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Original investigation

Efficacy of Pharmacotherapy for Smoking Cessation in Adolescent Smokers: A Meta-analysis of Randomized Controlled Trials

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Abstract

Introduction: This study aimed to evaluate the efficacy of pharmacotherapy for smoking cessation among adolescent smokers by using a meta-analysis of randomized controlled trials (RCTs).

Methods: PubMed, EMBASE, and Cochrane Library were searched from the inception to January 20, 2018. We included RCTs of pharmacotherapy for smoking cessation among adolescent smokers aged less than 20 years. Data were pooled using a random-effects meta-analysis. The primary outcome measures were a smoking abstinence rate and its relative risk (RR) at the longest follow-up period in each study validated by biochemical markers.

Results: Among a total of 1035 articles searched, nine RCTs, which involved 1188 adolescent smokers aged 12–20 years with 627 in the intervention group and 561 in the control group, were included in the final analysis. In the random-effects meta-analysis of all the nine trials, pharmacotherapy showed a increased abstinence rate (RR = 1.62; 95% confidence interval [CI] = 1.08 to 2.44, I^2 = 0.0%), compared with the control group. Subgroup meta-analyses by follow-up period showed an increased abstinence rate at 4 weeks (RR = 1.87; 95% CI = 1.22 to 2.87; n = 4) and a non-significantly increased abstinence rate during the longer term follow-up periods at 8, 12, 24, and 52 weeks.

Conclusions: The current meta-analysis suggests that pharmacotherapy can be considered as an aid for smoking cessation in the short-term period among adolescent smokers. However, further large RCTs are warranted to determine its long-term efficacy and safety.

Implications: In this meta-analysis of nine RCTs with 1188 adolescent smokers aged 12–20 years, pharmacotherapy showed an increased abstinence rate, compared with the control group. In the subgroup meta-analyses by follow-up period, it showed the increased abstinence rate at 4 weeks and no efficacy on abstinence during the longer term follow-up periods up to 52 weeks. Further large RCTs are warranted to determine the long-term efficacy and safety of pharmacotherapy in adolescent smokers.

Introduction

Tobacco use harms almost every organ of the body and is the leading preventable cause for the death of more than 7 million people every year.[1,2] Quitting smoking is very difficult for most smokers because of addiction to nicotine in tobacco products: Among 70% of smokers who would like to quit, only about 3% of smokers quit on their own.[3] Fortunately, the US Public Health Service Clinical Practice Guideline and Cochrane Collaboration's Database of Systematic Reviews have reached common conclusions that several types of counseling such as individual, group, and telephone counseling and pharmacological therapies such as nicotine replacement therapy (NRT), bupropion, and varenicline are effective for smoking cessation in adult smokers based on the results of systematic reviews and meta-analyses of randomized controlled trials (RCTs).[4–6]

In the meantime, it has been reported that more than 80% of dependent adult smokers start smoking when they are under 18 years of age and that early smoking initiation increases the risk of premature death.[7,8] Therefore, it is crucial that smoking initiation should be prevented during childhood and adolescence and that adolescent smokers should stop smoking as soon as possible. However, the proven effectiveness of behavioral support and pharmacotherapy in adult smokers cannot be applied to adolescent smokers because of the differences in smoking patterns, lifestyles, and attitudes between adults and adolescents.[9] According to the Clinical Practice Guideline from the Agency for Healthcare Research and Quality (AHRQ) in 2008, counseling was recommended for smoking cessation in adolescent smokers, but pharmacotherapy was not recommended due to a lack of evidence from RCTs.[4] Since then, a meta-analysis of six RCTs reported that pharmacotherapy for smoking cessation in adolescent smokers did not show a significant effect on abstinence rates,[10] and a systematic review concluded that there was some evidence of the efficacy of pharmacotherapy at the end of treatment but not at long-term periods.[11] Also, a recent meta-analysis published in the Cochrane Database of Systematic Reviews reported that there is limited evidence of the efficacy of behavioral support and smoking cessation medication on abstinence in the long term among young people.[12]

The current study aimed to revisit the efficacy and safety of pharmacotherapy for smoking cessation in adolescent smokers by using a meta-analysis of RCTs.

Methods

Search Strategy

We searched PubMed, EMBASE, and the Cochrane Library from their inception in January, 2018. We used the following keywords related to the study subject: "smoking," "adolescent," "nicotine replacement therapy," "nicotine gum," "nicotine patch," "nicotine spray," "nicotine inhaler," "nicotine lozenge," "bupropion," "varenicline," and "pharmacological therapy." We also reviewed the bibliographies of relevant articles in order to identify additional studies.

Study Selection

We included RCTs evaluating the efficacy of pharmacotherapy for smoking cessation among adolescent smokers. Following the World Health Organization (WHO), adolescents are defined as individuals in the 10–19 years age group. However, we also included trials for adolescent smokers involving early 20s as the upper age limit. There were no language restrictions. Two of the authors (S. -K. Myung and J. -Y. Park) independently assessed the eligibility of all studies based on the predetermined selection criteria. Disagreements between evaluators were resolved by discussion.

Data Extraction

In order to summarize general characteristics of the trials included in this analysis, the following data were extracted from the individual studies: study name along with the name of the first author and the year of publication, country, characteristics of study participants (number and age range), type and duration of pharmacotherapy, abstinence verification (self-report or biochemical validation), and definition and rate of abstinence in each group (intervention vs. control).

Assessment of Methodological Quality and Risk of Bias

We determined the methodological quality of each RCT using the Jadad score.[13] Points ranged from 0 to 5 were awarded to each study. The 5-point quality scale is composed of points for randomization (described as randomized, 1 point; table of random numbers or computer-generated randomization, additional 1 point), double blind (described as double blind, 1 point; use masking such as identical placebo, additional 1 point), and follow-up (state the numbers and reasons for withdrawal in each group; 1 point) in the report of each trial. Some critics have charged that the Jadad scale is oversimplistic and can show low consistency between different raters. Especially, the Cochrane Collaboration criticized that the scale does not cover one of the most important potential biases in randomized trials, namely allocation concealment. Thus, we estimated the risk of bias based on the Cochrane Risk of Bias Tool[14] and investigated whether there is any difference in the results of methodological quality assessment between the two tools.

Main and Subgroup Analysis

In the main analysis, we estimated the efficacy of all types of pharmacological therapies for smoking cessation among adolescent smokers using the longest-term follow-up data, which are less than 6 months, stricter abstinence rates (eg, longer abstinence rate and biochemical validated abstinence rate), and have at least one abstinent person in both groups. Also, we performed subgroup meta-analysis according to various factors as follows: type of pharmacotherapy (NRT, nicotine patch, nicotine gum, nicotine nasal spray, and bupropion), follow-up period (4, 8, 12, 24, and 52 weeks), Jadad score for study quality (5 points vs. <5 points), and number of low risk of bias (≥6 items vs. <6).

Statistical Analysis

We calculated a pooled relative risk (RR) with its 95% confidence interval (CI) using four values in cells of a 2 × 2 table based on an intention-to-treat analysis in the main and subgroup meta-analyses. We used a random-effects model meta-analysis on the basis of the DerSimonian and Laird method because individual trials were performed in the different populations. For the estimation of heterogeneity across trials, we used Higgins I^2, which measures the proportion of total variation.[15] An I^2 value of more than 50% was considered to indicate substantial heterogeneity. Publication bias was evaluated using the Begg's funnel plot and Egger's test.[16] If publication bias exists, the funnel plot is asymmetrical or the p value is found to be less than .05 by Egger's test. We used Stata SE version 10.0 software package (StataCorp, College Station, TX) for statistical analysis.

Results

General Characteristics of the Included Trials

A total of 1035 articles were retrieved after searching three databases and hand-searching relevant bibliographies. After excluding 404 duplicated articles and 615 articles that did not satisfy the selection criteria mentioned in the method section, the full texts of 16 articles were reviewed. Among these, seven articles were excluded for the following reasons: not relevant topic (n = 5), no data for abstinence (n = 1), and an identical trial (n = 1). A total of nine RCTs were included in the final analysis (Figure 1).[17–25]

Table 1 shows the general characteristics of the nine RCTs included in the final analysis. The included trials were published between 2003 and 2014, spanning 11 years. They were conducted in the United States (n = 6),[17,18,20,22–24] Austria (n = 1),[19] United Kingdom (n = 1),[21] and the Netherlands (n = 1).[25] The trials involved a total of 1188 adolescent smokers with 627 in the intervention group and 561 in the control group. The age of study participants ranged between 12 and 20 years. Pharmacological therapies included nicotine patch (21, 14, and 7 mg/day; 21 or 14 mg/day; 15, 10, and 5 mg/day; n = 5),[17,18,20,21,25] nicotine gum (2 or 4 mg/day; n = 1),[20] bupropion (150 or 300 mg/day; n = 4),[18,19,22,24] and nicotine nasal spray (whenever participants had strong cravings for a cigarette but not to exceed 40 mg/day; n = 1).[23] The duration of treatment and the longest follow-up period ranged between 6 and 12 weeks and between 10 weeks and 12 months. Except for Rubinstein et al.'s trial[23] with counseling only, all the remaining trials used placebos as controls. Counseling for smoking cessation was provided for both the intervention and control groups in all trials. For abstinence verification, Roddy et al.'s trial[21] used only exhaled carbon monoxide levels, whereas the remaining ones confirmed self-reported abstinence by using expired-air carbon monoxide levels less than or equal to 4, 5, 6, or 10 ppm, salivary cotinine levels less than or equal to 1 ng/mL or less than 20 ng/mL, or urinary cotinine levels less than or equal to 50 µg/L or 100 ng/mL. The abstinence rates in the intervention group ranged from 0% to 54.6% and those in the control group did from 2.5% to 18.2 % at 4–26 weeks.

Methodological Quality and Risk of Bias of the Included Trials

The Jadad score for the assessment of the methodological quality of the included trials showed 3 points in one trial,[23] 4 points in five trials,[17–20,24] and 5 points in three trials[21,22,25] (Supplementary Table 1); its mean across trials was 4.2. Also, as shown in Supplementary Table 2, the number of low risk of bias items based on the Cochrane Risk of Bias Tool was five in four trials,[17,19,20,24] six in two,[18,23] seven in three trials[21,22,25]; its mean across trials was 5.9.

Overall Efficacy of Pharmacotherapy for Smoking Cessation

In the random-effects meta-analysis of all the included RCTs, when based on the longest-term follow-up data in each study, pharmacotherapy increased a smoking abstinence rate (RR = 1.62; 95% CI = 1.08 to 2.44; I^2 = 0.0%; n = 9), compared with the control group (Figure 2). Smoking abstinence rates in the intervention group and the control group were 18.2% (95% CI = 15.2% to 21.2%) and 9.7% (95% CI = 7.3% to 12.0%) at 4 weeks (n = 4), 17.0% (95% CI = 13.3% to 20.8%) and 14.7% (95% CI = 11.1% to 18.3%) at 8 weeks (n = 3), 22.9% (95% CI = 9.2% to 36.6%) and 17.5% (95% CI = 3.4% to 31.5%) at 12 weeks (n = 3), 6.6% (95% CI = 4.7% to 8.5%) and 5.2% (95% CI = 3.5% to 6.9%) at 24 weeks (n = 3), and 4.4% (95% CI = 1.0% to 7.9%) and 6.6% (95% CI = 2.2% to 10.9%) at 52 weeks (n = 1), respectively (Supplementary Table 3).

Subgroup Meta-analysis by Various Factors

Table 2 shows the effects of pharmacotherapy for smoking cessation in adolescent smokers in the subgroup meta-analysis by various factors. In the subgroup meta-analysis by type of pharmacotherapy,

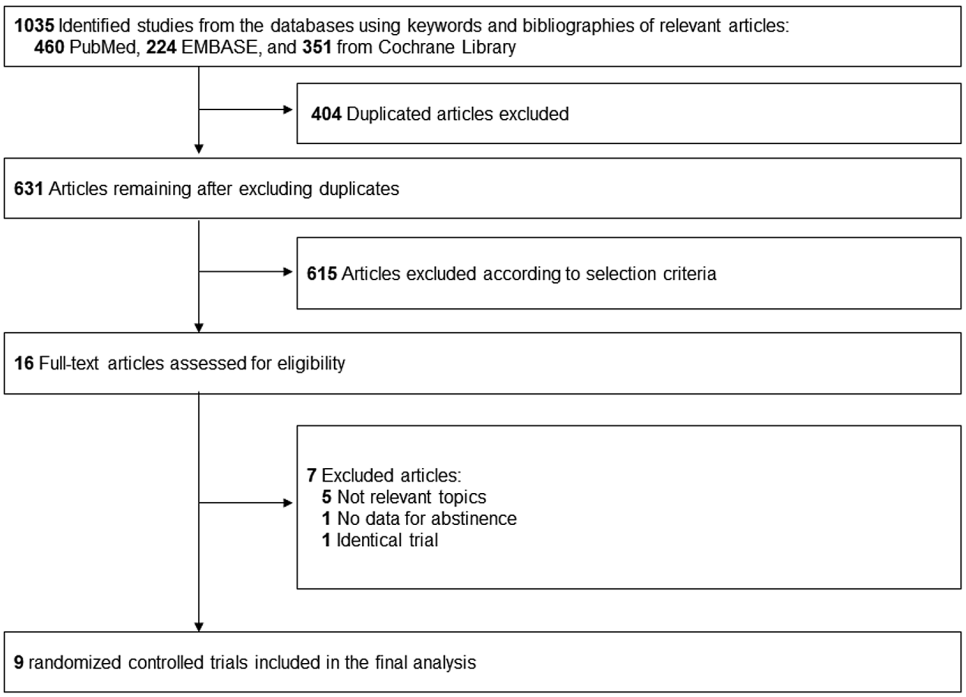

Figure 1. Flow diagram of identification of relevant trials.

Table 1. Characteristics of Randomized Controlled Trials of Pharmacological Therapy for Smoking Cessation in Adolescent Smokers Included in the Final Analysis ($n = 9$)

Study	Country	Participants	Type and duration of pharmacotherapy (longest follow-up period)	Abstinence verification	Abstinence definition	
					Abstinence rate in intervention group (%)	Abstinence rate in control group (%)
Hanson et al., 2003[17]	United States	100 young smokers aged 13–19 y who smoked at least 10 CPD for at least 6 mo	Nicotine patch (21, 14, and 7 mg/d) vs. placebo for 10 wk (10 wk)	Self-reported abstinence confirmed by expired-air CO levels ≤5 ppm	30-d point prevalence abstinence at 10 wk 10/50 (20)	9/50 (18)
Killen et al., 2004[18]	United States	211 adolescent smokers aged 15–18 y who smoked at least 10 CPD for at least 6 mo	Nicotine patch (21, 14, and 7 mg/d) plus bupropion (150 mg/d) vs. nicotine patch (21, 14, and 7 mg/d) plus placebo for 8 wk (26 wk)	Self-reported abstinence confirmed by salivary cotinine levels <20 ng/mL	7-d point prevalence abstinence at 26 wk 5/103(4.9)	5/108(4.6)
Niederhofer et al., 2004[19]	Austria	22 adolescent smokers aged 16–19 y	Bupropion (150 mg/d) vs. placebo for 90 d (90 d)	Self-reported abstinence confirmed by breath CO levels	Continuous abstinence at 90 d 6/11 (54.6)	2/11 (18.2)
Moolchan et al., 2005[20]	United States	120 adolescent smokers aged 13–17 y who smoked >10 CPD for at least 6 mo	Nicotine patch (21 or 14 mg/d) or nicotine gum (2 or 4 mg) vs. placebo for 12 wk (26 wk)	Self-reported abstinence confirmed by expired-air CO levels ≤6 ppm	Prolonged abstinence at 3 mo 9/80 (11.3)	1/40 (2.5)
Roddy et al., 2006[21]	United Kingdom	98 young smokers aged 14–20 y who were daily smokers	Nicotine patch (15, 10, and 5 mg/d) vs. placebo for 6 wk (13 wk)	Exhaled CO (levels not specified)	Point abstinence at 4 wk 5/49 (10.2)	2/49 (4.1)
Muramoto et al., 2007[22]	United States	207 adolescent smokers aged 14–17 y who smoked six or more CPD	Bupropion SR (300 mg/d) vs. placebo for 6 wk (26 wk)	Self-reported abstinence confirmed by exhaled CO levels ≤10 ppm or urinary cotinine levels ≤50 µg/L	7-d point prevalence abstinence at 6 wk confirmed by urinary cotinine levels 12/104 (11.5)	5/103 (4.9)
Rubinstein et al., 2008[23]	United States	39 adolescent smokers aged 15–18 y who smoked five or more CPD for at least 6 mo	Nicotine nasal spray vs. counseling only for 12 wk (12 wk)	Self-reported abstinence validated by expired-air CO levels <4 ppm	7-d point prevalence abstinence at 8 wk 0/22 (0)	2/17 (11.8)
Gray et al., 2011[24]	United States	134 adolescent smokers aged 12–21 y who smoked at least five CPD	Bupropion SR (300 mg/d) with CM and Bupropion SR with non-CM vs. placebo with CM and placebo with non-CM for 6 wk (12 wk)	Self-reported abstinence confirmed by urinary cotinine ≤100 ng/mL	7-d point prevalence abstinence at 12 wk 6/73 (8.2)	2/61 (3.3)
Scherphof et al., 2014[25]	The Netherlands	257 adolescent smokers aged 12–18 y who smoked at least seven CPD	Nicotine patch vs. placebo patch for 6 or 9 wk (12 mo)	Self-reported abstinence validated by salivary cotinine levels ≤1 ng/mL	30-d point prevalence abstinence at 6 mo 11/135(8.2)	7/122 (5.7)

Abbreviations: CM = contingency management; CO = carbon monoxide; CPD = cigarettes per day; SR = sustained release.

Table 2. Efficacy of Pharmacological Therapy for Smoking Cessation in Adolescent Smokers in the Subgroup Meta-analysis by Various Factors

Category	No. of trials	Summary RR (95 % CI)	Heterogeneity, I^2 (%)
All	9	1.62 (1.08 to 2.44)	0.0
Type of pharmacological therapy			
Nicotine replacement therapy	5	1.38 (0.79 to 2.42)	4.5
Nicotine patch	4	1.54 (0.87 to 2.74)	5.9
Nicotine gum	1	2.81 (0.28 to 24.09)	n.a.
Nicotine nasal spray	1	0.16 (0.01 to 3.06)	n.a.
Bupropion	4	2.03 (1.09 to 3.77)	0.0
Follow-up period			
4 wk	4	1.87 (1.22 to 2.87)	0.0
8 wk	3	1.15 (0.64 to 2.06)	14.0
12 wk	3	1.72 (0.72 to 4.10)	28.3
24 wk	3	1.34 (0.75 to 2.42)	0.0
52 wk	1	0.68 (0.24 to 1.90)	n.a.
Jadad score for study quality			
5 points	3	1.89 (1.01 to 3.52)	0.0
<5 points	6	1.49 (0.83 to 2.68)	10.8
No. of low risk of bias			
5	4	1.73 (0.94 to 3.18)	0.0
6	2	0.66 (0.13 to 3.33)	27.6
7	3	1.89 (1.01 to 3.52)	0.0

Abbreviations: CI = confidence interval; n.a. = not applicable; RR = relative risk.

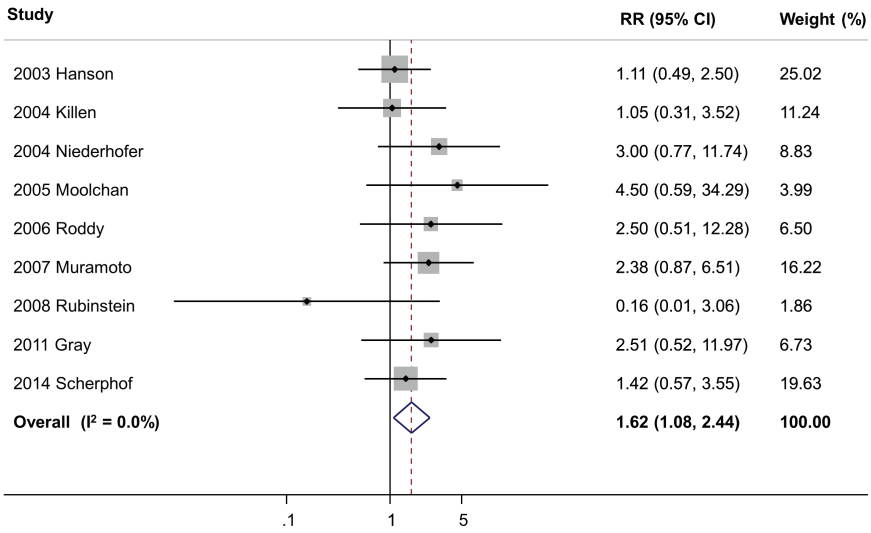

Figure 2. Efficacy of pharmacotherapy for smoking cessation among adolescent smokers in a random-effects model meta-analysis of randomized controlled trials ($n = 9$). Abbreviations: CI = confidence interval; RR = relative risk.

only the use of bupropion was associated with an increased abstinence rate (RR = 1.62; 95% CI = 1.08 to 2.44; $I^2 = 0.0\%$; $n = 4$), whereas other types such as NRT, nicotine patch, nicotine gum, and nicotine nasal spray had no effect on smoking abstinence.

Also, the subgroup meta-analysis by follow-up period showed an increased abstinence only during the short-term follow-up (4 weeks; RR = 1.87; 95% CI = 1.22 to 2.87; $I^2 = 0.0\%$; $n = 4$), whereas there was no effect during the longer term follow-up periods at 8, 12, 24, and 52 weeks.

Regarding the methodological quality of trials, the higher quality trials given 5 points based on the Jadad scale showed an increased abstinence (RR = 1.89; 95% CI = 1.01 to 3.52; $I^2 = 0.0\%$; $n = 3$), whereas no effect was found in the lower quality trials given less than 5 points. Similarly, the trials with seven low risk of bias items had an increased abstinence (RR = 1.89; 95% CI = 1.01 to 3.52; $I^2 = 0.0\%$; $n = 3$), whereas the trials with five and six low risk of bias items had no effect.

As shown in Supplementary Figure 1, publication bias was observed in the included trials: the funnel plot is asymmetrical, and p value for bias was .037.

Adverse Events

Supplementary Table 4 shows adverse events and serious adverse events reported in each trial. Three trials[20,21,25] reported that minor adverse events such as headache, pruritus or itching, erythema, sore throat, hiccups, shoulder or arm pain, abnormal dreams, and muscle pain were significantly more common in the pharmacological therapies than in the control group, whereas two trials[17,22] did that

headache or headache with cough was more common in the placebo group than in the bupropion group. The remaining three trials[18,19,24] suggested that there were no significant differences in the occurrence of adverse events.

Common adverse events related with the use of nicotine patch were itching (n = 16/49, 32.7%[21] and n = 31/48, 64.5%[17]), rash (n = 6/49, 12.2%[21] and n = 26/48, 54.2%[17]), sleep problems or abnormal dreams (n = 30/48, 62.5%[17]), joint or muscle pain (n = 28/48, 58.3%[17]), pain at nicotine patch site (n = 6/49, 12.2%[21]), and headache/dizziness (n = 2/49, 4%[21] and n = 20/48, 41.7%[17]). Those related with bupropion treatment included headache, irritability, insomnia, and dream disturbances. However, there were no significant differences between the intervention and control groups except for dream disturbances in one trial.[24]

Two serious adverse events and one medically important event during the study were reported in only one trial[22]: A 16-year-old boy in the bupropion 150 mg/day group was hospitalized for ingesting Jimson weed (Datura innoxia) for recreational purposes; a 16-year-old girl in the same group was hospitalized for a suicide attempt with the use of overdose of bupropion medication and other drugs; and a 16-year-old girl in the placebo group became pregnant shortly after her week 1 visit. Otherwise, no other serious adverse events were reported.

Discussion

In this meta-analysis of RCTs using the longest-term follow-up data less than 6 months in each trial based on an intention-to-treat analysis, we found that overall, pharmacotherapy had its efficacy on smoking cessation among adolescent smokers. However, subgroup meta-analysis showed that this efficacy was found only in the trials of bupropion, short-term follow-up of 4 weeks, higher quality with 5 points of the Jadad score, and seven items of low risk of bias.

As previously mentioned in the introduction section, although pharmacotherapy has proven its efficacy on smoking cessation in adult smokers and has been routinely used, the Clinical Practice Guideline from the AHRQ in 2008 recommended only counseling for smoking cessation in adolescent smokers because of a lack of evidence of the efficacy and safety of pharmacological therapy in those population from RCTs. Since then, several meta-analyses[10,12] and systematic review of RCTs[11] reported limited evidence of the efficacy of behavioral support as well as pharmacological therapy on smoking cessation in the long term among young people.

Our findings are different from those of our previous meta-analysis[10] published in 2011. Our previous one concluded that there was no significant effect of pharmacological therapy for smoking cessation among adolescent smokers based on the results from the meta-analysis of six RCTs (RR = 1.38; 95% CI = 0.92 to 2.07). On the other hand, the current meta-analysis of a total of nine RCTs with additional three RCTs showed an increased abstinence (RR = 1.62; 95% CI = 1.08 to 2.44). This difference is considered to be attributable to the addition of two additional published RCTs involving bupropion treatment. The current subgroup meta-analysis by type of NRT showed no significant changes in the number of the included RCTs and no significant efficacy like the previous meta-analysis. However, the current subgroup meta-analysis for bupropion showed its efficacy on smoking cessation in four RCTs (RR = 2.03; 95% CI = 1.09 to 3.77), whereas the previous meta-analysis showed no efficacy in two RCTs (RR = 1.24; 95% CI = 0.63 to 2.45).

Our findings are similar to those from the previous systematic review[11] in that there was some evidence of the efficacy of pharmacotherapy at the end of treatment but not at long-term periods. However, it did not provide meta-analytic findings on the efficacy of pharmacotherapy. Also, the recent meta-analysis published in the Cochrane Library in 2017 reported no clear evidence for the efficacy of pharmacotherapy for smoking cessation among young people. However, it included only three RCTs on NRT and one RCT on bupropion in the meta-analysis, whereas our study did a total of nine RCTs including those four RCTs. The reasons for exclusion of the five RCTs that were included in our meta-analysis were unclear and not presented in the article.

In our previous meta-analysis, we mentioned that no significant effect of pharmacotherapy on smoking cessation among adolescent smokers might be related with the low statistical power due to a small sample size.[10] Also, we suggested that at least 2920 participants are necessary to show a statistically significant difference between the intervention and control groups with a power of 80%, an α of 0.05, and the estimated smoking abstinence rates of 11.5% in the intervention group and 8.4% in the control group in the meta-analysis based on a sample-size calculation. However, although the current study included only a total of 1188 study participants, a significant difference between the two groups was observed. It might be mainly attributable to the inclusion of trials[19,24] with a larger discrepancy in abstinence rates between the intervention and control groups.

In our study, pharmacotherapy for smoking cessation in adolescent smokers showed minor adverse events such as headache, nausea, itching, and sleep problems similar to those in adult smokers. Overall, there were no significant differences in adverse events between the intervention and control groups. More important, out of nine RCTs, only one trial reported two serious adverse events in the bupropion group and one medically important event in the placebo group. However, there was no evidence that those events were directly related to the bupropion medication used in the trial.

Our study has several limitations. First, although we found that pharmacotherapy had a significant increased abstinence rate in the meta-analysis by using the longest-term follow-up data in each trial, no significant effect was observed in the longer term periods more than 4 weeks. Further long-term RCTs are warranted to confirm the long-term efficacy of pharmacotherapy in adolescent smokers. Second, there was publication bias in the main analysis. Thus, the efficacy of pharmacotherapy might be overestimated. Last, we were unable to evaluate whether or not the efficacy of pharmacotherapy for smoking cessation is different between boys and girls because none of the trials reported abstinence rates and adverse events separately in each gender.

Conclusion

The current meta-analysis found that pharmacotherapy for smoking cessation among adolescent smokers had a statistically significantly increased abstinence rate in the short-term period of 4 weeks and a nonstatistically significant increase in the longer term periods up to 24 weeks. Among the different types of pharmacotherapy, bupropion only showed a significant efficacy on smoking cessation. Furthermore, even though several minor adverse events were reported in each trial, there were no significant differences in the frequency of adverse events between the intervention and control groups. Also, there was no evidence that two serious adverse events and one medically important event reported in the only trial were directly related to the medication. Further large RCTs with higher quality and low risk of bias are warranted to determine the long-term efficacy and safety of pharmacotherapy for smoking cessation among adolescent smokers.

Supplementary Material

Supplementary data are available at *Nicotine and Tobacco Research* online.

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Declaration of Interests

None declared.

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S. -K. Myung and J. -Y. Park contributed equally to this work as co-first authors.

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