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# Pharmacotherapy Safety and Efficacy in Adolescent Smoking Cessation

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# **Pharmacotherapy Safety and Efficacy in Adolescent Smoking Cessation.**

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## ABSTRACT

**OBJECTIVE:** To determine whether or not pharmacotherapy is a safe and effective treatment option for smoking cessation in adolescents

**STUDY DESIGN:** Review of three English language primary studies published in 2007, 2008, and 2009

**DATA SOURCES:** Two Randomized double-blind placebo-controlled trials and one Randomized Control Study comparing pharmacotherapy, including nicotine nasal spray (NNS), Bupropion hydrochloride, and Varenline, at different doses to placebo, therapy, or both, were found using MEDLINE, OVID, PUBMED, and COCHRANE databases.

**OUTCOME MEASURED:** Measurement of efficacy included self reported reduction in number of cigarettes smoked per day, confirmed by reduction in exhaled carbon monoxide and saliva or urine cotinine levels; seven-day point prevalence of abstinence; and self-rated addiction scale (1-100%). Measurement of safety included reported incidence of side effects; degree of agreement with statement about side effects (“Strongly agree” to “strongly disagree”)

**RESULTS:** Muramoto et al. showed that Bupropion hydrochloride significantly increased the seven day point prevalence abstinence at six weeks compared to placebo (p-value = .03), but did not significantly affect the seven day point prevalence at 26 weeks (p-value = .28). The Faessel study highlighted a higher decrease in number of cigarettes smoked per day, but failed to include any p-values. Rubenstein, et al. failed to show any statistical difference between the arm that received only counseling and the arm that received counseling and NNS.

**CONCLUSION:** Of the three interventions used in the randomized control studies included in this review, only Bupropion hydrochloride demonstrated significant safety and efficacy as therapy for smoking cessation in adolescents. High relapse rate, however, necessitates that a longer trial of Bupropion be investigated in the future.

**KEYWORDS:** Smoking Cessation, Adolescents, Chantix, Varenline, Bupropion hydrochloride, Zyban, Pharmacotherapy

## **Introduction**

Tobacco use is the number one preventable contributor to serious morbidity and mortality in the United States. Of particular public health concern is the number of adolescent cigarette smokers. Over 90% of adult habitual tobacco users picked up the habit before their eighteenth birthday. Each year, nearly 1.5 million adolescents initiate smoking and 416,000 becoming daily smokers. In addition to an increased risk for heart disease, cancer, stroke, and associated premature mortality, adolescent smokers disproportionately develop a host of more immediate health consequences. These include reduced growth of lung function, persistent cough, shortness of breath, poorer overall health, fitness, and endurance, greater involvement in high risk behaviors, and poorer mental health. Despite increased awareness of these dangers, cigarette smoking among high school students has remained stable since 2003.<sup>1</sup>

Components of cigarettes and other tobacco products not only contain several harmful carcinogenic substances, but also those that stimulate receptors in the brain that contribute to addiction. In adolescents, signs and symptoms of addiction can present in as little as a few days following initiation of occasional tobacco use.<sup>2</sup> More than a quarter of children and adolescents who tried their first tobacco product before the age of 18 develop dependency by the same age.<sup>1</sup> Despite a high percentage of adolescent smokers who wish to quit, adolescents have the highest cessation attempt failure compared to any other population. Even with the help of non-pharmacologic interventions, the increase in successful cessation is statistically insignificant.<sup>3</sup>

Current first line medications for smoking cessation in adults include nicotine replacement therapies (transdermal patch, nasal spray, inhaler, gum), Bupropion hydrochloride (Zyban), and Varenline (Chantix). First line agents have been shown to double the success rate of quitting in this population. Norytptiline and clonidine are considered second line agents and

are not FDA approved for this purpose. Neither first nor second line agents, however, are FDA approved for the use in adolescent populations. Since most regular users start before age 18 and quickly become addicted, and the longer a person smokes the greater the risk of morbidity and premature mortality, it seems imperative that more intensive treatments for tobacco cessation be evaluated for the adolescent population.

### **Objective**

The objective of this systematic review is to determine whether or not pharmacotherapy is a safe and effective treatment option for smoking cessation in adolescents.

### **Methods**

A search for randomized control trials was conducted by the author via MEDLINE, OVID, PUBMED, and COCHRANE databases. Keywords utilized included Smoking Cessation, Adolescents, Chantix, Varenline, Bupropion hydrochloride, Zyban, Pharmacotherapy, and Nicotine Replacement Therapy (NRT). Only studies published in English in peer reviewed journals were considered for inclusion. In addition, a search was conducted in order to ensure that no Meta Analysis or Systematic Review of the topic of focus existed.

The three studies included in this review are randomized control trials that compare the use of different medications (Bupropion, Varenline, and Nicotine Nasal Spray) for smoking cessation in adolescents to either a placebo, therapy, or a combination of the two. All subjects were between the ages of twelve and eighteen, smoked at least three cigarettes a day, were not currently (or recently) on another pharmacologic agent for smoking cessation, and were otherwise healthy. More specific inclusion and exclusion criteria can be found in **Table 1**. Results of these studies were evaluated based on patient oriented outcomes. Reported statistics included p-value, RBI, ABI, NNT, mean change from baseline.

**Table 1: Demographics of Included Studies**

Characteristics of Studies Included in Systematic Review of Safety and Efficacy of Pharmacotherapy for Adolescent Smoking Cessation							
Study	Type	# of Pts	Age in yrs	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Faessel, USA, 2009	RCT double-blind	42	12-16	Smoke $\geq 3$ cigarettes/d Otherwise healthy	Regular EtOH/illicit drug use Crcl $< 80$ mL/min Donation $> 280$ mL blood within last 56 d Sensitivity to heparin or hx of HIT Use of meds other than acetaminophen in last 7 days Tx with investigational drug in last 30 days	1	Varenline 1 mg BID x 14 days
Rubinstein, USA, 2008	RCT	40	15-18	Smoke $\geq 5$ cigarettes/d for $\geq 5$ months Want to quit smoking	Previous/current use of nicotine replacement therapy Use of Bupropion hydrochloride in last 30 days	8	Nicotine Nasal Spray 1mg (4 sprays) PRN (not to exceed 40/d) x 6 wks w/ counseling before (2 wks), and during
Muramoto, USA, 2007	RCT double-blind	207	14-17	Smoke $\leq 6$ cigarettes/d Exhaled CO $\geq 10$ ppm At least 2 previous quit attempts	Current use of other Tobacco products, or smoking cessation therapies Current ADHD, depression, or other psychiatric disorder Use of psychoactive drug in last 4 weeks Significant CVD dz or risk of seizure Pregnancy or refusal to use contraceptives	92	SR Bupropion 300mg/d with brief counseling for 6 weeks

## **Outcomes Measured**

The efficacy of the tobacco cessation treatment was determined by reduction in use and desire to use tobacco products. Muramoto et al. focused on successful cessation of cigarette smoking. In this study, the seven day point prevalence of abstinence was calculated at various times throughout the study based on self reported cessation. Self report was confirmed by either exhaled carbon monoxide or urine cotinine levels. An exhaled carbon monoxide level of less than 10 ppm and a urine cotinine level of less than or equal to 50 microg/L are consistent with at least seven days of abstinence. Faessel et al. focused on reduction of the average number of cigarettes smoked per day by the end of the trial as measurement of efficacy of Varencline. Rubenstein et al. also measured the mean reduction of cigarettes smoked per day, but in addition used a self reported scale of addiction as measurement of the efficacy of nicotine nasal spray.

Safety of the different pharmacotherapy was determined by the number of subjects reporting side effects with the intervention of interest compared to the number of subjects reporting side effects on the placebo. No placebo was used in the Nicotine Nasal Spray trial, however, and therefore no comparison was possible.

## **Results**

All studies analyzed in this review were randomized control trials, two of which were double-blind, focused on patient oriented outcomes in an adolescent population of cigarette smokers, smoking at least three cigarettes per day. Each study met the inclusion criteria as listed above.

In the Muramoto study, participants were split into three groups, one that received a placebo, one that received 150mg Bupropion hydrochloride, and one that received 300mg Bupropion hydrochloride. All groups also received counseling for the six weeks during which

the medication was given. The most significant difference was found between the group that received the placebo and the group that received the higher dose of Bupropion hydrochloride.<sup>4</sup> For the purpose of this paper, only the dichotomous data from these two groups was analyzed. **Table 2** shows the seven day point prevalence abstinence at six and twenty-six weeks after the target quit date. At six weeks, 5 out of 89 of those in the placebo group and 12 out of 83 in the treatment group, had not smoked a cigarette in seven days (confirmed by a urine cotinine level of less than or equal to 50 microg/L). From this data, the absolute benefit increase was calculated to be 8.7% and number of patients needed to treat with bupropion hydrochloride in order for one adolescent to be abstinent from cigarettes for at least seven days was calculated to be twelve (p-value = .03). At twenty-six weeks, 6 of the remaining 58 subjects from the placebo group and 9 of the remaining 65 subjects from the 300mg Bupropion hydrochloride group, reported abstinence of seven days. This report was confirmed with a measurement of exhaled carbon monoxide of less than 10pmm. The ABI was calculated to be 3.2% with a NNT of 32 patients (p-value = .28).

**Table 2: Seven Day Point Prevalence Abstinence (Muramoto, 2007)**

	Placebo	Bupropion hydrochloride 300mg	P-value	CER	EER	RBI	ABI	NNT
6 wks* confirmed by urine cotinine levels	5 of 89	12 of 83	0.03	5.60%	14.30%	154.40%	8.70%	12 pts
26 wks* confirmed by exhaled CO	6 of 58	9 of 65	0.28	10.60%	13.80%	30.20%	3.20%	32 pts

\*Weeks following TQD (Target quit date)



Bupropion hydrochloride safety was determined by the incidence of the most common side effect reported: headache. While approximately 54% of the placebo group reported experiencing a headache during or immediately following administration of bupropion hydrochloride, only 44% of those receiving bupropion 300mg reported the same. The number needed to harm was therefore negative (-10), indicating that for every ten patients not treated with bupropion, one patient will experience a headache.

**Table 3: Incidence of Side Effects**

Intervention	SE	CER	EER	RRI	ARI	NNH
Varenicline	Any	14.29%	57.14%	300%	42.85%	3 pts
Bupropion hydrochloride	Headache	54.40%	44.20%	-18.80%	-10.20%	-10 pts

In the Faessel study, participants were broken up into a total of six groups. The subjects were split into two groups based on weight, and then into three subgroups that either received a low dose of varenline (.5 mg QD for the first week, .5 mg BID for the second week), a high dose of varenline (.5 mg BID for the first week, 1 mg BID for the second week), or a placebo. The high-body-weight group (>55 k) consisted of 35 subjects (65.7% male; 77.1% white; mean age, 15.2 years). For the purpose of this paper, the main focus is on the difference in data between the three subgroups from the high dose group. The data regarding the efficacy of the intervention was presented with continuous data. **Table 4** includes this data, as well as the calculations from the data converted into dichotomous form. The reduction in the average number of cigarettes smoked 16 days following initiation of pharmacotherapy in the high dose, low dose, and placebo subgroups were 58.9%, 44.4%, and 13.1%, respectively. The absolute benefit increase in the high-dose subgroup was 45.8%, with 3 patients needing to be treated with the higher dose varenline in order for one adolescent to reduce the number of cigarettes smoked

per day. In the low-dose group, ABI was 31.3%, with 4 patients needed to be treated. The study did not include any p-values.

**Table 4: Reduction in CPD with Varencline Therapy (Faessel, 2009)**

	Baseline	16 days	Reduction
Placebo	8.4	7.3	13.1%
Varencline (high dose)	9.5	3.9	58.9%
Varencline (low dose)	9	5.1	44.4%

CER	EER	RBI	ABI	NNT
13.1%	58.9%	77.8%	45.8%	3 pts
13.1%	44.4%	70.5%	31.3%	4 pts

Safety of the before mentioned intervention was addressed by number of patients reporting adverse events (AEs) and severity rating of such events. AEs were reported by 57.1% of subjects in both the high- and low-dose varencline subgroups and by 14.3% of subjects in the placebo group. The most common AEs were nausea, headache, vomiting, and dizziness. Of the AEs reported by at least one subject in any treatment group, 92% were mild in intensity.<sup>5</sup> Absolute risk increase in terms of these adverse events was determined to be 42.85%, with only 3 patients needing to be treated in order for at least one AE to occur.

The Rubenstein study was a randomized, open-label, 12-week trial, including adolescent smokers who were assigned to receive either weekly counseling alone for 8 weeks or 8 weeks of counseling along with 6 weeks of nicotine nasal spray (NNS). Since the intervention being tested was delivered via nasal spray and not a pill, no placebo was used. Therefore, the study was not blind. Of the original 40 participants, 15 of 23 in the NNS and counseling group, and 12 of 17 in the counseling alone group completed the study, including follow-up.

The primary outcome measured was self-reported continuous abstinence for at least 7 days, validated by a CO concentration of less than 4 ppm. An intention to treat analysis

was used to determine abstinence such that participants who did not complete the study were considered to still be smoking.<sup>6</sup> At 12 weeks following initiation of counseling, however, no subjects from either group had abstained from tobacco use. The mean reduction in cigarettes smoked per day in the group receiving both the NNS and counseling and the counseling only group was found to be 42% and 32%, respectively (p-value = .61). Similarly, all other measurement of efficacy of the NNS, including cravings, withdrawal, and self-rated addiction scale, failed to show statistical significance at twelve weeks (p-values .49-.91).

**Table 5: Nicotine Nasal Spray**

	p-value	CER	EER	RBI	ABI	NNT
CPD	0.61	32.0%	42.0%	31.3%	10.0%	10 pts
Cotinine	0.16	17.6%	-30.9%	-276%	-48.5%	-3 pts
Addiction	0.83	35.8%	18.8%	-47.5%	-17%	-6 pts

Addiction: self report based on scale of 1-100 (1 = No addiction)

CPD: Cigarettes per day (confirmed by exhaled CO < 4ppm)

Safety of NNS in the adolescent population was determined by ratings of adverse effects. 38.9% of participants either “agreed” or “strongly agreed” with the statement “The spray had lots of adverse effects”. The statistical significance of the incidence of such effects cannot be determined since no placebo arm existed for comparison.

## **Discussion**

All pharmacotherapy options discussed in this review have been proven to be safe and effective in aiding adults in tobacco use cessation. Few studies, however, have addressed these interventions in the adolescent population.

Overall limitations of these studies were largely due to problems related to the population being studied. To begin with, it is illegal for minors to purchase cigarettes.

Also, because the body is still undergoing significant growth and development during adolescence, more potential adverse effects of pharmacotherapy exist in this population. These adverse events can be related to immaturity of organ systems involved in metabolism of medication and that of the target organ of the medication, the brain, in addition to potentially halting or altering further growth and development. Since the subjects in these studies were minors, it was necessary to obtain informed consent from both the subjects and the subjects' parents. The stigma associated with committing illegal activity in addition to the potential risk of pharmacotherapy, greatly limits the size of the population willing to participate in these studies. The smaller the population, the more likely it is that any differences in outcome between the group that received the intervention and the group that did not are due to coincidence. With the exception of the Muramoto study, the studies included in this review did not include a large enough population for the results to have significance.

The Rubenstein study, which investigated NNS as the intervention, originally included only 40 subjects, only 27 of whom completed the study with follow-up. Furthermore, selection bias was created by offering monetary incentive to participate in the study, which may have also contributed to lack of motivation to quit, and therefore a lack of compliance. Poor compliance, as noted by 43% use of the NNS by the end of treatment despite continued tobacco use, is also attributed to the high incidence of adverse effects.<sup>6</sup> In addition, the lack of a placebo arm of the study could have contributed to a measurement bias. Subjects receiving the NNS may have felt compelled to report what they thought to be a more socially desirable response. The absence of a placebo also makes it impossible to determine whether the adverse effects were due to the delivery route of the nicotine, the

nicotine itself, or bias. The study ultimately concluded that due to the intolerability of side effects, NNS was not an efficacious intervention for smoking cessation in the population studied. Due to the before mentioned limitations, however, this conclusion cannot accurately be applied to the population of all adolescent tobacco users.

In addition to the small population included in the Faessel study, the fact that safety and efficacy of Varenline therapy was not the primary focus of the investigation limited the significance of the results. The primary limitation of this study was the short follow-up time of sixteen days, an inadequate period of time in which to determine continued effectiveness of the intervention. Number need to harm was found to be equal to number needed to treat in the high dose arm of the study, and greater than number needed to treat in the low dose arm. This finding suggests that varenline therapy is unlikely to aid in cessation without also causing side effects. Similar to the Rubenstein study, however, results of this study cannot be applied to all adolescent tobacco users because of the small population size, insufficient follow-up, and the absence of p-values demonstrating that observed differences were not due to coincidence. Of importance, this was the only study in which the subjects were not asked to stop tobacco use during pharmacotherapy administration.<sup>5</sup>

In contrast to the other two studies, Muramoto et al. demonstrated significantly positive results for the use of Bupropion hydrochloride as a smoking cessation therapy in an adolescent population. The difference in abstinence rates between the placebo group and the group receiving Bupropion hydrochloride 300mg at six weeks was found to be statistically significant (p-value = .03). The difference between the two groups at 26 weeks, however, was not significant (p-value = .28). In addition, a negative number

needed to harm indicates that Bupropion actually reduces certain adverse effects associated with nicotine withdrawal.

Study limitations included modification of the study protocol (follow-up shortened from 52 weeks after the quit date to 26 weeks) to adjust for recruitment changes and a prolonged accrual period. In addition, losses to follow-up made up more than 20% of the initial participants and no intention to treat analysis was performed. Furthermore, it was determined that confirmation of abstinence with urine cotinine levels was more accurate than confirmation with exhaled levels of CO; however, urine cotinine was only measured at weeks 1 and 6.<sup>4</sup>

### **Conclusion**

Only the Muramoto study investigating the safety and efficacy of Bupropion hydrochloride confirmed results with enough significance to have implications for the larger population of adolescent cigarette smokers. This study demonstrates that SR bupropion hydrochloride at 300 mg/d plus brief behavioral counseling has short-term efficacy in helping adolescent smokers quit, without significant adverse events. Six weeks of pharmacotherapy was determined to be too short, however, as many subjects later relapsed.<sup>4</sup> While further investigation into the ideal length of therapy is still needed, it is reasonable to recommend the use of Bupropion hydrochloride for smoking cessation in adolescents who have failed conventional methods of quitting. At this time, there is not enough evidence to suggest that either nicotine nasal spray or varenline is a safe or effective therapy for smoking cessation in the adolescent population.