# Bupropion

Section: 24. Medicines for mental and behavioural disorders > 24.5. Medicines for disorders due to psychoactive substance use > 24.5.2. Medicines for nicotine use disorders

ATC codes: N06AX12

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| **Indication** | Nicotine dependence ICD11 code: 6C4A.2Z |
| **INN** | Bupropion |
| **Medicine type** | Chemical agent |
| **List type** | Core |
| **Formulations** | **Oral > Solid:** 150 mg sustained-release (hydrochloride) |
| **EML status history** | First added in 2021 (TRS 1035) |
| **Sex** | All |
| **Age** | Adolescents and adults |
| **Therapeutic alternatives** | The recommendation is for this specific medicine |
| **Patent information** | Patents have expired in most jurisdictions<br>Read more about patents. |
| **Wikipedia** | Bupropion |
| **DrugBank** | Bupropion |

## Expert Committee recommendation

The Expert Committee noted that smoking is a major public health threat worldwide and causes substantial harm to human health as a cause of numerous cancers, and cardiovascular and pulmonary diseases. Currently, the EML only includes nicotine replacement therapy for smoking cessation (chewing gum and transdermal patches). The Expert Committee took into account the evidence shown in the application that there is high-certainty evidence that bupropion increases long-term smoking cessation rates as reported in a Cochrane review with more than 100 studies and that it is well tolerated overall. However, a synthesis of existing evidence also suggests an increased risk of adverse effects, particularly anxiety and agitation and these effects may increase the probability that people stop using the medicine. The Expert Committee recognized that smoking cessation interventions are among the most cost-effective public health interventions. Moreover, there is sufficient evidence on the affordability of bupropion for smoking cessation, although not for low- and middle-income countries. The availability of different treatment options may enhance procurement capacity, lower prices and increase affordability through competition. The Expert Committee also noted that no specialist training is required to prescribe or use the medicine. However, the success of medications for quitting smoking is improved when smokers are prepared to quit and receive quitting advice, counselling, and support from health care providers. The Expert Committee therefore noted that while the effectiveness of pharmacological interventions for smoking cessation is high, their success is dependent on a concomitant behavioural education approach such as counselling. In many countries, especially in low- and middle-income countries, the use of this approach as well as the strengthening of tobacco control policies are still not optimal. The Expert Committee noted that bupropion was mentioned in the WHO Report on the Global Tobacco Epidemic 2019 as non-nicotine pharmacological intervention to help people to quit smoking. Considering the body of evidence supporting the efficacy and tolerability of

bupropion, the Expert Committee recommended the inclusion of bupropion for smoking cessation in the core list of the EML. However, considering the limited evidence on bupropion's affordability in low- and middle-income countries, mechanisms to estimate costs in these countries need to be established with ministries of health.

## Background

Bupropion hydrochloride has not been evaluated before for inclusion on the EML. Nicotine replacement therapy (NRT), as chewing gum or transdermal patch formulations, has been included on the EML since 2009. The Expert Committee recommended listing on the basis of the public health need, high-quality evidence of effectiveness, and acceptable safety and cost–effectiveness. Other formulations were not recommended for inclusion at the time because less evidence was available of comparative safety, effectiveness and cost in different populations (1).

## Public health relevance

Tobacco smoking is still the leading cause of premature disability and death around the world (2). 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 gases: ammonia, butane, carbon monoxide (CO), hydrogen cyanide and toluene. More than half of all long-term smokers die from a disease caused by tobacco use, with an average loss of at least 10 years of life (3). Smoking causes 87% of lung cancer deaths, 61% of pulmonary disease deaths (chronic obstructive pulmonary disease (COPD) and emphysema) and one in three cancer deaths. For every person who dies from smoking, at least 30 people live with serious smoking-related illnesses (3). According to WHO (4): • The tobacco epidemic is one of the biggest public health threats the world has ever faced. • Globally, 1.3 million people use tobacco, of whom 80% live in low- and middle-income countries. • Tobacco use contributes to poverty by diverting household spending away 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 gross domestic product (GDP), with about 40% of the total economic cost borne by developing countries (5). The scale of human and economic harms that the tobacco industry imposes is large and preventable. In response, in 2003, WHO Member States unanimously adopted the WHO Framework Convention on Tobacco Control (WHO FCTC), which is currently endorsed by 182 Parties and covers 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, the WHO introduced MPOWER in 2007, with "O" related to offering treatment. The six MPOWER measures are: • Monitor tobacco use and prevention policies • Protect people from tobacco use • Offer help to quit tobacco use • Warn about the dangers of tobacco • Enforce bans on tobacco advertising, promotion and sponsorship • Raise taxes on tobacco. Quitting smoking brings health benefits and when smokers become aware of the dangers of tobacco use, most want to quit. Yet, without medications or cessation support, only about 4% of attempts to stop using tobacco will succeed. Professional support and proven cessation medications can more than double a tobacco user's chance of successfully quitting (5). As stated in the 2019 WHO report on the global tobacco epidemic (6), "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 a behavioural (or conditioned) habit of using tobacco. Hence, for maximal effectiveness, as recommended by clinical practice guidelines, tobacco dependence treatment engages a multipronged approach (7–9). Addiction can be treated with evidence-based medications for smoking cessation, and the behavioural habit can be treated through counselling and behaviour change programmes. Either cessation medication or counselling alone has evidence of effectiveness, but the best outcomes are with a combination of both approaches. The availability of interventions and their use are likely to vary. Having many cessation medication options available for clinicians and smokers for tobacco treatment is essential for tackling the significant global harms of tobacco use.

## Benefits

The efficacy of bupropion sustained release (SR) as an aid to smoking cessation has been demonstrated in many placebo-controlled, double-blind trials. The application describes three trials conducted by the manufacturer (GlaxoSmithKline, GSK) in non-depressed chronic cigarette smokers (n = 1940, smoking > 15 cigarettes a day) (10). In these trials, bupropion SR was used in conjunction with individual smoking cessation counselling. Treatment with bupropion SR was started at 150 mg a day while the participant was still smoking and then increased after 3 days to 150 mg twice daily. 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 in the specified week. The first trial (n = 615), conducted at three clinical centres, evaluated dose–response (11). Participants were treated for 7 weeks with one of three doses of bupropion SR (100, 150 or 300 mg a day) or placebo. Participants set a target quit date after 1 week of medication (usually day 8). Table 10 shows 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 a day) was more effective than placebo in helping participants achieve abstinence at week 6 and month 3. Treatment with bupropion at 150 mg or 300 mg a day was more effective than placebo in helping participants achieve abstinence at months 6 and 12. Rates of continuous abstinence from the target quit date to 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 the group that received 100 mg of bupropion ($P < 0.02$). Table 10. Dose–response trial: carbon monoxide-confirmed weekly point prevalence quit rates The second trial was a comparator combination treatment trial (n = 893) conducted at four clinics, which evaluated 9-week treatments of: bupropion SR 300 mg a day, nicotine patch 21 mg a day, a combination of bupropion SR 300 mg and nicotine patch 21 mg a day, and placebo (12). Nicotine patch 21 mg a day was added to treatment with bupropion SR after about 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 a day, respectively. The primary outcome was CO-verified point-prevalence abstinence at 6 and 12 months follow-up. Bupropion SR and the combination of bupropion SR and nicotine patch were better than placebo in helping participants to achieve and maintain abstinence from smoking (Table 11). The treatment combination of bupropion SR and nicotine patch showed the highest rates of continuous abstinence throughout the trial; however, the quit rates for the combination were not significantly higher than for bupropion SR alone ($P > 0.05$). Table 11. Comparator clinical trial: carbon monoxide-confirmed point prevalence quit rates The third trial, at five clinics, examined long-term maintenance treatment with bupropion SR (13). Participants (n = 784) received open-label bupropion SR 300 mg a day for 7 weeks. After 7 weeks, 429 participants who quit smoking while receiving bupropion SR were then randomized to receive bupropion SR 300 mg a 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 of drug therapy at week 52 (55% versus 42%, respectively; $P = 0.008$) and at week 78 (48% versus 38%, respectively; $P = 0.034$) but did not differ at the final follow-up visit at week 104 (42% versus 40%, respectively; $P > 0.05$). The median time to relapse was significantly greater for bupropion SR recipients than for placebo recipients (156 days versus 65 days; $P = 0.021$). 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% versus 42%; $P = 0.037$), but did not differ between groups after week 24. Another 6-month trial of long-term maintenance treatment with bupropion SR reported hazard ratios (HR) for relapse that statistically significantly favoured bupropion SR over placebo at 6 months, the end of treatment (HR 0.59, 95% CI 0.37 to 0.92) and at 12 months, the 6-month follow-up (HR 0.66, 95% CI 0.42 to 0.96) (14). However, the advantage of bupropion SR was lost on 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 attempts to quit using NRT. Across trials, during active treatment, withdrawal symptoms were significantly reduced in participants randomized to treatment with bupropion SR compared with placebo. Reductions in 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 preauthorization comparative clinical trials of varenicline versus bupropion SR for smoking cessation – studies A3051036 and A2051028 (15,16). The treatment arms were varenicline (1 mg twice daily), bupropion SR (150 mg twice daily) and placebo. In these 52-week duration studies, participants 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 minutes of smoking cessation counselling at each weekly treatment visit. Participants can smoke in the first week of medication dosing and set a date for stopping smoking. The primary endpoint of the two studies was 4-week continuous abstinence from smoking during weeks 9–12 confirmed by exhaled CO. 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 12. Compared with placebo, bupropion SR had significantly higher continuous abstinence rates at weeks 9–12 in both trials and at weeks 9–52 in one of the trials. Varenicline was superior to bupropion SR at weeks 9–12 in both trials and at weeks 9–52 in one of the trials. Table 12. Varenicline compared with bupropion SR for smoking cessation in the Pfizer comparative clinical trials Across both studies during active treatment, participant-reported outcome measures showed that craving and withdrawal (urge, negative effect and insomnia) were significantly lower in participants randomized to receive bupropion SR versus placebo. Bupropion SR also significantly reduced positive reinforcing effects of smoking during treatment compared with placebo. 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 smoking cessation in people who smoke cigarettes (17). The literature search was last updated in 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 on smoking treatment in pregnancy were excluded. When multiple doses of bupropion were compared in a trial, data from the 300 mg/day arm were used. The efficacy findings are summarized in the following list. • High-certainty evidence confirmed the benefit of bupropion SR compared with placebo as a single pharmacotherapy for smoking cessation (risk ratio (RR) 1.64, 95% CI 1.52 to 1.77; I2 = 15%; 45 studies, 17 866 participants). • Treatment effects of bupropion SR for quitting smoking were comparable across settings and types of behavioural support studied (group versus individual, low-intensity, i.e. routine care). • Treatment effects of bupropion SR for quitting smoking were comparable for participants with psychiatric conditions (RR 1.67, 95% CI 1.3 to 2.15; I2 = 0%; five studies, 2180 participants) and without a history of psychiatric conditions (RR 1.67, 95% CI 1.3 to 2.15; I2 = 23%; 42 studies, 15 686 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 stable on treatment. • Adding bupropion SR to NRT (RR 1.19, 95% CI 0.94 to 1.51; I2 = 52%; 12 studies, 3487 participants) or varenicline (RR 1.21, 95% CI 0.95 to 1.55; I2 = 15%; three studies, 1057 participants) did not appear to provide additional benefit compared with 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; I2 = 18%; 10 studies, 8230 participants), or bupropion SR and nortriptyline (RR 1.30 (favouring bupropion SR), 95% CI 0.93 to 1.82; I2 = 0%; three studies, 417 participants) for smoking cessation. • Bupropion SR had lower smoking cessation rates compared with varenicline (RR 0.71, 95% CI 0.64 to 0.79; I2 = 0%; six studies, 6286 participants). Smokers with COPD In a randomized, double-blind trial conducted by GSK, bupropion SR was evaluated in 404 participants with mild to moderate COPD defined as postbronchodilator forced expiratory volume 1/forced vital capacity (FEV1/FVC) < 70% and FEV1 per cent predicted normal value ≥ 50%, and a diagnosis of chronic bronchitis, emphysema and/or small airways disease (18). Participants aged 36 to 76 years were randomized to bupropion SR 300 mg a 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 started at 150 mg a 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. Participants treated with bupropion SR had higher abstinence rates than those who received the placebo in the last 4 weeks of treatment (22% versus 12%, P = 0.011). Continuous abstinence rates from weeks 4–12 and weeks 4–26 were also significantly higher in participants receiving bupropion SR than in those taking the placebo (18% versus 10% (P = 0.021) and 16%

versus 9%, (P = 0.040)). Furthermore, symptoms of tobacco craving and withdrawal were reduced in those receiving bupropion SR. Smokers with cardiovascular disease Several randomized controlled trials and meta-analyses have examined use of bupropion SR for treating smoking in adults with cardiovascular disease (CVD). A randomized, double-blind, multicentre 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 a day (15). Participants received bupropion SR (150 mg twice daily) 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 week 4 to week 7. Secondary endpoints were continuous abstinence at weeks 4–12, 4–26 and 4–52. Continuous smoking abstinence rates from weeks 4–7 were significantly higher in participants receiving bupropion SR compared with placebo (43% versus 19%, OR 3.27, 95% CI 2.24 to 4.84). Continuous abstinence rates from weeks 4–26 and 4–52 continued to be more than double for bupropion SR compared with placebo (27% versus 11% and 22% versus 9%, both P < 0.001). In both groups, no clinically significant changes in blood pressure and heart rate were seen throughout the treatment phase. After 7 weeks of bupropion SR treatment, more than twice as many smokers with CVD had quit smoking at 1 year compared with those receiving placebo. A randomized controlled trial evaluated the safety and efficacy of bupropion SR in 247 hospitalized smokers with acute CVD (19). Participants were treated for 12 weeks with bupropion SR 300 mg or placebo. Counselling was provided to all participants in the hospital and for 12 weeks following discharge. Cotinine-confirmed abstinence outcomes were reported at 3 months (end-of-treatment) and 12 months. Validated tobacco abstinence rates in the bupropion SR and placebo groups were 37% versus 27% (OR 1.61, 95% CI 0.94 to 2.76) at 3 months and 25% versus 21% (OR 1.23, 95% CI 0.68 to 2.23) at 12 months. The adjusted OR, after controlling for cigarettes smoked a day, depression symptoms, prior bupropion SR use, hypertension and length of stay, was 1.91 (95% CI 1.06 to 3.40) at 3 months and 1.51 (95% CI 0.81 to 2.83) at 12 months. Bupropion SR and placebo groups did not differ in cardiovascular mortality at 12 months (0% versus 2%), in blood pressure at follow-up or in cardiovascular events at end-of-treatment (16% versus 14%, incidence rate ratio (IRR) 1.22 (95% CI 0.64 to 2.33) or at 12 months (26% versus 18%, IRR 1.56, 95% CI 0.91 to 2.69). The investigators concluded that bupropion SR improved short-term but not long-term smoking cessation rates compared with intensive counselling and appeared to be safe in hospitalized smokers with acute CVD. A meta-analysis of three randomized controlled trials (773 participants) was conducted to determine the efficacy and safety of bupropion SR therapy started in hospital for smoking cessation in patients with CVD (20). Participants were predominantly men (range of means 69–84%) and hospitalized with acute coronary syndrome (range of means 66–100%). Treatment duration ranged from 8 to 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 to 1.45) but not continuous abstinence (RR 1.19, 95% CI 0.97 to 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 to 1.48) or continuous abstinence (RR 1.16, 95% CI 0.90 to 1.50). Pooled analysis results for major adverse cardiac and cerebrovascular events were inconclusive (RR 1.28, 95% CI 0.93 to 1.78). Bupropion SR improved abstinence over placebo at the end of treatment but not at 12 months. A network meta-analysis was conducted to evaluate the efficacy and safety of pharmacological smoking cessation interventions in CVD patients in randomized controlled trials (21). 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 the inclusion criteria. Varenicline (one trial, RR 2.64, 95% CI 1.34 to 5.21) and bupropion SR (four trials, RR 1.42, 95% CI 1.01 to 2.01) were associated with greater abstinence than placebo, while the evidence for NRTs was inconclusive (two trials, RR 1.22, 95% CI 0.72 to 2.06). Smokers with current depression Five trials, all with relatively small sample sizes, reported results of bupropion SR (with or without NRT) versus placebo in smokers with current depression. A meta-analysis of effects across the five trials resulted in a positive, although not significant, effect for the outcome of abstinence at 6 months or longer follow-up (five trials (n = 410); RR 1.37, 95% CI 0.83 to 2.27) (22). Smokers with and without a history of psychiatric disorders Bupropion SR was evaluated in the EAGLES (Evaluating Adverse Events in a Global Smoking Cessation Study) trial, 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)

(23). Participants aged 18 to 75 years, smoking > 10 cigarettes a day were randomized 1:1:1:1 to bupropion SR 150 mg twice daily, varenicline 1 mg twice daily and nicotine patch 21 mg a 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. 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. For the outcome of continuous abstinence rates measured 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 (Table 13 and Table 14). In addition, varenicline showed significantly greater efficacy than bupropion SR and nicotine patch at both weeks 9–12 and 9–24, while no significant differences were found between bupropion SR and nicotine patch in either time period. Table 13. Treatment comparisons for continuous abstinence from tobacco use in smokers with and without psychiatric disorders, weeks 9–12 Table 14. Treatment comparisons for smoking cessation in smokers with and without psychiatric disorders, weeks 9–24 Healthy adolescent smokers Four published trials have evaluated bupropion SR for treating smoking in adolescent groups (24–27), with one of the trials receiving support from GSK (25). Two of the studies were limited to short-term (i.e. 12-week) follow-up (24,27). One study evaluated 7-week treatment of bupropion SR at 300 mg or 150 mg a day versus placebo in 312 adolescents aged 14–17 years (25). At 6-months follow-up, CO-confirmed 7-day point prevalence abstinence was 8.7% for bupropion SR 300 mg, 1.9% for bupropion SR 150 mg and 5.8% for placebo; RR 1.49 (95% CI 0.55 to 4.02) for bupropion SR 300 mg versus placebo. The second study examined bupropion SR in combination with nicotine patch versus nicotine patch alone in a sample of 211 adolescents with an average age of 17 years (26). In addition to the medications, all participants received weekly 45-minute group sessions with skills training. Compliance with bupropion SR and patch therapy was 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 still smoking) was 7.8% for bupropion SR plus patch and 7.4% for patch alone (RR 1.05, 95% CI 0.41 to 2.69). The third study examined bupropion SR versus placebo with or without contingency management in 134 participants between the ages of 12 and 21 years (24). CO-confirmed 7-day point prevalence abstinence at 12-week follow-up, combined across contingency management conditions, were 8.2% for bupropion SR versus 3.3% for placebo (calculated pooled effects OR for bupropion SR 2.6, 95% CI 0.5 to 13.6). The fourth study compared 8 weeks of bupropion SR versus varenicline in 29 adolescents aged 15 to 20 years (27). Quit rates, reported as cotinine-confirmed 7-day point prevalence abstinence at 12-week follow-up, were 0% for varenicline versus 7.1% for bupropion SR.

## Harms

A systematic review of the clinical effectiveness and cost–effectiveness of bupropion SR and NRT for smoking cessation published in 2002 included a comprehensive assessment of safety and adverse events from participant use of bupropion SR (28). The only adverse events reported 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 20.0%) 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 (five trials) and the exclusion criteria for participants in those trials. A 2008 community-based observational cohort study evaluated the safety of bupropion in 11 735 participants (29). The most commonly reported adverse events reported were insomnia, nausea and/or vomiting and dizziness. Adverse effects of bupropion SR are experienced more often than with NRT although the discontinuation rate is similar between the two therapies (30). About 9% of participants using either bupropion SR or NRT will discontinue treatment and a further 13% will stop treatment temporarily (31). Participants in community-based observational studies report experiencing adverse effects at a higher rate than participants in clinical trials (32, 33); however these community-based studies may include individuals who are unable to distinguish between withdrawal-related symptoms and medication-related symptoms. The main safety concern with bupropion is the risk of seizures. Seizures have been reported to occur at a rate of about 0.1% in depressed patients treated with up to 300 mg a day (34). In a review of 221 clinical papers involving over 4000 participants, no seizures were reported (35). In a

2014 Cochrane review of antidepressants for smoking cessation, 10 seizures were reported out of 13 000 participants treated with bupropion (36). The risk of seizure 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 people with a seizure disorder, current or prior diagnosis of anorexia nervosa or bulimia, or in those going through abrupt discontinuation of alcohol, benzodiazepines, barbiturates and antiepileptic drugs (34). Pooled data from 10 randomized trials of bupropion SR found the most commonly observed side-effects to be insomnia, headache, dry mouth, rash and/or pruritus, rhinitis and nausea and/or vomiting (30). The EAGLES trial evaluated the neuropsychiatric safety and efficacy of varenicline, bupropion SR and nicotine patch in 8144 smokers with and without psychiatric disorders (23). In the bupropion SR arm of the trial, for the primary comparison of bupropion SR versus placebo, the risk difference for neuropsychiatric adverse events was 0.85 (95% CI –0.13 to 2.15), i.e. no statistically significant increased risk of neuropsychiatric adverse events in the composite endpoint with bupropion SR treatment. Following the EAGLES trial results and analysis, the US Food and Drug Administration 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 results of the EAGLES trial but 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 15. Table 15. Most frequently reported treatment-emergent adverse events (in ≥ 5% of participants in any treatment arm), EAGLES overall safety population A 2020 Cochrane systematic review of antidepressants for smoking cessation included 87 studies involving bupropion SR treatment, 46 of which measured safety outcomes (17). The review concluded that bupropion SR was associated with an increased risk of adverse events (RR 1.14, 95 CI 1.11 to 1.18), although there was methodological and clinical variance between the included studies. Among 21 studies (10 625 participants) reporting serious adverse events, there was no clear evidence of increased risk (RR 1.16, 95% CI 0.90 to 1.48). However, smokers randomized to receive bupropion SR were more likely to report symptoms of anxiety (RR 1.42, 95% CI 1.21 to 1.67) and insomnia (RR 1.78, 95% CI 1.62 to 1.96) and experience psychiatric adverse events (RR 1.25, 95% CI 1.15 to 1.27). The authors took a different view of the EAGLES trial (23) and suggested that bupropion SR does increase the risk of 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. The severity criteria for the components of the composite endpoint in the EAGLES trial were imposed to minimize the inclusion of less clinically significant events, including some typically associated with nicotine withdrawal, and thus increase the specificity of the endpoint. After the EAGLES trial, a study using a separate endpoint examined cardiovascular events in 8058 smokers (38). The primary endpoint was the time to the development of a major adverse cardiovascular event (cardiovascular death, nonfatal myocardial infarction or nonfatal stroke) during treatment. The secondary endpoint was the occurrence of a major adverse cardiovascular event and other relevant cardiovascular events (e.g. 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 major adverse cardiovascular event; < 0.8% for a major adverse cardiovascular event plus other relevant cardiovascular events) and did not differ significantly by treatment. No significant differences were observed between treatment groups in time to cardiovascular events, blood pressure or heart rate. There was no significant difference in time to onset of a major adverse cardiovascular event for either varenicline or bupropion treatment versus placebo (varenicline: HR 0.29, 95% CI 0.05 to 1.68 and bupropion: HR 0.50, 95% CI 0.10 to 2.50). The authors concluded that there was no evidence that the use of smoking cessation pharmacotherapies increased the risk of serious cardiovascular adverse events during or after treatment.

## Cost / cost effectiveness

The first economic analysis of bupropion for smoking cessation was conducted in 2000 (41) using data from a 1999 double-blind trial (12). The study examined 12-month outcome data from 893 smokers who were treated with either 9 weeks of bupropion (150 mg twice daily), 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 with nicotine patch and combination therapy, 9 weeks of bupropion treatment was determined to be the most cost-beneficial treatment. Another study developed an economic model to assess the costs and benefits to United States (US) payers of covering bupropion SR as a medication for smoking cessation (42). The model used a cohort of 100 000 employees and 60 000 dependents who were followed until retirement at 65 years or death at 85 years. If the costs of bupropion SR were covered, the overall decrease in health care costs over a 20-year period ranged from US$ 7.9 million to US$ 8.8 million; for every dollar spent covering smoking cessation, US$ 4.10–4.69 in health care costs were saved. For the employer scenarios, health care costs over 20 years decreased by US$ 8.3–14.0 million, and smoking-related indirect costs decreased an additional US$ 5.1–7.7 million; for every dollar spent covering smoking cessation, US$ 5.04–6.48 was saved. An Australian study calculated the incremental cost–effectiveness ratio of bupropion and NRT compared with the current practice scenario (mass media campaigns and taxation on cigarettes which were widespread in Australia in 2000) (43). The outcome measure was disability-adjusted life year (DALY) averted in Australian dollars (AU$). DALYs averted is equivalent to the number of healthy life years gained. The authors concluded that providing bupropion to current smokers who are motivated to quit would cost AU$ 7900 (95% uncertainty interval AU$ 6000 to AU$ 10 500) for each DALY averted; NRT patches would cost AU$ 17 000 (AU$ 9000 to AU$ 28 000) for each DALY averted, with similar results even if used as a second-line treatment after 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 (44). This study included a cohort of 612 851 male and 780 970 female smokers constructed to represent the 2001 population of Sweden aged 35 years and older. This cost–utility study of a smoking cessation programme measured cost per quality-adjusted life year (QALY) gained by using bupropion SR and nicotine gum or nicotine patch. The incremental costs per QALY gained were relatively low for bupropion compared with nicotine patches, about € 725 for men and € 535 for women. The authors concluded bupropion was a cost-effective therapy for smoking cessation. Researchers from Spain evaluated the cost–effectiveness of smoking cessation therapies, NRT and bupropion SR (45). For bupropion, the cost–effectiveness ratios at 5 years were € 70 939 and € 37 305 per death prevented and per year of life saved, respectively. When a 20-year time period was applied, the net savings were € 28 166 per death prevented and € 3265 per year of life saved. The cost–effectiveness ratios for both nicotine gum and patches were higher than that for bupropion. The authors concluded that bupropion treatment for 1 year would prevent a greater number of deaths than the alternative strategies (about 3000 deaths in a time period 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 that examined minimal and intensive smoking interventions delivered by medical professionals (46). The study 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 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 with NRT across all time periods. At 10 years, the costs per QALY gained for bupropion and NRT were € 3400 and € 4900, respectively. The authors noted that the cost–effectiveness ratios compared favourably to other cost-effective practices in the Netherlands, such as breast cancer screening (€ 4000 per life year gained) or influenza vaccination in elderly people (€ 1800 per life year gained). A number of economic evaluations of the cost–effectiveness of varenicline compared with 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, COPD, coronary heart disease, stroke and asthma exacerbations (47–51). These studies were completed in Europe and South Korea and found varenicline to be a cost-effective strategy despite the initial higher cost of varenicline. Adopting a population level or public health view, then a variety of cessation strategies will be required to help smokers around the world. For example, a 2010 report to the Canadian health ministry 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 (52). Of these interventions, the report concluded that varenicline, bupropion and NRT, followed by physician advice to quit and nursing interventions to be the most effective strategies. In a review of smoking cessation interventions to inform the development of national guidelines, researchers

examined the affordability of such interventions according to country income level (39). The researchers used World Bank categories of low, middle and high income and estimated the incremental cost–effectiveness ratios for effective interventions for each category. The authors suggested that bupropion SR, similar to all medications for smoking cessation (except nortriptyline and cytisine), was affordable in middle- and high-income countries 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. When assessing interventions and their costs, the evidence from economic studies strongly suggests that greater use of medications, including bupropion SR, generates net savings in tobacco-related health costs. The 2020 US Surgeon General's report concluded that the smoking cessation medications approved by the US Food and Drug Administration were cost-effective and increased the likelihood of successful quitting, and that combinations of therapies further increased the likelihood of quitting (53).

## WHO guidelines

WHO treatment guidelines for smoking cessation therapies are not currently available. The 2019 WHO report on the global tobacco epidemic recommends offering help to quit tobacco use as one of the key measures in the MPOWER strategy (6). The report recognizes that both behavioural cessation support and nicotine-replacement and non-nicotine pharmacotherapies are effective in helping people to quit tobacco use. Combining both behavioural and pharmacotherapy interventions, however, is more effective and can double the chances of successfully quitting (39). The 2003 WHO policy recommendations on smoking cessation and treatment of tobacco dependence note that a variety of behavioural and pharmacological therapies for smoking cessation have proved effective, but that no single approach should be emphasized to the exclusion of the others because the therapies vary widely in their efficacy, acceptability, cost–effectiveness and their cost on an individual and population basis (40).

## Availability

Bupropion SR is widely available globally, in originator and generic brands.


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