

# A Meta-Analysis of the Efficacy of Bupropion Sustained-Release for Smoking Cessation in Heavy Smokers

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Cigarette smoking damages just about every organ in the body and reduces overall health. Even with the prevalence of accessible nicotine replacement therapies and behavioral counseling, there remains a need for alternative therapies to improve the odds of successfully abstaining from smoking in the long term. Bupropion sustained-release (SR) is a pharmacological, prescription-only intervention that is approved as a first-line treatment for smoking cessation. This meta-analysis examines the effectiveness of bupropion sustained-release for smoking cessation amongst heavy smokers, defined as those who consistently smoke at least fifteen or more cigarettes per day. Across five qualifying studies, bupropion SR increased odds of cessation over placebo treatment at six and twelve months. Bupropion SR is a well-tolerated, non-nicotinic therapy for smoking cessation. Treatment with bupropion SR reduces initial cravings and withdrawal effects but does not appear to address the multi-faceted problem of cigarette addiction, resulting in decreased abstinence rates over time. An integrated approach incorporating bupropion SR with other interventions, such as nicotine replacement therapies and psychotherapy, may provide the necessary means to achieve lasting cessation and promote well-being.

Abbreviations: AE– adverse effect; CI – confidence interval; cpd – cigarettes per day; DA – dopamine; NE – norepinephrine; NRT – nicotine replacement therapy; OR odds ratio; SAE – serious adverse effect; SR sustained-release

Keywords: nicotine addiction; nicotine replacement therapy; NRT; pharmacological therapy; Wellbutrin SR; Zyban

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## Introduction

Cigarette use continues to be a major preventable cause of morbidity and mortality, and each year more than 480,000 people die from diseases associated with cigarette smoking in the United States (“The Health Consequences of Smoking–50 Years of Progress,” 2014). Smoking increases the likelihood of developing a myriad of complications including but not limited to coronary heart disease, stroke, chronic obstructive pulmonary disease (COPD), several types of cancers, infertility, and erectile dysfunction. Aside from the complications caused by cigarette smoking lie several hidden costs of the habit, some of which include a decrease in productivity, increase in healthcare expenditures, and complications caused by

second-hand smoke (Ekpu and Brown, 2015). Of the annual smoking-attributable mortalities, 41,000 resulted from second-hand smoke exposure.

Quitting smoking presents a long list of benefits including a reduced risk of stroke, diabetes, coronary heart disease, several types of cancers, autoimmune diseases such as arthritis, and other diseases associated with cigarette use (“The Health Consequences of Smoking–50 Years of Progress,” 2014). Prognoses in cancer patients also improve following sustained abstinence from smoking. The rate of decline in pulmonary function, which increases in smoking individuals, returns to that of never smokers with sustained abstinence. Despite the benefits

of and recent attempts to promote smoking cessation, an estimated 36.5 million people in the U.S. smoked cigarettes in 2015, and more than 16 million of those Americans currently live with an illness caused by smoking (“The Health Consequences of Smoking—50 Years of Progress,” 2014). In 2015, 68% of the 36.5 million smokers expressed interest in quitting and over half of that smoking population has attempted to quit within the past year (Babb et al., 2017). Smoking cessation generally requires several attempts before long-term termination is achieved. According to the American Cancer Society, it can take more than 10 attempts to successfully abstain from smoking (Chaiton et al., 2016). Nicotine replacement therapies (NRTs) such as nicotine patches (NicoDerm), gum and lozenges (Nicorette) increase the likelihood of successful smoking cessation attempts (Fiore et al., 2008). Still, other forms of pharmacotherapies are needed.

The nicotine in cigarettes is quickly absorbed by the small airways and alveoli of the lungs and reaches the brain within 10-20 seconds after the first puff (Henningfield et al., 1993). Once in the brain, nicotine activates nicotinic cholinergic receptors in the mesolimbic pathway, facilitating the release of dopamine (DA) in the nucleus accumbens. This pathway is known to play an important role in the perception of pleasure as well as reinforcing the rewards and cravings associated with cigarette smoking (Corrigall et al., 1992). Nicotine also augments the release of glutamate and gamma-aminobutyric acid (GABA), and over time, results in an enhanced responsiveness to nicotine. (Benowitz, 2010). Repeated exposure to nicotine due to smoking results in desensitization of the nicotinic cholinergic receptors. This desensitization is thought to participate in an increased tolerance of and dependence to nicotine (Govind et al., 2009). Withdrawal symptoms are thought to be associated with altered noradrenergic activity within the locus coeruleus (Zwar and Richmond, 2002).

Bupropion is licensed as a first-line treatment for smoking cessation (Wilkes, 2008) with a recommended dosage of 300mg per day, given as one tablet (150mg) twice a day (GlaxoSmithKline, 2016). The FDA approved

the drug in 1985 under the marketed name Wellbutrin® (Wilkes, 2008) with a recommended dosage of 300mg per day, given as one tablet (150mg) twice a day (GlaxoSmithKline, 2016). Currently Zyban®, Wellbutrin SR®, and generic bupropion sustained-release (SR) tablets all contain the same formulation of the pharmacologically active ingredient, bupropion hydrochloride.

Bupropion acts as a selective inhibitor of the neuronal reuptake of the catecholamine neurotransmitters dopamine and norepinephrine (NE; Ascher et al., 1995). The mechanism of action of bupropion appears to enhance neurotransmission of both dopamine and norepinephrine via inhibition of the DA and NE transporters (Fava et al., 2005). The mechanism is also thought to be related to a reduction in the re-uptake of dopamine in the mesolimbic pathway (Ascher et al., 1995) along with a reduction in the re-uptake of norepinephrine in the locus coeruleus (Ferry, 1999). Bupropion also exhibits nicotinic receptor-blocking activity, which likely contributes to a reduction in reinforcement that is followed after smoking a cigarette (Slemmer et al., 2000). The exact mechanism of action of bupropion in aiding with the ability to abstain from smoking, however, is not fully understood.

### *Aim*

A widely accepted definition for heavy smoking does not exist and varies between 15 and 25 cigarettes per day (cpd). The Centers for Disease Control and Prevention (CDC), for example, defines heavy smoking as more than 25 cpd (“Cigarette Smoking Among Adults,” 2005). In order to encompass all cutoff points for heavy smoking, this study defines heavy smokers as individuals who smoke fifteen or more cpd.

Heavy smoking individuals are less likely to quit smoking than light to moderate smokers (Nordstrom et al., 2000). Research suggests that heavy smokers are at an increased risk of tobacco-related morbidity and mortality (Kawachi et al., 1993). While casual and heavy smokers may smoke for the rewarding effects of nicotine, heavy smokers are more likely to continually smoke in order to prevent withdrawal symptoms, which occurs when

plasma nicotine levels fall (Benowitz, 2010). Since bupropion inhibits the reuptake of NE and this neurotransmitter is associated with withdrawal symptoms, a heavy smoking population was set as the focus of this meta-analysis.

To date, no meta-analysis has examined the effectiveness of bupropion SR for heavy smokers, the population with the lowest odds of achieving unassisted smoking cessation. A meta-analysis by Scharf and Shiffman (2004) examined smoking cessation rates with treatment with bupropion SR between men and women. The analysis did not find any significant differences between genders, though women were less successful regardless of treatment. Wu et al. (2006) published a meta-analysis that examined the effectiveness of different smoking cessation interventions. The study found that both NRTs and bupropion were more effective than placebo at twelve months. There have also been multiple reviews summarizing the efficacy, pharmacological profile, and safety of bupropion since its discovery as a smoking cessation agent. Richmond and Zwar published the largest review of bupropion in 2003. This systematic review included 22 papers and poster presentations that focused on a broad smoking population with or without comorbidities. There have also been systematic reviews that assess the efficacy of bupropion on smoking cessation in hospitalized smokers (Rigotti et al., 2008) and the effectiveness of combination therapy (bupropion plus NRTs) versus bupropion versus varenicline (Chantix®; Mills et al., 2012). Other reviews have evaluated smoking cessation in a general smoking population (Wilkes, 2008) as well as special populations with co-occurring conditions (Ranney et al., 2006). This meta-analysis aims to establish the degree to which bupropion SR is able to increase the odds of heavy smokers that are motivated to quit, abstain from smoking in the long-term.

## Materials and Methods

### *Search Methods*

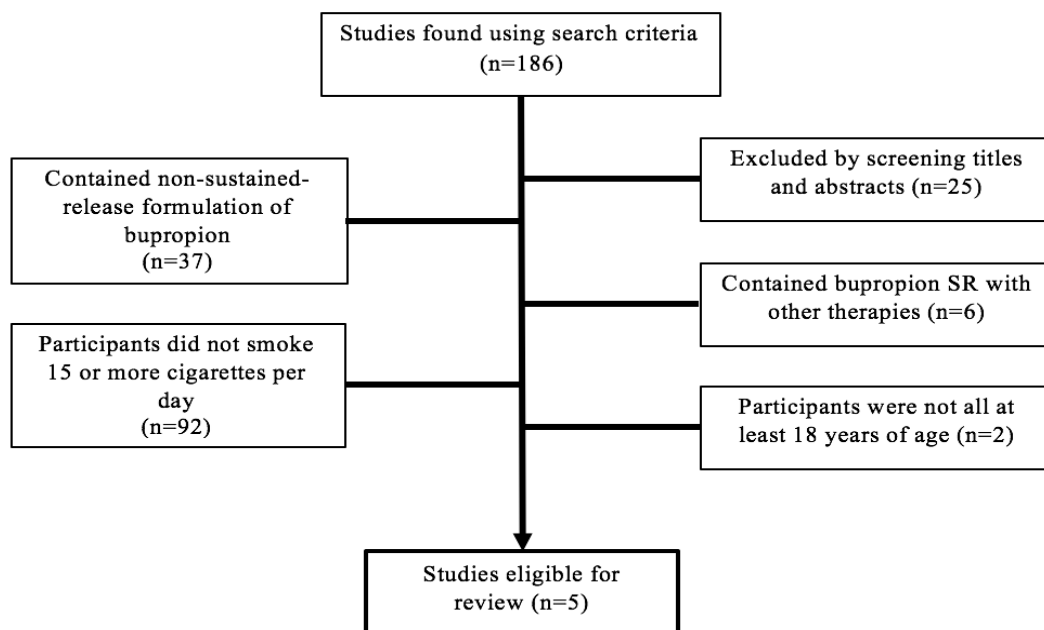
Studies for this review were collected from PubMed, Google Scholar, EBSCOhost,

and ClinicalTrials.gov using the following terms: bupropion, bupropion SR, nicotine addiction, nicotine replacement therapy, pharmacological therapy, smoking cessation Wellbutrin SR®, Wellbutrin®, and Zyban®. Citation mining was also used for all reviews found involving bupropion. A total of 186 studies were found and screened (Figure 1).

### *Selection Criteria*

Titles and abstracts were initially screened. Studies with more ambiguous titles/abstracts were further screened for the selection criteria. In order for a study to be eligible for review, it had to include the use of the sustained-release formulation of bupropion, therefore excluding 37 studies. The sustained-release formulation was chosen over the two other formulations of bupropion (immediate-release and extended-release) because Zyban®, the first brand to be approved for the cessation of smoking, was sustained-release and most extensively studied. Six studies were excluded for using the sustained-release formulation of bupropion in conjunction with additional pharmacological interventions such as Chantix® or nicotine replacement therapies in order to maintain an exclusive focus on the efficacy of bupropion. One study used in the analysis had several treatment arms; one of which received NRTs plus bupropion SR, another that only received bupropion SR, and a placebo arm (Jorenby et al., 1999). Only the latter two arms were used in the analysis. Participants in the studies must have smoked at least 15 cigarettes per day for at least the last month in order to be eligible for review. This criterion significantly narrowed the pool of studies by 92 and was chosen to evaluate the efficacy of bupropion in alleviating a heavy dependence on nicotine.

Participants must have been 18 years old or older at the time the study was initiated. This criterion was established for two reasons: the majority of the studies were carried out in nations where the legal smoking age was 18, and there is limited clinical evidence examining the differences of the effects of nicotine in adolescents and adults (Rupprecht et al., 2015). This criterion excluded two studies, one that focused on an adolescent population and one that contained a portion of underage participants



**Figure 1.** Trial selection for the meta-analysis. Studies were included/excluded based on the whether or not they contained criteria specific for the analysis.

within the study. Studies whose participants had a current mental disorder or disease pathology were omitted, excluding 19 more studies. The studies that included participants with existing mental disorders either did not screen for or did not specify whether the participants were taking medication for their condition; this may affect the effectiveness of bupropion, especially considering that many of the drugs used to treat mental conditions exert their effects on DA or NE. Studies were not excluded for containing participants with a history of mental health disorders. One study had an exclusion criterion that included a history of mental illness, though this study was included in the analysis (Jorenby et al., 1999).

The number of articles excluded as described in Figure 1 are best estimates, as studies may have shown up more than once using the search criteria. In order to obtain proper estimates, articles containing more than one potential exclusion criteria were marked and cross referenced with other excluded articles. A total of five studies were eligible after being screened for all inclusion/exclusion criteria.

### *Study Characteristics*

Every study had a placebo group that received a pill identical in size and shape to the treatment group. All five of the studies were placebo-controlled, double-blind, randomized trials. Participants across all studies were current smokers who were otherwise healthy, and were interested or motivated to quit. The number of participants at the beginning of each study is shown in the “Study Population” column of Figure 1. Each study administered bupropion SR in 150mg tablets that were taken twice a day for a total daily dose of 300mg. Dosing across all studies followed an initial dose of 150mg per day, given as a single dose in the morning. After three days, the dose was then increased to the target adult dose (300mg) given as 150mg tablets twice a day (GlaxoSmithKline, 2016). Every study except Tonstad et al. (2001), which did not specify a target quit date, set a target quit date during the baseline visit, which was the eighth day of taking the medication. Participants were allowed to smoke during the first seven days of taking the medication. The treatment period varied among studies. Tonstad et al. (2001) and Hurt et al. (1997) used a seven-week, double-blind treatment period. Hays et al. (2001) used a seven-week open-label treatment period

where every participant received treatment, then double blind for weeks 8 through 52 for individuals who were continuously abstinent throughout the duration of the treatment period. This study also had the greatest percentage of abstinent participants in both treatment and placebo groups when compared to other studies, suggesting that sustained treatment promotes abstinence. Jorenby et al. (1999) utilized a nine-week treatment period and Gonzales et al. (2001) used a 12-week treatment period.

Validation of smoking abstinence during clinic visits was self-reported by participants across all studies and confirmed by exhaled carbon monoxide (CO) levels. There were differences in the number and frequency of visits across the studies (see Table 1). All five studies reported smoking abstinence using point-prevalence and continuous abstinence rates. Velicer et al. (1992) define continuous abstinence as not smoking since the last follow-up. Individuals who have not smoked since the last follow-up are considered to have remained abstinent without relapse. Point prevalence abstinence, also defined by Velicer et al. (1992) is not smoking for the last seven days. Both methods of assessing abstinence rates were used in the analysis, as they are highly correlated ( $r = .82-.99$ ; Velicer and Prochaska, 2004). Tonstad et al. (2001) measured 'slips allowed' abstinence rates. Slips allowed abstinence rates are defined as smoking for a maximum of six consecutive days or for a total of nine days during the treatment phase and follow-up phase. This method allowed a participant in the study to smoke during the treatment and follow-up periods and still be considered abstinent. There was no data regarding how many participants smoked during the study and were considered abstinent.

Depending on the study, participants received brief counseling during all visits, self-help material, and/or phone calls during the treatment and follow-up periods. Each counseling session was 15 minutes or less and was limited to the number of visits during the study, which varied among the studies. The effects of counseling on abstinence rates was not measured, though the general presence of counseling would not produce relative differences in abstinence rates. Since personal

counseling sessions were the main form of counseling in the studies, it is unlikely that other counseling methods produced significant differences in abstinence rates. No information regarding the extent of counseling was available for Tonstad et al. (2001; Table 1).

### *Adverse Effects*

An adverse effect (AE) is defined by the U.S. Food and Drug Administration (FDA) as an untoward occurrence that is associated with the use of a drug (Code of Federal Regulations, 2016). An AE is considered serious if it requires or prolongs hospitalization, becomes persistent or disrupts normal life, becomes life threatening, or results in death.

Adverse effects and serious adverse effects (SAEs) were observed in all studies. Two of most common AEs across all studies were insomnia and dry mouth, which occurred significantly more in the treatment group in Jorenby et al. (1999) and Hurt et al. (1997). Headache was also a frequently observed AE, though there was no significant difference in occurrence between treatment and placebo groups in four studies. Tonstad et al. (2001) did not mention the significance of AEs between treatment and control groups. Twenty-five SAEs were noted in all studies across both groups, 21 of them being reported in the treatment group. One SAE in Gonzales et al. (2001) and two in Jorenby et al. (1999) were attributed to bupropion, all of which were rashes that improved with termination of medication and treatment. Tonstad et al. (2001) noted six SAEs in the treatment group, of which allergic reactions were most frequent. There were no fatal adverse reactions across all studies.

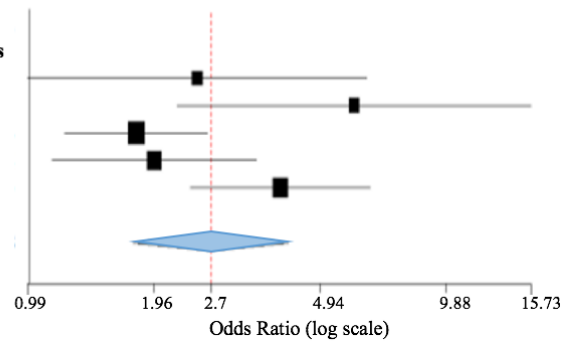
Each study contained participants who discontinued the study before the treatment period was over. The main reasons for incompleteness of the studies included withdrawal of consent due to scheduling conflicts or lack of perceived benefits, protocol deviation, AEs, administrative reasons, death, and abandonment. No deaths during any of the studies were attributed to bupropion.

### *Analysis*

The software used to perform the random binary effects analysis was

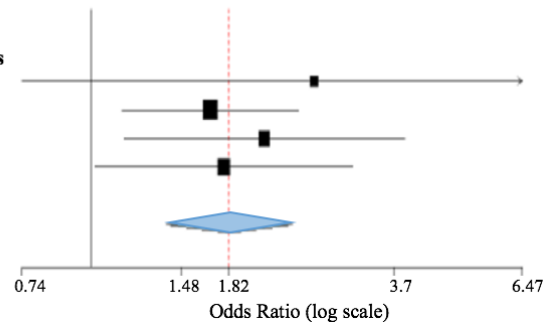
**a. Six Month Abstinence**

Studies	OR [95% CI]	Treatment Abstinent	Placebo Abstinent	Weights
Tonstad et al. (2001)	2.51 [0.99, 6.38]	64/183	6/34	13.24%
Gonzales et al. (2001)	5.94 [2.25, 15.73]	27/226	5/224	12.53%
Hays et al. (2001)	1.79 [1.21, 2.66]	145/214	116/215	27.67%
Hurt et al. (1997)	1.98 [1.13, 3.47]	42/156	24/153	22.22%
Jorenby et al. (1999)	3.96 [2.42, 6.49]	85/178	30/160	24.33%
<b>Overall (<math>I^2=59\%</math>, <math>P=0.04</math>)</b>	<b>2.70 [1.76, 4.14]</b>	<b>363/957</b>	<b>181/786</b>	



**b. Twelve Month Abstinence**

Studies	OR [95% CI]	Treatment Abstinent	Placebo Abstinent	Weights
Tonstad et al. (2001)	2.63 [0.74, 9.32]	41/145	3/23	4.66%
Hays et al. (2001)	1.67 [1.14, 2.45]	118/214	91/215	51.27%
Hurt et al. (1997)	2.12 [1.15, 3.89]	36/156	19/153	20.22%
Jorenby et al. (1999)	1.78 [1.01, 3.11]	74/169	25/82	23.85%
<b>Overall (<math>I^2=0\%</math>, <math>P=0.86</math>)</b>	<b>1.82 [1.38, 2.39]</b>	<b>269/684</b>	<b>138/473</b>	



**Figure 2.** Figures 2a and 2b show the results of meta-analysis for treatment effects for six- and twelve-month abstinence rates, respectively.

OpenMeta[Analyst] (Wallace et al., 2012). All odds ratios (ORs), confidence intervals (CIs), heterogeneity tests ( $I^2$ ), P-values, and weights were calculated by the software. An OR greater than one signifies that the results favor bupropion over placebo, and vice versa for an OR less than one. The 95% CI signifies the range of plausible values in the population given the sample data available. The ORs and CIs in Figures 2a and 2b are presented on a logarithmic scale, allowing the CIs to be symmetrical from the means when comparing ORs less than one to those greater than 1. Heterogeneity tests were provided with their own respective P-values for Figures 2a and 2b. P-values were also provided for the overall treatment effects at six and twelve months.

**Results**

*Six-Month Abstinence Rates*

Each study in the analysis reported abstinence rates at six months. Treatment with bupropion SR increased rates of abstinence

when compared to placebo. Compared to placebo (23.0%), 37.9% of participants treated with bupropion were abstinent. The overall treatment effect was 2.70 ( $P = 0.001$ ), 95% CI [1.76, 4.14] (Figure 2a). Gonzales et al. (2001) had the greatest treatment effect (OR = 5.94, 95% CI [2.25, 15.73]) despite having the lowest number of abstinent participants in both placebo and treatment groups. There was significant heterogeneity in the results at six months ( $I^2 = 59\%$ ,  $P = 0.04$ ), indicating moderate to substantial variance among the studies.

*Twelve-Month Abstinence Rates*

Four of the five studies included in the analysis (all except Gonzales et al., 2001) also reported abstinence rates at twelve months. Integrating across these studies, 39.3% of the treatment group had remained abstinent for a year, compared to 29.2% in the placebo group. The treatment effect was 1.82 ( $P = 0.001$ ), 95% CI [1.38, 2.39] (Figure 2b). There was no evidence of heterogeneity ( $I^2 = 0\%$ ,  $P = 0.86$ ).

## Discussion

Treatment with bupropion SR produced greater cessation rates than placebo across all studies. Meta-analysis shows that bupropion SR is almost three times more effective than placebo in helping individuals abstain from smoking at six months and almost two times more effective than placebo at one year. The CI for six month rates [1.76, 4.14] suggests that the effect could be anywhere from a near two-fold increase in cessation rates up to a four-fold increase in cessation rates.

Gonzales et al. (2001) focused on participants who were previously treated with bupropion. This study had the greatest treatment effect on six-month abstinence rates, which suggests that odds of quitting can increase with subsequent treatments. The presence of heterogeneity for six-month abstinence rates can be attributed to a prolonged treatment period in Hays et al. (2001), which resulted in the highest abstinence rates in both groups. Some heterogeneity can also be associated with Gonzales et al. (2001), whose participants have previously been treated with bupropion. It is worth noting, though, that the untreated odds of successful cessation are very low (23%), so even with the increased odds due to treatment it was still a minority of patients who successfully quit (38%).

A prolonged treatment period (greater than twelve weeks) appears to increase abstinence rates, despite the fact that the OR of the study that included a 52-week treatment period (Hays et al., 2001) was below the overall OR for both six- and twelve-month abstinence rates. Interestingly, this study did not note significant differences in abstinence rates between treatment and placebo groups at one year, despite the high rates of abstinence. Given that nicotine withdrawal is a major cause for relapse, the target daily dose (300mg) appears to effectively blunt the unpleasant withdrawal symptoms associated with smoking cessation. Only twelve participants across all studies reported having withdrawal symptoms after the target quit date.

Tonstad et al. (2001) reported the greatest OR at twelve months, but it is possible

that this was partially attributed to the design method, which allowed participants to smoke for six consecutive days or nine days total during the treatment and follow-up periods and still be considered abstinent.

Treatment of bupropion SR appears to be an effective pharmacological intervention for smoking cessation. The review shows good evidence that bupropion SR is a useful, non-nicotinic treatment for quitting smoking in heavy smokers. Bupropion SR is reportedly well tolerated with minimal AEs. In fact, there were more participants that did not complete any study due to scheduling conflicts than due to AEs from treatment. Treatment may be even more effective in light smokers, as heavy smokers are subject to more intense cravings and withdrawal symptoms (Chandra et al., 2011), or in combination with NRTs or other interventions.

Though the overall OR favors bupropion SR over placebo at one year, this seems to be a weaker advantage than at six months, and the CI indicates there may be as little as only a 38% improvement in the odds of cessation. Bupropion SR increased odds of quitting from a very low baseline, so the majority of treated patients still failed to successfully cease smoking. The observed decrease in abstinence rates over time, however, do not necessarily signify that treatment is becoming less effective in terms of its modulatory effects on neurotransmitters, since bupropion's activity as a nicotinic antagonist decreases the rewarding effects of nicotine. Smoking is a behavioral habit as well as a physiological addiction to nicotine. With the purpose of finding a more efficacious treatment plan for those motivated to quit smoking, perhaps bupropion SR can be utilized as part of a multi-faceted approach, introducing psychotherapy and NRTs to achieve lasting cessation.

**Table 1.** A summary of the studies used for meta-analysis.

**Summary of Studies**

<b>Study</b>	<b>Study Population (Enrolled/Completed)</b>	<b>Continuous abstinence % at 6 months (Treatment vs. Placebo)</b>	<b>Continuous abstinence % at 12 months (Treatment vs. Placebo)</b>	<b>Treatment Period (weeks)</b>	<b>Frequency of Validation</b>	<b>Extent of counseling</b>
Tonstad et al. (2006)	710/572	35.0 vs 19.0	28.0 vs 13.0	7	At visits during weeks 4, 12, 26 and 52	No information available
Gonzales et al. (2001)	450/414	12.0 vs 2.0	No information available	12	At visits during weeks 1-7, 9, 12, and at 6 months	Brief counseling during visits, phone calls during follow-up
Hays et al. (1997)	784/317	67.8 vs 54.0	55.1 vs 42.3	52	At visits during weeks 1-6, 8-10, 12, 16, 20, 24, 28, 36, 40, 44, 48, and 52	Self-help material, brief counseling (15 min) during visits
Hurt et al. (1997)	309/198	26.9 vs 15.7	23.1 vs 12.4	7	At visits during weeks 1-8, 12, 26, and 52	Self-help material, brief counseling during visits, phone calls during treatment & follow-up
Jorenby et al. (1999)	404/251	34.8 vs 18.8	30.3 vs 15.6	9	At at visits during weeks 1-10, 12, 26, and 52	Brief counseling (15 min) during visits, phone calls during treatment & follow-up



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