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Efficacy and Tolerability of Pharmacotherapies to Aid Smoking Cessation in Adolescents

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Abstract

Adolescent smoking remains a public health problem. Despite concerns regarding adolescent nicotine dependence, few well-designed smoking cessation studies have been conducted with teen smokers. This is particularly true regarding pharmacological treatments for nicotine dependence. Currently, pharmacological aids are not recommended for treating adolescent nicotine dependence, as efficacy has not been shown in this population. This review includes studies that have examined the efficacy of pharmacotherapy for smoking abstinence and/or reduction in cigarette consumption among adolescent smokers who want to quit smoking, lab-based adolescent studies that have examined the effectiveness of these medications in reducing cravings and/or withdrawal symptoms, and/or studies that have assessed the tolerability of medications for smoking cessation in adolescent smokers. This review provides information on the pharmacologic action of each medication, the efficacy of each medication for adolescent smoking cessation, the tolerability of each medication based on reported adverse events, and compliance with the medication protocols. Thirteen relevant articles were identified and included in the review. Nicotine patch, nicotine gum, nicotine nasal spray, bupropion, and varenicline have been studied in adolescent smokers. The adverse events reported in the studies on pharmacology for adolescent smoking suggest that the side effect profiles for nicotine replacement therapy, bupropion, and varenicline are similar to those reported in adult studies. There is some evidence of efficacy of nicotine patch and bupropion at end of treatment (efficacy of varenicline has not been assessed), but none of the medications included in this review were efficacious in promoting long-term smoking cessation among adolescent smokers. It is noted that many of the study protocols did not follow the recommended dose or length of pharmacotherapy for adults, rendering it difficult to determine the true efficacy of medication for adolescent smoking cessation. Future efficacy studies are warranted before recommending pharmacotherapy for adolescent smoking cessation.

1. Adolescent Smoking and Pharmacotherapy

Adolescent smoking remains a high priority public health concern. The U.S. Department of Health and Human Services has retained the goal of reducing adolescent smoking rates in the Healthy People 2020 initiative.[1] Although smoking rates have declined in the United States in the past decade,[2,3] 20% of 12th graders were current smokers in 2009, with 11.2% of 12th graders smoking on a daily basis and 5% smoking at least a half a pack a day.[3]

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Considering that over 80% of adult smokers begin smoking prior to age of 18,[4] it is imperative to develop effective smoking cessation programs for adolescent smokers.

Relatively few well-designed smoking cessation studies have been conducted with teen smokers. This is particularly true regarding pharmacological treatments for nicotine dependence. To date, nicotine replacement, bupropion (Zyban), and varenicline have been approved as therapies for adult smokers and the recommended treatment for adult nicotine dependence is a combination of psychotherapy and pharmacotherapy.[5] In contrast, it is unclear whether pharmacotherapy is efficacious, or safe, for use with adolescent smokers. Given recent evidence that adolescents experience craving and withdrawal symptoms associated with smoking cessation, pharmacotherapy may be useful in alleviating these symptoms, thereby increasing the chances of abstinence in teens.[6–9]

This review includes studies that examined the efficacy of pharmacotherapy for smoking abstinence and/or reduction in cigarette consumption among adolescent smokers who want to quit smoking, lab-based adolescent studies that examined the effectiveness of pharmacotherapy in reducing cravings and/or withdrawal symptoms, and/or studies that assessed the tolerability of medications for smoking cessation in adolescent smokers. This review provides information on the pharmacologic action, efficacy, and safety/tolerability of each medication, as well as compliance with the medication protocols.

2. Methods

2.1. Study Identification and Inclusion

Searches were conducted through the PubMed and PsycINFO online databases (through May 2011) and were limited to “English Language” and “Human.” The following keywords were used in the initial search “smoking cessation”, “adolescent OR teen” and then limited by the separate use of the following terms: “bupropion”, “Zyban”, “nicotine replacement therapy”, “varenicline”, “Chantix”, “nicotine patch”, “nicotine gum”, “nicotine nasal spray”, and “pharmacotherapy.” Only studies that targeted adolescent smokers for recruitment and enrollment were included. In addition, studies referenced in relevant review articles, meta-analyses, and all selected articles were examined.

The searches yielded 14 relevant studies that included pharmacotherapy for adolescent nicotine dependence. One study was excluded from the review because the focus was on reduction of smoking among adolescents that did not want to quit and did not include data on adverse events.[10] The following medications have been studied regarding their efficacy for smoking cessation in adolescent smokers: nicotine patch (NP), nicotine gum (NG), nicotine nasal spray (NNS), and bupropion (Zyban). One study examined the tolerability/safety of the use of varenicline in adolescents. Intent-to-treat analyses were performed in all studies that examined efficacy of medications.

3. Nicotine replacement therapy

This review focuses on nicotine replacement therapy (NRT) that has been evaluated for smoking cessation among adolescent smokers (nicotine patch, gum, and spray); however, there are other nicotine replacement products approved for smoking cessation, including a nicotine inhaler, a nicotine lozenge and, in some countries outside of the United States, a nicotine sublingual tablet. Nicotine replacement therapy (NRT) replaces the nicotine delivered while smoking to reduce craving and withdrawal symptoms and is available in different forms and dosages depending on the number of cigarettes smoked.[11,12] Tobacco use must be discontinued when implementing NRT to avoid toxic levels of nicotine within the body. Precautions for use of NRT should be taken in persons under the age of 18,

women who are pregnant or breastfeeding, and for all persons with recent (≤ 2 weeks) myocardial infarction, serious underlying arrhythmias, and/or serious or worsening angina pectoris. An additional precaution for use of nicotine gum should be taken for persons with temporomandibular joint disease.[13] Additional precautions should be taken when nicotine nasal spray is used in persons with underlying chronic nasal disorders and severe reactive airway disease. The use of NRT in adolescents is not currently recommended as a component of adolescent tobacco treatment because efficacy has not been established in this population.[5]

Nicotine gum (NG) and nicotine patch (NP) were originally approved by the Food and Drug Administration (FDA) in the United States as prescription-only medications for the treatment of adult nicotine dependence. In 1996, both NG and NP became available in the U.S. without a prescription for persons 18 years or older. In 1996, the FDA also approved nicotine nasal spray (NNS) as a prescription-only NRT for adult smokers. NG delivers nicotine through the mouth with doses of 2 or 4 mg, and smokers are advised to chew one piece every 1 – 2 hours, depending on the amount of cigarettes smoked daily. [5] NP delivers nicotine through the skin in a steady dose. NP is available in 7, 14, and 21 mg doses worn over 24 hours, or in 5, 10, and 15 mg doses available in a 16-hour patch.[12] NNS delivers nicotine through the mucous membrane of the nose. One dose is two sprays (one in each nostril). One dose is 1 mg of nicotine, with 1 – 2 doses recommended per hour.[5]

3.1. Summary of the literature on NRT in adolescent smokers

3.1.1. Lab-based studies—One study examined NRT in a controlled environment to determine if adolescent smokers experience nicotine withdrawal and whether brief treatment with NRT alleviates withdrawal symptoms.[7] Adolescents (n = 92) attended two, 8-hour sessions conducted on consecutive Saturdays. During each session, heart rate and blood pressure were assessed at 2-hour intervals and subjective withdrawal symptoms were reported at 4-hour intervals. During Session 1, participants were allowed to resume their normal activities, including smoking. At Session 2, participants were not permitted to use tobacco products during the eight-hour session, and were required to wear a placebo patch or 15 mg/16-hour nicotine patch. The results revealed that adolescents do experience withdrawal symptoms when deprived of nicotine; however, none of the between-group comparisons (active NP vs. placebo patch) for withdrawal symptoms were significant, suggesting that the patch does not alleviate all withdrawal symptoms, at least in the short-term. Only itchiness was reported significantly more often in the active NP group than the placebo group. One teen removed the patch after experiencing nausea one hour after patch application and was excluded from the study. None of the adverse events rated by participants as severe at Session 2 were deemed to be truly severe by the study physician.

3.1.2. Open-label studies—The earliest study to use NRT with adolescent smokers was conducted by Smith and colleagues in 1996.[14] Participants (n = 22) were provided with 22 mg/24-hour NP for six weeks and then 11 mg/24-hour NP for two weeks along with weekly school-based individual behavioral counseling and group support. Of the 22 participants, three (13.6%) had biologically verified point prevalence abstinence at the end of treatment (Week 8). Only one (4.5%) continued to be smoke-free at three and six months after initiation of patch use. Despite low abstinence rates, a decrease in withdrawal symptoms and a significant reduction in daily smoking were observed. At least one adverse event was reported by 82% participants, with the most common being a skin reaction. None of the adverse events were of more than moderate intensity or deemed life-threatening or serious. No adverse events were associated with discontinuation of patch therapy.

Hurt et al. conducted a larger open-label study (n = 101) that coupled six weeks of 15 mg/16-hour NP therapy with an optional brief individual counseling session at the first clinic visit.[15] At the end of treatment (Week 6), 10.9% of participants were abstinent. By the 6-month follow-up visit, only 5.0% were abstinent. By Week 2 of NP therapy, mean withdrawal scores had significantly reduced from baseline and remained lower through Week 6. At least one adverse event was reported by 87% of participants with the most common being upper respiratory tract infections (44%) and headache (43%). There was no difference in the frequency of adverse events in those who completed patch therapy compared to those who did not. During the course of treatment, 30 participants dropped out of the study prior to completion of patch treatment, with five discontinuing treatment due to patch-related adverse events.

3.1.3. Randomized clinical trials (RCT)—The first randomized, double-blind, placebo-controlled study of NRT was conducted by Hanson et al. in 2003.[16] Initial dose and titration schedules were based on the teens' level of cigarette consumption. Participants (n = 100) received 10 weeks of NP therapy and cognitive-behavioral therapy and a contingency management procedure. There were no significant differences between groups in biologically verified, 7-day point prevalence abstinence at end of treatment (Week 10) (28.0% NP vs. 24.0% placebo), 30-day point prevalence abstinence (20.0% NP vs. 18.0% placebo), or continuous abstinence from the quit date. Compared to the placebo patch group, the active NP group experienced a significantly lower craving score and overall withdrawal symptom score. Participants in the placebo patch group reported more headaches than those in the active NP group (75.6% vs. 56.3%, respectively). None reported dropping out as a result of an adverse event and no significant differences in dropout rates or medication compliance were observed across the treatment groups.

A community-based, double-blind pilot RCT was conducted by Roddy and colleagues with 98 regular smokers (defined as > 1 cigarette per day or < 1 cigarette per day but reported past or anticipated withdrawal).[17] Smokers were randomized to receive either active NP (n = 49) or placebo patches (n = 49) for six weeks, along with weekly brief counseling sessions. NP dose was 15 mg/10 mg/5 mg per day for two weeks each. At four weeks, five smokers in the NP group (10.2%) and two in the placebo group (4.1%) achieved biologically verified point prevalence abstinence; none were abstinent at 13 weeks. Of the 98 randomized smokers, only three in the active group and five in the placebo group completed the full six weeks of treatment, with a median number of weeks of patch therapy with counseling of one week. One participant in the NP group and one in placebo group withdrew because of adverse events (details not reported). The most common adverse event reported was itching.

Moolchan and colleagues[18] examined the efficacy of 12 weeks of NP and NG therapy (plus cognitive-behavioral group therapy) in treating adolescent nicotine dependence using a double-blind, double-dummy, randomized 3-arm trial: 1) active NP and placebo gum (NP group; n = 34), 2) active NG and placebo patch (NG group; n = 46), and 3) placebo gum and placebo patch (placebo group; n = 40). NG dose was 4 mg for those smoking at least 25 cigarettes per day; otherwise the given dose was 2 mg. NP dose was 21 mg/24-hour if the participant weighed at least 100 pounds and smoked at least 20 cigarettes per day at baseline; otherwise the dose was 14 mg/24-hour. Biologically verified prolonged abstinence rates were 17.7% for the NP group, 6.5% for the NG group, and 2.5% for the placebo group. The difference between the NP group and placebo group was statistically significant. There were no statistically significant differences between the NP and NG groups, or NG versus placebo groups. Biologically verfied point prevalence abstinence rates at end of treatment (Week 12) and at the 6-month follow-up (three months after the end of treatment) were highly concordant but not significantly associated with treatment group (20.6% NP, 8.7%

NG, 5% placebo). Active medication was associated with a significant increase in adverse events for the following symptoms: sore throat and hiccups for NG vs. placebo, shoulder/arm pain and erythema for NP vs. placebo, and pruritus for NP vs. placebo and for NG vs. placebo. Compliance in the NG group was significantly lower than in the placebo group. Mean compliance rates across groups were higher for the patch than the gum; however, study completion rates did not differ significantly by treatment group.

Finally, Rubinstein et al. conducted a pilot randomized trial of nicotine nasal spray (NNS) in 40 adolescent smokers.[19] Participants were assigned to receive either weekly group counseling for eight weeks (n = 17) or eight weeks of counseling plus six weeks of NNS (n = 23). Participants were advised to use the spray whenever they had strong cravings for a cigarette (not to exceed 40 doses per day). There was no significant difference in biologically verified continuous abstinence (at least seven days) between groups at the end of treatment (eight weeks): two participants in the counseling only group quit smoking and none of those in the NNS plus counseling group quit. Nicotine nasal spray use was low, with only 26% of participants assigned to NNS plus counseling group reporting daily use during the first week and only 43% still using their spray by the end of treatment (median of < 1 spray per day). The most commonly reported side effects were nasal irritation and burning (34.8%) and complaints about taste and smell (13%).

3.2. Summary of efficacy

See Table I for efficacy data by study. End of treatment point prevalence rates ranged from 0% (NNS) [19] to 28.0% (NP).[16] Of the three studies that reported 6-month follow-up data, abstinence rates also varied, with a low of 4.5%[4] and a high of 20.6%[18] (both NP studies). Of the four randomized clinical trials with NP, only one reported significantly lower rates of abstinence at end of treatment (defined as prolonged abstinence) for those in the NP group compared to those in the placebo group.[18] There were no significant differences in abstinence rates for NG versus placebo[18] or NNS versus placebo.[19]

Most studies reported statistically significant decreases in smoking and/or reductions in withdrawal and craving scores from baseline. Given the small number of trials, it is difficult to ascertain whether NRT is an effective aid in smoking cessation. The data do suggest that NP therapy is more efficacious than the other nicotine replacement products that have been evaluated in adolescent smokers; however, the higher abstinence rates could be due to lower medication compliance rates with NG and NNS among adolescents. Data also suggest that NP therapy may be most effective when the dose is determined by the number of cigarettes smoked per day and is used for at least 10 weeks in conjunction with psychotherapy. The two studies[17,18] that followed this protocol reported longer-term cessation rates similar to those found in the adult literature.[13] The lowest abstinence rates at 6-month follow-up for NP therapy were seen in the study that provided minimal counseling and used the 15 mg/16-hour for a total of six weeks;[15] however, we were unable to determine if these lower abstinence rates were statistically significant from the other studies or if these differences were due to study factors unrelated to medication.

3.3. Safety/tolerability

None of the studies reported any severe or life-threatening side effects. The adverse events reported by adolescents for NRT were similar to those reported by adult smokers.[13,20] Commonly reported adverse events in adolescents using NP included: local skin reactions, headache, nausea/vomiting, tiredness, sleep disturbances, joint/muscle ache and lightheadedness/dizziness. One study reported a high incidence of upper respiratory tract infections; however, it is unclear if this was related to patch use as there was no placebo control.[15] In the one study that assessed NG, [18] sore throat, hiccups and pruritus were

higher in those using NG compared to placebo. Finally, the most common side effects for NNS were nasal irritation/burning and complaints of taste and smell [19]. See Table II for detailed adverse events by study.

Of the NRT studies, only three reported discontinuation of study medication during treatment due to an adverse event.[7,15,17] Hurt et al reported five participants discontinued NP[15] and Roddy and colleagues reported 2 discontinuations (1 in NP group, 1 in placebo group) [17]; neither study stated the nature of the adverse events. One adolescent in the Killen et al. study removed NP after experiencing nausea one hour after patch application was excluded from study participation. [7]

In general, NRT is well tolerated in adolescents with the possible exception of the nicotine nasal spray. Although use of the NNS did not result in severe or life-threatening adverse events, compliance rates were low and appeared due, in part, to the unpleasant side effects associated with the spray.[19]

3.4. Compliance rates

NP had the highest compliance rates. Hanson et al.[16] reported that among participants who completed their visits, self-reported compliance with use of active NP was 84.2% through six weeks postquit and 67.2% during the 4-week dose reduction period. Hurt et al. [15] reported that NP use was reported in daily diaries for 85% +/− 20% of the days of patch therapy. Roddy et al. reported the lowest compliance rates of patch use (NP and placebo), with a median duration of one week and only eight out of 98 participants completing the 6-week treatment. [17] In the Moolchan study,[18] compliance rates for gum (mean: 38.5–50.7%) were lower than compliance for patch use (mean: 78.4–82.8%) and compliance for NG was significantly lower than the placebo group. Compliance rates for NNS also were low and appeared due to the unpleasant side effects. During the first week of spray use, only 26% of participants assigned to the NNS used their spray every day and 57% stopped using their spray after only one week. [19]

3.5. Special considerations for use in adolescent smokers

Controversy remains over the use of NRT in adolescents. Studies with animals indicate that nicotine can elicit neuronal damage and long-term changes in synaptic function, suggesting that there could be long-term adverse consequences of nicotine exposure in adolescence.[21] Therefore, several studies suggest that NRT should not be given to teen smokers especially since evidence of efficacy is lacking.[22] However, too few studies have been conducted to conclude that NRT is not effective. If NRT proves to be efficacious in treating adolescent nicotine dependence, NRT risks are likely minimal regarding nicotine's effect on the adolescent brain if adolescent smokers are already ingesting nicotine through cigarettes. Further, if NRT aids in helping teens quit, the reduced exposure to nicotine and other carcinogens through quitting smoking would have significant health effects over the lifetime.

4. Bupropion

Bupropion was initially marketed as an atypical antidepressant and was approved in 1997, under the name Zyban, as the first non-nicotine medication to aid in smoking cessation for adults. Bupropion inhibits the reuptake of dopamine and norepinephrine in the central nervous system[5,13] and may function as a nicotinic actetylcholine-receptor antagonist.[23] Contraindications for bupropion include: underlying seizure disorders, concomitant bupropion therapy, current or prior diagnosis of anorexia or bulimia nervosa, simultaneous abrupt discontinuation of alcohol or sedatives and/or benzodiazepines, and monoamine oxidase inhibitor therapy in previous 14 days. Extreme caution should be used in prescribing

bupropion to anyone with a previous history of seizures or cranial trauma, those taking medications that might lower the seizure threshold, patients with severe hepatic cirrhosis, women who are pregnant or breastfeeding, and persons under the age of 18.[13] In 2009, the FDA mandated a “black box” warning highlighting the risk of neuropsychiatric symptoms, including changes in behavior, hostility, agitation, depressed mood, suicidal thoughts and behavior, and attempted suicides, in patients taking bupropion for smoking cessation. Bupropion also has a black box warning that describes the increased risk of suicidal thoughts and behaviors in children and adolescents being treated with antidepressant medications (see Section 4.5).[24] The use of bupropion in adolescent smokers currently is not supported by the Clinical Practice Guidelines for Treating Tobacco Use and Dependence because of the insufficient evidence of its effectiveness in promoting smoking cessation in this population.[5]

4.1. Summary of the literature on bupropion in adolescent smokers

4.1.1. Open-label studies—One open-label pilot study has been conducted using 300 mg/day bupropion SR in adolescents for the treatment of nicotine dependence. Upadhyaya et al. examined the use of this medication in 16 adolescent smokers, 11 of who had comorbid attention-deficit/hyperactivity disorder (ADHD).[25] Participants received brupropion SR for six weeks and two smoking cessation counseling sessions. Analyses were conducted with participants who took at least one dose of medication during the study (n = 15); 31.3% of adolescents were abstinent after four weeks of taking bupropion SR; however, end of treatment cessation rates (six weeks) and the cut-off for expired air CO were not specified. Three participants withdrew from the study due to medication side effects (side effects not specified) and one was withdrawn after taking an overdose of the study medication in a suicidal gesture. Dosage was reduced to 150 mg/day for one participant that experienced a gastrointestinal side effect.

4.1.2. Randomized clinical trials (RCT)—Four RCTs have assessed the efficacy of bupropion for smoking cessation with adolescents.[26–29] Niederhofer and Huber examined immediate release bupropion for nicotine dependence with adolescents in an outpatient setting who were randomly assigned to receive 150 mg/day of bupropion or placebo for 90 days.[26] Participants underwent inpatient nicotine withdrawal treatment using NRT prior to beginning treatment with bupropion. Those who achieved abstinence for at least five days (n = 22) were then randomized to one of the two treatment groups. Participants received psychotherapy and 90 days of bupropion or placebo. Treatment failure was defined as the first relapse (> 15 cigarettes over three days) or non-attendance at the 30 and/or 90-day assessments. Continuous abstinence rates at the 90-day assessment were higher for those in the bupropion group (55%) than in the placebo group (18%). Further, the mean cumulative abstinence duration was significantly greater in the bupropion group than in the placebo group (78.4 +/− 39.6 days vs. 30.2 +/− 19.2 days, respectively). Interpretation of these results is difficult, as many aspects of this study are not comparable to other study protocols, including the definition of relapse, the use of NRT prior to bupropion treatment, and the unspecified CO level used to confirm abstinence. With regard to adverse events, there were no significant differences between the bupropion and placebo groups.

In the only study to examine bupropion SR in combination with NP therapy, Killen and colleagues randomized adolescent smokers (n = 211) to receive eight weeks of NP therapy and nine weeks of either 150 mg/day bupropion SR or placebo pills.[27] Group skills training sessions were provided on a weekly basis. No statistically significant differences in biologically verified point prevalence abstinence were found between treatment groups at end of treatment (Week 10) or at the 26-week follow-up. At end of treatment, 28% of the NP + placebo group and 23% of the NP + bupropion SR group were abstinent. Although,

abstinence rates did not differ significantly at end of treatment, participants in the bupropion SR group with a detectable level of bupropion metabolite at Week 5 had significantly lower levels of smoking during treatment than participants without a detectable level, suggesting that bupropion SR might have aided in smoking cessation if used as directed. At 26 weeks, abstinence rates were 7% for the NP + placebo group and 8% for the NP + bupropion SR group. Analyses revealed that there was no significant difference between treatment groups in time to relapse. None of the adverse events rated as severe by those in either group were deemed truly severe by the lead study physician.

In the only multi-dose RCT of bupropion SR for adolescent smoking cessation, Muramoto and colleagues recruited 312 adolescents for a study that included weekly brief individual counseling and six weeks of either 300 mg/day bupropion SR (n = 104), 150 mg/day bupropion SR (n = 105), or placebo (n = 103).[28] At end of treatment (Week 6), there were no significant differences between groups in biologically verified 30-day prolonged abstinence. The biologically verified point prevalence abstinence rates at end of treatment were 14.5%, 10.7%, and 5.6% for those in the 300 mg/day, 150 mg/day, and placebo arms, respectively. The difference in abstinence rates for those in the 300 mg/day group versus placebo group was significant. By week 26, neither bupropion SR group had significantly higher abstinence rates than the placebo group: 13.9% in the 300 mg/day group, 3.1% in the 150 mg/day group, and 10.3% in the placebo group. There was a significant difference in the number of headache and cough between placebo and active treatment groups, with the placebo group reporting more cough than the 300 mg/day group and more headache than both active medication groups. Two serious adverse events occurred during the study. One participant in the 150 mg/day group deliberately ingested Jimson weed and was hospitalized for anticholinergic crisis and another participant in the 150 mg/day group with an undisclosed extensive history of depression and undisclosed probable eating disorder was hospitalized for intentional overdose of the study medication, other drugs, and alcohol in an apparent suicide attempt.

Finally, Gray and colleagues examined the efficacy of 300 mg/day bupropion SR and contingency management (CM).[29] In this 6-week RCT, 134 adolescent smokers were randomized to one of four groups: bupropion SR + CM (n = 37), bupropion SR + non-CM (n = 36), placebo + CM, (n = 29), and placebo + non-CM (n = 32). The primary outcome was biologically verified point prevalence abstinence measured weekly from Week 3 to Week 6, with a final follow-up at 12 weeks. Abstinence rates at end of treatment (Week 6) were 27.0% for bupropion SR + CM, 8.3% for bupropion SR + non-CM, 10.3% for placebo + CM, and 9.4% for placebo + non-CM. There was a significant difference in end of treatment abstinence rates between the bupropion SR + CM and the brupropion SR + non-CM ($p < .05$), and a marginally significant difference between the bupropion + CM group and the placebo + non-CM group, $p < .10$. At the 12-week follow-up, abstinence rates were 10.8% for bupropion SR + CM, 5.6% for bupropion SR + non-CM, 0% for placebo + CM, and 6.3% for placebo + non-CM. There were no significant differences between the groups at the 12-week follow-up, although the bupropion SR + CM group had marginally higher rates of abstinence at the 12-week follow-up compared to the placebo + CM group, $p < .10$. At least one adverse event was experienced by 57% of participants with headaches, insomnia, dream disturbances, and irritability reported by more than 20% of participants in at least one treatment group. Adverse events were more common in the active medication groups (pooled) than in the placebo (pooled) groups (64% vs. 48%, respectively); however, equal numbers of participants from active medication groups versus placebo groups discontinued medication due to adverse events and/or tolerability issues (n = 3 each). Over the course of enrollment, five participants in the active medication groups reduced from 300 mg/day to 150 mg/day.

4.2. Summary of efficacy

See Table I for efficacy data by study. End of treatment abstinence rates in the three studies that used 150 mg/day bupropion were 55%,[26] 23%[27] and 10.7%.[28] Only one of these studies reported a statistically significant difference in favor of bupropion SR at end of treatment.[26] Abstinence rates in the bupropion groups at follow-up (Week 26) for the two studies that reported these data were low (8%[27] and 3.1%[28]) and did not differ significantly from the placebo groups. The differences in abstinence rates are likely a result of differences in study protocols. Niederhofer and Huber[26] only included adolescents who were able to maintain abstinence for five days prior to inclusion in the study, thus lessening the generalizability of this study to hard to treat populations. Further, continuous abstinence (i.e., no relapse) served as the outcome measure, and, as noted previously, the definition of relapse is not consistent with that recommended by smoking cessation experts. [30] Killen and colleagues[27] combined NP with bupropion SR and the rate of abstinence in this group was similar to the NP plus placebo group. This suggests that the NP and/or group skills training may have been responsible for the higher abstinence rates than were reported in the Muramoto study.[28]

The end of treatment abstinence rates in studies that used a higher dose of bupropion SR were as follows: 31.3%,[25] 14.5%,[28] and 27% and 8.3%[29] for those in the bupropion SR + CM and bupropion SR + no CM groups, respectively. Muramoto reported a statistically significant difference between the 300 mg/day bupropion group and the placebo group at end of treatment (14.5% vs. 5.6%, respectively), but this was not maintained at 26-week follow-up.[28] The only significant differences in abstinence rates at end of treatment in Gray's 4-arm trial was between bupropion SR + CM and bupropion SR + non-CM, with the combined treatment producing the highest abstinence rates.[29]

The abstinence rates reported in the adolescent smoking cessation literature for bupropion versus placebo provide some support for the use of 300 mg/day for increased end of treatment abstinence; however, none of the treatments resulted in significantly higher abstinence rates ($p < .05$) at longer-term follow-up compared to placebo. This is not similar to adult studies that have found a significant effect of bupropion versus placebo in abstinence at 6-month follow-up or greater.[31]

One explanation for this difference is that the protocols for the adolescent studies did not follow the recommended adult dosage of 150 mg/day bupropion SR for the first three days and then an increase to 300 mg/day for seven to 12 weeks. Only two adolescent studies[26,27] provided more than six weeks of bupropion SR treatment, but both used 150 mg/day. Of the two, only Killen et al. provided longer-term follow-up data. [27] This study reported low compliance rates, rendering it difficult to ascertain if 150 mg/day bupropion SR for nine weeks is effective in treating adolescent smoking cessation, or if the lack of differences between groups was due to non-compliance. The finding that participants with detectable levels of the bupropion metabolite had significantly lower levels of smoking during treatment compared to those without a detectable level, suggests that this dose of bupropion might be efficacious if compliance rates were higher.

None of the studies with 300 mg/day bupropion SR were longer than six weeks in duration. The full dose was well tolerated by adolescent smokers and resulted in higher end of treatment abstinence than 150 mg/day bupropion SR in the only adolescent multi-dose study. However, similar to the few multi-dose studies in adults, the higher dose did not produce a better outcome at follow-up.[32,33]

Given that none of the studies that have examined the use of bupropion SR for adolescent nicotine dependence followed the dosage recommendations for adult smokers, a future study that adheres to these guidelines is warranted.

4.3. Safety/tolerability

The most common adverse events reported by adolescent smokers were similar to those reported by their adult counterparts [13] (See Table II). Of the four RCTs, two found no differences in the number of reported adverse events for those in the active medication versus the placebo group.[26,27] In Muramoto et al.'s study, the placebo group reported significantly more headache than both active medication groups and more cough than the 300 mg/day group.[28] Gray and colleagues found that headache, irritability and dream disturbances were more common in the active bupropion SR groups than in the placebo medication groups.[29]

Three of the five studies reported at least one discontinuation of medication during treatment. [25,28,29] Upadhyaya reported three participants that discontinued medication (two pregnancies and one intentional overdose of study medication).[25] Muramoto reported eight participants discontinued active medication early for the following adverse events: feeling depressed, irritable, or angry; sleep disturbance; headache; urticaria; anxiety; heart palpitations; suicide attempt; an anticholinergic crisis related to recreational drug use; and pregnancy.[28] Finally, Gray reported that three participants discontinued active medication, but did not state the adverse events that prompted bupropion SR cessation.[29] Only two studies reported whether dosage was reduced over the course of the study. One participant in the study by Upadhyaya[25] and five participants in the Gray study[29] were reduced from 300 mg/day to 150 mg/day.

Although bupropion SR was generally well tolerated by adolescent smokers, hospitalizations occurred on three occasions. One was due to the intentional ingestion of Jimson weed in combination with bupropion SR, resulting in an anticholinergic crisis.[28] The other two were hospitalizations due to intentional suicide attempts.[25,28] Most of the studies screened out any potential participant who had a previous psychiatric history or history of depressive symptoms.

4.4. Compliance rates

Three of the five studies provided compliance data, but the methods used to assess compliance varied across the three studies.[25,27,29] In Killen et al.,[27] 22% of participants reporting use of all pills on at least six weeks and 44% reporting use of all pills on two treatment weeks or less. This was the only study to measure bupropion metabolite levels. They found that at Week 5, 38% had measurable levels of the drug metabolites in their urine. Upadhyaya and colleagues[25] estimated compliance by counting the number of returned tablets. Compliance was considered to be satisfactory with the average number of missed doses ranging from 0.4 to 3.2 each week. Finally, in the Gray et al. study,[29] compliance was documented by participants in daily self-report diaries and confirmed with weekly pill counts. There was no significant difference between medication groups and placebo groups in medication adherence (85% vs. 83% of dispensed doses, respectively).

4.5. Special considerations for use in adolescent smokers

Zyban contains the same active ingredient as the antidepressant medications Wellbutrin, Wellbutrin SR, and Wellbutrin XL. In 2004, the FDA directed manufacturers to add a "black box" to the health professional label of all antidepressants warning that antidepressants increased the risk compared to placebo of suicidal thinking and suicidal behavior in

children, adolescents, and young adults in short-term studies of major depressive disorder and other psychiatric disorders.

In the RCTs with bupropion SR for smoking cessation in adolescent smokers, two adverse events were deemed to be intentional suicide attempts.[25,28] Although bupropion carries a warning of increased suicidal ideation and behavior, no RCTs have compared bupropion to placebo for the treatment of depression in children and adolescents. Thus, the manufacturers of all medications marketed as antidepressants were mandated by the FDA to provide this warning, regardless of whether RCTs were conducted on each specific antidepressant.[34]

Despite the lack of data from RCTs regarding the increased risk of suicidal thinking and behavior in children or teens taking bupropion versus placebo, any child or adolescent prescribed bupropion for smoking cessation should be carefully monitored for changes in behavior, hostility, agitation, depressed mood, and suicide-related events, including ideation, behavior, and attempted suicide.

5. Varenicline

In 2006, the United States FDA approved varenicline as a prescription-only pharmacological aid for adult smoking cessation. It is also an approved smoking cessation aid in some countries outside of the U.S. Varenicline is a selective nicotinic acetylcholine receptor partial antagonist that binds to the $\alpha_4\beta_2$ receptor subtype, thereby reducing the reinforcing effects of nicotine. Due to its mixed agonist-antagonist properties, varenicline is effective at relieving craving and withdrawal during abstinence and blocking the reinforcing effects of smoking.[35] Smokers begin varenicline a week prior to their quit date, titrating from 0.5 mg on days 1 – 3 to 0.5 mg twice a day on days 4 – 7. After the titration week, the recommended dose is 1 mg twice a day for 12 weeks. Precautions should be taken when prescribing varenicline to smokers with impaired renal function, women who are pregnant or breastfeeding, and persons under the age of 18.[13] Safety and efficacy have not been established in smokers with serious psychiatric conditions. In 2009, a black box warning was mandated by the FDA due to neuropsychiatric symptoms reported postmarket, including: changes in behavior, hostility, agitation, depressed moods, suicidal thoughts and behaviors, and attempted suicide.[5,36]

5.1. Literature on varenicline in adolescent smokers

One RCT examined the pharmacokinetics, safety and tolerability of varenicline in adolescent smokers.[37] Adolescents (age 12–16 years) who smoked at least three cigarettes per day were divided into high-body weight (>55 kg; n = 35) and low-body weight (≤ 55 kg; n = 37) groups and then were randomized to receive 14 days of the standard adult dose of varenicline, a lower dose of varenicline, or placebo in a 2:2:1 ratio. The standard and lower doses in the high-body weight group were 1 mg BID and 0.5 mg BID, respectively. The two doses for the low-body weight group were 0.5 mg BID and 0.5 mg once daily. Those receiving doses > 0.5 mg once daily underwent dose titration during the first week. There was a 4-day follow-up period at the conclusion of the 14-day active-treatment period. Although participants were not specifically asked to quit smoking, a reduction in the mean number of cigarettes smoked daily was observed over the course of the study in all active treatment groups. For those in the high-body weight group, the average numbers of cigarettes smoked per day by treatment group were similar on day 1 (mean: 8.6 – 9.6 cigarettes). At day 16, those in the standard dose varenicline group smoked a mean of 3.9 cigarettes, those in the lower dose smoked 5.1 cigarettes, while those in the placebo group smoked a mean of 7.3 cigarettes. Although the low-body weight groups also reduced their consumption from day 1 (mean: 5.6 – 7.3), the reduction in smoking was similar for the three treatment groups. Among high-body weight participants, 57.1% of the participants in

the standard and lower dose groups and 14.3% of those in the placebo groups reported an adverse event. Among the low-body weight group, adverse events were numerically greater in the varenicline groups compared to the high-body weight group, with 64.3%, 73.3%, and 12.5% of participants reporting an adverse event in the 0.5 mg BID varenicline, 0.5 mg once daily varenicline, and placebo groups, respectively. Similar to adult studies with varenicline, [35] the most common adverse events were nausea, headache, vomiting, and dizziness. Except for one case of severe nausea, all adverse events were mild or moderate and resolved during the study. Psychiatric adverse events considered to be treatment-related were abnormal dreams (n = 2 participants) and mild, transient anger (n = 1 participant). No participants discontinued medication or had their dosage reduced due do to an adverse event.

Although these preliminary results look promising, future RCTs for adolescent smoking cessation need to be conducted using the recommended 12-week dosing schedule to fully assess efficacy and tolerability in this population. Similar to bupropion SR, varenicline also includes a “black box” warning that serious neuropsychiatric events have been reported in patients taking varenicline for smoking cessation;[36] therefore, adolescents should be carefully assessed and monitored for any changes in mood and behavior.

6. Conclusion

Studies that include pharmacotherapy interventions for adolescent smoking cessation are hard to conduct. Often, researchers are faced with difficulties such as recruiting minors and obtaining informed consent, high attrition rates at both end of treatment and longer-term follow-ups, and/or a lack of medication compliance. Many study protocols have not followed the recommended dose or length of pharmacotherapy for adults, rendering it difficult to determine the true efficacy of medication for adolescent smoking cessation. This is likely due to concern of the tolerability of these medications in teens. The adverse events reported in the studies on pharmacotherapy for adolescent smoking suggest that the side effect profiles for NRT, bupropion, and varenicline are similar to those reported in adult studies. However, most of these studies did not include teens with current or past psychiatric disorders. Given the black box warnings for bupropion and varenicline, researchers need to carefully monitor adolescents for any changes in mood and/or behaviors.

When interpreting the results of each study, some caveats should be noted. One is that the measurements of self-reported and biologically verified abstinence are not consistent across studies (see Table I). For example, some studies utilized prolonged abstinence (also called sustained, continuous, or maintained) which is typically defined as complete abstinence throughout the duration of the study except for a two week “grace period” after the initial quit attempt, whereas others use a less conservative measure called point-prevalence abstinence. Point-prevalence abstinence is defined as not smoking (sometimes it is clarified ‘not even a puff’) within a consecutive number of days (usually 7 or 30 days) from the time of the assessment. In addition, some studies biologically verified abstinence using either cotinine, a metabolite of nicotine and considered a more sensitive measure of nicotine exposure, while others used expired air carbon monoxide, which has a relatively short half-life. Another consideration when interpreting the findings of these studies is that most included psychosocial treatments to varying degrees. This variation could contribute to the differences in abstinence rates across studies. Finally, given the difficulty in recruiting adolescents to smoking cessation studies and/or due to the nature of the study (i.e., smaller pilot studies), there might not have been enough statistical power to detect significant differences in studies with small sample sizes.

In summary, there is some evidence of efficacy of nicotine patch and bupropion at end of treatment, but none of the medications included in this review were efficacious in promoting

long-term smoking cessation among adolescent smokers. The one varenicline study did report reduced numbers of cigarettes in those who received varenlicine versus placebo, even though participants were not told to quit smoking or reduce cigarette consumption. This finding, along with evidence of tolerability of side effects, warrants further study of varenlicine as a potential pharmacotherapy for adolescent nicotine dependence. Given the relatively low abstinence rates for adolescent psychosocial interventions alone (9.14%)[38], and the few studies that have utilized medication protocols recommended for adult smokers, use of pharmacotherapy for adolescent smoking cessation merits continued investigation.

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Table I

Summary of studies on the efficacy of pharmacotherapies for adolescent smoking cessation

Study	Design	Length of Med Tx	Demographics	Abstinence Criteria	End of Treatment Abstinence	Follow-up Abstinence	Completion Rates
NRT							
Smith et al., 1996[14]	NR open label (n = 22) NP: 22mg/24 h for 6 wks; 11mg/24 h for last 2 wks Individual counseling and group support	8 weeks	100% White 68% female Mean age: 15.9 ± 1.2 yrs Mean CPD: 23.3 ± 5.0	7-day PP and CO < 9 ppm	13.6%	4.5% at both 3 and 6 mo f/u	86.4% completed to the 6 mo f/u
Hurt et al., 2000[15]	NR open label (n = 101) NP: 15 mg/16 h Brief counseling at participant's request at the first clinic visit	6 weeks	95.0% White 40.6% female Mean age: 16.5 ± 1.1 yrs Median CPD: 20.0	7-day PP before each visit and CO < 9 ppm	10.9%	5.0% at 6 mo f/u	70.3% completed 6 wks of NP; 57.4% completed 6 mo f/u
Hanson et al., 2003[16]	Double-blind PC RCT (n = 100) NP: If ≥ 15 CPD: 21 mg/24 h for 6 wks, 14 mg/24 h for 2 wks, 7 mg/24 h for 2 wks; if < 15 cpd: 14 mg/24 h for 6 wks and 7 mg/24 h for 4 wks CBT ≥ once a week and CM	10 weeks	86.9% White 47% female Mean age: 16.8 ± 1.5 yrs Mean CPD: 16.3 ± 4.9	7-day PP and CO < 6 ppm 30-day PP and CO < 6 ppm	7-day PP: 28.0% NP vs. 24.0% placebo, *NS* 30-day PP: 20.0% NP vs. 18.0% placebo, *NS*	No follow-up	53% completed treatment
Roddy et al., 2006[17]	Double-blind PC RCT (n = 98) NP: 15 mg/day for 2 weeks, 10 mg/day for 2 weeks, 5 mg for 2 weeks 10–15 minutes of weekly behavioral counseling	6 weeks	% female: 64% NP, 56% placebo Mean age: 14.9 yrs NP, 14.7 yrs placebo Median CO: 12.9 ppm NP, 11.8 ppm placebo	PP and CO (# of days for PP and CO cut-off for biological verification were not reported)	4 weeks: 10.2% NP vs. 4.1% placebo, significance not reported; no data for end of treatment (6 weeks)	13 weeks: 0% in both NP and placebo groups	6.1% of NP group and 10.2% completed 6 weeks of treatment
Moolchan et al., 2005[18]	Double-blind PC RCT (n = 120) 3 groups: active NP + placebo gum, active NG + placebo patch, placebo patch + placebo gum NP: 21 mg/24 h NP if weighed ≥ 100 lbs and smoked ≥ 20 CPD; if not, received 14mg/24 h	12 weeks	72.5% White 70% female Mean age: 15.2 ± 1.33 yrs Mean CPD: 18.8 ± 8.56 75% had at least 1 psychiatric diagnosis	PA with 2 week grace period after quit date 7-day PP and CO levels < 7 ppm at end of treatment and 6 mo f/u	PA: 17.7% NP vs. 2.5% placebo, $p = .043$. 6.5% NG vs. 2.5% placebo 7-day PP: 20.6% NP vs. 5% placebo, *NS* 8.7% NG vs. 5% placebo, *NS*	6 mo f/u: 20.6% NP vs. 5% (placebo), *NS* 8.7% NG vs. 5% (placebo), *NS*	41.3% of NG group, 52.9% of NP group and 40.0% of placebo group completed study

Study	Design	Length of Med Tx	Demographics	Abstinence Criteria	End of Treatment Abstinence	Follow-up Abstinence	Completion Rates
	NG: 2 mg if smoking ≤ 24 CPD or 4 mg if > 24 CPD Group CBT at each treatment visit						
Rubinstein et al., 2008[19]	Open label RCT (n = 40) Either weekly group counseling alone (control) for 8 weeks or 8 weeks of counseling + 6 weeks of NNS	6 weeks	< 50% the sample was White 54% female Mean age: 16.7 ± .99 Mean CPD: 9.9 ± 6.4	Continuous abstinence for at least 7 days and CO < 4 ppm	0% NNS + counseling vs. 11.8% control, *NS*	Abstinence data not reported for 12 week f/u; no significant difference between groups for cigarette reduction	Completed end of treatment: 83% of NNS plus counseling and 76% of control Completed 12 wk f/u: 65% of NNS plus counseling and 70% of control
Bupropion							
Upadhyaya et al., 2004[25]	NR Open label (n = 16) 300 mg/day bupropion SR[a] (if weighed less than 90 lbs, received 150 mg/day) Two 30-min individual smoking cessation counseling sessions	6 weeks	87.5% White 37.5% female Mean age: 18 yrs Mean CPD: 18.06 68.8% had comorbid ADHD	Difference in average CPD and CO between baseline and postmedication (at least 4 week trial)	31.3% quit after 4 weeks (end of treatment data was not reported)	No follow-up	9 completed ≥ 4 weeks
Niederhofer & Huber, 2004[26]	Double-blind PC RCT (n = 22) Those who were abstinent for ≥ 5 days using NRT were randomized to either 150 mg/day bupropion or placebo for 90 days Received psychosocial and behavioral treatment; hospitalized for an entire day if relapsed during treatment	90 days	Race/ethnicity not reported 50% female Mean age: 17.4 ± 0.3 yrs bupropion group, 17.1 ± 1.0 yrs placebo group CPD > 10	Time to first treatment failure: either relapse (more than 15 cigarettes over 3 days) or non-attendance at 30 and/or 90 days. Mean cumulative abstinence with CO verification at 30 and 90 days	% abstinent throughout 90 days of treatment: 55% bupropion vs. 18% placebo, p = .0014. Cumulative abstinence duration: 78.4 ± 39.6 days bupropion vs. 30.2 ± 7 19.2 placebo, *p* = 0.0042	No follow-up	Not reported
Killen et al., 2004[27]	Double-blind PC RCT (n = 211) 2 groups: NP + placebo pill and NP + 150 mg/day bupropion SR Group skills training weekly for 10 weeks	8 weeks NP 9 weeks bupropion SR or placebo	% White: 54.63% NP + placebo, 45.63% NP + bupropion SR 31% of each treatment group was female Mean age: 17.32 ± 0.80 yrs NP + placebo, 17.32 ± 0.73 yrs NP + bupropion SR Mean CPD: 15.65 ± 6.40 NP + placebo, 15.12 ± 5.33 NP + bupropion SR	End of Treatment: 7-day PP and CO < 9 ppm Week 26: 7-day PP and saliva cotinine level < 20 ng/ml	28% NP + placebo vs. 23% NP + bupropion SR, *NS*	Week 26 f/u: 7% NP + placebo vs. 8% NP + bupropion SR, *NS*	80% attended at least 8 sessions

Study	Design	Length of Med Tx	Demographics	Abstinence Criteria	End of Treatment Abstinence	Follow-up Abstinence	Completion Rates
Muramoto et al., 2007[28]	Double-blind PC RCT (n = 312) 3 groups: 150 mg/day bupropion SR, 300 mg/day bupropion SR [a], or placebo Weekly brief (10–20 min) individual therapy	6 weeks	% White: 70.9% placebo, 73.3% 150 mg, 77.9% 300 mg % female: 41.7% placebo, 53.3% 150 mg, 42.3% 300 mg Median age for all groups: 16 yrs Median CPD: 11 placebo, 10 150 mg, 12 300 mg	End of Treatment: 7-day PP and urinary cotinine ≤ 50 μg/L 30-day PA and CO level < 10 ppm at each visit and urinary cotinine ≤ 50 μg/L at Wk 2 and 6 Wk 26: 7-day PP and urinary cotinine ≤ 50 μg/L	5.6% placebo vs. 10.7% 150 mg, *NS* 5.6% placebo vs. 14.5% 300 mg, $p = .03$ No significant differences in 30-day PA	Week 26 f/u: 10.3% placebo, 3.1% 150 mg, $p = .05$ 10.3% placebo vs. 13.9% 300 mg, *NS*	Week 26 completion: 57.3% placebo, 64.8% 150 mg/day, 63.5% of 300 mg/day
Gray et al., 2011[29]	Double-blind PC RCT (n = 134) 4 groups: 300 mg/day bupropion SR[a] + contingency management (CM), 300 mg/day bupropion SR[a] + non-CM, placebo + CM, placebo + non-CM[a]	6 weeks	% White: 94.6% bupropion SR + CM, 86.1% bupropion SR + non-CM, 89.7% placebo + CM, 84.4% placebo + non-CM % female: 43.2% bupropion SR + CM, 38.9% bupropion SR+ non-CM, 37.9% placebo + CM, 46.9% placebo + non-CM Mean age: 18.4 ± 1.9 bupropion SR+ CM, 18.4 ± 1.9, bupropion SR+ non-CM, 18.1 ± 1.9 placebo + CM, 19.0 ± 1.8 placebo + non-CM Mean CPD: 11.3 ± 6.3 bupropion SR + CM, 11.5 ± 8.1 bupropion SR + non-CM, 11.2 ± 6.4 placebo + CM, 9.1 ± 4.5 placebo + non-CM	7-day PP (if reported ≤ 2 cigarettes on ≤ 2 days in a given week, considered abstinent if urinary cotinine ≤ 100 ng/ml)	27.0% bupropion SR + CM, 8.3% bupropion SR+ non-CM, 10.3% placebo + CM, 9.4% placebo + non-CM Signficant difference between bupropion SR + CM vs. bupropion SR + non-CM, $p < .05$	12-week f/u: 10.8% bupropion SR+ CM, 5.6% bupropion SR + non-CM, 0% placebo + CM, 6.3% placebo + non-CM No significant differences between groups	31% completed all treatment visits 22% completed all treatment visits + 12-week f/u

[a] 150 mg/day bupropion SR for 3 days and increased to 300mg/day bupropion SR on day 4

Notes: NRT = nicotine replacement therapy; NR = non-randomized; RCT = randomized clinical trial; PC = placebo controlled; NP = nicotine patch; NG = nicotine gum; NNS = nicotine nasal spray; CPD = cigarettes per day; PP = point prevalence abstinence; PA = prolonged abstinence; ppm = parts per million; f/u = follow-up, *NS* = not significant. NOTE. Table does not include studies that did not assess smoking cessation efficacy [7, 36]

Table II

Summary of adverse events and tolerability of pharmacotherapies for adolescent smoking cessation

Study	Adverse Events (AE)	Different from Placebo Group?*	Serious AE?	Medication reductions due to AE	Medication compliance	Discontinued medication due to AE
NP						
Smith et al., 1996[14] n = 22	82% reported ≥ 1 AE; AE with ≥ 10% occurrence: 68% skin reaction; 41% headache; 41% nausea and vomiting; 41% tiredness; 27% dizziness; 23% arm pain	NA	No	Not reported	Not reported	No
Hurt et al., 2000[15] n = 101	87% reported ≥ 1 AE; 44% upper respiratory tract infections; 43% headache; 13% nausea and/or vomiting; 12% skin reaction; 10% sleep disturbance	NA	No	Not reported	Reported NP use of 85% ± 20% of days of treatment for those who completed the 6 week tx (n = 91)	N = 5; AEs not specified
Killen et al., 2001[7] n = 92	# of participants that reported severe AE in NP group: 8 itching, 4 dizziness, 1 joint/muscle aches, 1 headache, 1 dry mouth, 1 redness # of participants reporting severe AEs in placebo group: 3 dizziness, 1 dry mouth, 1 itching	More itching in the NP group vs. placebo group	No; none deemed severe by study physician	No	All included in analysis complied with 8-hour patch use	N = 1; removed NP after experiencing nausea 1 hr after applying NP (data excluded from analysis)
Hanson et al., 2003[16] n = 100	≥ 1 AE: 97.9% in NP and 93.3% in placebo patch Active NP AEs: 64.5% itching at NP site; 62.5% sleep problems or abnormal dreams; 58.3% joint or muscle aches; 54.2% redness at NP site; 41.7% lightheadedness/dizziness; 43.8% stomachaches	More headaches in placebo group vs. active NP group	No	Not reported	Through 6 wks postquit: 84.2% active NP and 85.0% placebo. During 4-wk dose reduction: 67.2% NP and 68.5% placebo	No
Roddy et al., 2006[17] n = 98	30 AEs reported in NP group: 16 itching, 6 rash, 6 pain or paraesthesia at patch site, 2 dizziness, nausea or headache 17 AEs reported in placebo group: 7 itching, 3 rash, 4 pain or paraesthesia at patch site, 3 dizziness, nausea or headache	AEs more common in NP than placebo group; significance not reported	No	Not reported	Median # of weeks of patch therapy with counseling was 1 week	N = 2 (1 in NP group, 1 in placebo group); AEs not specified
NP and NG						
Moolchan et al., 2005[18] n = 120	Of 745 total AEs: 130 pruritus; 111 erythema; 86 headache; 67 fatigue; 63 viral infection; 43 insomnia; 32 cough; 31 nausea; 30 jaw pain; 26 anxiety; 24 sore throat; 22 hiccup; 22 dyspepsia; 18 shoulder or arm pain; 15 dizziness; 10 congestion; 10 edema; 3 constipation; 2 diarrhea; 18 “other”	Higher rates of erythema, shoulder/arm pain, and pruritus for active NP vs. placebo Higher rates of sore throat, hiccups, and pruritus for active NG vs. placebo	No	Not reported	Mean daily use of patch: 78.4% active NP + placebo gum, 82.8% active NG + placebo patch, 80.9% placebo group, *NS* Gum use during the first month: 38.5% active NG + placebo patch; 42.1% placebo gum + active NP; 50.7% placebo group Active NG group had lower compliance than placebo group, $p = .02$	Not reported
NNS						

Study	Adverse Events (AE)	Different from Placebo Group?*	Serious AE?	Medication reductions due to AE	Medication compliance	Discontinued medication due to AE
Rubinstein et al., 2008[19] n = 40	34.8% reported nasal irritation and burning; 13% reported complaints about the taste and smell 38.9% in NSS group agreed or strongly agreed that the spray had “lots of side effects”	Control did not include a placebo medication group	No	Not reported	57% stopped use of NNS after 1 week 26% assigned to NNS used spray everyday during the first week, (median = 1.14 sprays/day 43% still using by end of treatment (median = .64 sprays/day)	Not reported
Bupropion						
Upadhyaya et al., 2004[25] n = 16	# of participants reporting AE (only those reported by > 1 participant): 7 headache; 6 insomnia; 5 decreased appetite; 3 cough; 3 heartburn; 2 dizziness; 2 heart pounding/ palpitations; 2 migraine headache; 2 nausea; 2 blurred vision; 2 tremor; 2 bad taste; 2 yellow urine	NA	1 intentional overdose of study medication in apparent suicide attempt	1 reduced to 150 mg/day due to gastrointestinal AE	Average number of missed doses ranged from 0.4 to 3.2 each week	N = 6 (3 voluntarily withdrew due to AE; 2 withdrawn due to pregnancy; 1 withdrawn due to overdose of study medication in apparent suicide attempt)
Niederhofer & Huber, 2004[26] n = 22	Frequencies of AEs in bupropion group: 7.7% neurologic or psychological effects; 6.4% cardiovascular or pulmonary effects; 3.4% gastrointestinal effects; 3.1% muscular effects; 2.9% cardiac effects	No	No	Not reported	Not reported	No
Muramoto et al., 2007[28] n = 312	Reported by ≥ 4% of participants: Headache (49.5% 150 mg/day, 44.2% 300 mg/day); cough (16.2% 150 mg/day, 12.5% 300 mg/day); throat symptom/concern (17.1% 150 mg/day, 17.3% 300 mg/day); sleep disturbance (11.4% 150 mg/ day, 14.3% 300 mg/day); nausea (17.5% 150 mg/ day, 9.7% 300 mg/day)	Headache occurred more often in the placebo vs. both active bupropion SR groups Cough occurred more in the placebo group vs. 300 mg/day bupropion SR group	2 serious AEs resulting in hospitalization (150 mg/day group): 1 for anticholinergic crisis after ingestion of Jimson weed for recreational purposes; 1 for apparent suicide attempt	Not reported	Not reported	N = 8 in active bupropion SR groups (AEs were: feeling depressed, irritable or angry; sleep disturbance; headache; urticaria; anxiety; heart palpitations; suicide attempt; anticholinergic crisis related to recreational drug use; pregnancy)
Gray et al., 2011[29] n = 134	57% of participants experienced ≥ 1 AE > 20% of participants in ≥ 1 treatment group reported the following: headaches, insomnia, irritability, dream disturbances	AEs more common in bupropion SR groups (pooled) vs. placebo groups (pooled) All dream disturbances (n = 9) occurred in active bupropion SR groups	No	5 participants reduced from 300 mg/day bupropion SR to 150 bupropion SR mg/day	Participants receiving bupropion SR took 85% of dispensed doses compared to 83% in the placebo group, *NS*	N = 6 (3 in active bupropion SR groups, 3 in placebo groups); AEs not specified

Study	Adverse Events (AE)	Different from Placebo Group?*	Serious AE?	Medication reductions due to AE	Medication compliance	Discontinued medication due to AE
Bupropion SR and NP						
Killen et al., 2004[27] n = 211	# of participants that reported severe AE in the bupropion SR + NP group: 3 nausea; 2 dizziness; 1 dimness of vision; 1 skin rash; 1 confusion; 1 digestive problems; 1 headache; 12 “other.” # of participants that reported moderate AE in bupropion SR + NP group: 4 nausea; 3 skin rash; 2 headache; 1 digestive problems; 1 agitation; 1 dizziness; 12 “other”	No	No	Not reported	At Wk 5, 38% of participants in the bupropion SR + NP group had measurable levels of bupropion metabolite in urine; 22% reported using all pills on at least 6 treatment weeks; 44% reported using all pills on 2 treatment weeks or less	No
Varenicline						
Faessel et al., 2009[37] n = 72	Most frequently reported AEs in varenicline groups: nausea (mainly in females), headache, vomiting, dizziness Psychiatric AEs considered to be treatment related: abnormal dreams (2 participants) and mild, transient anger (1 participant) > 92% of AEs reported by ≥ 1 participant in any treatment group were mild in intensity % in the high body weight groups reporting ≥ 1 AE: 57.1% in both the 1 mg BID varenicline and 0.5 mg BID; 14.3% in placebo group % in the low body weight groups reporting ≥ 1 AE: 64.3% in 0.5 mg BID group, 73.3% 0.5 mg once daily group, 12.5% in placebo group AEs numerically more common in low vs. high body weight, but unrelated to dose	Yes, numerically more AEs in varenicline groups vs. placebo groups	No	None	1 participant in the low-body weight 0.5 mg once daily was discontinued because of lack of compliance and 1 in placebo withdrew consent but not reported if either were due to medication compliance	No

Notes: NP = nicotine patch; NG = nicotine gum; NSS = nicotine nasal spray; BID = twice a day; AE = adverse event(s); NA = not applicable; *NS* = not significant

*significant at $p < .05$ or lower