During Weeks 8 and 9 of the trial, the patch was tapered to 14 and 7 mg per day, respectively. The primary outcome was CO-verified point-prevalence abstinence at 6 and 12 months follow-up. Findings demonstrated the superiority of bupropion SR and the combination of bupropion SR and nicotine patch over placebo in helping participants to achieve and maintain abstinence from smoking (see Table 2). Although the treatment combination of bupropion SR and nicotine patch displayed the highest rates of continuous abstinence throughout the trial, the quit rates for the combination were not significantly higher (p □ 0.05) than for bupropion SR alone.

**Table 2. Comparator Clinical Trial: CO-Confirmed Point Prevalence Quit Rates by Group**

| Treatment groups (9-weeks): | 6 months | 12 months |
|---|---|---|
| Bupropion SR 300 mg plus nicotine patch 21 mg, n=245 | 38.8%[a] | 35.5%[a] |
| Bupropion SR 300 mg, n=244 | 34.8% [a] | 30.3% [a] |
| Nicotine patch 21 mg, n=244 | 21.3%[b] | 16.4% [b] |
| Placebo, n=151 | 18.8%[b] | 15.6% [b] |

[a,b] indicate comparisons different at p<.05

The third trial, at five clinical centers, examined long-term maintenance treatment with bupropion SR (20). Participants (N=784) received open-label bupropion SR 300 mg per day for 7 weeks. Of participants who quit smoking while receiving bupropion SR, 429 were then randomized to bupropion SR 300 mg per day or placebo for a total trial duration of 1 year. Abstinence from smoking was determined by self-report and verified by expired air CO levels. Smoking point prevalence abstinence was significantly higher in the bupropion SR group than in the placebo group at the end (week 52) of drug therapy (55% vs. 42%, respectively; p=.008) and at week 78 (48% vs. 38%; p=.034) but did not differ at the final (week 104) follow-up visit (42% vs. 40%). The median time to relapse was significantly greater for bupropion SR recipients than for placebo recipients (156 days vs. 65 days; p=.021). The continuous abstinence rate was higher in the bupropion SR group than in the placebo group at study week 24 (17 weeks after randomization) (52% vs. 42%; p=.037), but did not differ between groups after week 24.

Another trial, of 6-months long-term maintenance treatment with bupropion SR, reported hazard ratios (HR) for relapse statistically significant for bupropion SR at 6-months (end-of-treatment) (HR = 0.59, 95% CI = 0.37-0.92) and at 12-months (6-month follow-up) (HR = 0.66, 95% CI = 0.42-0.96) (21). However, bupropion SR's advantage dissipated upon stopping the drug.

Quit rates in clinical trials are influenced by the population selected. Quit rates in an unselected population may be lower than the above rates. Quit rates for bupropion SR were similar in participants with and without prior quit attempts using NRT.

Across trials, during active treatment, withdrawal symptoms were significantly reduced in participants randomized to treatment with bupropion SR compared with placebo. Reductions on the following withdrawal symptoms were most pronounced: irritability, frustration, or anger; anxiety; difficulty concentrating; restlessness; and depressed mood or negative affect. Depending on the trial and the measure used, treatment with bupropion SR showed evidence of reduction in craving for cigarettes or urge to smoke compared with placebo.

Pfizer conducted two identically designed double-blind pre-authorization varenicline vs. bupropion SR comparative clinical trials for smoking cessation (22, 23). The arms were varenicline (1 mg BID), bupropion SR (150 mg BID), and placebo. In these 52-week duration studies, patients received treatment for 12 weeks, followed by a 40-week non-treatment phase. In addition to an educational

booklet on smoking cessation, participants received up to 10 min of smoking cessation counselling at each weekly treatment visit. Patients set a date to stop smoking with medication dosing starting 1 week prior. The primary endpoint of the two studies was CO-confirmed, 4-week continuous abstinence from smoking during weeks 9-12. After the 40-week non-treatment phase, a key secondary endpoint for both studies was the continuous abstinence during weeks 9-52. The continuous abstinence rates during weeks 9-12 and 9-52 from these studies are shown in Table 3. Bupropion SR had significantly higher continuous abstinence rates at weeks 9-12 in both trials and at weeks 9-52 in one of the two trials. Varenicline was superior to bupropion SR at weeks 9-12 in both trials and at weeks 9-52 in one of the two trials.

**Table 3. Varenicline vs Bupropion SR in Pfizer Comparative Clinical Trials**

| | Gonzales et al. (23) (n=1025) | | Jorenby et al. (22) (n=1027) | |
|---|---|---|---|---|
| | CA Wk 9-12 | CA Wk 9-52 | CA Wk 9-12 | CA Wk 9-52 |
| Varenicline 2 mg/day | 44.0% | 21.9% | 43.9% | 23.0% |
| Bupropion SR 300 mg/day | 29.5% | 16.1% | 29.8% | 14.6% |
| Placebo | 17.7% | 8.4% | 17.6% | 10.3% |
| OR varenicline vs placebo | 3.85*** | 3.09*** | 3.85*** | 2.66*** |
| OR bupropion vs placebo | 2.00*** | 2.09** | 1.99*** | 1.50 |
| OR varenicline vs bupropion | 1.96*** | 1.46 | 1.90*** | 1.77** |

CA = Continuous Abstinence, Wk = Week, OR = Odds Ratio, *** p<.001, ** p<.01, * p<.05

Across both studies during active treatment, patient reported outcome measures demonstrated that craving and withdrawal (urge, negative affect, insomnia) were significantly reduced in patients randomized to bupropion SR vs. placebo. Bupropion SR also significantly reduced positive reinforcing effects of smoking during treatment vs. placebo.

**Use in Smokers with Chronic Obstructive Pulmonary Disease (COPD)**

In a randomized, double-blind trial conducted by GSK, bupropion SR was evaluated in 404 participants with mild-to-moderate COPD defined as FEV1 $\geq$ 35%, FEV1/FVC $\leq$ 70%, and a diagnosis of chronic bronchitis, emphysema, and/or small airways disease (24). Participants aged 36 to 76 years were randomized to bupropion SR 300 mg per day (n=204) or placebo (n=200) and treated for 12 weeks. All participants were chronic smokers with a smoking history of about 51 pack years. Treatment with bupropion SR was initiated at 150 mg per day for 3 days while the participant was still smoking and increased to 150 mg twice daily for the remaining treatment period. Abstinence from smoking was determined by participant daily diaries and verified by CO levels in expired air. Quitters were defined as participants who were abstinent during the last 4 weeks of treatment. Table 4 shows quit rates in the COPD Trial. Bupropion SR-treated patients had higher abstinence rates than placebo-treated patients during the last 4 weeks of treatment (22% *vs* 12%, p=0.011). Continuous abstinence rates from weeks 4-12 (18% vs 10% and weeks 4-26 (16% vs 9%) also were also higher in participants receiving bupropion SR than in those taking placebo (p<0.05). Furthermore, symptoms of tobacco craving and withdrawal were attenuated in those receiving bupropion SR. Twenty-seven participants discontinued study medication because of an adverse event (placebo=13, bupropion SR=14). The most common adverse events leading to discontinuation of study drug were anxiety (n=5) and insomnia (n=4) for the bupropion SR group, and headache (n=3) for the participants receiving placebo.

**Table 4. COPD Trial: Quit Rates (95% CI) by Treatment Group**

| Treatment groups (12-weeks): | CA Wk 9-12 | CA Wk 4-12 | CA Wk 4-26 |
|---|---|---|---|
| Bupropion SR 300 mg/day, n=204 | 22% (17-27)* | 18%* | 16%* |
| Placebo, n=200 | 12% (8-16) | 10% | 9% |

CA=Continuous Abstinence, Wk=Week, * indicates significantly different from placebo p<.05

**Use in Smokers with Cardiovascular Disease (CVD)**

Several randomized controlled trials and meta-analyses have examined use of bupropion SR for treating smoking in adults with CVD.

The first, a trial funded by GSK, investigated the safety and efficacy of bupropion SR in promoting abstinence from smoking in 629 participants with CVD who smoked > 10 cigarettes per day (22). Participants were randomized in a double-blind, multicenter study to receive bupropion SR (150 mg BID) or placebo for 7 weeks with brief motivational support, with a follow-up assessment at 52 weeks. The primary efficacy endpoint was continuous abstinence from smoking from weeks 4-7. Secondary endpoints were continuous abstinence at weeks 4-12, 4-26, and 4-52. Safety was evaluated throughout the study. Continuous smoking abstinence rates from weeks 4-7 were significantly higher in participants receiving bupropion SR compared with placebo (43% vs. 19%, OR=3.27, 95% CI: 2.24-4.84; p<.001). Continuous abstinence rates from weeks 4-26 and 4-52 continued to be more than double for bupropion SR compared with placebo (27% vs. 11% and 22% vs. 9%, both p<.001). In both groups, there were no clinically significant changes in blood pressure and heart rate throughout the treatment phase. Overall, 6% of the participants (n=36) discontinued study medication due to an adverse event (bupropion SR, n=17; placebo, n=19). After 7 weeks of bupropion SR treatment, more than twice as many smokers with CVD had quit smoking at 1 year compared with placebo. The safety profile of bupropion SR was similar to that previously observed in general smoking populations.

Rigotti et al. (25) conducted a randomized controlled trial with 247 hospitalized patients with acute CVD (i.e., patients admitted with MI or unstable angina, CABG, or other cardiovascular conditions with documented CAD) treated for 12 weeks with bupropion SR 300 mg or placebo. Cotinine-confirmed abstinence outcomes were reported at 3-months (end-of-treatment) and 12 months. The study was funded by grants from NHLBI, the NIH General Clinical Research Centers Program, and an unrestricted research grant from GSK (GSK provided free drug and placebo and an unrestricted research grant to permit data collection to be completed when NHLBI funds were exhausted). Validated tobacco abstinence rates in bupropion SR and placebo groups were 37% vs 27% (OR=1.61, 95% CI: 0.94-2.76; p=.08) at 3 months and 25% vs 21% (OR=1.23, 95% CI: 0.68-2.23, p=.49) at 12 months. The adjusted OR, after controlling for cigarettes per day, depression symptoms, prior bupropion SR use, hypertension, and length of stay, was 1.91 (95% CI: 1.06-3.40, p=.03) at 3 months and 1.51 (95% CI: 0.81-2.83) at 12 months. Bupropion SR and placebo groups did not differ in cardiovascular mortality at 12 months (0% vs 2%), in blood pressure at follow-up, or in cardiovascular events at end-of-treatment (16% vs 14%, incidence rate ratio [IRR]=1.22 (95% CI: 0.64-2.33) or 12 months (26% vs 18%, IRR=1.56, 95% CI: 0.91-2.69). The investigators concluded that bupropion SR improved short-term but not long-term smoking cessation rates over intensive counselling and appeared to be safe in hospitalized smokers with acute CVD.

A meta-analysis was conducted to determine the efficacy and safety of bupropion SR therapy started in-hospital for smoking cessation in patients with CVD (26). Three randomized controlled trials with 773 participants were included in the analyses, predominantly men (range of means, 69%-84%) and hospitalized with acute coronary syndrome (range of means, 66%-100%). Treatment duration ranged from 8-12 weeks. At the end of treatment, bupropion SR was associated with a significant increase in

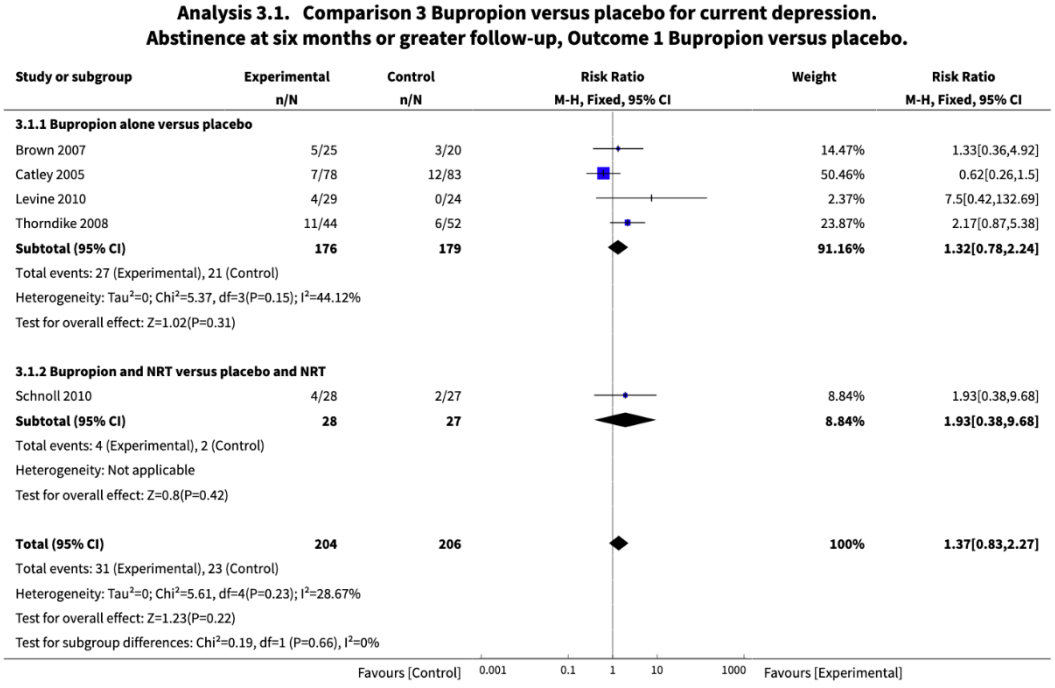
point prevalence abstinence (RR=1.21; 95% CI: 1.02-1.45) but not continuous abstinence (RR=1.19; 95% CI: 0.97-1.45). At 12 months, bupropion SR was not associated with a significant increase in point prevalence abstinence (RR=1.17; 95% CI: 0.92-1.48) or continuous abstinence (RR=1.16; 95% CI: 0.90-1.50). Pooled analysis results for major adverse cardiac and cerebrovascular events were inconclusive (RR=1.28; 95% CI: 0.93-1.78). Bupropion SR improved abstinence over placebo at the end of treatment but not at 12 months. Inconsistent reporting of safety data made the safety profile of bupropion SR therapy in this patient population unclear.

A network meta-analysis was conducted to evaluate the efficacy and safety of pharmacological smoking cessation interventions in CVD patients in randomized controlled trials (27). Smoking abstinence at 6 and 12 months was examined, using the most rigorous criteria reported. Data were pooled across studies for direct comparisons using random-effects models. Network meta-analysis using a graph-theoretical approach was used to generate the indirect comparisons. Seven randomized controlled trials (n=2809) met inclusion criteria. Varenicline (1 trial, RR=2.64; 95% CI: 1.34-5.21) and bupropion SR (4 trials, RR=1.42; 95% CI: 1.01-2.01) were associated with greater abstinence than placebo, while the evidence for NRTs was inconclusive (2 trials, RR=1.22; 95% CI: 0.72-2.06).

**Study in Smokers with Current Depression**

Five trials, all with relatively small sample sizes, reported results of bupropion SR vs. placebo in smokers with current depression. A meta-analysis of effects across the five trials resulted in a positive, although not significant, effect (5 trials, N = 410, RR = 1.37, 95% CI 0.83 to 2.27) (28).

**Figure 1. Smoking cessation outcomes in smokers with current depression: bupropion SR vs placebo, with or without NRT (28)**




**Study in Participants with and without a History of Psychiatric Disorders**

Conducted by GSK and Pfizer, with guidance from the FDA, bupropion SR was evaluated in a randomized, double-blind, active- and placebo-controlled trial that included participants without a history of psychiatric disorder (non-psychiatric cohort, n=3912) and participants with a history of

psychiatric disorder (psychiatric cohort, n=4003) (29). Participants aged 18 to 75 years, smoking > 10 cigarettes per day were randomized 1:1:1:1 to bupropion SR 150 mg BID, varenicline 1 mg BID, nicotine patch 21 mg per day with taper, or placebo for a treatment period of 12 weeks. Participants were then followed for another 12 weeks post-treatment. The primary focus of the trial was safety in estimating the occurrence of neuropsychiatric adverse events (AEs). The main efficacy objectives were measuring continuous abstinence for Weeks 9-12 and Weeks 9-24 in participants with and without a psychiatric diagnosis. The primary comparisons were bupropion SR versus placebo and varenicline versus placebo. Nicotine patch was included as an active control, and study drugs were given via a triple dummy design, i.e., all patients took 3 drugs, which were either 1 active plus 2 placebo or all 3 were placebo. This allowed for comparison of active treatments, as well as comparison to placebo.

Figure 2 shows the continuous abstinence rates for the non-psychiatric and psychiatric cohorts and for the sample overall at weeks 9-12 and weeks 9-24. In both cohorts and overall, all active treatments (including bupropion SR) showed significantly greater efficacy in smoking cessation compared with placebo as measured at both Weeks 9-12 and 9-24 (Tables 5 & 6). In addition, varenicline showed significantly greater efficacy compared with bupropion SR and compared with nicotine patch at both Weeks 9-12 and 9-24, while the bupropion SR−patch differences were not significant in either timeframe (Tables 5 & 6).

**Figure 2. Continuous Abstinence Outcomes for Non-Psychiatric and Psychiatric Cohorts and for the Sample Overall: Weeks 9-12 and Weeks 9-24 (29)**

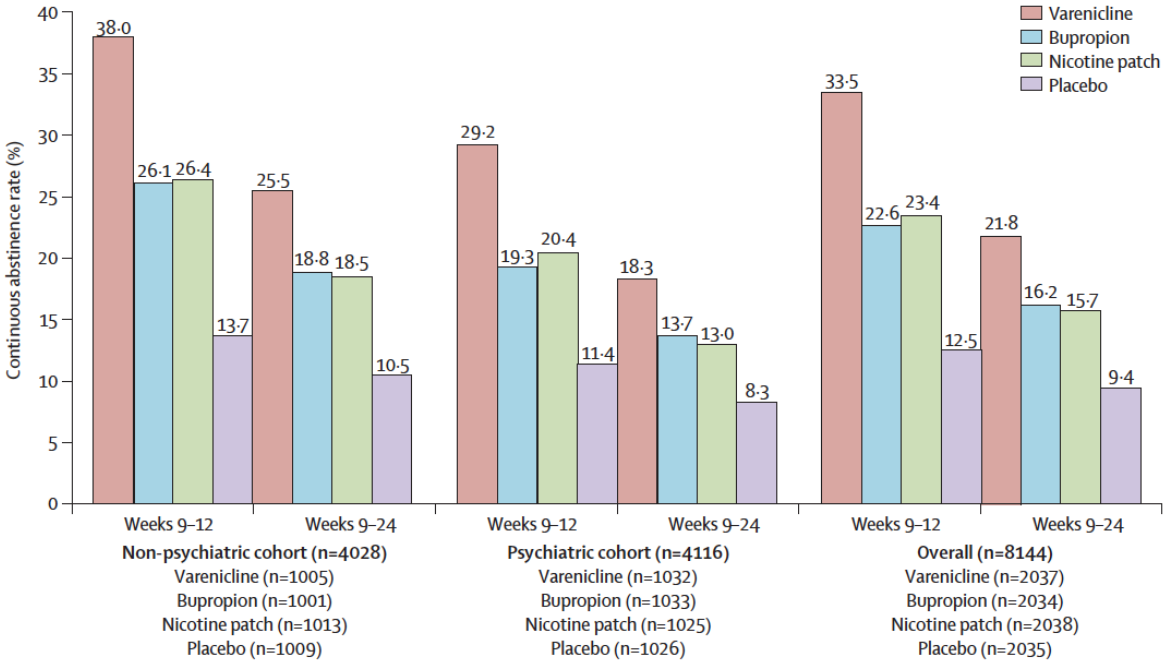


**Table 5. Odds Ratios (95% CI) for Treatment Comparisons: Weeks 9-12**

| Treatment Comparisons | Non-Psychiatric Cohort | Psychiatric Cohort | Overall |
|---|---|---|---|
| Bupropion vs Placebo | 2.26 (1.80, 2.85) | 1.87 (1.46, 2.39) | 2.07 (1.75, 2.45) |
| Bupropion vs Patch | 0.98 (0.80, 1.20) | 0.94 (0.75, 1.16) | 0.96 (0.83, 1.11) |
| Bupropion vs Varenicline | 0.56 (0.47, 0.68) | 0.57 (0.47, 0.71) | 0.57 (0.50, 0.65) |
| Varenicline vs Placebo | 4.00 (3.20, 5.00) | 3.24 (2.56, 4.11) | 3.61 (3.07, 4.24) |
| Varenicline vs Patch | 1.74 (1.43, 2.10) | 1.62 (1.32, 1.99) | 1.68 (1.46, 1.93) |
| Patch vs Placebo | 2.30 (1.83, 2.90) | 2.00 (1.56, 2.55) | 2.15 (1.82, 2.54) |

**Table 6. Odds Ratios (95% CI) for Treatment Comparisons: Weeks 9-24**

| Treatment Comparisons | Non-Psychiatric Cohort | Psychiatric Cohort | Overall |
|---|---|---|---|
| Bupropion vs Placebo | 2.00 (1.54, 2.59) | 1.77 (1.33, 2.36) | 1.89 (1.56, 2.29) |
| Bupropion vs Patch | 1.02 (0.81, 1.28) | 1.07 (0.83, 1.39) | 1.04 (0.88, 1.24) |
| Bupropion vs Varenicline | 0.67 (0.54, 0.83) | 0.71 (0.56, 0.90) | 0.69 (0.59, 0.81) |
| Varenicline vs Placebo | 2.99 (2.33, 3.83) | 2.50 (1.90, 3.29) | 2.74 (2.28, 3.30) |
| Varenicline vs Patch | 1.52 (1.23, 1.89) | 1.51 (1.19, 1.93) | 1.52 (1.29, 1.78) |
| Patch vs Placebo | 1.96 (1.51, 2.54) | 1.65 (1.24, 2.20) | 1.81 (1.49, 2.19) |

**Study in Healthy Adolescent Smokers**

Four published trials have evaluated bupropion SR for treating smoking in adolescent samples (30-33), with one of the trials receiving support from GSK (31). Two of the studies were limited to short-term (i.e., 12-week) follow-up (30, 33).

Muramoto et al. evaluated 7-week treatment of bupropion SR at 300 mg or 150 mg per day vs. placebo in 312 adolescents aged 14 to 17 (31). The study was funded by the National Cancer Institute, the Robert Wood Johnson Foundation, and GSK. At 6-months follow-up, CO-confirmed 7-day point prevalence abstinence was 9/104 (8.7%) for bupropion SR 300 mg, 2/105 (1.9%) for bupropion SR 150 mg, and 6/103 (5.8%) for placebo, with a RR=1.49 (0.55, 4.02) for bupropion SR 300 mg vs. placebo.

Killen et al. examined bupropion SR in combination with nicotine patch versus nicotine patch alone in a sample of 211 adolescents recruited from continuation high schools with an average age of 17 (32). In addition to the medications, all participants received weekly 45-min group sessions with skills training. Compliance with bupropion SR and patch therapy was characterized as low, and over a third of participants in both groups was lost to follow-up at 6-months. Intention-to-treat cotinine-validated 7-day point prevalence abstinence at 6 months (assuming those lost to follow-up were smoking) were 8/103 (7.8%) for bupropion SR plus patch and 8/108 (7.4%) for patch alone, RR (95% CI) of 1.05 (0.41, 2.69).

Gray et al. examined bupropion SR vs. placebo paired with or without contingency management in a sample of 134 participants between the ages of 12 and 21 (30). CO-confirmed 7-day point-prevalence abstinence at 12-week follow-up, collapsing across contingency management conditions, were: 6/73 (8.2%) for bupropion SR vs. 2/71 (2.8%) for placebo, with a calculated pooled effects OR (95% CI) of 2.6 (0.5, 13.6).

In a second trial, Gray et al. tested 8-weeks of bupropion SR vs. varenicline in 29 adolescents aged 15 to 20 (33). Quit rates, reported as cotinine-confirmed 7-day point prevalence abstinence at 12-week follow-up, were: 0/15 (0%) for varenicline vs. 1/14 (7.1%) for bupropion SR.

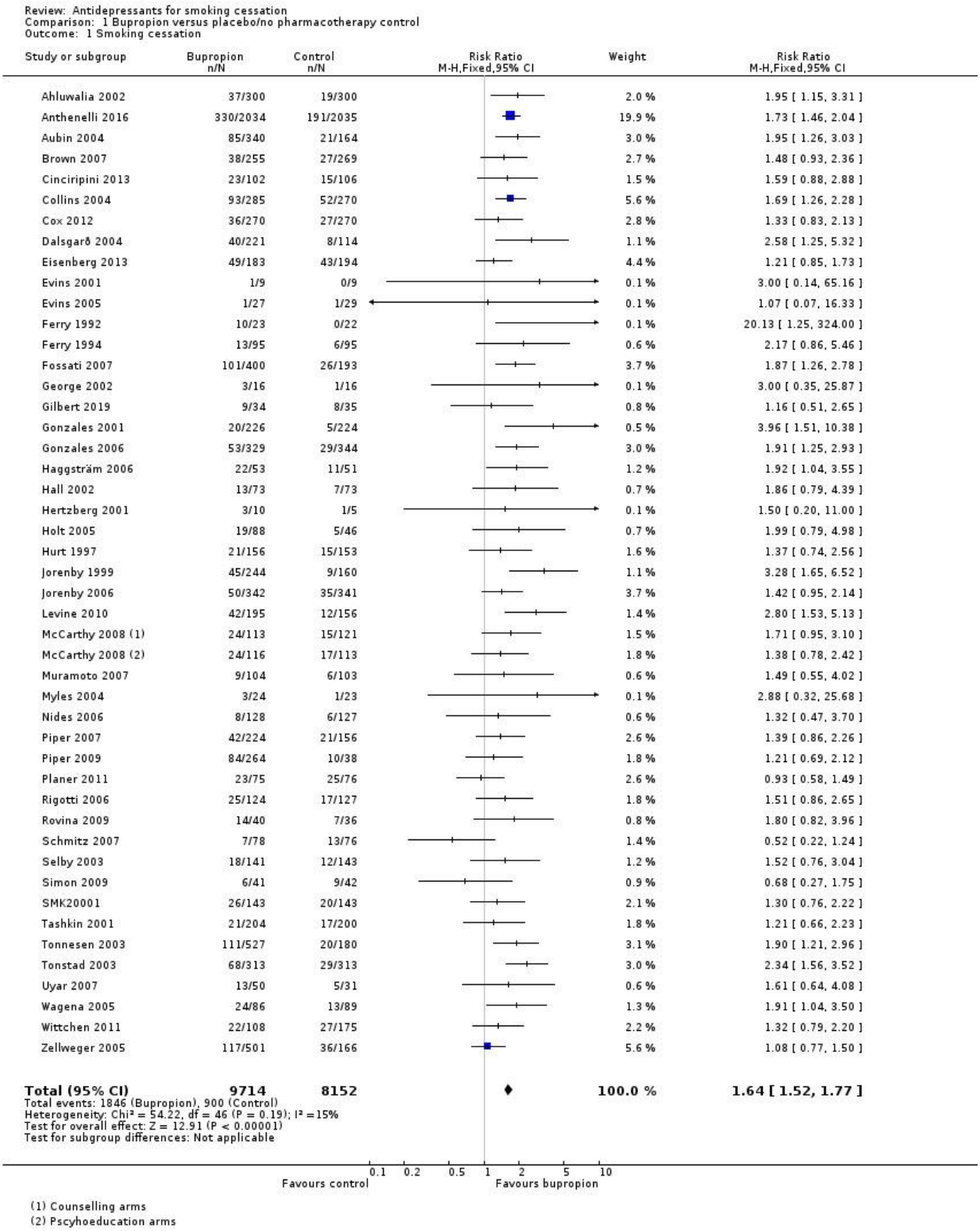
In the four studies of bupropion SR with adolescents, the medication was well-tolerated with an AE profile similar to that observed in healthy adult smokers and no notable findings for neuropsychiatric AEs.

**Meta-Analysis Findings**

A Cochrane meta-analysis was conducted to assess the evidence for the efficacy, safety, and tolerability of medications with antidepressant properties, including bupropion SR, in assisting long-term tobacco smoking cessation in people who smoke cigarettes (34). The literature search was last updated May 2019 and was restricted to randomized controlled trials with smoking cessation treatment outcomes reported at 6 months or longer. The meta-analysis included samples of any age; studies of treating smoking in pregnancy were excluded. When multiple doses of bupropion were compared in a trial, data from the 300 mg/day arm was used. The efficacy findings are summarized here for bupropion SR as a single therapy relative to placebo, NRT, varenicline, and nortriptyline; and for bupropion SR as a combination therapy with NRT or varenicline relative to NRT and varenicline alone, respectively. The figures below come from the Cochrane publication. Conclusions from the meta-analysis regarding bupropion SR's safety and tolerability as a smoking cessation aid are summarized in section 10.

- High-certainty evidence confirmed the benefit of bupropion SR as a single pharmacotherapy for smoking cessation (RR=1.64, 95% CI: 1.52 to 1.77; $I^2$=15%; 45 studies, 17866 participants, see Figure 3).
- Treatment effects of bupropion SR for quitting smoking were comparable across settings and types of behavioural support studied (group vs. individual, low-intensity).
- Treatment effects of bupropion SR for quitting smoking were comparable for participants with psychiatric conditions (RR=1.67, 95% CI: 1.3,2.15; $I^2$=0% 5 studies, 2180 participants) and without a history of psychiatric conditions (RR=1.67, 95% CI: 1.3,2.15; $I^2$=23%, 42 studies, 15686 participants). Trials comparing bupropion SR to placebo found no evidence of an interaction between depression and bupropion SR treatment effects. The samples were recruited as motivated to quit, and those with psychiatric conditions were stably treated.
- Adding bupropion SR to NRT (RR=1.19, 95% CI: 0.94 to 1.51; $I^2$=52%; 12 studies, 3487 participants, Figure 4) or varenicline (RR=1.21, 95% CI: 0.95 to 1.55; $I^2$=15%; 3 studies, 1057 participants, Figure 5) did not appear to provide additional benefit compared to treatment with NRT or varenicline alone, respectively.
- The evidence does not suggest a difference in the efficacy of bupropion SR and NRT (RR=0.99, 95% CI: 0.91 to 1.09; $I^2$=18%; 10 studies, 8230 participants, Figure 6), or bupropion SR and nortriptyline (RR=1.30 (favouring bupropion SR), 95% CI: 0.93 to 1.82; $I^2$=0%; 3 studies, 417 participants), for smoking cessation.
- Bupropion SR had inferior smoking cessation rates to varenicline (RR=0.71, 95%: CI: 0.64 to 0.79; $I^2$=0%; 6 studies, 6286 participants, Figure 7).

**Figure 3. Smoking cessation outcomes: bupropion SR vs placebo or a no pharmacotherapy control group (34)**




(1) Counselling arms
(2) Pscyhoeducation arms

**Figure 4. Smoking cessation outcomes: bupropion SR & NRT vs NRT alone (34)**

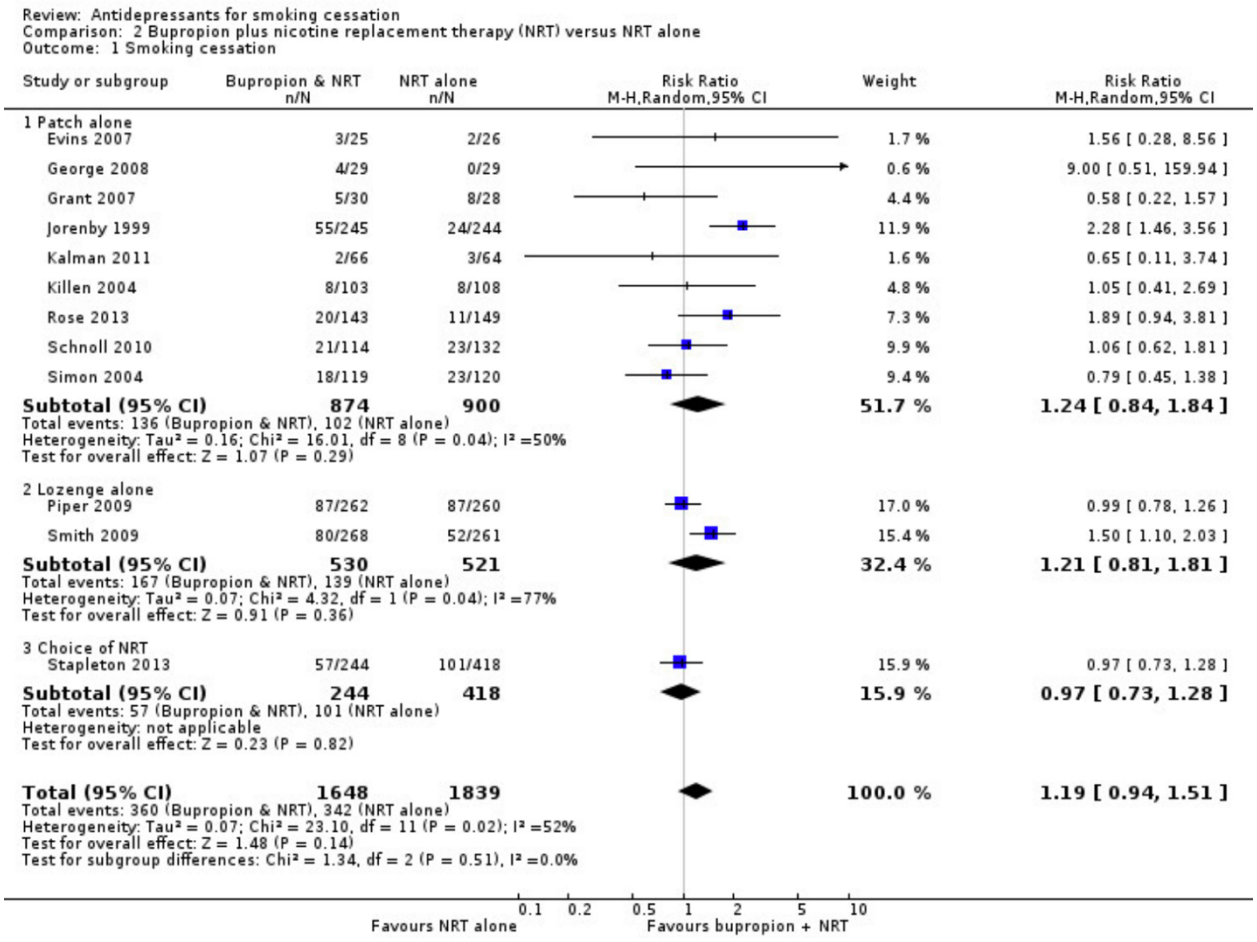
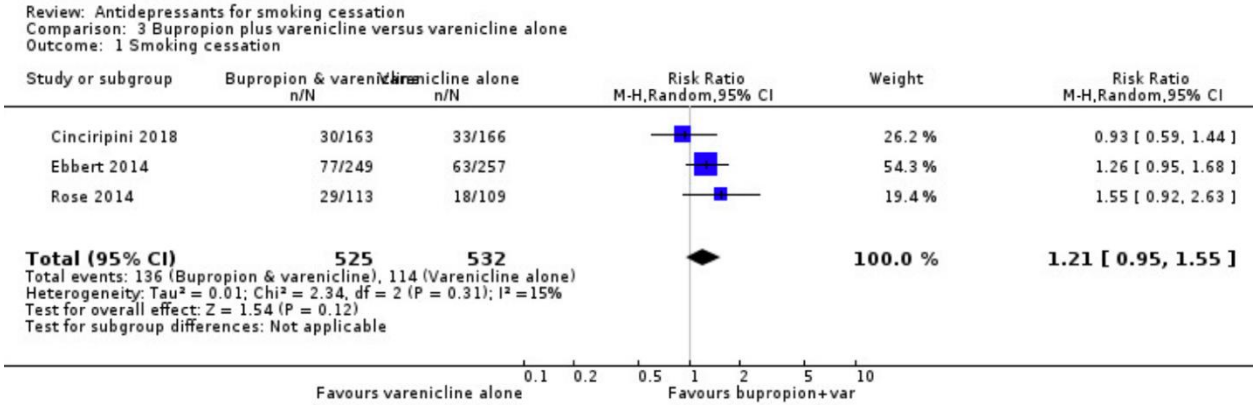
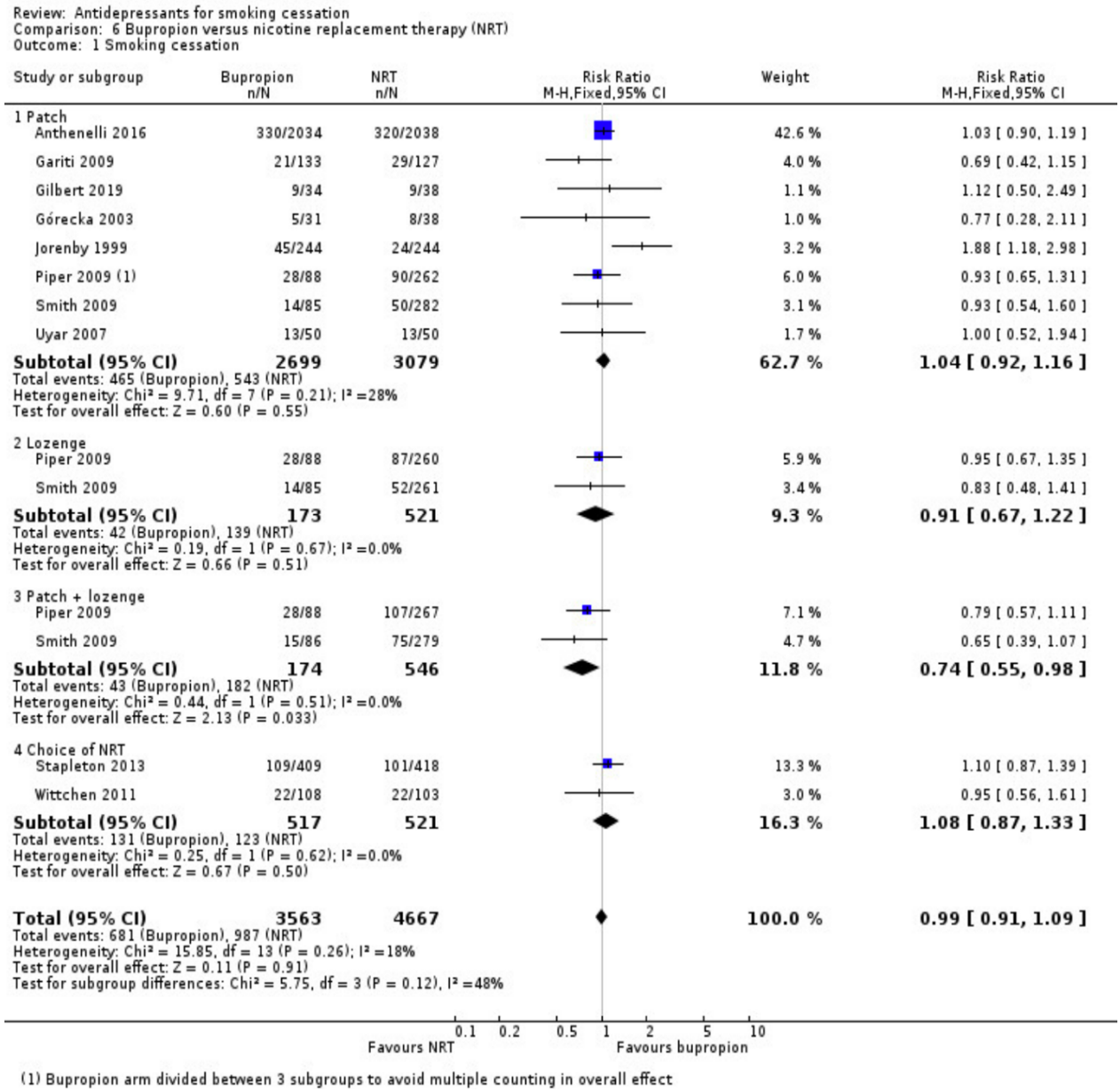



**Figure 5. Smoking cessation outcomes: bupropion SR & varenicline vs varenicline alone (34)**

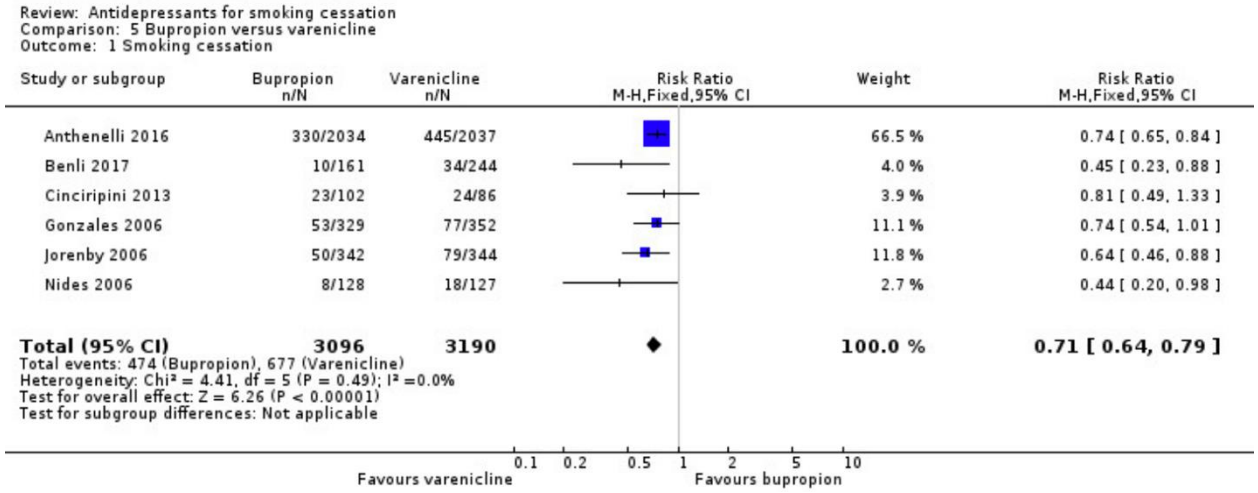


## Figure 6. Smoking cessation outcomes: bupropion SR vs NRT (34)




(1) Bupropion arm divided between 3 subgroups to avoid multiple counting in overall effect

## Figure 7. Smoking cessation outcomes: bupropion SR vs varenicline (34)



## 10. Review of harms and toxicity: summary of evidence of safety.

### Estimate of total patient exposure to date

It is difficult to know how many people have taken bupropion SR for smoking cessation since it was first approved in the US in 1997, but the number is likely in the tens of millions of individuals living in high income countries.

### Description of adverse effects/reactions

In an early assessment of safety from the use of bupropion for smoking cessation, the National Institute for Clinical Excellence in England [now the National Institute for Health and Care Excellence] (NICE) published a large systematic review in 2002 of the clinical and cost effectiveness of bupropion SR and nicotine replacement therapy (NRT) for smoking cessation (35). This report included a comprehensive assessment of safety and adverse events from patient use of bupropion SR. The authors reported the only adverse events that were statistically significantly more common with bupropion SR (100 or 300 mg/day) than with placebo were insomnia (34.6% and 42.4% compared with 20%) and dry mouth (12.8% and 10.7% compared with 4.5%). This review was limited by the small number of randomized trials at the time (n=5) and the exclusion criteria of patients in those trials.

From a large community-based observational cohort study of 11,735 patients the most commonly reported adverse events reported were insomnia, nausea/vomiting and dizziness (36).

Adverse effects of bupropion SR are experienced more often than with NRT though the discontinuation rate is similar between the two therapies (37). Approximately 9% of patients using either bupropion SR or NRT will discontinue treatment and a further 13% will stop treatment temporarily (38). Community-based observational studies include patients who report experiencing adverse effects at a higher rate than clinical trials (39, 40), however these studies may include individuals who are unable to distinguish between withdrawal-related symptoms and medication-related symptoms.

The major safety issue with bupropion is risk of seizures, however, the reported frequency of seizures is rare. Seizures have been reported to occur at a rate of approximately 0.1% (41). In a review of 221 clinical papers involving over 4000 patients, no seizures were reported (42). In the 2014 Cochrane review there were 10 seizures among 13,000 bupropion-treated patients (43).

Seizure risk is dose-related and risk can be minimized by gradually increasing the dose and limiting the daily dose to 300 mg. Regardless, bupropion SR is contraindicated in patients with a seizure disorder, current or prior diagnosis of anorexia nervosa or bulimia, or undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs.

### Allergic reactions

Bupropion SR is generally well tolerated. In their review of 221 clinical papers, Richmond & Zwar (42) reported allergic reactions occurring at a rate of approximately 3%.

A summary of the side effects experienced with bupropion SR are presented in Table 7.

**Table 7. Prevalence of side effects of bupropion SR (range %)**

| Reported side effect | Placebo % | Bupropion % |
|---|---|---|
| Insomnia | 9–21 | 24–42 |
| Headache | 3–33 | 4–33 |
| Dry mouth | 4–24 | 6–28 |
| Rash/Pruritus | 7 | 15 |
| Rhinitis | 12–17 | 10–14 |
| Nausea/Vomiting | 5–6 | 9–13 |
| Dizziness | 1–6 | 2–11 |
| Anxiety | 5–11 | 5–9 |
| Flu syndrome | 6–11 | 4–9 |
| Taste perversion | 5 | 6 |
| Constipation | 1 | 5-6 |
| Sweating | 3 | 5 |
| Mood disorder | 4 | 4 |

Source: Wilkes, 2008 (37)

## Toxicity

There have been a few published papers that document the effects from overdose (44, 45). Common effects have included tachycardia, drowsiness, hallucinations and convulsions.

## Summary of FDA warning

After the non-nicotine medication varenicline was approved for smoking cessation treatment by the US Food and Drug Administration (FDA) in 2006, post-market reports of neuropsychiatric events in patients using the medication led the FDA to require the manufacturers of both varenicline and bupropion SR to include a black box warning to highlight the risk of serious mental health events for prescribers and patients. In addition, the FDA required the development of a post-marketing clinical trial to collect data on smoking cessation treatments and their correlation to neuropsychiatric events.

The EAGLES trial (Evaluating Adverse Events in a Global Smoking Cessation Study) (29) was designed to measure the neuropsychiatric safety and efficacy of varenicline, bupropion SR, and nicotine patch in smokers with and without psychiatric disorders. The clinical trial was completed in 2016 and to-date is the largest trial involving smoking cessation medications with 8144 subjects enrolled at 140 centres in 16 countries. In the bupropion SR arm of the EAGLES trial, the primary comparison of bupropion SR vs placebo had a risk difference greater than zero and a 95% CI including zero, showing no statistically significant increased risk of neuropsychiatric adverse events in the composite endpoint with bupropion SR treatment (0.85 [-0.35, 2.05].

In December 2016, following the EAGLES trial results and analysis, the FDA reported that the risk of mental health side effects from smoking cessation medications was '**lower than previously suspected**.' New medication labelling was to include updated EAGLES trial results but the medication guide no longer required a risk evaluation and mitigation strategy. The most frequently reported adverse events for each medication in the EAGLES trial are reported in Table 8.

**Table 8. Most Frequently Reported Treatment-Emergent Adverse Events (≥5% of Subjects in any Treatment Arm), EAGLES Study Overall Safety Population**

| System Organ Class<br>Preferred Term | Study Overall | | | |
|---|---|---|---|---|
| | Varenicline (N=2016) | Bupropion (N=2006) | NRT (N=2022) | Placebo (N=2014) |
| Subjects with Adverse Events | 1503 (74.6) | 1446 (72.1) | 1436 (71.0) | 1345 (66.8) |
| Gastrointestinal Disorders | 786 (39.0) | 527 (26.3) | 481 (23.8) | 414 (20.6) |
| Nausea | 511 (25. 3) | 201 (10.0) | 199 (9.8) | 137 (6.8) |
| Dry mouth | 66 (3.3) | 146 (7.3) | 59 (2.9) | 64 (3.2) |
| General Disorders and Administration Site Conditions | 270 (13.4) | 241 (12.0) | 404 (20.0) | 229 (11.4) |
| Application site pruritus | 22 (1.1) | 12 (0.6) | 109 (5.4) | 16 (0.8) |
| Fatigue | 124 (6.2) | 57 (2.8) | 75 (3.7) | 83 (4.1) |
| Infections and Infestations | 533 (26.4) | 475 (23.7) | 495 (24.5) | 506 (25.1) |
| Nasopharyngitis | 174 (8.6) | 156 (7.8) | 126 (6.2) | 135 (6.7) |
| Upper respiratory tract infection | 109 (5.4) | 104 (5.2) | 97 (4.8) | 115 (5.7) |
| Nervous System Disorders | 440 (21.8) | 440 (21.9) | 443 (21.9) | 374 (18.6) |
| Headache | 245 (12.2) | 186 (9.3) | 233 (11.5) | 199 (9.9) |
| Psychiatric Disorders | 720 (35.7) | 767 (38.2) | 722 (35.7) | 613 (30.4) |
| Anxiety | 132 (6.5) | 169 (8.4) | 138 (6.8) | 120 (6.0) |
| Irritability | 82 (4.1) | 71 (3.5) | 108 (5.3) | 104 (5.2) |
| Abnormal dreams | 201 (10.0) | 131 (6.5) | 251 (12.4) | 92 (4.6) |
| Insomnia | 189 (9.4) | 245 (12.2) | 196 (9.7) | 139 (6.9) |

N=total number of subjects per treatment arm; NRT=nicotine replacement therapy.
Subjects are only counted once per treatment for each row but may be counted in multiple rows.
Includes all subjects who received at least 1 partial dose of study treatment.
Treatment-emergent=during treatment plus 30 days.
MedDRA v18.0
Source: FDA Advisory Committee Sponsor Briefing Document 2016 (46)

**Drug interactions and contraindications**

Evidence suggests a potential interaction for drugs affecting the cytochrome P-450 (CYP) 2D6 isoenzyme. These drugs would include tricyclic antidepressants, selective serotonin reuptake inhibitors, b-blockers, type 1C antiarrhythmic agents, and certain antipsychotic medications. There is a significant effect on the P-450 system based on discontinuing cigarettes (down-regulation due to markedly less exposure to cigarette smoke toxins). This results in drugs that are metabolized via the

P-450 pathway possibly developing increased serum levels at the same dose. But this effect is independent of whether someone uses a medication to quit (including NRT because it isn't a nicotine effect). In addition, based on the manufacturer labelling, bupropion SR should be used with caution in patients at an increased risk of seizure including: severe head injury; arteriovenous malformation; CNS tumour or CNS infection; severe stroke; concomitant use of other medications that lower the seizure threshold, metabolic disorders (e.g., hypoglycaemia, hyponatremia, severe hepatic impairment, and hypoxia), use of illicit drugs (e.g., cocaine), or abuse or misuse of prescription drugs such as CNS stimulants (47).

**Summary of safety profile from 2020 Cochrane Review**

The most recent 2020 Cochrane review update, antidepressants for smoking cessation (48), represents the largest review to-date with a total of 87 studies involving bupropion SR.

Below is a summary of the outcomes tabulated from the 46 studies that measured specific safety outcomes. These outcomes have been reported in studies of antidepressants.

| Outcome | No. of studies | Participants | Effect size (95%CI) |
|---|---|---|---|
| Psychiatric conditions | 5 | 2180 | 1.67 [1.30, 2.15] |
| Non-psychiatric | 42 | 15686 | 1.63 [1.51, 1.77] |
| Adverse events | 19 | 10893 | 1.14 [1.11, 1.18] |
| Serious adverse events | 21 | 10625 | 1.16 [0.90, 1.48] |
| Psychiatric adverse events | 6 | 4439 | 1.25 [1.15, 1.37] |
| Seizures | 13 | 7344 | 2.93 [0.64, 13.37] |
| Overdoses | 5 | 5585 | 2.15 [0.23, 19.86] |
| Suicide attempts | 10 | 6484 | 1.62 [0.29, 8.92] |
| Death by suicide | 14 | 8822 | 0.34 [0.01, 8.26] |
| All-cause mortality | 21 | 11403 | 0.89 [0.42, 1.87] |
| Anxiety | 11 | 7406 | 1.42 [1.21, 1.67] |
| Insomnia | 22 | 11077 | 1.78 [1.62, 1.96] |
| Dropouts due to drug | 25 | 12340 | 1.37 [1.21, 1.56] |

Source: Howes et al., 2020, Cochrane Review (48)

For the overall assessment of safety, the 2020 Cochrane review concluded that taking bupropion SR increased adverse events (RR 1.14, 1.11-1.18), although there was methodological and clinical variance between the included studies. In the meta-analysis of 21 studies, they **did not** find clear evidence of an increase in **serious adverse events** (RR 1.16, 0.90-1.48). There was, however, evidence that smokers randomized to receive bupropion SR were more likely to report symptoms of anxiety (RR 1.42,1.21 to 1.67) and insomnia (RR 1.78, 1.62 to 1.96). In addition, the Cochrane

authors took a different view of the EAGLES trial (29) and suggested that bupropion SR does increase psychiatric adverse events when considered broadly. They reached this conclusion by including psychiatric adverse events of any severity in their meta-analysis, whereas the EAGLES trial used a composite measure of only moderate and severe intensity psychiatric events in the primary analysis. Severity criteria for the components of the composite endpoint in the EAGLES trial were imposed to minimize inclusion of less clinically significant events, including some typically associated with nicotine withdrawal and thus increase the specificity of the endpoint.

**Cardiovascular Safety**

From the EAGLES trial a separate endpoint examined cardiovascular events that included 8058 smokers (49). The primary end point was the time to development of a major adverse cardiovascular event (MACE: cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) during treatment; secondary end points were the occurrence of MACE and other pertinent cardiovascular events (MACE+: MACE or new-onset or worsening peripheral vascular disease requiring intervention, coronary revascularization, or hospitalization for unstable angina). The incidence of cardiovascular events during treatment and follow-up was low (<0.5% for MACE; <0.8% for MACE+) and did not differ significantly by treatment. No significant treatment differences were observed in time to cardiovascular events, blood pressure, or heart rate. There was no significant difference in time to onset of MACE for either varenicline or bupropion treatment vs placebo (varenicline: hazard ratio, 0.29; 95% CI, 0.05-1.68 and bupropion: hazard ratio, 0.50; 95% CI, 0.10-2.50). The authors conclude that there was no evidence that the use of smoking cessation pharmacotherapies increased the risk of serious cardiovascular adverse events during or after treatment.

**11. Summary of available data on comparative cost and cost-effectiveness of the medicine.**

The introduction of bupropion hydrochloride sustained release (SR) marked a major change in the options available for smoking cessation pharmacotherapy. After more than 20 years of experience across different groups of smokers, the preponderance of evidence suggests bupropion SR consistently produces improved odds of successful cessation in adult smokers. In addition, the evidence supports bupropion as a cost-effective medication when considering the costs of treatment compared to the resulting benefits in terms of avoided mortality, morbidity, and the costs of care for smoking-related diseases. This assessment has been sustained across two decades of research and across multiple countries.

This section provides a summary of the national studies and systematic reviews that have evaluated the cost-effectiveness of bupropion SR for smoking cessation. All of these studies assessed the benefit of treatment as either cost per year of life saved, quality adjusted life year (QALY), or disability adjusted life year (DALY).

Following the landmark studies of Hurt et al. (6) and Jorenby et al. (19), bupropion SR was quickly adopted as an effective and useful oral non-nicotine treatment for smoking cessation. Nielsen and Fiore (50) conducted the first economic analysis of bupropion for smoking cessation using the original US study of Jorenby and colleagues (19). They examined 12-month outcome data from the double-blind study with 893 smokers who were treated with either 9 weeks of bupropion (2x150mg), nicotine patch, bupropion plus patch or placebo. The analysis followed a traditional cost benefit approach to predict the net benefit to a payer after 1-year based on the effectiveness of the intervention (quit rates), the cost of the intervention, the cost of not quitting and the benefit of quitting. Compared to nicotine patch and combination therapy, 9 weeks of bupropion treatment was determined to be the most cost beneficial.

Halpern and colleagues (51) developed an economic model to assess the costs and benefits of US payers covering bupropion SR as a medication for smoking cessation. The model involved a cohort of 100,000 employees and 60,000 dependents who were followed until retirement at age 65 or death at age 85. If the costs of bupropion SR were covered the overall decrease in health care costs over a 20-year period ranged from $7.9 million to $8.8 million; for every dollar spent covering smoking cessation, $4.10- $4.69 in health care costs was saved. For the employer scenarios, health care costs over 20 years decreased by $8.3 million to $14.0 million, and smoking-related indirect costs decreased an additional $5.1 million to $7.7 million; for every dollar spent covering smoking cessation, $5.04 to $6.48 was saved.

In a study from Australia, Bertram and colleagues (52) calculated the incremental cost-effectiveness ratio (ICER) of bupropion and NRT compared with the current practice scenario in year 2000. Their outcome measure was disability-adjusted life year (DALY) averted in Australian dollars. DALYs averted is equivalent to the number of healthy life years gained. The authors concluded that providing bupropion to current smokers who are motivated to quit would cost A$7900 (95% uncertainty interval A$6000 to A$10 500) for each DALY averted; NRT patches would cost A$17 000 (A$9000 to A$28 000) for each DALY averted, with similar results even if used as a second-line treatment following initial failure to quit using bupropion. In addition, the authors noted that NRT and bupropion were more cost-effective than other medicines included in the public reimbursement list that are primarily focused on prevention, such as statins for lowering cholesterol.

Nicotine patch and bupropion SR were compared using the Global Health Outcomes simulation model with 20 years follow-up in Sweden (53). This study involved a cohort of 612,851 male and 780,970 female smokers constructed to represent the 2001 population of Sweden ages 35 years and older. This cost utility study of a smoking cessation program measured cost per QALY gained for bupropion SR and nicotine gum/nicotine patch. The incremental costs per QALY gained were relatively low for bupropion in comparison to nicotine patches, approximately €725 for men and approximately €535 for women. The authors concluded bupropion was a cost-effective therapy for smoking cessation.

Researchers from Spain evaluated the cost-effectiveness of treatment with bupropion SR (54). The ratio at 5 years was 70,939 euros per death prevented and 37,305 euros per year of life saved. When the time horizon was increased to 20 years, the net savings were 28,166 and 3,265 euros, respectively. The cost-effectiveness ratios for both nicotine gums and patches were higher than that for bupropion. The authors concluded bupropion treatment for 1 year would prevent a greater number of deaths than the alternative strategies (approximately 3,000 deaths in a time horizon of 20 years) due to the decrease in the number of smokers.

In 2005, researchers from The Netherlands reported the results of a dynamic modelling study examining minimal and intensive smoking interventions delivered by medical professionals (55). The researchers projected future gains in life years, QALYs, and savings in health care costs over 1 year, 10 years, and on a permanent basis (up to 75 years). For treatment with bupropion SR or nicotine replacement therapy (NRT), the intervention included counselling from a pulmonary nurse and physician, and either 9 or 12 weeks of pharmacotherapy. Overall, costs per life year and QALY gained were lower for bupropion treatment compared to NRT. This finding was consistent across time horizons and in the permanent implementation status. The 10-year model results are tabulated below.

10-year simulation of adjusted costs and gains from NRT or bupropion SR with Dutch smokers (euros, year 2000 prices)

| Intervention | QALYs gained | Intervention costs per QALY | Cost per QALY gained |
|---|---|---|---|
| NRT + counselling | 37 000 | 8100 | 4900 |
| Bupropion + counselling | 43 000 | 6600 | 3400 |

Source: Feenstra et al. (55) NRT was either patches or gum. Values discounted 4%.

The authors noted that the ratios presented above were very favourable and compared to other cost-effective practices in The Netherlands, such as breast cancer screening (€4000 per life year gained) or influenza vaccination in the elderly (€1800 per life year gained).

A number of economic evaluations of the cost-effectiveness of varenicline compared to bupropion and NRT have been published based on the Benefits of Smoking Cessation on Outcomes (BENESCO) model, a Markov state-transition model developed by Pfizer, which includes health states for lung cancer, chronic obstructive pulmonary disease, coronary heart disease, stroke and asthma exacerbations (56-60). These studies were completed in various countries in Europe and South Korea and found varenicline to be a cost-effective strategy despite the initial higher cost of varenicline.

However, if one adopts a population level or public health view, then a variety of cessation strategies will be required to assist smokers around the world. For example, a 2010 report to the Ministry of Health in Canada (61) concluded that pharmacotherapy, physician advice to quit, nursing interventions, hospital-based interventions, and proactive telephone counselling were all likely to be both effective and cost-effective in the short-term. Among these interventions they found varenicline, bupropion and nicotine replacement therapies, followed by physician advice to quit and nursing interventions to be the most effective strategies.

In a review of smoking cessation interventions to inform national guideline development, West and colleagues (62) examined affordability by stratifying at the country level using World Bank categories of low, middle and high income. The authors estimated incremental cost-effectiveness ratios (ICERs) for effective interventions for countries in different World Bank income categories. ICERs give the incremental cost incurred for an incremental health outcome, usually expressed as cost per life-year gained or QALY gained. ICERs can be used to assess the affordability of interventions globally by accounting for income levels in relevant countries.

The authors suggested that bupropion SR, similar to all medications for smoking cessation except nortriptyline and cytisine, was affordable in middle and high income but not in low-income countries. However, additional research is necessary, including country-level analysis, before a conclusion can be reached that specific smoking cessation medications are not affordable relative to their benefits in low-income countries.

Overall, smoking cessation interventions are considered among the most cost-effective public health interventions. While the cost of some tobacco cessation methods, such as physician advice and automated texts, is low their efficacy is also low. Pharmacotherapies have increased costs but also achieve higher efficacy rates. When assessing interventions and their costs, the evidence from economic studies strongly suggests that the greater use of medications, including bupropion SR, generate net savings in tobacco-related health costs. The 2020 US Surgeon General's report (63) concluded that FDA approved smoking cessation medications were cost-effective, increase the likelihood of successful quitting, and that combinations of therapies further increase the likelihood of quitting.

**12. Summary of regulatory status and market availability of the medicine.**

Bupropion is widely available globally, including innovator and generic brands. By the end of 2018, bupropion was available in the following 98 countries (64).

Afghanistan
Andorra
Antigua and Barbuda
Argentina
Australia
Austria
Azerbaijan
Bahamas
Bahrain
Bangladesh
Barbados
Belize
Belgium
Bosnia and Herzegovina
Brazil
Cameroon
Canada
Chile
China
Colombia
Congo
Costa Rica
Côte d'Ivoire
Croatia
Cyprus
Czech Republic
Denmark
Dominican Republic
El Salvador
Estonia
Ethiopia
Fiji
Finland
France
Gabon
Germany
Guatemala
Guyana
Iceland
India
Iran (Islamic Republic of)
Iraq
Ireland
Israel
Italy
Jamaica
Kazakhstan
Kenya
Latvia
Lithuania
Luxembourg
Malta
Mauritius
Mexico
Monaco
Morocco
Mozambique
Netherlands
New Zealand
Nicaragua
Nigeria
Norway
Pakistan
Palau
Panama
Peru
Poland
Portugal
Qatar
Republic of Korea
Romania
Saint Kitts and Nevis
Saint Lucia
Saudi Arabia
Senegal
Serbia
Seychelles
Singapore
Slovakia
Slovenia
South Africa
Spain
Suriname
Swaziland
Sweden
Switzerland
Syrian Arab Republic
Thailand
The former Yugoslav Republic of Macedonia
Trinidad and Tobago
Turkey
Turkmenistan
United Kingdom of Great Britain and Northern Ireland
United States of America
Uruguay
Vanuatu
Venezuela
West Bank and Gaza Strip

**13. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopeia).**

Reference standards for bupropion hydrochloride are included in the United States Pharmacopoeia.

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