

REVIEW ARTICLE

Smoking Cessation Treatment for Adolescents

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Cigarette smoking in the adolescent population remains a public health concern. A significant portion of the adolescent population currently uses tobacco. Nicotine is particularly addicting in adolescents, and quitting is difficult. The goals for adolescent cigarette smoking efforts must include both primary prevention and smoking cessation. Bupropion and nicotine replacement therapies—including nicotine patches, gum, and nasal spray—have been studied to a limited extent in the adolescent population. Varenicline has not been evaluated as a treatment modality in adolescents. Long-term quit rates in the pharmacotherapy trials have not been optimal; however, decreases in cigarettes smoked per day have been observed. Several evidence-based guidelines include recommendations for smoking cessation in adolescents that include counseling and pharmacotherapy. Pharmacotherapy may be instituted for some adolescents in addition to counseling and behavioral interventions. Therapy should be individualized, based on smoking patterns, patient preferences, and concomitant disease states. Smoking cessation support for parents should be instituted as well. The pharmacist can play a large role in helping the adolescent quit smoking. Further studies evaluating pharmacotherapy options for smoking cessation in adolescents are necessary. If pharmacotherapy is used, it should be individualized and combined with psychosocial and behavioral interventions.

KEYWORDS adolescent, bupropion, nicotine replacement therapy, smoking cessation, varenicline

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INTRODUCTION

National surveillance data indicate that while adolescent cigarette smoking has declined over recent years, it is still a significant problem.¹⁻³ According to the Youth Risk Behavior Surveillance System (YRBSS) 2009 data, 19.5% of high school students smoked cigarettes.¹ The YRBSS 2009 and the Monitoring the Future study 2009 showed that 6.5% of 8th graders, 13.5% of 9th graders, 13% to 18% of 10th graders, 22% of 11th graders, and 20% to 25% of 12th graders reported smoking in the month prior to being surveyed.^{1,2} Data also show that most people who start smoking are younger than 18 years old.³ In 2000, the estimated number of potential smoking-related

future deaths among children age 0 to 17 years in the United States was more than 6.4 million.⁴

Tobacco use in adolescence is associated with

ABBREVIATIONS AAP, American Academy of Pediatrics; ADHD, attention deficit hyperactivity disorder; CO, carbon monoxide; DHHS, Department of Health and Human Services; DoD, Department of Defense; FDA, Food and Drug Administration; ICSI, Institute for Clinical Systems Improvement; NICE, National Institute for Health and Clinical Excellence; NRT, nicotine replacement therapy; ppm, parts per million; OTC, over the counter; SR, sustained release; VA, Veterans Affairs; YRBSS, Youth Risk Behavior Surveillance System

both physical and social consequences. Smoking at an early age is more likely to lead to nicotine addiction than starting at a later age. Nicotine may be particularly addicting to adolescents, and adolescents may not fully realize the potential to become addicted or the difficulty in quitting.⁵ Nicotine addiction occurs rapidly in

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Table 1. Evidence-based Smoking Cessation Guidelines and Reports*

Organization	Publication
U.S. Department of Health and Human Services	Treating Tobacco Use and Dependence: 2008 Update—Clinical Practice Guideline ¹²
Department of Veterans Affairs / Department of Defense	VA/DoD Clinical Practice Guideline for the Management of Tobacco Use ¹³
Institute for Clinical Systems Improvement	Health Care Guideline: Preventive Services for Children and Adolescent, 15 th edition ¹⁴
National Institute for Health and Clinical Excellence	Smoking cessation services in primary care, pharmacies, local authorities and workplaces, particularly for manual working groups, pregnant women and hard to reach communities (Public health guidance) ¹⁵
American Academy of Pediatrics Committee on Substance Abuse	Tobacco as a substance of abuse (Technical report) ⁵
American Cancer Society	Cancer Prevention & Early Detection Facts & Figures 2009 ¹⁰

*VA/DoD indicates Department of Veterans Affairs/Department of Defense.

adolescents; 25% of adolescents who smoke show signs of addiction within 1 month. In addition to nicotine dependence, cigarette smoking causes many well-known ill effects, including increased pulmonary and cardiovascular diseases and increased risk for lung cancer. Behaviors such as being involved in fights, carrying weapons, attempting suicide, engaging in high-risk sexual behavior, and using alcohol and other drugs are also more likely to occur in adolescents who smoke cigarettes.^{6,7}

Adolescents who regularly use tobacco have as much difficulty with cessation, withdrawal symptoms, and relapse as adults. The Fagerström Test for Nicotine Dependence (and modified versions) is used to assess nicotine dependence.⁸ Results of the questionnaire are interpreted similarly to the interpretation method used for adults; scores equal to or greater than 6 (scale 0-10) indicate a high degree of dependence. According to the YRBSS, approximately half (50.8%) of adolescents who currently smoked cigarettes tried to quit in the previous 12 months.¹ The Centers for Disease Control and Prevention analyzed survey data from the YRBSS and found that very few high school students (12%) who ever smoked cigarettes daily were able to successfully quit smoking, although most (61%) had tried.⁹

To reduce mortality and morbidity from tobacco use, the goal must be two-fold: 1) prevent initiation of cigarette smoking and 2) help current smokers quit. The American Cancer Society

2015 Nationwide Objectives include reducing the proportion of high school students who currently smoke to less than 10% and who use smokeless tobacco to less than 1%.¹⁰ Additionally, Healthy People 2010 aims to reduce adolescent use of tobacco products from the 1999 baseline of 40% to 21%, and the use of cigarettes specifically from 35% to 16% (Objective 27-2).¹¹

LITERATURE REVIEW

The following is a review of the pharmacotherapy literature regarding options for nicotine dependence in the adolescent population. Included will be a discussion of efficacy, safety, and other issues surrounding the use of bupropion and nicotine replacement therapy (NRT) specific to this population. Although the importance of behavioral therapy and counseling is recognized, it is beyond the scope of this review to include a detailed account of its effectiveness. The reader is referred to treatment guidelines and primary literature for more information on behavioral interventions. In addition, noncigarette forms of tobacco (e.g., chewing tobacco) will not be discussed.

EVIDENCE-BASED GUIDELINES

Several guidelines, position statements, and resources are available for guiding smoking cessation programs for the adolescent population (Table 1). The American Cancer Society recom-

mends that youth be included in smoking cessation initiatives, recognizing that support and encouragement are important for this age group in particular.¹⁰ The United States Department of Health and Human Services (DHHS), the Department of Veterans Affairs (VA)/Department of Defense (DoD), the Institute for Clinical Systems Improvement (ICSI), and the National Institute for Health and Clinical Excellence (NICE) have published recommendations for smoking cessation among adolescents.¹²⁻¹⁵ The American Academy of Pediatrics (AAP) Committee on Substance Abuse published a technical report describing tobacco as a substance of abuse in pediatric and adolescent patients; in the report, the committee encouraged education, prevention, screening, and treatment.⁵ While the AAP's recommendations for treatment guidance differ from those of the DHHS guidelines, AAP strongly encourages behavioral interventions and recommends that pediatricians familiarize themselves with pharmacotherapies such as nicotine replacement, bupropion, and varenicline.

In their guidelines, both the DHHS and the VA/DoD state that all pediatric patients and their parents should be routinely screened for tobacco use by their health care professionals.^{12,13} Health care professionals are advised to send a strong message of abstinence and to offer cessation advice and interventions when either the adolescent patients or their parents smoke. In contrast with the 2000 DHHS guidelines, the 2008 update does not recommend the use of medications to treat nicotine dependence in adolescents.¹² Although the DHHS recognizes that NRT has been shown to be safe in adolescents, the lack of long-term efficacy data for NRT or bupropion prompted the deletion of this recommendation. The guideline now recommends counseling and behavioral interventions for this group. Specific methods and recommendations are discussed in further detail in the guideline.

The VA/DoD guidelines also recommend counseling and behavioral interventions for adolescents. However, adolescent patients who have evidence of nicotine dependence and who express a desire to quit tobacco use may be offered NRT or bupropion sustained release (SR). Nonetheless, pharmacotherapy is listed as an intervention that "may be considered"; within the guidelines, pharmacotherapy is considered as grade C evidence, because of positive results in a small amount of good-to-fair literature.¹³

In contrast, the ICSI guidelines recommend pharmacotherapy to aid smoking cessation efforts.¹⁴ The guidelines state that providers should address tobacco use status and provide cessation services at every opportunity. Services should include counseling and other support systems plus medications for smoking cessation in all patients who do not have contraindications. Specific medications are not specified.

NRTs with behavioral interventions are recommended in the NICE guidelines for patients with nicotine dependence beginning at age 12 years.¹⁵ The NICE guidelines state to avoid varenicline and bupropion in patients younger than 18 years. They recommend that a careful consideration of risks and benefits should be employed by the provider and explained to the patient and the legal guardian.

Incongruence among the guidelines exists regarding the use of pharmacotherapy for the adolescent population. Clinical trials in this population are limited, and recent safety concerns with antidepressant medications make the decision controversial despite positive efficacy results.

PHARMACOTHERAPY OPTIONS

No smoking cessation medications are FDA-approved for use in children or adolescents (younger than 18 years; Table 2). NRT and bupropion, the 2 mainstay pharmacotherapeutic aids for smoking cessation treatment, have been studied specifically for smoking cessation to a limited extent in the adolescent population (Table 3). Although bupropion has many uses, it is not labeled for use in children younger than 18 years for any indication. A black box warning, recently added to all antidepressants (including proprietary bupropion, Zyban GlaxoSmithKline, Raleigh, NC) warns about the increased risk of suicidal thinking and behavior in children, adolescents, and young adults younger than age 24 years being treated for depression.¹⁶ Because patients with depression are already at increased risk for suicide and definite attribution to the medication may not be clear, it is reasonable to closely monitor patients in this age group receiving antidepressants, especially during the first 2 months of therapy.

Nicotine Replacement Therapy

Monotherapy with NRT has been evaluated

Table 2. Smoking Cessation Pharmacotherapy Available in the United States*,† 16, 28, 35-37

Therapy	Brand Name	Strengths	FDA-Approved Adult Dosing	Availability	Studied in Adolescents	Quit Date
Nicotine Replacement Therapy						
Gum‡	Nicorette®	2 mg, 4 mg	The 4-mg strength should be used by patients who smoke 25 or more cigarettes a day; otherwise the 2-mg strength should be used. Wk 1 to 6: one piece every 1- 2 hr Wk 7 to 9: one piece every 2- 4 hr Wk 10 to 12: one piece every 4-8 hr	OTC	Yes	
Inhaler	Nicotrol Inhaler®	4 mg	6-16 cartridges a day for up to 12 wks	Rx	No	
Lozenge	Commit™, Nicorette® mini	2 mg, 4 mg	The 4-mg strength should be used by patients who smoke their first cigarette within 30 minutes of waking; otherwise, the 2-mg strength should be used. Wk 1-6: one lozenge every 1- 2 hr Wk 7- 9: one lozenge every 2- 4 hr Wk 10-12: one lozenge every 4-8 hr	OTC	No	Prior to beginning nicotine replacement therapy
Nasal Spray	Nicotrol® NS	0.5 mg / spray	1- 2 sprays per hr up to a maximum of 80 sprays per day	Rx	Yes	
Transdermal Patch‡	Nicoderm CQ®	7, 14, 21 mg / 24 hr	For patients who smoke >10 cigarettes daily: Step 1: one 21-mg patch daily for wks 1-6. Step 2: one 14-mg patch daily for wks 7-8. Step 3: one 7-mg patch daily for wks 9-10. For patients who smoke < 10 cigarettes daily: begin with the 14-mg patch daily for 6 wks, followed by the 7-mg patch for 2 wks	OTC	Yes	
Non-Nicotine Therapy						
Bupropion SR‡	Zyban®	150-mg sustained release tablets	150 mg by mouth in the morning for 3 days, then increase to 150 mg by mouth twice daily	Rx	Yes	1 week after starting therapy
Varenicline	Chantix®	0.5-, 1-mg tablets	0.5 mg by mouth in the morning for 3 days. Increase to 0.5 mg by mouth twice daily for 4 days. Then, increase to 1 mg by mouth twice daily.	Rx	No	

*OTC indicates over the counter; and Rx, prescription product.

†None are FDA-approved for use in patients younger than 18 years.

‡Generics available

Table 3. Smoking Cessation Pharmacotherapy Trials in Adolescents*

Reference	Treatments (n)	Therapy Length (Follow-up)	Smoking Cessation†	Smoking Rate: Mean (SD) Cigarettes Per Day
Nicotine Replacement Trials				
Smith, et al. ¹⁷	Nicotine patch, n=22 (open label)	8 wks	13.6% (95% CI, 2.9%-34.9%)	Baseline: 23.3 (5) 8 wks: 1.6 (1.6)
		(6 mo)	4.5% (95% CI, 0.1%-22.8%)	6 mo: 9.4 (7.4)
Hurt, et al. ¹⁸	Nicotine patch, n=101 (open label)	6 wks	10.9% (95% CI, 5.6%-18.7%)	Baseline: 18.2 (6.2) 6 wks: 2.5 (3.5)
		(6 mo)	5% (95% CI, 1.6%-11.2%)	6 mo: 9.4 (6.5)
Hanson, et al. ¹⁹	Nicotine patch, n=50	10 wks	28% (SD 0.45) [‡]	Baseline: 16.3 10 wks: 3.7 (combined)
	Placebo, n=50		24% (SD 0.43)	
Moolchan, et al. ²⁰	Nicotine patch + placebo gum, n=34	12 wks	17.7% [§]	¶Baseline: 7.7 (6.45) 12 wks: -80.4%
	Nicotine gum + placebo patch, n=46		6.5% [‡]	¶Baseline: 18.9 (8.96) 12 wks: -85.1%
	Placebo patch + placebo gum, n=40		2.5%	¶Baseline: 19.6 (9.7) 12 wks: -89.6%
Rubinstein, et al. ²¹	Nicotine nasal spray + counseling, n=23	12 wks	0% [‡]	Baseline: 10.6 (7.2) 12 wks: 4.8 (3.1)
	Counseling only, n=17		11%	Baseline: 8.8 (5.1) 12 wks: 7.8 (7.1)
Nicotine Replacement Therapy and Bupropion				
Killen, et al. ²³	Bupropion SR, n=108	8 wks NRT + 9 wks bupropion or placebo	23%	Not specified
	Placebo, n=103		28%	
Bupropion Trials				
Muramoto, et al. ²⁴	Bupropion SR 150 mg daily, n=105	6 wks	27% [‡]	Not measured
	Bupropion SR 150 mg twice daily, n=104		34% [§]	
	Placebo, n=103		20%	
Niederhofer, et al. ²⁵	Bupropion, n=11	90 days	55% [§]	90 days: Reduced in 5.4% of subjects
	Placebo, n=11		18%	90 days: Reduced in 5.9% of subjects
Upadhyaya, et al. ³⁰	Bupropion, n=16 (ADHD, n=11)	4 wks	31.25%	Baseline: 18.06 4 wks: <5 (not specified) [#]

*NRT indicates nicotine replacement therapy; SD, standard deviation; Tx, treatment; and wks, weeks.

†Time points for defining abstinence varied by study. Please refer to text.

#Not statistically significant vs placebo

§Statistically significant vs placebo

¶Primary endpoint: percentage reduction in smoking rate; not statistically significant vs placebo

#Statistically significant vs baseline (primary endpoint)

in adolescent smokers in 5 controlled trials since the mid-1990s, demonstrating varied effectiveness.¹⁷⁻²¹ In 3 of the trials, researchers investigated the nicotine patch. In 1 trial, researchers investigated both the nicotine patch and nicotine gum, and in the other trial, researchers investigated nicotine nasal spray.

An open-label trial was conducted involving 22 adolescents between the ages of 13 and 17 years who smoked at least 20 cigarettes per day for at least 6 months.¹⁷ In addition to group behavioral counseling, all patients received a 22 mg/day nicotine patch for 6 weeks, then an 11 mg/day patch for 2 weeks. Patients with other substance abuse disorders were excluded. The patient population was all white and 32% male, with a mean age of 15.9 ± 1.2 years and a mean smoking rate (number of cigarettes per day) of 23.5 ± 5 , and had been smoking for a mean of 2.6 ± 1.6 years. Most (68%) had a Fagerström Tolerance Questionnaire (original) score of at least 7. Only about one-third had tried to quit smoking previously, and most (86%) reported "less than 1 week" as the longest time without a cigarette. Nineteen of the patients (85%) completed the trial through the 6-month follow-up visit; the other 3 patients dropped out because of compliance issues. At week 8 (end of treatment phase), 3 patients (14%) self reported abstinence and had a confirmed carbon monoxide (CO) level of 8 ppm or less. At the 3- and 6-month follow-ups, only 1 person (5%) reported continued abstinence (not confirmed objectively). Mean withdrawal scores, as measured by the Hughes-Hatsukami Questionnaire, decreased for weeks 2 through 8 compared with baseline (not specified, but less than 2 [mild] at all points including baseline). A reduction in mean smoking rate (cigarettes per day \pm SD) was reported throughout the treatment phase and at week 8 was 1.6 ± 1.6 , compared with baseline of 23.5 ± 5 . Smoking cessation rates were dismal in this short-term trial, but a substantial reduction in cigarettes per day was observed.

To evaluate the effect of the nicotine patch on smoking cessation rates, researchers conducted a larger, open-label trial involving 101 adolescent patients aged 13 to 17 years who smoked at least 10 cigarettes per day for at least 1 year.¹⁸ All patients received a nicotine patch 15 mg/16 hours for 6 weeks, in addition to individual brief counseling sessions only as requested. The patient

population was 95% white, 59% male, and had a median age of 16 years; median number of cigarettes per day, 20 (range, 10-40); and median years of smoking, 3 (range, 1-8). The patients in this trial reported several other medical or psychological issues: alcohol abuse history (24%), history of major depression (24%), other substance abuse (20%), and attention deficit hyperactivity disorder (ADHD; 16%). Approximately one-quarter of the study population had a Fagerström Test for Nicotine Dependence (revised) score of at least 7. Seventy-one patients completed the therapy (80% of 30 non-completers withdrew consent, 17% dropped out because of adverse effects, and 3% were unavailable for follow-up). At week 6 of treatment, the CO-confirmed, 7-day abstinence rate was 10.9% (11 of 101 patients). At 6 months, the rate fell to 5% (5 patients). Although the cessation rate was low, withdrawal scores (not specified, but all less than 2 [mild] at all points) decreased significantly from baseline during weeks 2 through 6 ($p \leq 0.05$). In addition, the smoking rate (mean cigarettes per day \pm SD) was reduced from baseline (18.2 ± 6.2) to the 6th week (2.5 ± 3.5) and at the 6-month follow-up (9.4 ± 6.5). Smoking cessation rates were low in a very difficult-to-treat population (i.e., with high dependence scores and concomitant diagnoses), but a reduction in cigarettes per day occurred at the end of treatment and at the 6-month follow-up.

A double-blind, randomized, placebo-controlled 10-week trial evaluating the efficacy of nicotine patch therapy for reducing nicotine withdrawal was conducted in 100 adolescents aged 13 to 19 years.¹⁹ Patients were included if they smoked at least 10 cigarettes per day for at least 6 months. Patients who smoked at least 15 cigarettes per day were given the 21-mg/day patch for 6 weeks, then the 14-mg/day patch for 2 weeks, and the 7-mg/day patch for the final 2 weeks. Patients who smoked between 10 and 14 cigarettes per day received the 14-mg/day patch for 6 weeks, followed by the 7-mg/day patch for 4 weeks. In addition, patients received individual counseling at each visit and were rewarded with gift certificates for successful completion. Patients with comorbid substance abuse disorders were not included. The Nicotine Withdrawal Symptoms Checklist was used to evaluate the primary endpoint. Overall, 87% of the participants were white, and 43% were male; patients had a mean age of 16.8 ± 1.5 years and smoked

16.3 ± 4.9 cigarettes per day. The nicotine patch resulted in a significantly lower nicotine craving score ($p = 0.011$) and lower overall withdrawal score compared with placebo ($p = 0.025$) at 2 weeks (scores not specified). The 7-day abstinence rate was 28% in the active group vs 24% in the placebo group at 10 weeks ($p = 0.65$). Among non-quitters, the number of cigarettes per day (smoking rate) decreased from the pre-quit visit (16.3) to the visit 10 weeks after the quit day (3.7). Slightly higher quit rates were obtained in this study compared with those of other NRT studies, although the difference between groups was not significant. As in other studies, the number of cigarettes per day decreased.

Because a reduction in smoking rates was observed in previous trials as a secondary endpoint, a double-blind, placebo-controlled trial was designed to assess the impact of the nicotine patch and nicotine gum therapy on smoking rates.²⁰ Patients aged 13 to 17 years ($n=100$) who smoked at least 10 cigarettes per day for at least 6 months were enrolled. Patients with other drug or alcohol abuse disorders were excluded. Patients were randomized to 1 of 3 groups: 1) active patch + placebo gum ($n=34$), 2) active gum + placebo patch ($n=46$), or 3) placebo patch + placebo gum ($n=40$). Patients received the 21-mg/day patch (14-mg patch for patients < 45 kg who smoked < 20 cigarettes per day), 2-mg gum (for those who smoked ≤ 24 cigarettes per day), and 4-mg gum (for those who smoked > 24 cigarettes per day). In addition, 45-minute individual behavioral counseling sessions were completed at each visit. The patient population was 75% white and 30% male, with a mean age of 15.2 ± 1.3 years and a smoking rate of 18.8 ± 8.6 cigarettes per day for 2.6 ± 1.6 years. Many participants had a concurrent psychiatric diagnosis. The mean score on a modified Fagerström Test for Nicotine Dependence Questionnaire was 7.04 ± 1.29 at baseline. Approximately half ($n=53$) of the patients completed the trial (53% patch, 41% gum, 40% placebo). All 3 groups had a reduction in smoking rate by the end of the 12-week treatment phase, but the differences among groups were not significant (-80.4% patch, -85.1% gum, -89.6% placebo). Continuous abstinence beginning 2 weeks after randomization was statistically significant for the patch (17.7%; 6 of 34) vs placebo (2.5%; 1 of 40; $p = 0.043$), but not the gum (6.5%; 3 of 46) vs placebo ($p = 0.62$) or when comparing combined

NRT arms with placebo ($p = 0.066$). Although a decrease occurred in all groups from baseline, a statistically significant reduction in cigarettes per day was not observed among groups.

The first trial evaluating the nicotine nasal spray (Nicotrol NS, Pfizer, New York, NY) in adolescents was an open-label trial that randomized 40 adolescent smokers aged 15 to 18 years to either counseling only for 8 weeks ($n=17$) or counseling for 8 weeks plus nicotine nasal spray for the last 6 weeks ($n=23$).²¹ Participants smoked at least 5 cigarettes per day for at least 6 months and had a desire to quit smoking. The patients were instructed to use 1 dose (1 spray in each nostril; 1 mg nicotine) when they had strong cravings, up to a maximum of 40 doses per day. Almost half of the patients were white, 46% were male, and the mean age was 16.7 ± 0.9 years. The mean smoking rate at baseline was 9.9 cigarettes per day. Approximately half of the participants had previously used NRT in the form of the patch (28%) or gum (23%). The median use of the nasal spray was 1.14 sprays per day (range, 0.14-3). At 8 weeks, smoking cessation rates were not statistically different between the groups (11.8% in counseling-only group vs none in the nicotine nasal spray group, $p = 0.16$). Smoking rates decreased in both groups, from 8.8 at baseline in the counseling group to 6.4 cigarettes per day at 8 weeks (28% decrease) versus 10.6 cigarettes per day for the nasal spray group at baseline to 5 cigarettes per day at 8 weeks (50% decrease; $p = 0.1$). Adverse effects were common and almost 40% of patients reported that the nasal spray had "lots of side effects." The authors suggested that the low success may have been attributed to the low use of the nasal spray (possibly secondary to adverse effects), lack of motivation, or under-reporting of cigarettes smoked per day.

Adverse effects were common in these trials, but were not severe and were not a frequent cause for dropping out.¹⁷⁻²⁰ Nasal irritation and burning were commonly reported in the trial evaluating the nicotine nasal spray.²¹ Some of the more common adverse effects included skin reactions at patch application site, sleep problems, insomnia, abnormal dreams, joint or muscle pain, pruritus, fatigue, headache, nausea, and dizziness.

Despite the safety observed in short-term trials and the guideline recommendations for the use of NRT, not all are in agreement with this modality for adolescents. As previously mentioned,

the 2008 DHHS guidelines do not recommend the use of pharmacotherapy. The authors of one literature review voiced concerns about the high susceptibility to nicotine dependence and the strong influence that even early and limited nicotine exposure (i.e., experimenting 1 time) in the adolescent has on later development of nicotine addiction and cigarette smoking.²² These authors also suggested that similar to the nicotine in cigarettes, NRT may have the potential for “priming the brain for nicotine addiction” and may also lead to other drug use. They suggested that on the basis of limited support for NRT efficacy and potential for increased addiction, NRT should not be loosely recommended to this patient population.²²

Nicotine Replacement Therapy and Bupropion

A trial has been conducted with adolescent smokers comparing NRT alone with NRT plus bupropion.²³ This was a randomized, double-blind, placebo-controlled trial evaluating effects on smoking cessation in smokers (n=211) between the ages of 15 to 18 years. Patients were included who had smoked at least 10 cigarettes per day, had smoked for at least 6 months, had tried and failed to quit smoking at least once previously, and had scored at least a 10 on a modified version of the Fagerström Tolerance Questionnaire. All of the patients received group-based skills training (groups of 8 met weekly) and a nicotine patch for 8 weeks (if the patient smoked more than 15 cigarettes per day: 21-mg patch in weeks 1-4, 14-mg patch in weeks 5-6, 7-mg patch in weeks 7-8; if the patient smoked 10-15 cigarettes per day: 14-mg patch in weeks 1-6, 7-mg patch in weeks 7-8). They were then randomized to receive either placebo (n=108) or bupropion SR 150 mg (n=103) daily for 9 weeks, starting the week prior to the quit date. The study population was approximately 50% white and 69% male, with a mean age of 17 years and a smoking rate of approximately 15 cigarettes per day. Compliance with the treatments was low with 29% of patients reporting daily patch use for at least 5 weeks and 22% of patients reporting taking the oral medication (bupropion or placebo) daily for at least 6 weeks. Abstinence rates between the groups did not statistically differ at week 10 (23% abstinent in the bupropion group and 28% abstinent in the placebo group) or at week 26 (8% in the bupropion group and 7% in the placebo

group; p-values were not stated). Time to relapse also did not differ between the groups. Adverse events were not specified, but were reported to be similar between the groups (22 events reported in the bupropion group and 25 events reported in the placebo group). Abstinence rates were less than one-third for both groups at week 10 and less than 10% at week 26, also similar between both groups.

Bupropion

Two studies were identified in which researchers evaluated bupropion SR for tobacco cessation in adolescents.^{24,25} A randomized, double-blind, placebo-controlled trial was conducted to evaluate the safety and efficacy of 2 doses of bupropion SR (150 mg once daily [n=105] and 150 mg twice daily [n=104]) compared with placebo (n=103).²⁴ Patients were 14 to 17 years old, smoked at least 6 cigarettes per day, had an exhaled CO level greater than or equal to 10 ppm, had at least 2 previous quit attempts, weighed at least 40.5 kg, were English literate, and were motivated to quit smoking. Patients received treatment or placebo for 6 weeks and were followed for 26 weeks. They received brief counseling during their visits on the pre-quit visit, quit date, and then weekly for 7 weeks with no additional behavioral therapy thereafter. Most of the study population was white (74%) and male (54%), with a median age of 16 years and a smoking rate of approximately 11 cigarettes per day (median). Quit rates for the bupropion 150 mg/day group did not differ statistically from the placebo group at any time. The bupropion 300 mg/day group had significantly higher 7-day abstinence rates compared with the placebo group at week 6 (150 mg/day, 27% abstinent; 300 mg/day, 34% abstinent; placebo 20% abstinent; p = 0.02 for placebo vs 300 mg). No statistically significant differences in abstinence rates appeared among the groups following treatment cessation. Headache and cough were more commonly reported in the bupropion groups compared with those in the placebo group. There was one attempted suicide by a 16-year old female patient with a medical history significant for depression and an eating disorder. In summary, quit rates were higher for the 300 mg group at the end of treatment, but differences in abstinence did not persist.

A placebo-controlled study of bupropion included patients who were classified as nicotine

dependent in accordance with criteria in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; the patients were ages 16 to 19 years and had a breath CO level greater than 10 ppm.²⁵ During the 5 days prior to the study, the patients received inpatient nicotine withdrawal treatment with NRT. They were then randomly assigned to receive either bupropion 150 mg daily (n=11) or placebo for 90 days (n=11). All patients received psychosocial and behavioral treatment. During relapses, patients received inpatient care with nicotine withdrawal treatment and continued on the study medication. The mean age of patients was 17 years, and a similar number of males and females were randomized to each group. More patients in the bupropion group (55%) remained continuously abstinent at 90 days compared with those receiving placebo (18%). A reduction in the number of cigarettes smoked per day occurred in 5.4% of patients receiving bupropion compared with 5.9% of patients on placebo. No significant differences in adverse effects were reported between bupropion and placebo. A high level of abstinence was obtained at 90 days, but the external validity of this trial is low because of the inpatient component.

An abstract on the evaluation of bupropion SR and contingency management, bupropion alone, placebo plus contingency management, and placebo was presented at the 56th Annual Meeting of the American Academy of Child & Adolescent Psychiatry in October 2009. While results appear to favor combination treatment, assessment cannot be completed until the results are published in full.

Varenicline

Clinical trial data for varenicline (Chantix, Pfizer, New York, NY) are lacking for the adolescent or pediatric population. The results of a safety, tolerability, and pharmacokinetic study of varenicline in adolescent smokers were published in early 2009.²⁶ Subjects were 12 to 16 years old (n=72) and smoked at least 3 cigarettes per day; they were stratified by weight (high-body weight, > 55 kg; low-body weight, ≤ 55 kg). High-body weight subjects were randomized to 1 mg twice daily (large dose), 0.5 mg twice daily (small dose), or placebo. Low-body weight subjects were randomized to 0.5 mg twice daily (large dose), 0.5 mg once daily (small dose), or placebo for 14 days. In the high-body weight

group, pharmacokinetic parameters, including maximum concentration and renal clearance, were similar to those of adults. In low-body weight subjects, the volume of distribution was decreased, and maximum concentration and area under the curve were increased. It appears that these increases can be managed with a reduction in the usual recommended adult dose. Adverse effects included nausea, vomiting, dizziness, and headache in more than half of the patients. The only treatment-related psychiatric adverse events were abnormal dreams (n=2) and transient anger (n=1). Most side effects were mild, and none required discontinuation.

The FDA requires the manufacturer of varenicline to conduct a subsequent trial to determine the effectiveness of the drug in achieving and maintaining smoking cessation in adolescents.²⁷ It should be noted that as a result of post-marketing surveillance, the varenicline labeling now includes a black box warning that serious neuropsychiatric symptoms—including changes in behavior, agitation, hostility, suicidal ideation and behavior, and depressed mood—have been observed in adult patients taking varenicline.²⁸

TOBACCO CESSATION THERAPY FOR PATIENTS WITH CONCOMITANT ATTENTION DEFICIT HYPERACTIVITY DISORDER

Tobacco use is associated with depression, ADHD, alcohol and other drug abuse and dependence, and other psychiatric disorders. ADHD, especially with active symptoms, is a significant risk factor for (early) initiation of cigarette smoking in children and adolescents. Nicotine may be used by patients with ADHD to control symptoms because it improves attentiveness. As an adjunctive or alternative therapy to stimulants for ADHD, bupropion is an attractive option for treating the co-occurrence of ADHD and tobacco use in adolescents.²⁹ Bupropion has been studied in adolescent patients with ADHD to evaluate the effectiveness for smoking cessation and for preventing the initiation of smoking in this high-risk group.

In an open-label study including 16 participants (11 with ADHD) aged 12 to 19 years, the effectiveness of bupropion SR for smoking cessation was evaluated.³⁰ In addition to 2 counseling sessions, subjects weighing less than 41 kg were

given 150 mg once daily, while those weighing more than 41 kg received 150 mg once daily for 3 days then 150 mg twice daily. At 4 weeks, only 9 patients remained in the trial; data were analyzed for 15 patients. The population was 88% white and 62% male, with a mean age of 18 years. Although the minimum smoking rate to be eligible for the trial was 5 cigarettes per day, the mean for the study sample was 18 cigarettes per day (range, 6 to 40). After 4 weeks of therapy, the cigarette smoking rate and exhaled CO levels decreased significantly ($p = 0.00$ and $p = 0.04$, respectively), with no change in self-reported ADHD symptoms. Approximately one-third (31.25%, 5 of 16) were cigarette free at 4 weeks.

The association between ADHD and the risk for initiation of smoking prompted a double-blind, placebo-controlled trial of bupropion for the prevention of smoking initiation in participants ages 9 to 18 years with ADHD ($n=99$).³¹ Subjects had experimented with smoking in the past, but did not have a history of regular tobacco use. Patients were randomized to titrated bupropion (150 mg daily up to a maximum 300 mg per day by week 3) or matching placebo for up to 6.5 years. Data were analyzed for subjects who were followed at least 4 weeks ($n=28$, bupropion; $n=29$, placebo). The sample was 80% white, 70% male, and had a mean age of 13 ± 2.3 years, and approximately half of each group used stimulant medications for ADHD symptoms. As determined by a positive cotinine screen, 46% of the bupropion group and 28% of the placebo group ($p = 0.14$) smoked at some point during the follow-up period. Bupropion was not more effective than placebo for preventing the initiation of smoking in this small study.

ISSUES SURROUNDING NICOTINE REPLACEMENT THERAPY

In a survey of Canadian youths, more than 75% indicated they would like to quit smoking, and many had attempted quitting more than once in the previous year.³² Most of those indicating they had intentions to quit said they would never use telephone quitlines, the Internet, a doctor, teachers, school counselors, or group meetings at school. However, more than half indicated they would try NRT, advice from friends, or attempts to quit on their own. This survey gives insight into the methods that may interest this patient population.

Similarly, adolescents in another survey indicated that they wished to quit smoking, but needed assistance to do so.³³ In focus groups of British youths, half indicated that they would like to quit smoking, but many had experienced difficulty in accomplishing this. Initially, they had a low opinion of NRT based on their beliefs, experimental use, varied success of family members, cost, and availability. After brief education about NRT product forms and effectiveness, many expressed interest in trying NRT to help them quit smoking. They also expressed interest in counseling sessions.

A survey of physician practices related to adolescent smoking cessation assistance provided information about treating tobacco dependence and NRT prescriptions.³⁴ Of the pediatricians surveyed, 50% noted that they urged smokers to quit, and 30% documented smoking status. However, they did not always refer patients to outside cessation programs (10%) or follow-up with the patients after their quit dates (3%). While many considered NRT safe (45%), only 17% were currently prescribing it to adolescent smokers. Most pediatricians thought NRT was moderately-to-highly effective, but many (55%) indicated that they were not confident they could effectively help adolescents use NRT. Almost half (44%) of the physicians thought that their competence for helping adolescents quit smoking was low. The most commonly recommended NRT was the transdermal patch (81%), followed by nicotine gum (53%). Forty-four percent prescribed bupropion to their patients.

NRTs such as nicotine patches, gum, and lozenges are available over the counter (OTC) in the United States. Sale of these OTC products is restricted to persons at least 18 years of age. The packages for Nicorette gum (GlaxoSmithKline, Raleigh, NC), Commit lozenges (GlaxoSmithKline, Raleigh, NC), and NicoDerm CQ (GlaxoSmithKline, Raleigh, NC) specifically state, "Not for sale to those under age 18 years of age. If you are under 18, ask a doctor before use."³⁵ Therefore, while the OTC purchase of NRT is not permitted by adolescents, adolescents may obtain the products under the supervision of a physician via a prescription. Other forms of NRT such as the nicotine inhaler (Nicotrol Inhaler, Pfizer, New York, NY) and nicotine nasal spray (Nicotrol NS, Pfizer, New York, NY) are only available with a prescription. Labeling for

the nicotine nasal spray does not recommend use in patients younger than 18 years because it has not been evaluated for this population.³⁶ However, inherent in the Nicotrol Inhaler labeling is the recognition that while none of the NRT products have been evaluated for those younger than 18 years, there does not seem to be medical risk for nicotine-dependent adolescents who use them. The labeling states that if potential benefit outweighs risk, the inhaler may be used in older adolescents for tobacco dependence.³⁷

The authors of one critique of NRT regulatory practices endorsed the sale of NRT to patients younger than 18 years and proposed the age limit be lowered to 12 years of age.³⁸ The authors recognized that these patients are already being exposed to nicotine in a more dangerous way through cigarette smoking, are dependent upon nicotine, and will require the best available therapies to overcome their addiction (including NRT). It was the authors' belief that if the patient is ready to quit, the patient should not be denied therapy on the basis of an arbitrarily chosen age restriction. Additional support for the expanded access of NRT to adolescents is provided by a cross-sectional survey of drug counselors (n=501).³⁹ The results of this survey indicated a low rate of NRT abuse (4.6%).

Access has been recognized as a potential barrier for adolescents to obtain NRT.^{38,40} In a mock buying scenario study, the ability of a minor to purchase OTC nicotine patches and gum was assessed.⁴⁰ A 15-year old female attempted to buy these products without identification in 207 businesses in Memphis, Tennessee. In stores that stocked both gum and patches (n=165), the buyer was able to purchase the product in most stores (81%). While assistance from store personnel was required in approximately half (58%) of the stores, age verification was not performed in most (79%). The pharmacist was the second most common person to provide this assistance (30%). If she was asked her age, the store was less likely to sell the product versus stores where she was not asked (9% vs 99%, $p < 0.001$). The authors concluded that the age restrictions did not present a large barrier to adolescents obtaining NRT products. However, they suggest that efforts to promote proper use of NRT (e.g., by the pharmacist) could be incorporated at the point of sale.

While access to NRT may be a hurdle to overcome, this must be weighed against inappropri-

ate use. A survey was conducted of 11th grade students to estimate NRT use in both smoking and nonsmoking adolescents and to determine how and why they used NRT.⁴¹ The report included surveys from 4,078 students (54.9% of those who never smoked, 26% experimental smokers, 13.1% regular smokers, and 5.9% former smokers). The use of nicotine gum or patches was reported by 5.3% of the total group; 16% of this subgroup used it every day. NRT was used by less than 1% of those who had never smoked, but they represented 18% of those reporting use of NRT. The reasons for using NRT included trying to quit smoking (28.2%) and using it when they could not smoke (22.4%). Approximately 30% used NRT concurrently while smoking. The results of this survey indicate several conclusions, including that many adolescents want to quit smoking and seek out pharmacologic therapy to assist them. However, it also indicates that many are not using it according to instructions and are continuing to smoke while using NRT. In addition, use of NRT for reasons other than smoking cessation (e.g., among those who have never smoked) is also occurring. The youths in this study indicated that obtaining NRT was relatively easy through friends, siblings, parents, physicians, or direct self-purchase.

DISCUSSION

The need for smoking cessation and primary prevention in the adolescent population has been established. What remains unknown is the best way to accomplish this. The studies included in this review are a start, but more are needed to define the role of pharmacotherapy. Many of the studies have been small and short term, and many have not been randomized, blinded, or placebo-controlled. Smoking cessation rates in the trials were less than desirable, with the highest rates, around 30%, in the studies with real-world, outpatient settings. Many studies with NRT had cessation rates less than 15%. Additionally, although cessation of smoking occurred in many of the studies at the end of the treatment phase, longer-term follow-up of the patients demonstrated that many do not remain abstinent after stopping treatment. A recent meta-analysis of tobacco cessation interventions in adolescents concluded that pharmacotherapy trials (n=2) were not effective for maintaining

abstinence at 6 months and recommended more studies with a minimum of 6 months duration.⁴² Some of the poor response in the trials reviewed may be explained by poor adherence to therapy, concomitant psychiatric diagnoses, other substance abuse disorders, high baseline smoking rates, and inadequate duration of therapy (i.e., less than 12 weeks). The lack of pharmacokinetic data for these smoking cessation medications in the adolescent population and, therefore, lack of accurate dosing, may also lead to poor response. Additionally, many of the subjects in the NRT and bupropion trials lived in homes with other smokers, started smoking at young ages, and had other barriers to successfully quitting. It should be noted that the participants in some of the trials were compensated for participation, which may provide some degree of motivation to enroll in the trial. Parental knowledge of participation in these trials was required for all patients younger than the age of 18 years, which may have limited participation by some adolescents who did not want their parents to know they smoked.

The decision to use pharmacotherapy should be individualized and should be administered in addition to cognitive-behavioral counseling and support. Short-term use of NRT and bupropion did not show major safety issues in the samples studied. While none of the efficacy evidence for pharmacotherapy is overwhelmingly positive, some success was documented and some form of intervention (e.g., psychosocial, behavioral, pharmacologic) is necessary. Either NRT or bupropion may be considered. Patient preference for type of therapy (bupropion vs NRT) and specific NRT (e.g., patch vs gum) should be considered, and the NRT dose should be individualized based on smoking patterns. Patients with concomitant depression may benefit from the antidepressant properties of bupropion. Similarly, patients with ADHD may benefit from the positive effects bupropion may have on ADHD symptoms. In light of recent concerns regarding suicidal ideation in adolescents beginning antidepressant therapy, patients starting bupropion should be carefully monitored for behavioral changes. Bupropion should not be used in patients with eating disorders such as anorexia or bulimia, or in patients with seizure disorders. Although a safety and pharmacokinetic study has been published on varenicline in adolescents, in light of recent safety concerns and a lack of clinical trial data, it may be

best to avoid the use of varenicline outside of a clinical trial until efficacy and longer-term safety data are available for adolescents.

The guidelines published by various groups are divided on the issue of pharmacotherapy for adolescents. Recurrent, frequent assessment of smoking status, encouragement of smoking cessation, and behavioral or counseling interventions are consistently recommended by the guidelines. Support for smoking cessation by parents who smoke is also emphasized and recognized as extremely important for the health of their children. Pharmacists may be in a great position to help the parents quit smoking.

The practitioner recommending NRT should be cognizant of the potential barriers to therapy in the adolescent patient population. They may need to take steps to ensure access, such as providing a written prescription, and collaborating and communicating closely with local pharmacists. In addition to barriers, healthcare providers should also consider the potential for inappropriate use and/or abuse of NRT.

Pharmacists can play an important role with these aspects of patient care. They can ensure access to NRT through proper methods, such as with physician supervision via a prescription. The pharmacist can help the patient by assessing readiness to quit and understanding the appropriate way to use NRT, including quitting procedures with timing of NRT, proper dose selection, management of side effects, and providing psychological support. Pharmacists can also help with appropriate use of bupropion therapy by determining appropriate candidates, counseling the patients about the risks of psychiatric side effects, monitoring the patient for behavioral changes, and optimizing the plan for quitting with the patient. They should also encourage parent and peer involvement and support.

Identifying school or community-based support programs aimed at adolescents may be one such way. Focusing on consequences that may be important to adolescents such as odor, bad breath, cough, teeth and nail discoloration, wrinkles, and perception by others, may be a great way to motivate them to quit. The Monitoring the Future study indicated that most adolescents view cigarette smoking negatively, including that smoking is a dirty habit, smoking reflects poor judgment, and the majority dislike being near people who are smoking.² It may be

Table 4. Resources for Smoking Cessation Initiatives*

Resource	Organization	Location
Cancer Prevention & Early Detection Facts & Figures 2009	ACS	http://www.cancer.org/downloads/STT/860009web_6-4-09.pdf
<i>Tobacco Cessation - You Can Quit Smoking Now!</i> (includes Clinical Practice Guideline Treating Tobacco Use and Dependence: 2008 Update)	U.S. DHHS Office of the Surgeon General	http://www.surgeongeneral.gov/tobacco/ http://www.surgeongeneral.gov/tobacco/treating_tobacco_use08.pdf
<i>Healthy People 2010</i>	U.S. DHHS	http://www.healthypeople.gov/
<i>I Quit! What to Do When You're Sick of Smoking, Chewing, or Dipping</i> (booklet for young people)	CDC	http://www.cdc.gov/tobacco/quit_smoking/how_to_quit/iquit/index.htm
<i>Youth Tobacco Cessation: A Guide for Making Informed Decisions</i>	CDC	http://www.cdc.gov/tobacco/quit_smoking/cessation/youth_tobacco_cessation/index.htm#
<i>Youth Tobacco Prevention Resource Website</i>	CDC	http://www.cdc.gov/tobacco/youth/index.htm

*ACS indicates American Cancer Society; CDC, Centers for Disease Control and Prevention; and U.S. DHHS, United States Department of Health and Human Services.

of particular importance to some adolescents that most indicated they would prefer to date people who do not smoke (81% of 8th graders, 80% of 10th graders, and 75% of 12th graders).

Follow-up is essential during smoking cessation attempts. The pharmacist is in a great position to inquire about success, motivate if relapse occurs, and reassess the therapeutic plan as needed. The pharmacist also has a responsibility to monitor for misuse of NRT, in both smoking and nonsmoking adolescents. Because adolescents become quickly dependent on nicotine, primary prevention strategies should also be incorporated into practice. These may include not selling cigarettes or other forms of tobacco in the pharmacy, displaying posters and models that depict consequences of tobacco use, regularly assessing smoking status, reinforcing abstinence, encouraging open communication, and being a positive role model by not smoking. Several online resources are available to aid the pharmacist with smoking cessation initiatives (Table 4).

CONCLUSION

Smoking remains a problem in the adolescent population, and national organizations are emphasizing the resources to help them quit. There is an overall lack of large, long-term studies evaluating the use of pharmacotherapy for

smoking cessation in the adolescent population. However, some evidence exists from short-term trials that bupropion and NRT are beneficial to aid adolescents in smoking cessation and to reduce the number of cigarettes smoked per day. The decision to use pharmacotherapy should be individualized and should be combined with psychosocial and behavioral interventions. The pharmacist can play a large role in adolescent smoking cessation efforts.

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