Nicotine & Tobacco Research, Volume 14, Number 2 (February 2012) 234–239

Brief Report

Varenicline versus Bupropion XL for Smoking Cessation in Older Adolescents: A Randomized, Double-Blind Pilot Trial

Kevin M. Gray, M.D.,[1] *Matthew J. Carpenter, Ph.D.,*[1,2] *A. Lee Lewis, M.D.,*[1] *Erin M. Klintworth, B.A.,*[1] *& Himanshu P. Upadhyaya, M.B.B.S., M.S.*[1]

[1] *Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC*
[2] *Hollings Cancer Center, Medical University of South Carolina, Charleston, SC*
Himanshu P. Upadhyaya is now at Eli Lilly and Company

Corresponding Author: Kevin M. Gray, M.D., *Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, 67 President Street, MSC861, Charleston, SC 29425, USA. Telephone: 843-792-6330; Fax: 843-792-8206; E-mail: graykm@musc.edu*

Received March 21, 2011; accepted May 20, 2011

Abstract

Introduction: Despite tremendous potential public health impact, little work has focused on development of evidence-based smoking cessation treatments for adolescents, including pharmacotherapies. No prior studies have explored the feasibility and safety of varenicline and bupropion XL, 2 potentially promising pharmacotherapies, as smoking cessation treatments in adolescents.

Methods: Treatment-seeking older adolescent smokers (ages 15–20) were randomized (double-blind) to varenicline ($n = 15$) or bupropion XL ($n = 14$), with 1-week titration and active treatment for 7 weeks. Structured safety, tolerability, and efficacy assessments (cotinine-confirmed 7-day point prevalence abstinence) were conducted weekly.

Results: There were no serious adverse events. Two participants discontinued bupropion XL due to adverse effects, and none discontinued varenicline. Over the course of treatment, participants receiving varenicline reduced from 14.1 ± 6.3 (mean ± *SD*) to 0.9 ± 2.1 cigarettes/day (CPD, 4 achieved abstinence), while those receiving bupropion XL reduced from 15.8 ± 4.4 to 3.1 ± 4.0 CPD (2 achieved abstinence).

Conclusions: These preliminary results support the feasibility and safety of conducting adequately powered, placebo-controlled efficacy studies of varenicline and bupropion XL for adolescent smoking cessation.

Introduction

Almost all adult smokers began smoking during adolescence, and youth smoking rates range, in steadily increasing numbers, from 6% of 14-year olds to 37% of 21-year olds (Backinger, Fagan, Matthews, & Grana, 2003; Substance Abuse and Mental Health Services Administration, 2008). Daily smoking, a particularly concerning predictor of long-term smoking and adverse health outcomes, is uncommon in younger adolescents (3% of 8th graders, 7% of 10th graders), but increasingly prevalent as older adolescents transition into adulthood (11% of 12th graders and 17% of 21-year olds; Johnston, O'Malley, Bachman, & Schulenberg, 2011; Substance Abuse and Mental Health Services Administration, 2008). Nearly two-thirds of young smokers may be interested in quitting, but only 4%–6% of unassisted quit attempts are successful (Chassin, Presson, Pitts, & Sherman, 2000; Stanton, McClelland, Elwood, Ferry, & Silva, 1996; Zhu, Sun, Billings, Choi, & Malarcher, 1999).

Surprisingly, few controlled studies have evaluated adolescent smoking cessation programs, and almost all have exclusively focused on psychosocial treatments, yielding generally discouraging results. For example, a meta-analysis of 48 studies showed a mean quit rate of 9.1%, compared with 6.2% among control groups (Sussman, Sun, & Dent, 2006). In the interest of enhancing these modest quit rates, and in light of clear evidence that adolescent smokers experience nicotine withdrawal and craving (Jacobsen et al., 2005; Killen et al., 2001; Prokhorov et al., 2001), a handful of recent studies have explored the potential impact of pharmacotherapy for adolescent smokers. Only six controlled cessation trials to date, most enrolling predominantly older adolescents, have investigated bupropion SR (Gray et al., 2011 [mean age 18]; Killen et al., 2004 [mean age 17]; Muramoto, Leischow, Sherrill, Matthews, & Strayer, 2007 [mean age 16]) and/or nicotine replacement therapy (Hanson, Allen, Jensen, & Hatsukami, 2003 [mean age 17]; Moolchan et al., 2005 [mean age 15]; Rubinstein, Benowitz, Auerback, & Moscicki, 2008 [mean age 17]). Results, while mixed, suggest that some pharmacotherapies may complement psychosocial treatment and enhance cessation outcomes.

Bupropion SR trials in adolescents support the efficacy of the 300 mg/day dose, but not the 150-mg dose (Gray et al., 2011; Killen et al., 2004; Muramoto et al., 2007). Twice daily dosing, which is necessary for 300 mg/day of bupropion SR, introduces

doi: 10.1093/ntr/ntr130
Advance Access published on July 20, 2011

concerns about multidose medication adherence, a common issue among adolescents (McGuinness & Worley, 2010) that may diminish efficacy (Charach, Volpe, Boydell, & Gearing, 2008). Bupropion XL, administered once daily (300 mg), may allow for improved adherence and persistence with treatment (McLaughlin, Hogue, & Stang, 2007; Stang, Suppapanaya, Hogue, Park, & Rigney, 2007; Stang, Young, & Hogue, 2007). However, there have been no previous published smoking cessation studies of bupropion XL in adolescents or adults.

Varenicline has demonstrated superior efficacy in adults compared with bupropion SR and nicotine patch (Aubin et al., 2008; Eisenberg et al., 2008; Gonzales et al., 2006; Jorenby et al., 2006; Nides et al., 2006), but each of these trials was based on a sample of adult smokers (e.g., mean age ≥42 for each trial). The only prior study of varenicline for adolescent smokers was limited in scope (Faessel, Ravva, & Williams, 2009). This 2-week pharmacokinetic study supported the short-term safety of varenicline and provided guidance on dosing in adolescents, but did not evaluate its smoking cessation efficacy and safety.

Given the shortage of prior smoking cessation pharmacotherapy trials focused on young smokers, and the potential promise of varenicline and bupropion XL, the present study sought to evaluate, via a double-blind randomized design, the feasibility and safety of both within an older adolescent population.

Methods

Participant Eligibility and Recruitment

To enroll in the study, adolescents were required to (a) be 14–20 years old; (b) smoke at least five cigarettes/day (CPD; but not use other tobacco products); (c) express interest in quitting, including at least one prior unsuccessful quit attempt; (d) not be pregnant and use birth control to avoid pregnancy; (e) lack current non-nicotine substance use disorders; (f) have no unstable psychiatric or medical illness; (g) have no history of suicidal, homicidal, or aggressive behavior; (h) have no history of seizures or eating disorders; and (i) not be taking current pharmacotherapy for smoking cessation treatment or medications metabolized by CYP2B6 or CYP2D6. Recruitment occurred primarily through community media advertisements (e.g., flyers, newspaper advertisements, etc.). If an initial telephone screen suggested potential eligibility, adolescents were scheduled for an informed consent and baseline assessment visit. Participant consent was obtained for all adolescents aged 18 years or older, whereas parental consent and participant assent were obtained for those less than 18 years old. The U.S. Food and Drug Administration (FDA) approved the Investigational New Drug application for the conduct of this study. The procedures followed were approved by the university institutional review board and were in accord with the Helsinki Declaration of 1975.

Screening and Baseline Assessments

Comprehensive psychiatric assessment (Sheehan et al., 1998, 2010), physical examination, laboratory testing (complete blood count, comprehensive metabolic panel, urine pregnancy test, and urine drug screen), and electrocardiogram were performed. A thorough smoking history was obtained, and baseline nicotine dependence was assessed using the Modified Fagerström Tolerance Questionnaire (Prokhorov et al., 2000) and the Hooked on Nicotine Checklist (DiFranza et al., 2002).

Randomization and Treatment

Eligible participants in both groups were given quit smoking brochures, instructed to set a quit date within 2 weeks of medication initiation, and randomized to receive an 8-week double-blind course of varenicline or bupropion XL. Varenicline participants ≥55 kg received 0.5 mg daily for 3 days, 0.5 mg twice daily for 4 days, and then 1 mg twice daily thereafter. Those <55 kg received 0.5 mg daily for 7 days and then 0.5 mg twice daily thereafter (Faessel et al., 2009). Bupropion XL participants received 150 mg daily for 7 days and then 300 mg daily thereafter. The university investigational drug service encased medications in identical-appearing capsules and dispensed them in weekly blister packs with specific instructions on day/time for each dose. Placebo capsules were used at times when no active medication was scheduled (i.e., evening dose for participants randomized to bupropion XL, to match evening dose of varenicline). We recognize that this design element undermined the potential adherence advantage of bupropion XL once daily dosing, but judged that maintenance of the treatment blind was of primary importance.

Participants were seen weekly during the 8-week medication trial and returned for posttreatment follow-up assessment at Week 12. At all visits, the study physician provided brief individual cessation counseling (≤10 min) and structured safety assessment.

Measures

Safety

A thorough safety evaluation was conducted at each visit (weekly during active treatment): (a) physician evaluation of physical and neuropsychiatric adverse events via open-ended interview and comprehensive, structured review of systems (Kalachnik, 2001), (b) Columbia Suicide Severity Rating Scale (Meyer et al., 2010; Posner et al., 2007) and the Beck Depression Inventory II (BDI; Beck, Steer, & Brown, 1996; Subramaniam, Harell, Huntley, & Tracy, 2009) to assess neuropsychiatric events, (c) urine pregnancy testing (females only), and (d) vital sign measurement.

Adherence

Medication diaries and weekly pill counts (inspection of blister packs and documentation of missed doses) were used to measure adherence.

Efficacy

Participants completed a 30-day cigarette timeline followback at the assessment visit and daily cigarette diaries (collected weekly) throughout treatment (Harris et al., 2009; Sobell, Sobell, Leo, & Cancilla, 1988). Carbon monoxide breathalyzer and urine cotinine testing (NicAlert, Nymox Pharmaceuticals) were used to biologically verify smoking status.

Urine cotinine-verified 7-day point prevalence abstinence was assessed at each study visit beyond the scheduled quit date.

Analyses

The pilot nature of the protocol precluded powered statistical analyses of safety or efficacy. Results are thus generally descriptive in nature. Nonetheless, generalized estimating equations (GEE)

Table 1. Participant Baseline Characteristics

	Varenicline ($n = 15$)	Bupropion XL ($n = 14$)
Age, $M \pm SD$	19.1 ± 0.6 (range 18–20)	18.7 ± 1.5 (range 15–20)
% Female	47	57
CPD		
Weekdays	14.1 ± 6.2	15.5 ± 4.7
Weekends	16.4 ± 8.9	18.8 ± 6.5
Years as a daily smoker	3.8 ± 2.1	2.8 ± 1.4
Age became a daily smoker	15.4 ± 2.2	15.9 ± 1.3
Number of past quit attempts	1.6 ± 1.2	1.3 ± 1.0
% Living with another smoker	87	64
mFTQ (range 0–9)	6.1 ± 2.1	7.2 ± 2.2
HONC (range 0–10)	6.8 ± 1.6	7.8 ± 2.1

Note. CPD = cigarettes/day; mFTQ = Modified Fagerström Tolerance Questionnaire and HONC = hooked on nicotine checklist.

were used to assess for time effects on secondary outcomes of smoking behavior (CPD, abstinence). Given (a) the study's small sample, (b) our secondary focus on efficacy, and (c) no placebo control group, we did not anticipate any medication effects or time × medication interactions. CPD and medication adherence were calculated only among participants retained in the study at each corresponding time point.

Results

Participants

Twenty-nine participants (age range 15–20 years) enrolled over an 8-month recruitment period and were randomized to treatment (15 to varenicline and 14 to bupropion XL). Sample characteristics are detailed in Table 1. There were no significant differences between treatment groups among these variables.

Safety

There were no FDA-defined serious adverse events in either treatment group. None of the varenicline participants discontinued medication. One participant randomized to bupropion XL discontinued medication due to increased anxiety and another discontinued due to "feeling too focused." Adverse events occurring in more than one varenicline participant included insomnia (4), nausea (3), and headache (2). Adverse events occurring in more than one bupropion XL participant included vivid dreams (5), insomnia (2), nausea (2), and chest discomfort (2). No suicidal behavior or ideation was observed in either treatment group, and no participants reported clinically significant depressive symptoms on BDI.

Adherence

Varenicline participants took 80% of dispensed doses, and bupropion XL participants took 79% of dispensed doses.

Efficacy

Smoking outcomes (CPD, abstinence by week) are detailed in Table 2. GEE analysis revealed significant ($p < .01$) time effects for both outcomes over the course of treatment and as expected no significant treatment (varenicline vs. bupropion XL) effects or interactions.

Discussion

Results of this preliminary pilot trial support the feasibility and safety of conducting older adolescent smoking cessation trials with varenicline and bupropion XL. While both medications carry FDA "black box warnings" related to potential neuropsychiatric adverse effects, they were generally well tolerated and were not associated with depressive symptoms or suicidality as assessed by comprehensive, validated evaluation methods. Additionally, smoking outcomes (detailed in Table 2), while preliminary, are encouraging, and though our design did not include a placebo control, suggest that both medications could be efficacious. We believe these findings warrant larger, adequately powered (and controlled) clinical trials within older adolescent smokers.

Table 2. Smoking Outcomes, by Study Week

	Week									
	Baseline	1	2	3	4	5	6	7	8	12[a]
Participants retained (n)										
Varenicline	15	14	12	11	10	10	9	9	9	4
Bupropion XL	14	14	12	12	12	11	8	8	7	5
CPD ($M \pm SD$)[b,c]										
Varenicline	14.1 ± 6.3	8.8 ± 4.3	4.2 ± 3.9	2.6 ± 3.3	1.8 ± 3.8	0.8 ± 1.2	0.7 ± 1.1	1.2 ± 1.5	0.9 ± 2.1	0.9 ± 0.8
Bupropion XL	15.8 ± 4.4	11.9 ± 7.1	5.9 ± 4.6	5.2 ± 4.6	5.0 ± 5.0	4.9 ± 5.2	4.4 ± 4.8	5.3 ± 6.4	3.1 ± 4.0	7.0 ± 4.4
Participants achieving 7-day point prevalence abstinence (n)[c,d]										
Varenicline	N/A			2	3	4	3	2	1	0
Bupropion XL				2	2	2	1	2	2	1

Note. CPD = cigarettes/day and N/A = not applicable.

[a]Treatment concluded at Week 8, posttreatment follow-up occurred at Week 12.

[b]Among participants retained at each time point.

[c]Significant time effect during treatment, $p < .01$.

[d]Zero cigarettes in a week, confirmed by urine cotinine testing.

Interpretation of findings should be tempered by study limitations, most notably the lack of power within the small sample to comprehensively assess safety, tolerability, and efficacy of these medications. While the double-blind nature of the randomized treatment was a methodological strength, inclusion of a placebo treatment group would have allowed for additional comparisons. Another concern is poor participant retention, a pervasive challenge in adolescent smoking cessation studies that undermines the ability to detect effects over time. For this reason, we caution readers not to over-interpret abstinence outcomes (Table 2), which are provided for descriptive purposes only. To address attrition, future studies should incorporate innovative techniques, such as retention-targeted contingency management (Carroll et al., 2006; Festinger, Marlowe, Dugosh, Croft, & Arabia, 2008; Ledgerwood, Alessi, Hanson, Godley, & Petry, 2008; Sinha, Easton, Renee-Aubin, & Caroll, 2003), and should be conservatively powered in anticipation of elevated dropout rates compared with adult studies.

Despite these limitations, findings provide a novel addition to the nascent older adolescent smoking cessation pharmacotherapy literature. Varenicline and bupropion XL, never before investigated as cessation treatments in young smokers, appear to be viable candidates for further study based on the present results. Future studies to comprehensively evaluate their safety, tolerability, and efficacy in older adolescents should incorporate a fully powered sample, a longer course of treatment (12 weeks), and posttreatment follow-up over several months to allow for more direct comparison with the well-established adult smoking cessation pharmacotherapy literature. One would expect, based on findings to date, lower absolute rates of abstinence among older adolescents versus adults, but it is unclear how effect sizes (odds ratios) would compare between these two age groups. What is clear is that, given the prevalence and significant public health impact of older adolescent smoking, as well as the limits of the current cessation evidence base, further studies of pharmacotherapy for older adolescent smoking cessation will be critical contributions to the field.

Funding

Medical University of South Carolina Hollings Cancer Center Pilot Research Program and the National Institutes of Health (K12DA000357, K23DA020482, R25DA020537, and UL1RR029882).

Declaration of Interests

Dr. Upadhyaya is an employee and stockholder of Eli Lilly and Company. The other authors do not have potential conflicts to declare.

Acknowledgments

The authors would like to thank participants and their families and gratefully acknowledge the efforts of the Medical University of South Carolina (MUSC) Investigational Drug Service and the MUSC Clinical and Translational Research Center clinical support staff.

References

Aubin, H. J., Bobak, A., Britton, J. R., Oncken, C., Billing, C. B., Jr., Gong, J., et al. (2008). Varenicline versus transdermal nicotine patch for smoking cessation: Results from a randomized open-label trial. *Thorax*, *63*, 717–724. doi:10.1136/thx.2007.090647

Backinger, C. L., Fagan, P., Matthews, E., & Grana, R. (2003). Adolescent and young adult tobacco prevention and cessation: Current status and future directions. *Tobacco Control*, *12*(Suppl. 4), IV46–IV53. doi:10.1136/tc.12.suppl_4.iv46

Beck, T. A., Steer, R. A., & Brown, G. K. (1996). *Beck Depression Inventory manual* (2nd ed.). San Antonio, TX: Psychological Corporation.

Carroll, K. M., Easton, C. J., Nich, C., Hunkele, K. A., Neavins, T. M., Sinha, R., et al. (2006). The use of contingency management and motivationa/skills-building therapy to treat young adults with marijuana dependence. *Journal of Consulting and Clinical Psychology*, *74*, 955–966. doi:10.1037/0022-006X.74.5.955

Charach, A., Volpe, T., Boydell, K. M., & Gearing, R. E. (2008). A theoretical approach to medication adherence for children and youth with psychiatric disorders. *Harvard Review of Psychiatry*, *16*, 126–135. doi:10.1080/10673220802069715

Chassin, L., Presson, C. C., Pitts, S. C., & Sherman, S. J. (2000). The natural history of cigarette smoking from adolescence to adulthood in a midwestern community sample: Multiple trajectories and their psychosocial correlates. *Health Psychology*, *19*, 223–231. doi:10.1037/0278-6133.19.3.223

DiFranza, J. R., Savageau, J. A., Fletcher, K., Ockene, J. K., Rigotti, N. A., McNeill, A. D., et al. (2002). Measuring the loss of autonomy over nicotine use in adolescents: The DANDY (Development and Assessment of Nicotine Dependence in Youths) study. *Archives of Pediatrics and Adolescent Medicine*, *156*, 397–403. Retrieved from http://archpedi.ama-assn.org/cgi/content/full/156/4/397

Eisenberg, M. J., Filion, K. B., Yavin, D., Bélisle, P., Mottillo, S., Joseph, L., et al. (2008). Pharmacotherapies for smoking cessation: A meta-analysis of randomized controlled trials. *Canadian Medical Association Journal*, *179*, 135–144. doi:10.1503/cmaj.070256

Faessel, H., Ravva, P., & Williams, K. (2009). Pharmacokinetics, safety, and tolerability of varenicline in health adolescent smokers: A multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Clinical Therapeutics*, *31*, 177–189. doi:10.1016/j.clinthera.2009.01.003

Festinger, D. S., Marlowe, D. B., Dugosh, K. L., Croft, J. R., & Arabia, P. L. (2008). Higher magnitude cash payments improve research follow-up rates without increasing drug use or perceived coercion. *Drug and Alcohol Dependence*, *96*, 128–135. doi:10.1016/j.drugalcdep.2008.02.007

Gonzales, D., Rennard, S. I., Nides, M., Oncken, C., Azoulay, S., Billing, C. B., et al. (2006). Varenicline, an $\alpha_4\beta_2$ nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion

and placebo for smoking cessation: A randomized controlled trial. *Journal of the American Medical Association*, *296*, 47–55. doi:10.1001/jama.296.1.47

Gray, K. M., Carpenter, M. J., Baker, N. L., Hartwell, K. J., Lewis, A. L., Hiott, D. W., et al. (2011). Bupropion SR and contingency management for adolescent smoking cessation. *Journal of Substance Abuse Treatment*, *40*, 77–86. doi:10.1016/j.jsat.2010.08.010

Hanson, K., Allen, S., Jensen, S., & Hatsukami, D. (2003). Treatment of adolescent smokers with the nicotine patch. *Nicotine and Tobacco Research*, *5*, 515–526. doi:10.1080/1462220031000118559

Harris, K. J., Golbeck, A. L., Cronk, N. J., Catley, D., Conway, K., & Williams, K. B. (2009). Timeline follow-back versus global self-reports of tobacco smoking: A comparison of findings with nondaily smokers. *Psychology of Addictive Behaviors*, *23*, 368–372. doi:10.1037/a0015270

Jacobsen, L. K., Krystal, J. H., Mencl, W. E., Westerveld, M., Frost, S. J., & Pugh, K. R. (2005). Effects of smoking and smoking abstinence on cognition in adolescent tobacco smokers. *Biological Psychiatry*, *57*, 56–66. doi:10.1016/j.biopsych.2004.10.022

Johnston, L. D., O'Malley, P. M., Bachman, J. G., & Schulenberg, J. E. (2011). *Monitoring the future national results on adolescent drug use: Overview of key findings, 2010*. Ann Arbor, MI: Institute for Social Research, The University of Michigan. Retrieved from http://monitoringthefuture.org/pubs/monographs/mtf-overview2010.pdfon

Jorenby, D. E., Hays, J. T., Rigotti, N. A., Azoulay, S., Watsky, E. J., Williams, K. E., et al. (2006). Efficacy of varenicline an $\alpha_4\beta_2$ nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: A randomized controlled trial. *Journal of the American Medical Association*, *296*, 56–63. doi:10.1001/jama.296.1.56

Kalachnik, J. E. (2001). *Standardized monitoring for psychopharmacologic medication side effects. Manual for the Monitoring of Side Effects Scale (MOSES)*. Columbia, SC: University of South Carolina, School of Medicine, Department of Pediatrics, Center for Disability Resources, and the South Carolina Department of Disabilities and Special Needs.

Killen, J. D., Ammerman, S., Rohas, N., Varady, J., Haydel, F., & Robinson, T. N. (2001). Do adolescent smokers experience withdrawal effects when deprived of nicotine? *Experimental and Clinical Psychopharmacology*, *9*, 176–182. doi:10.1037/1064-1297.9.2.176

Killen, J. D., Robinson, T. N., Ammerman, S., Hayward, C., Rogers, J., Stone, C., et al. (2004). Randomized clinical trial of the efficacy of bupropion combined with nicotine patch in the treatment of adolescent smokers. *Journal of Consulting and Clinical Psychology*, *72*, 729–735. doi:10.1037/0022-006X.72.4.729

Ledgerwood, D. M., Alessi, S. M., Hanson, T., Godley, M. D., & Petry, N. M. (2008). Contingency management for attendance to group substance abuse treatment administered by clinicians in community clinics. *Journal of Applied Behavioral Analysis*, *41*, 517–526. doi:10.1901/jaba.2008.41-517

McGuinness, T. M., & Worley, J. (2010). Promoting adherence to psychotropic medication for youth-part 1. *Journal of Psychosocial Nursing and Mental Health Services*, *48*, 19–22. doi:10.3928/02793695-20100831-03

McLaughlin, T., Hogue, S. L., & Stang, P. E. (2007). Once-daily bupropion associated with improved patient adherence compared with twice-daily bupropion in treatment of depression. *American Journal of Therapeutics*, *14*, 221–225. doi:10.1097/01.mjt.0000208273.80496.3f

Meyer, R. E., Salzman, C., Youngstrom, E. A., Clayton, P. J., Goodwin, F. K., Mann, J. J., et al. (2010). Suicidality and risk of suicide—Definition, drug safety concerns, and a necessary target for drug development: A consensus statement. *Journal of Clinical Psychiatry*, *71*, e1–e21. doi:10.4088/JCP.10cs06070blu

Moolchan, E. T., Robinson, M. L., Ernst, M., Cadet, J. L., Pickworth, W. B., Heishman, S. J., et al. (2005). Safety and efficacy of the nicotine patch and gum for the treatment of adolescent tobacco addiction. *Pediatrics*, *115*, e407–e414. doi:10.1542/peds.2004-1894

Muramoto, M. L., Leischow, S. J., Sherrill, D., Matthews, E., & Strayer, L. J. (2007). Randomized, double-blind, placebo-controlled trial of 2 dosages of sustained-release bupropion for adolescent smoking cessation. *Archives of Pediatrics and Adolescent Medicine*, *161*, 1068–1074. doi:10.1001/archpedi.161.11.1068

Nides, M., Oncken, C., Gonzales, D., Rennard, S., Watsky, E. J., Anziano, R., et al. (2006). Smoking cessation with varenicline, a selective alpha4beta2 nicotinic receptor partial agonist: Results from a 7-week, randomized, placebo- and bupropion-controlled trial with 1-year follow-up. *Archives of Internal Medicine*, *166*, 1561–1568. doi:10.1001/archinte.166.15.1561

Posner, K., Brent, D., Lucas, C., Gould, M., Stanley, B., Brown, G., et al. (2007). *Columbia-Suicide Severity Rating Scale (C-SSRS)*, New York, NY: The Research Foundation for Mental Hygiene, Inc.

Prokhorov, A. V., De Moor, C., Pallonen, U. E., Hudmon, K. S., Koehly, L., & Hu, S. (2000). Validation of the modified Fagerström tolerance questionnaire with salivary cotinine among adolescents. *Addictive Behaviors*, *25*, 429–433. doi:10.1016/S0306-4603(98)00132-4

Prokhorov, A. V., Hudmon, K. S., de Moor, C. A., Kelder, S. H., Conroy, J. L., & Ordway, N. (2001). Nicotine dependence, withdrawal symptoms, and adolescents' readiness to quit smoking. *Nicotine and Tobacco Research*, *3*, 151–155. doi:10.1016/S0306-4603(98)00132-4

Rubinstein, M. L., Benowitz, N. L., Auerback, G. M., & Moscicki, A. B. (2008). A randomized trial of nicotine nasal spray in adolescent smokers. *Pediatrics*, *122*, e595–e600. doi:10.1542/peds.2008-0501

Sheehan, D. V., Lecrubier, Y., Harnett-Sheehan, K., Amorim, P., Janavs, J., Weiller, E., et al. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview

for DSM-IV and ICD-10. *Journal of Clinical Psychiatry*, *59*, S22–S33.

Sheehan, D. V., Sheehan, K. H., Shytle, R. D., Janavs, J., Bannon, Y., Rogers, J. E., et al. (2010). Reliability and validity of the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID). *Journal of Clinical Psychiatry*, *71*, 313–326. doi:10.4088/JCP.09m05305whi

Sinha, R., Easton, C., Renee-Aubin, L., & Carroll, K. M. (2003). Engaging young probation-referred marijuana-abusing individuals in treatment: A pilot trial. *American Journal on Addictions*, *12*, 314–323. doi:10.1111/j.1521-0391.2003.tb00546.x

Sobell, L. C., Sobell, M. B., Leo, G. I., & Cancilla, A. (1988). Reliability of a timeline method: Assessing normal drinkers' reports of recent drinking and a comparative evaluation across several populations. *British Journal of Addiction*, *83*, 393–402. doi:10.1111/j.1360-0443.1988.tb00485.x

Stang, P., Suppapanaya, N., Hogue, S. L., Park, D., & Rigney, U. (2007). Persistence with once-daily versus twice-daily bupropion for the treatment of depression in a large managed-care population. *American Journal of Therapeutics*, *14*, 241–246. doi:10.1097/MJT.0b013e31802b59e4

Stang, P., Young, S., & Hogue, S. (2007). Better patient persistence with once-daily bupropion compared with twice-daily bupropion. *American Journal of Therapeutics*, *14*, 20–24. doi:10.1097/MJT.0b013e31802b5954

Stanton, W. R., McClelland, M., Elwood, C., Ferry, D., & Silva, P. A. (1996). Prevalence, reliability and bias of adolescents' reports of smoking and quitting. *Addiction*, *91*, 1705–1714. doi:0965-2140/96/111705-10

Subramaniam, G., Harrell, P., Huntley, E., & Tracy, M. (2009). Beck Depression Inventory for depression screening in substance-abusing adolescents. *Journal of Substance Abuse Treatment*, *37*, 25–31. doi:10.1016/j.jsat.2008.09.008

Substance Abuse and Mental Health Services Administration. (2008). *Results from the 2007 National Survey on Drug Use and Health: National Findings*. NSDUH Series H-34, DHHS Publication No. SMA 08–4343. Rockville, MD: Office of Applied Studies. Retrieved from http://oas.samhsa.gov/NSDUH/2k7NSDUH/2k7results.cfm#Ch4on

Sussman, S., Sun, P., & Dent, C. W. (2006). A meta-analysis of teen cigarette smoking cessation. *Health Psychology*, *25*, 549–557. doi:10.1037/0278-6133.25.5.549

Zhu, S. H., Sun, J., Billings, S. C., Choi, W. S., & Malarcher, A. (1999). Predictors of smoking cessation in U.S. adolescents. *American Journal of Preventive Medicine*, *16*, 202–207. doi:10.1016/S0749-3797(98)00157-3