Appendix 3.1
Evidence Tables

List of Tables

Table A3.1-1 Studies on aerosolized nicotine and dependence, by dependency criteria

A. A strong desire or sense of compulsion to take the substance[a]

Study	Design/population	Findings
McQueen et al. (2011)	• Interviews with people at MidWest Vapefest • Meetings with members of MidWest Vapers Group • Sample size = 15	• Participants reported not "having the same sense of urgency about vaping that I had about smoking. . . . I go all day without vaping, and it doesn't occur to me."
Dawkins et al. (2013)	• Survey of users of two popular brands of e-cigarettes in the United Kingdom • Sample size = 1,347	• 18% of current and former smokers craved e-cigarettes as much as tobacco. • 23% used an e-cigarette within 5 minutes of waking. • 49% used e-cigarettes within 6–30 minutes of waking.
Goniewicz et al. (2013)	• Survey of e-cigarette users in Poland • Sample size = 179	• 98% used e-cigarettes every day. • 44% used e-cigarettes within 30 minutes of waking.
Etter (2015)	• Cross-sectional survey in English and French of daily e-cigarette users who had quit smoking in the previous 2 months • Sample size = 374	• 38% reported "definitely" and 23% "a lot" about having strong urges to use e-cigarettes today. • 68% reported "definitely" feeling an irresistible urge to use e-cigarettes "after a few hours without using an e-cigarette." • Perceived effect of e-cigarettes on craving to smoke was associated with dependence on e-cigarettes and time to first puff of e-cigarettes after waking.
Etter and Eissenberg (2015)	• Survey of daily e-cigarette users from outside the United States • Sample size = 1,284	• 30.7% of people who used e-cigarettes containing nicotine reported they likely would not be able to stop using e-cigarettes. • 28.2% reported that it would be "very difficult" or "impossible" to stop using e-cigarettes. • 27.5% reported not being able to stop e-cigarette use.
Foulds et al. (2015)	• Survey of e-cigarette users who were former cigarette smokers • Sample size = 3,609	• 35% had strong cravings to use e-cigarettes. • 6.8% woke up at night to use e-cigarettes. • 93% had strong cravings to smoke a conventional cigarette. • 41.2% reported waking up at night to smoke cigarettes prior to quitting.

[a]Most of the evidence for this criterion comes from subjective reports of users regarding their experiences with e-cigarettes.

B. A persistent desire or unsuccessful efforts to reduce or control substance use[b]

Study	Design/population	Findings
Dawkins et al. (2013)	• Survey of users of two popular brands of e-cigarettes in the United Kingdom • Sample size = 1,347	• 12% of people who were attempting to reduce e-cigarette use reported being "very" or "extremely" successful.
Etter and Eissenberg (2015)	• Survey of daily e-cigarette users from outside the United States • Sample size = 1,284	• Of people who used e-cigarettes containing nicotine: – 30.7% reported they would likely not be able to stop using e-cigarettes. – 28.2% reported that it would be "very difficult" or "impossible" to stop using e-cigarettes. – 27.5% reported not being able to stop e-cigarette use.

[b]As applied to the use of e-cigarettes, there is little support for this criterion because of limited data on users of e-cigarettes trying to quit e-cigarette use. Many people report using e-cigarettes to replace, reduce, or avoid relapsing to cigarette use (Etter and Bullen 2011; Adkison et al. 2013; Dawkins et al. 2013; Vickerman et al. 2013; Etter and Eissenberg 2015) and may have no intention of stopping all nicotine or tobacco use.

Table A3.1-1 Continued

C. A physiological withdrawal state when substance use is reduced or ceased[c]

Study	Design/population	Findings
Vansickel and Eissenberg (2013)	• Experienced users of e-cigarettes who puffed in one session with four phases: baseline, 10-puff bout, *ad libitum* bout, and rest period • Sample size = 8	• Significant reductions in anxiety, "restlessness," and intention to smoke from abstinence to post-electronic-cigarette use. • Significant increases in "feel awake," "calm you down," and "concentrate" from abstinence to post-electronic-cigarette use.
Dawkins and Corcoran (2014)	• Regular users of e-cigarettes who engaged in 10- and 60-minute puffing bouts with e-cigarettes • Sample size = 14	• Significantly higher ratings of "urge to smoke" and nicotine-related withdrawal symptoms at tobacco-abstinent baseline compared with post-electronic-cigarette use.
Spindle et al. (2015)	• Experienced users of e-cigarettes who preferred two sessions with 10-puff bouts • Sample size = 13	• Significant reductions in "anxious," "urge to use an e-cigarette," "craving an e-cigarette," and "impatient" from tobacco-abstinent baseline to post-electronic- cigarette use. • Increases in "awake," "calm," and "concentrate" from tobacco-abstinent baseline to post-electronic-cigarette use.
St. Helen et al. (2016)	• E-cigarette users recruited over the Internet participated in a 1-day research ward study. Subjects took 15 puffs from their usual brand of e-cigarette. Exhaled breath was trapped in gas-washing bottles, and blood was sampled before and several times after use. • Thirteen healthy, experienced adult e-cigarette users (6 females and 7 males).	E-cigarettes delivered a mean of 1.3 mg (95% CI, 0.9–1.8) of nicotine, and 94% of the inhaled dose, 1.2 mg (0.8–1.7), was systemically retained. Mean maximum plasma nicotine concentration (C_{max}) was 8.4 ng/mL (95% CI, 5.4–11.5) and time of maximal concentration (T_{max}) was 2 to 5 minutes; one participant had T_{max} of 30 minutes. In this study, 89% and 92% of vegetable glycerin and propylene glycol, respectively, was systemically retained. Heart rate increased by an average of 8.0 beats per minute after 5 minutes. Withdrawal and urge to smoke decreased, and the e-cigarettes were described as satisfying.

[c]Results of these studies may be confounded by the use of conventional cigarettes by many users of e-cigarettes.

D. Use the same (or closely related) substance with the intention of relieving or avoiding withdrawal symptoms

Study	Design/population	Findings
Bullen et al. (2010)	• Single-blind, randomized, repeated-measures, crossover trial of users of the Ruyan V8 e-cigarette in New Zealand • Dependent smokers were randomized to 16 mg or 0 mg nicotine e-cigarettes. • Sample size = 40	• Significant reduction in desire to smoke for users of 16 mg nicotine e-cigarettes compared with users of 0 mg nicotine e-cigarettes. • Other withdrawal symptoms—such as irritability, restlessness, and poor concentration—were not dependent on dose.
Vansickel et al. (2010)	• Smokers who never used e-cigarettes who engaged in two 10-puff bouts of four Latin-square order conditions: own-brand cigarette, NPRO e-cigarette, Hydro e-cigarette, and sham cigarette • Sample size = 32	• Two brands of e-cigarettes significantly decreased ratings of tobacco abstinence symptoms, but to a lesser magnitude than conventional cigarettes.

Table A3.1-1 D Continued

Study	Design/population	Findings
Etter and Bullen (2011)	• Survey in English and French of visitors to websites and Internet forums related to e-cigarettes and smoking cessation • Sample size = 3,587	• 50% reported that e-cigarette use may relieve cravings where smoking is prohibited. • 60% reported that e-cigarettes may satisfy the desire to smoke. • 51% reported that e-cigarette use may help with quitting smoking. • 55% reported that e-cigarette use may help with reducing cigarette smoking. • 79% reported using e-cigarettes to deal with cravings for tobacco. • 67% reported using e-cigarettes to deal with withdrawal symptoms. • 77% reported using e-cigarettes to help with quitting smoking or avoiding relapse to conventional cigarettes.
Adkison et al. (2013)	• Data from Wave 8 of the International Tobacco Control Four-Country Survey • Sample size (had tried an e-cigarette) = 450	• 75.4% reported using e-cigarettes to help reduce smoking. • 85.1% reported using e-cigarettes to help quit smoking.
Bullen et al. (2013)	• Randomized, controlled, superiority trial in Auckland, New Zealand • Sample size = 657 • People were randomized (289 to nicotine e-cigarettes, 295 to patches, and 73 to placebo e-cigarettes) and were included in the intention-to-treat analysis.	• At 6 months, verified abstinence was – 7.3% (21 of 289) with nicotine e-cigarettes; – 5.8% (17 of 295) with patches; and – 4.1% (3 of 73) with placebo e-cigarettes. • Risk difference for nicotine e-cigarette *vs.* patches 1.51 [95% CI, –2.49 to 5.51]; for nicotine e-cigarettes *vs.* placebo e-cigarettes 3.16 [95% CI, –2.29 to 8.61]). • No significant differences in adverse events between products.
Caponnetto et al. (2013)	• 12-month randomized controlled trial of smoking reduction/abstinence in smokers not in the process of quitting • Sample size = 300 • Group 1 received 7.2 mg nicotine e-cigarettes for 12 weeks. • Group 2 received 7.2 mg nicotine e-cigarettes for 6 weeks followed by 5.4 mg nicotine e-cigarettes for 6 weeks. • Group 3 received placebo (no nicotine) e-cigarettes for 12 weeks.	• Declines in cig/day use and levels of exhaled carbon monoxide were observed at each study visit in all three study groups. • In smokers not intending to quit, the use of e-cigarettes, with or without nicotine, decreased cigarette consumption and elicited enduring tobacco abstinence without causing significant side effects.
Dawkins et al. (2013)	• Survey of users of two popular brands of e-cigarettes in the United Kingdom • Sample size = 1,347	• 76% reported initiating e-cigarette use as a "complete alternative to smoking." • 67% reported wanting a "complete alternative to smoking." • 7% reported initiating e-cigarette use to quit smoking. • E-cigarette use was associated with decreased cravings for tobacco cigarettes: 91% reported substantial decreases in cravings for conventional cigarettes.

Table A3.1-1 D Continued

Study	Design/population	Findings
Dockrell et al. (2013)	• Survey of smokers in Great Britain who had and had not used e-cigarettes • Sample size = 1,380	• 50% reported that e-cigarette use may relieve cravings where smoking is prohibited. • 60% reported that e-cigarette use may satisfy the desire to smoke. • 51% reported that e-cigarette use may help with quitting smoking. • 55% reported that e-cigarette use may help with reducing cigarette smoking.
Vansickel and Eissenberg (2013)	• Experienced users of e-cigarettes who puffed in one session with four phases: baseline, 10-puff bout, *ad libitum* bout, and rest period • Sample size = 8	• Significant reductions in "anxious," "restlessness," and intention to smoke from abstinence to post-electronic-cigarette use. • Significant increases in "feel awake," "calm you down," and "concentrate" from abstinence to post-electronic-cigarette use.
Vickerman et al. (2013)	• Survey of quitline users in six states • Sample size (ever users of e-cigarettes) = 765	• 51% reported using e-cigarettes to help quit other types of tobacco use. • 15% reported using e-cigarettes to replace other types of tobacco use. • 7% reported using e-cigarettes to reduce other types of tobacco use.
Dawkins and Corcoran (2014)	• Regular users of e-cigarettes who engaged in 10- and 60-minute puffing bouts with e-cigarettes • Sample size = 14	• Significant reductions in urge to smoke and nicotine-related withdrawal symptoms after 10- and 60-minute puff periods.
Grana et al. (2014)	• Survey of current smoking in the United States • Sample size = 949	• E-cigarette use at baseline did not significantly predict quitting 1 year later. • E-cigarette use by smokers was not followed by greater quitting.
Norton et al. (2014)	• Smokers who abstained from conventional cigarettes and used only e-cigarettes for 72 hours • Lab-monitored e-cigarette puffing sessions that occurred before and after the 72-hour period • Sample size = 32	• Initial use of e-cigarettes did not significantly reduce scores on either scale of the Questionnaire on Smoking Urges.
Wagener et al. (2014)	• E-cigarette-naïve smokers sampled three e-cigarettes for a <10-minute puffing bout, followed by *ad libitum* e-cigarette use for 1 week. • Sample size = 19	• No significant changes in nicotine withdrawal symptoms from baseline to post-electronic-cigarette use.
Etter (2015)	• Cross-sectional survey in English and French of daily e-cigarette users who had quit smoking in the previous 2 months • Sample size = 374	• 25% reported that addiction to e-cigarettes is the same strength as addiction to conventional cigarettes. • 2% reported that addiction to e-cigarettes is stronger than addiction to conventional cigarettes.
Etter and Eissenberg (2015)	• Survey of daily e-cigarette users from outside the United States • Sample size = 1,284	• 65% of users of e-cigarettes with nicotine reported that it is "very true" or "extremely true" that they use e-cigarettes to deal with cravings for cigarettes. • 82% reported using e-cigarettes to help with quitting smoking or avoiding relapse to conventional cigarettes.

Table A3.1-1 D Continued

Study	Design/population	Findings
Lechner et al. (2015)	• Current smokers were randomized to a crossover design using a first- and second-generation e-cigarette on two separate days. • Sample size = 22	• Significant reductions in nicotine withdrawal symptoms after e-cigarette use. • Greater reductions in nicotine withdrawal symptoms after use of the 2nd-generation e-cigarette compared with the 1st-generation e-cigarette.
Spindle et al. (2015)	• Experienced users of e-cigarettes who preferred two sessions with 10-puff bouts • Sample size = 13	• Significant reductions in "anxious," "urge to use an e-cigarette," "craving an e-cigarette," and "impatient" from tobacco-abstinent baseline to post-electronic-cigarette use. • Increases in "awake," "calm," and "concentrate" from tobacco-abstinent baseline to post-electronic-cigarette use.

E. Tolerance to the effects of the substance

Study	Design/population	Findings
Farsalinos et al. (2013)	• Interviews with experienced users of e-cigarettes who had completely substituted e-cigarettes for conventional cigarettes for at least 1 month • Sample size = 111	• 16.2% reported increasing the level of nicotine in e-cigarette liquid to achieve smoking abstinence. • No users reported decreasing the level of nicotine in e-cigarette liquid before smoking cessation. • The majority of e-cigarette users also used conventional cigarettes (Sutfin et al. 2013; Aboaziza and Eissenberg 2015; Barnett et al. 2015) and were likely already dependent on nicotine.
Polosa et al. (2014)	• Prospective observational study in Italy, evaluating smoking reduction or abstinence in smokers not intending to quit using an e-cigarette • 6-month intervention using e-cigarettes, with follow-ups through 24 months • Sample size = 24	• Four participants upgraded their initial e-cigarette to a higher performing e-cigarette.

Table A3.1-1 Continued

F. Preoccupation with substance use, as manifested by important alternative pleasures or interests being given up or reduced because of substance use, or by spending a great deal of time in activities necessary to obtain and take the substance or recover from its effects[d]

Study	Design/population	Findings
Etter and Bullen (2011)	• Survey in English and French of visitors to websites and Internet forums related to e-cigarettes and smoking cessation • Sample size = 3,587	• 39% reported using e-cigarettes to deal with situations in which smoking is not allowed.
Dawkins et al. (2013)	• Survey of users of two popular brands of e-cigarettes in the United Kingdom • Sample size = 1,347	• 13% reported using e-cigarettes more than conventional cigarettes because e-cigarette use is permitted in places where smoking is not.
Vickerman et al. (2013)	• Survey of quitline users in six states • Sample size (ever users of e-cigarettes) = 765	• 5.4% reported using e-cigarettes in places where tobacco is not allowed.
Mimms (2014)	• Article from onvaping.com posted in Vaping Tips	• Text and videos explain how to use the "stealth vaping" technique.
Bohrer (2015)	• Article from vapenewsmagazine.com	• "Stealth vaping" is a style of e-cigarette use that is not easily detected by others.

[d]Criterion may be slightly less relevant for nicotine than other substances of abuse.

G. Persistent substance use despite clear evidence of harmful consequences[e]

Study	Design/population	Findings
Adkison et al. (2013)	• Data from Wave 8 of the International Tobacco Control Four-Country Survey • Sample size (had tried an e-cigarette) = 450	• 66–82% of respondents who were aware of e-cigarettes believed that e-cigarettes are less harmful than conventional cigarettes.
Dockrell et al. (2013)	• Survey of smokers in Great Britain who had and had not used e-cigarettes • Sample size = 1,380	• 71% of smokers believed that e-cigarettes are safer than tobacco cigarettes. • 28% of smokers believed that e-cigarettes are safer than nicotine replacement therapies.
Goniewicz et al. (2013)	• Survey of e-cigarette users in Poland • Sample size = 179	• 82% did not think that e-cigarettes are completely safe but thought that they were less dangerous than conventional cigarettes.
Carroll Chapman and Wu (2014)	• Review of articles focused on e-cigarette use • Sample size = 21 studies	• 54% believed e-cigarettes are safer than tobacco.

Note: **CI** = confidence interval; **mg** = milligram.

[e]As applied to the use of e-cigarettes, there is little support for this criterion because of limited data on the health effects of e-cigarette use. Notably, e-cigarette use is often associated with replacing or reducing the use of conventional cigarettes (Etter and Bullen 2011; Adkison et al. 2013; Dawkins et al. 2013; Vickerman et al. 2013; Etter and Eissenberg 2015). Although various potentially harmful ingredients have been identified in e-cigarettes, their levels may be substantially lower than those found in conventional cigarettes (McAuley et al. 2012; Goniewicz et al. 2014a,b; Tayyarah and Long 2014). Additionally, some people who have replaced at least some cigarettes with e-cigarettes report improvements in their health (McQueen et al. 2011; Dawkins et al. 2013; Farsalinos et al. 2013; Hua et al. 2013; Polosa et al. 2014; Etter 2015).

Table A3.1-2 Human studies on the effects of nicotine exposure on adolescent users

Study	Design/population	Outcomes examined	Findings
Kandel et al. (1992)	• Representative cohort study • 1,160 young adults in grades 10 and 11 in public high schools in the state of New York • Followed at intervals and ending 18–19 years after baseline (to 35 years of age)	Personal interviews were conducted to assess licit and illicit drug use and psychotropic drug use. The sequence of progression was analyzed.	Four stages of progression were identified: legal drugs (alcohol or cigarettes); marijuana; illicit drugs other than marijuana; and medically prescribed psychotropic drugs. Progression to illicit drug use among males was dependent on prior alcohol use. Progression to marijuana use among females was dependent on either cigarette or alcohol use. Age of onset and frequency of use at lower stages of drug use were strong predictors of progression.
Lewinsohn et al. (1999)	• Longitudinal cohort study • 684 high school students, 14–18 years of age, from nine high schools in western Oregon • Followed to age 24	Participants were randomly selected and evaluated for alcohol, cannabis, and other drug use or dependence. Lifetime tobacco use, age at onset of smoking, and frequency or quantity of smoking and quit efforts during adolescence were assessed through interviews. Diagnosis of substance abuse or dependence was made using DSM-IV.	Lifetime smoking among older adolescents was significantly associated with future alcohol, cannabis, illicit drug, and multiple drug use disorders during young adulthood. Being a former smoker did not reduce the risk of future substance use disorders but was associated with a reduced risk of alcohol use disorder. Among daily smokers, earlier age at onset of smoking predicted future substance use disorders.
DiFranza et al. (2000)	• Longitudinal cohort study • 681 students, 12–13 years of age, in 7th grade in seven public schools in two cities in Massachusetts • Followed for 1 year	Interviews were conducted to collect detailed information about tobacco use. The latency time to onset of symptoms of nicotine dependence was measured from the time a student first smoked at least once per month.	Ninety-five students initiated occasional smoking; 22% of them (n = 21) reported symptoms of nicotine dependence within 4 weeks of initiating occasional smoking. Sixty (63%) reported one or more symptoms of nicotine dependence; 62% of them (37) reported symptoms of dependence before smoking daily.
Lai et al. (2000)	• Population-based survey • 17,809 respondents, 12 years of age or older, from the NHSDA (U.S. civilian, noninstitutionalized population)	Univariate and multiple logistic regression analyses were used to assess independent associations between cigarette smoking and use of other drugs. Results were adjusted for race and gender and stratified by age. The study excluded those with illicit drug use before smoking.	Participants who smoked cigarettes were significantly more likely than never smokers to use cocaine, heroin, crack, and marijuana, even after adjusting for potential confounders.

Table A3.1-2 Continued

Study	Design/population	Outcomes examined	Findings
Hanna et al. (2001)	• Participants 12–16 years of age in the NHANES III (U.S. civilian, noninstitutionalized population)	Associations between smoking and other drug or alcohol use and behavior problems were assessed using multivariate logistic regression, controlling for potential confounders. Smoking status, age of onset of regular smoking, alcohol use, and illicit drug use were determined from interviews. Outcomes assessed included depression or dysthymia, on the basis of DSM-III criteria; school problems, including repeating grades, suspension, or expulsion; use of birth control pills or pregnancy; and psychosocial skills.	Onset of regular smoking at 13 years of age or younger was associated with difficulty getting along with peers. Regular smoking was associated with alcohol use, illicit drug use, and school problems, regardless of onset of regular smoking. Smoking was not associated with depression or dysthymia but was associated with pregnancy.
DiFranza et al. (2002)	• Longitudinal cohort study • 679 urban 7th grade students, 12–13 years of age, from seven schools in two cities in central Massachusetts • Followed for 1 year	Interviews were conducted to collect detailed information about tobacco use. The latency time to onset of symptoms of nicotine dependence was measured from the time a student first smoked at least once per month.	Of 332 students who used tobacco, 40% reported dependence symptoms. The median latency from onset of monthly smoking to dependence symptoms was 21 days for girls and 183 days for boys. Median frequency of use at the onset of symptoms was two cigarettes, 1 day per week. The presence of dependence symptoms predicted continued smoking. No minimum dose or duration of nicotine use required for symptoms was identified.
Wagner and Anthony (2002)	• Population-based survey • 44,624 U.S. household civilian, noninstitutionalized residents 12–25 years of age	Two mechanisms were studied to help account for prior observations about the "stepping-stone" or "gateway" sequences that link the use of alcohol, tobacco, marijuana, and cocaine.	Users of tobacco and alcohol were more likely than nonusers to have an opportunity to try marijuana and more likely to use marijuana if given the opportunity.
Isensee et al. (2003)	• Longitudinal study • Analysis included 3,021 randomly selected subjects, 14–24 years of age at baseline, from the Early Developmental Stages of Psychopathology Study from Munich, Germany. • Follow-up = 4 years	Baseline and 4-year follow-up data were used to assess bidirectional associations between smoking and nicotine dependence and panic and other anxiety disorders. Cox regression with time-dependent covariates was used to adjust for potential confounders. Diagnostic assessments were on the basis of the Munich-Composite International Diagnostic Interview. Panic attack and panic disorder, social phobia, phobia not otherwise specified, posttraumatic stress disorder, generalized anxiety disorder, agoraphobia, and obsessive-compulsive disorder were defined according to DSM-IV criteria.	Panic attacks and panic disorder were strongly associated with occasional and regular smoking and nicotine dependence. Prospective analyses found significant associations between regular smoking and nicotine dependence and new-onset panic attacks and between nicotine dependence and onset of panic disorder. In regression analysis with adjustment for confounders, nicotine dependence was associated with panic attacks but not panic disorder.

Table A3.1-2 Continued

Study	Design/population	Outcomes examined	Findings
O'Loughlin et al. (2003)	• Longitudinal cohort study • 1,267 students in 7th grade who were enrolled in the McGill University Study on the Natural History of Nicotine Dependence • Convenience sample from seven English and three French secondary schools in Montreal, Canada • Followed for 6 years	Associations between five indicators of nicotine dependence and monthly, weekly, and daily smoking vs. less frequent smoking were assessed. Of the five indicators of nicotine dependence, one was based on the criteria for tobacco dependence in the ICD-10 and one on the HONC, and the remainder included three clusters of symptoms.	More than 16% of past 3-month smokers, more than 19% of weekly smokers, and nearly 70% of daily smokers were tobacco-dependent. Nicotine dependence and cravings were significantly associated with frequency of smoking.
Audrain-McGovern et al. (2004)	• Longitudinal cohort study • 1,123 students in 9th grade in public high schools in northern Virginia • Followed through the end of 12th grade	Data were collected on smoking practices, novelty seeking, academic performance, substance use, peer smoking, physical activity, sports participation, and receptivity to tobacco advertisements.	Four smoking trajectories were identified: never smokers, experimenters, earlier/faster smoking adopters, and later/slower smoking adopters. Earlier/faster smoking adopters were characterized by high novelty-seeking personality, depressive symptoms, poorer academic performance, and receptivity to tobacco advertising.
John et al. (2004)	• Population-based study • 1,601 current and 836 former smokers, 18–64 years of age, from northern Germany	Among adult smokers, this study assessed the relationship between (a) age of smoking initiation, any quit attempts, and a single nicotine dependence criterion, and (b) amount of lifetime smoking. Participants were given the Composite International Diagnostic Interview and the Fagerström Test for Nicotine Dependence.	The rates at which smokers who started smoking at a young age, had made five or more quit attempts, and met criteria for nicotine dependence increased with lifetime amount of smoking.
Jacobsen et al. (2005)	• 73 persons (41 daily smokers and 32 nonsmokers), 14–18 years of age • Exposure to nicotine (or not) was similar with respect to age, gender, and education level.	The study assessed several outcomes in daily smokers and nonsmokers: verbal working memory; verbal learning and memory; selected, divided, and sustained attention; mood; nicotine withdrawal; and tobacco craving. Analyses were controlled for general intelligence, reading achievement, parental education attainment, baseline affective symptoms, and lifetime exposure to alcohol and cannabis.	In adolescent smokers, cessation of tobacco use increased tobacco craving, symptoms of withdrawal, and depressed mood. Adolescent smokers had impairments in accuracy of working memory regardless of how recently they had started smoking. Performance decrements were more severe with earlier age at onset of smoking. Adolescent smokers experienced further disruption of working memory and verbal memory during smoking cessation. Male smokers initiated smoking at earlier ages than females and were more impaired during tests of selective and divided attention than were female smokers and nonsmokers.

Table A3.1-2 Continued

Study	Design/population	Outcomes examined	Findings
Lejuez et al. (2005)	• Cross-sectional analysis • 125 students, predominantly African American, in grades 5–12 • Ever smokers (even a puff) and never smokers	The relationship between propensity for risk taking and ever smoking was assessed using the standard and adolescent BART, as administered to ever and never smokers. The Sensation Seeking Scale and Eysenck Impulsiveness Scale were also administered.	Ever smokers and never smokers differed on propensity for risk taking; higher BART scores and higher self-reported impulsive sensation-seeking scores were associated with greater odds of ever smoking.
Biederman et al. (2006)	• Secondary analysis of a case-control family genetic study • 300 females, 12 years of age and older, 97 with ADHD and 203 without ADHD • Females with ADHD were selected from referrals to a pediatric psychopharmacology clinic at a major academic center and from pediatric clinics of a major health maintenance organization. • Controls were selected from the pediatric clinics.	Chronology of substance use was determined from participant recall of age at first use and age at which criteria for abuse or dependence were met. Survival models were used to assess whether cigarette smoking was associated with later alcohol and drug use and dependence. Results were adjusted for gender.	A history of cigarette smoking was significantly associated with subsequent use of alcohol and drugs and with the development of alcohol and drug use disorders. The association was stronger in youth with ADHD than in controls.
Brook et al. (2007)	• Longitudinal cohort study • Students in grades 7–10, of African American or Puerto Rican race/ethnicity, in East Harlem, New York City • Followed until they were in their mid-20s	Adolescents were assessed for tobacco, alcohol, and illicit drug use and dependence. Logistic regression was used to examine potential associations between patterns of cigarette use and subsequent alcohol and drug use and dependence. Results were controlled for ethnicity and gender.	Participants who had started smoking by age 14 and continued to smoke in their 20s were more likely than nonsmokers, smokers who quit by their mid-20s, or smokers who started smoking between 19 and 24 years of age to be diagnosed at follow-up with alcohol dependence and dependence on illicit drugs. Smokers who started between 19 and 24 years of age were more likely than nonsmokers to become drug but not alcohol-dependent.
DiFranza et al. (2007)	• Longitudinal cohort study • 217 students in 6th grade who had inhaled tobacco smoke • Six communities in Massachusetts • Followed for 4 years	Outcomes included loss of autonomy as judged by using the HONC. Tobacco dependence was assessed using ICD-10 criteria. Cox regression analysis was used to assess independent associations between potential predictors and outcomes.	Fifty-eight percent of the students lost autonomy, and 38% developed ICD-10 dependence. Predictors of progression to loss of autonomy and tobacco dependence included a feeling of relaxation with the first cigarette and depressed mood.

Table A3.1-2 Continued

Study	Design/population	Outcomes examined	Findings
Jacobsen et al. (2007b)	• Cross-sectional analysis • 67 adolescent smokers and nonsmokers, with and without prenatal exposure to maternal smoking • Groups were similar with respect to age, education attainment, IQ, years of parental education, and symptoms of inattention.	Diffusion tensor anisotropy and magnetic resonance imaging were used to examine white matter microstructure. The study assessed auditory attention and compared outcomes between exposed and unexposed participants.	Prenatal and adolescent exposure to tobacco smoke were both associated with increased fractional anisotropy in anterior cortical white matter. Adolescent smoking was associated with increased fractional anisotropy of regions of the internal capsule that contain auditory thalamocortical and corticofugal fibers. Fractional anisotropy of the posterior limb of the left internal capsule was positively correlated with reaction time during performance of an auditory attention task in smokers but not in nonsmokers. Development of anterior cortical and internal capsule fibers may be particularly vulnerable to disruption of cholinergic signaling induced by nicotine in tobacco smoke. Disruption of auditory corticofugal fibers may interfere with the ability of these fibers to modulate ascending auditory signals, leading to greater noise and reduced efficiency of neurocircuitry that support auditory processing.
Kandel et al. (2007)	• Longitudinal study • 353 students in grades 6–10 in public schools in Chicago • One parent (usually the mother) • Followed for 2 years	Household interviews were conducted three times during the study period. Time to nicotine dependence criteria, per DSM-IV, and full dependence syndrome were assessed. Other potential risk factors assessed included race, gender, one or both parents ever being nicotine-dependent, positive diagnostic screen for conduct disorder, pleasant experience with first tobacco use, marijuana use before tobacco use, alcohol use before tobacco use, peer smoking, depressive symptoms, positive screen for anxiety disorder, academic performance, and pubertal stage.	Twenty-five percent of the students experienced nicotine dependence within 23 months of onset of tobacco use. Tolerance, impaired control, and nicotine withdrawal were experienced most frequently.
Musso et al. (2007)	• Cross-sectional analysis • 27 White participants (15 regular smokers and 12 never smokers), 18–25 years of age, who were recruited through a newspaper advertisement	Event-related functional magnetic resonance imaging was used to assess prefrontal attentional network function in young adults.	Prefrontal attentional network activity was significantly reduced in smokers compared with nonsmokers. Number of years of smoking was associated with the extent of diminished attentional network activity.

Table A3.1-2 Continued

Study	Design/population	Outcomes examined	Findings
Bronisch et al. (2008)	• Longitudinal cohort study • 3,021 adolescents and young adult participants, 14–24 years of age at baseline, from the Early Development Stages of Psychopathology Study, randomly selected from population registers in Munich, Germany • Followed for an average of 42 months	Participants were assessed for smoking behaviors, nicotine dependence, suicide ideation, and suicide attempts using the standardized Munich-Composite International Diagnostic Interview.	Occasional and regular smoking and nicotine dependence at baseline were strongly associated with suicide ideation and suicide attempts. Associations remained significant when participants with major depression were excluded.
Wilens et al. (2008)	• Longitudinal cohort study • 166 people (80 with ADHD and 86 control probands), 15–25 years of age, in Massachusetts • Follow-up at 5 years for females and 10 years for males	This study assessed nicotine dependence in ADHD and control individuals. Nicotine dependence was assessed using the mFTQ.	Smokers with ADHD had significantly higher scores on the mFTQ than smokers without ADHD. The study found a positive linear relationship between the mFTQ score and ADHD symptoms of inattention and hyperactivity. Parental smoking, peer smoking, and living with a smoker all increased the risk for smoking among those with ADHD compared with controls.
Boden et al. (2010)	• Longitudinal birth cohort study • 1,055 children from the Christchurch Health and Development Study in Christchurch, New Zealand • Followed from birth to 25 years of age	This study assessed the relationships between smoking and depression in early adulthood using fixed-effects regression and structural equation modeling. Depression was assessed at 18, 21, and 25 years of age using a structured mental health interview. Smoking status and nicotine dependence also were assessed at 18, 21, and 25 years of age.	The study found significant associations between nicotine dependence symptoms and depressive symptoms. Findings remained significant after adjusting for potential confounders, including nonobserved genetic and environmental factors. Structural equation modeling suggested that the best-fitting causal model was one in which nicotine dependence led to depression. Use of daily cigarette intake, instead of nicotine dependence measures, produced similar findings.
Dierker and Mermelstein (2010)	• Longitudinal cohort study • 694 students in grades 9 and 10 from high schools in metropolitan Chicago: 594 students had smoked fewer than 100 cigarettes in their lifetime, and 152 students had smoked 100 or more cigarettes in their lifetime. • Participants were drawn from the Social and Emotional Contexts of Adolescent Smoking Patterns Study.	Nicotine dependence was assessed at baseline and at 24 months using the NDSS, modified for adolescents. Logistic regression was used to assess the association between nicotine dependence (determined by NDSS total score and endorsement of individual symptoms) at baseline and smoking behavior at 24 months. Results were adjusted for gender, number of days smoked in the past 30 days, number of cigarettes smoked in the past 7 days, and other tobacco use (chewing tobacco, snuff, or dip; cigars, cigarillos, or little cigars; and bidis or kreteks) in the past 30 days.	Among students who had smoked fewer than 100 cigarettes, high levels of nicotine dependence symptoms at baseline and individual symptoms predicted current and daily smoking behavior at 24-month follow-up; this finding was significant after controlling for baseline smoking (quantity and frequency), gender, and other tobacco use. Among students who had smoked 100 or more cigarettes but were smoking fewer than 5 cigarettes/day, the level of nicotine dependence and individual symptoms did not predict smoking behavior at 24-month follow-up.

Table A3.1-2 Continued

Study	Design/population	Outcomes examined	Findings
McKenzie et al. (2010)	• Prospective cohort study of adolescent and young adult health • Sample size = 1,943 • Teens were assessed 6 times in monthly intervals, with two follow-up assessments during young adulthood (Wave 7, 1998; Wave 8, 2001–2003)	Adolescent depression and anxiety symptoms were assessed using the Revised Clinical Interview Schedule (CIS-R). Young adult tobacco use was defined as daily use (6 or 7 days per week) and dependent use as ≥4 on the Fagerström Test for Nicotine Dependence).	Among adolescent "less than daily" smokers, those with high levels of depression and anxiety symptoms had an increased risk of nicotine dependence in young adulthood compared with young adults who had low levels of adolescent depression and anxiety symptoms, after adjusting for potential confounding factors. Among adolescent "daily" smokers, those with high levels of depression and anxiety symptoms had an almost twofold increase in the odds of reporting nicotine dependence in young adulthood compared with young adults with low levels of adolescent depression and anxiety symptoms.
Griesler et al. (2011)	• Longitudinal cohort study • 814 adolescent smokers in grades 6–10 and their mothers, as selected from the Transition to Nicotine Dependence study • Adolescent participants were recruited from public schools in Chicago. • Participants were followed for 2 years (five follow-ups for adolescents and three follow-ups for mothers).	Data from participants were obtained through computerized household interviews. Selected DSM-IV psychiatric disorders were ascertained annually from both adolescents and their mothers. Adolescent smoking, other tobacco use, DSM-IV nicotine dependence symptoms, and abuse and dependence on other substances were assessed. Maternal lifetime smoking, DSM-IV nicotine dependence symptoms, DSM-IV depression, and delinquency were also assessed. Cox proportional hazards models were used to estimate effects of (a) psychiatric disorders on the onset of nicotine dependence, and (b) nicotine dependence on psychiatric disorders. Multivariate models were used to control for psychiatric comorbidity and factors associated with nicotine dependence and psychiatric disorders.	Among lifetime smokers, 53.7% experienced at least one nicotine dependence criterion; 26.1%, full dependence; 14.1%, an anxiety disorder; 18.8%, a mood disorder; and 29.5%, a disruptive disorder. Nicotine-dependent youth had higher rates of individual and multiple disorders than those not dependent. After adjusting for covariates, mood disorder and nicotine dependence did not predict each other, but anxiety disorder predicted nicotine dependence. Bidirectional influences were observed for disruptive disorder and nicotine dependence. Predictors of full nicotine dependence included earlier age at onset of tobacco use; high initial pleasant sensitivity to tobacco; alcohol and illicit drug use, abuse, and dependence; and parental nicotine dependence.
Jamal et al. (2011)	• Longitudinal cohort study • 1,055 participants in the Netherlands Study of Depression and Anxiety Disorders who developed psychopathology after starting smoking	Time to onset of psychopathology after starting smoking was assessed. Smoking behavior was measured by questionnaire; age at onset of smoking was defined as the age at which the participant began smoking regularly. Lifetime diagnosis and age at onset of depression and anxiety disorders were ascertained using the lifetime version of the Composite International Diagnostic Interview (version 2.1). Hierarchical multiple linear regression was used to examine the outcome of time between the onset of smoking and the onset of psychopathology. Results were adjusted for several potential confounders.	The time between the onset of smoking and the onset of depression was 5 years shorter for early-onset than late-onset smokers. A greater percentage of early-onset than late-onset smokers had the first onset of psychopathology within the first 5 years of starting smoking. Age at onset of smoking predicted the onset of psychopathology after adjusting for gender, education, and childhood trauma. When anxiety and depression disorder were examined separately, the pattern was true only for anxiety disorders.

Table A3.1-2 Continued

Study	Design/population	Outcomes examined	Findings
Rubinstein et al. (2011)	• Cross-sectional analysis • 12 adolescent smokers (1–5 cigarettes/day) and 12 nonsmokers, all 13–17 years of age	Functional magnetic resonance imaging was used to assess responses to natural reinforcers (visual cues representing pleasurable foods).	Food images elicited greater activations in nonsmokers in multiple areas of the brain, including the insula, inferior frontal region, and rolandic operculum. Versus nonsmokers, smokers did not demonstrate greater blood oxygenation-level-dependent activations in any region of the brain.
Cengelli et al. (2012)	• Systematic review of longitudinal, population-based studies • Adolescent and young adult smokers	Determinants of self-initiated smoking cessation lasting at least 6 months	Five factors robustly predicted quitting: not having friends who smoked, not having intention to smoke in the future, resisting peer pressure to smoke, being older at first use of cigarette, and having negative beliefs about smoking.
Moylan et al. (2012)	• Systematic review of population-based observational studies • Random samples of adolescents and adults from Germany, the Netherlands, New Zealand, and the United States	The studies in the review investigated associations between cigarette smoking, nicotine dependence, and anxiety disorders using recognized, structured clinical diagnostic criteria.	Evidence suggests that some baseline anxiety disorders are risk factors for smoking initiation and nicotine dependence, but the evidence is heterogeneous. The evidence more consistently suggests that smoking and nicotine dependence are risk factors for the development of some anxiety disorders, such as panic disorder and generalized anxiety disorder, but the evidence is not consistent across studies.
Dierker et al. (2012)	• Face-to-face survey of adolescents (13–17 years of age) • Sample size = 10,123	This study investigated the occurrence of nicotine dependence following the achievement of previous smoking milestones (initiation, weekly, and daily smoking).	Among adolescents who had ever smoked (36%), 40.7% had reached weekly smoking levels and 32.8% had reached daily smoking. Essentially one in five (19.6%) adolescents who had ever smoked met criteria for nicotine dependence. An earlier age of smoking initiation, a shorter time since the onset of smoking, and faster transitions between smoking milestones were independently associated with the onset of daily smoking and nicotine dependence.
Zhan et al. (2012)	• Cohort study of 9th- and 10th-grade students • Sample size = 12,970	This study investigated the natural course of nicotine dependence from first use/early initiation to actual dependence.	Nicotine dependence symptoms were reported before reaching 100 cigarettes for a substantial number of adolescents (from 9.4% to 58.8% for individual symptoms).

Table A3.1-2 Continued

Study	Design/population	Outcomes examined	Findings
Cavalca et al. (2013)	• Cross-sectional analysis • 39 adolescents (22 smokers and 17 nonsmokers) from high schools in Connecticut • Smokers used five or more cigarettes per day. • Nonsmokers reported never smoking in their lifetime.	This study assessed associations between smoking status and risk-taking behaviors. Smoking status was confirmed with urine cotinine level. Risk-taking behavior was measured using the standard BART and modified BART to include a peer component. Personality measures of impulsivity (assessed with the Barratt Impulsiveness Scale 11) and the degree to which subjects acted autonomously with peers (assessed with the Resistance to Peer Influence tool) were also measured.	Smokers showed more risk-taking behaviors using the modified BART than with the standard BART.
Galván et al. (2013)	• Cross-sectional analysis • 18 daily smokers and 25 nonsmokers, 17–21 years of age	This study compared brain function related to decision making in youth and young adult smokers and nonsmokers. The BART was administered to smokers and nonsmokers using functional magnetic resonance imaging to identify neural correlates of risky decision making.	Level of risk modulated the brain activities in the right dorsolateral and ventrolateral prefrontal cortices more in smokers than nonsmokers.
Kendler et al. (2014)	• Monozygotic co-twin control study • 175 male and 69 female twin pairs • Virginia Adult Twin Study of Psychiatric and Substance Use Disorders	Pairs were selected for discordant age at onset of regular smoking to study the association between age of onset of regular smoking and risk for later nicotine dependence. Nicotine dependence was assessed using the Fagerström Test for Nicotine Dependence and level of craving. Chi-square tests and t-tests were used to conduct comparisons.	Twins who began smoking earlier had significantly higher scores on the Fagerström Test during their periods of heaviest smoking. Findings were consistent for male and female twin pairs. Craving for cigarettes when unable to smoke was also higher in the early-onset member of both groups. Early-onset twins did not differ from later-onset twins in symptoms of alcohol or cannabis use; maximal level of cannabis use; or sedative, stimulant, or cocaine use.
Tjora et al. (2014)	• Longitudinal cohort study • 924 students in grade 7 in the Norwegian Longitudinal Health Behaviour Study • Followed from 13 to 30 years of age	Cross-sectional and longitudinal analyses were conducted. The study measured daily smoking and depressed mood in nine waves. Depression and depressed mood were measured with an inventory developed by Alsaker (1992) and Holsen and colleagues (2000). Longitudinal models assessed depression predicting smoking, smoking predicting depression, and smoking and depression influencing each other from Waves 1 to 2 and Waves 2 to 3; the three models were compared with indices of fit.	Cross-sectional analyses found an association between early adolescent depression and early adolescent smoking. Longitudinal analyses showed early adolescent smoking predicting early adolescent depression and vice versa in Waves 1–2 and 2–3, and supporting reciprocal causal effects between smoking and depression that are established in early adolescence and maintained into adulthood.

Table A3.1-2 Continued

Study	Design/population	Outcomes examined	Findings
Treur et al. (2015)	• Cross-sectional and longitudinal study • 1,987 adult and 648 adolescent monozygotic twin pairs from the Netherlands Twin Registry, concordant and discordant for smoking	This study compared twins, in which pairs were concordant and discordant for tobacco exposure, for attention problems. Adult comparisons were cross-sectional, and adolescents were studied longitudinally from birth to approximately 18 years of age.	Adult twins who had ever smoked had more attention problems than their never-smoking co-twins. Longitudinal analysis showed greater increases in attention problems from adolescence to adulthood in twins who ever smoked than in never-smoking co-twins. In childhood and adolescence, ever-smoking twins had more attention problems than never-smoking co-twins; scores were similar before smoking was initiated and after both twins started smoking.

Notes: **ADHD =** attention deficit hyperactivity disorder; **BART** = Balloon Analogue Risk Task; **DSM-III** = Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition; **DSM-IV** = Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; **HONC** = Hooked on Nicotine Checklist; **ICD-10** = International Statistical Classification of Diseases and Related Health Problems, 10th revision; **IQ** = intelligence quotient; **mFTQ** = modified Fagerström Tolerance Questionnaire; **NDSS** = Nicotine Dependence Syndrome Scale; **NHANES III** = Third National Health and Nutrition Examination Survey; **NHSDA** = National Household Survey on Drug Abuse.

Table A3.1-3 Preclinical/animal studies on adolescent nicotine exposure

Study	Species/exposure	Measures	Outcome/findings	Comments
Williams and Kanagasabai (1984)	• Sprague-Dawley rats were mated and assigned to control and nicotine groups. • Animals were weighed at regular intervals and killed on day 20 of pregnancy.	• Fetal and placental weights were recorded, and analysis of fetal body water, fat, protein, and DNA carried out. • Rates of maternal adipose tissue lipolysis and lipogenesis were measured.	• Weight gains of mothers in the nicotine group were lower in the first and second weeks of pregnancy but similar to controls in the third week. • Fetal body weight, DNA, protein, and percentage water content were similar in the two groups. Mean fetal body fat (g/kg) was significantly higher in the nicotine group (96.2) than in controls (72.0). • Rates of maternal lipolysis were also higher in the nicotine group.	—
Newman et al. (1999)	• Rat offspring were exposed to nicotine through implantation of osmotic minipumps in dams at levels of 0.75, 1.5, and 3.0 mg/kg/day for 19 days prenatally and 16 days postnatally.	• Gestation length, body weight, litter size, sex difference, and locomotor activity.	• No significant effects were shown for gestation length, litter size, or male-to-female pup ratio. • Higher percentage of pup deaths resulted from nicotine-exposed dams than from control dams. • Significantly less litter body weight was shown in nicotine-exposed offspring on P1 when compared with controls. However, these offspring surpassed the control groups in litter body weight on P14 and P21. • Hyperactivity was shown in offspring exposed to prenatal/postnatal nicotine at levels of 0.75 and 3.0 mg/kg/day on P14, but not on P21 or at the 1.5 mg/kg/day condition.	Results are consistent with the hypothesis that rat offspring are susceptible to the neurochemical and neurobehavioral effects of prenatal/postnatal nicotine exposure.

Table A3.1-3 Continued

Study	Species/exposure	Measures	Outcome/findings	Comments
Grove et al. (2001)	• Pregnant rhesus monkeys were treated with nicotine tartrate (1.5 mg/kg x d) starting on day 26 of pregnancy and then through day 160 of gestation.	• Weight of offspring at birth • P1 plasma leptin level	• Nicotine exposure had no significant effect on absolute birth weights of the neonatal monkeys, although there was a 10% reduction in birth weights with nicotine exposure when they were normalized to maternal weight. • P1 plasma leptin levels were significantly reduced by about 50% in the nicotine treatment group compared with saline controls, suggesting that the infant monkeys exposed to nicotine may also have had lower body fat levels.	Findings from this study suggest that nicotine exposure during pregnancy may increase energy expenditure in the developing fetus through actions on hypothalamic systems, resulting in lower birth weights and body fat levels.
Adriani et al. (2002)	• Outbred CD-1 mice in early (P28–P35), middle (P37–48), and late (P50–P61) adolescence • Oral self-administration (10 mg/L nicotine)	• Reinforcing effects of nicotine—oral self-administration with two-bottle choice (addiction/rewarding)	• Early adolescents showed significant preference for nicotine-containing solution (intake was 1.15 ± 0.04 mg/kg on final day); middle adolescents had no preference; late adolescents showed aversion to nicotine.	Early adolescents (P28–P35) were the only group to increase consumption when nicotine content was lowered.
Vastola et al. (2002)	• Male and female Sprague-Dawley rats • Conditioned with saline or nicotine (weight of salt was 0.6 mg/kg, s.c.) was begun on P28 or P58. • Testing occurred on P40 or P70, respectively, in a biased CPP paradigm.	• Rewarding effects of nicotine • CPP	• Adolescent rats of both genders showed a significant place preference for nicotine, while adults did not. • Nicotine-induced locomotion during CPP testing also showed age effects. • Adults were sensitive to motor-suppressing effects of nicotine, while adolescents showed some sensitization after multiple exposures.	Adolescents were more sensitive than adults to the rewarding and locomotor-activating effects of nicotine. A possible mechanism for this age difference is an increase in NAc dopamine tone across development that leads to decreased stimulation of mesolimbic structures and less sensitivity to nicotine.

Table A3.1-3 Continued

Study	Species/exposure	Measures	Outcome/findings	Comments
Levin et al. (2003)	• Female Sprague-Dawley rats (~P54 or ~P84 start); acute and chronic nicotine i.v. self-administration; 0.01–0.8 mg/kg/infusion for acute-dose response; 0.03 mg/kg/infusion for chronic testing	• Reinforcing effects of nicotine—adult vs. adolescent onset of acute and chronic i.v. self-administration	• Adolescents had almost double the rate of self-administration as adults at 0.03 mg/kg/infusion during chronic testing.	Adolescent onset of self-administration resulted in greater nicotine intake, and this effect persisted into adulthood.
Slawecki et al. (2003)	• Sprague-Dawley rats • Transdermal nicotine patches delivered 5 mg/kg/day nicotine from P31 to P36. • Testing occurred at least 10 days after nicotine exposure.	• Emotional responding in adulthood	• Nicotine-exposed rats had lower ambulatory counts, center-square crosses, and latency to retreat than nonexposed rats. • In a modified open-field test with food in the center, exposed rats approached food and spent significantly less time with food than unexposed rats.	Adolescent nicotine produced lasting increases in anxiety-like behavior, even when a food reward was available. The mechanism may be enhanced CRF signaling in the amygdala.
Belluzzi et al. (2004)	• Sprague-Dawley rats at P28, P38, or P90 • Single-trial CPP with 0.125–0.5 mg/kg nicotine	• Rewarding effects of nicotine • Single-trial CPP (addiction/rewarding)	• Early adolescents (P28) showed CPP for 0.5 mg/kg nicotine, a subthreshold dose.	Early adolescents showed greater sensitivity to the rewarding effects of a single nicotine injection (0.5 mg/kg). Adults and late adolescents (P38) did not develop place preference for any dose.
Schochet et al. (2005)	• Male Sprague-Dawley rats • Rats received acute injections of saline or nicotine (0.1 or 0.4 mg/kg, s.c.) at 30 days of age or 70 days of age.	• Nicotine-induced neural activation	• Age-related differences were found in baseline levels of arc and *cFos*, with adolescents having higher expression than adults. • Nicotine produced greater arc induction in adolescent PFC regions than adults, especially in the ventrolateral orbital cortex and somatosensory cortex. • *cFos* and *NGFI-B* were upregulated by nicotine in an age-independent manner.	Adolescents may have higher baseline neuronal activity, and nicotine exposure during this time may have more profound activational effects in regions mediating reward and executive function than in adulthood. This may help explain age-related behavioral differences seen in responses to nicotine.

Table A3.1-3 Continued

Study	Species/exposure	Measures	Outcome/findings	Comments
Chen and Kelly (2005)	• Pregnant Sprague-Dawley rats • Rats were given 0-, 15-, or 25-mg nicotine pellets throughout pregnancy. • One group of offspring received 1 or 2 mg/kg/day nicotine during early postnatal period. • One group of offspring received no nicotine.	• Body weight of offspring • Neonatal thyroid status	• Nicotine treatment significantly increased body weight in female offspring starting on P35 and continued into adulthood. • This increase was seen initially in male offspring but did not persist into adulthood.	Findings support other studies reporting a higher body weight among children born to mothers who smoked during pregnancy. Data from this study on thyroid status suggest that cigarette smoking-induced alterations in thyroid status might be mediated through compounds in cigarettes other than nicotine.
Cohen et al. (2005)	• Offspring of Wistar and mutant mice lacking beta2 and nAChR subunit • Pregnant mice were implanted with osmotic minipumps that delivered either water or a controlled dose of nicotine.	• Sympathoadrenal system development in offspring • Breathing and arousal reflexes in offspring	• Newborn Wistar pups exposed to nicotine exhibited all of the deficits associated with maternal tobacco and nicotine use and linked to poor neonatal outcome: growth restriction, unstable breathing, and impaired arousal and catecholamine biosynthesis. • Similar deficits were detected in offspring lacking beta2-containing nAChRs.	Article suggests that the underlying mechanisms of nicotine's detrimental side effects on a range of crucial defensive reflexes involve loss of function of nAChR subtypes, possibly via activity-dependent desensitization.
Holloway et al. (2005)	• Offspring of female Wistar rats were given either saline (vehicle) or nicotine (1 mg/kg^{-1} day^{-1}) during pregnancy and lactation.	• Effect of fetal and neonatal exposure to nicotine, the major addictive component of cigarettes, on postnatal growth, adiposity, and glucose homeostasis	• Exposure to nicotine resulted in increased postnatal growth and adiposity. Nicotine exposure also resulted in dysglycemia at 7 and 26 weeks of age. Serum insulin concentrations were decreased in the pups exposed to nicotine at birth. This was associated with increased beta cell apoptosis (pups of saline-treated mothers, 8.8 (±1.21% apoptotic beta cells; pups of nicotine-treated mothers, 27.8 (±3.1%) apoptotic beta cells).	Fetal and neonatal exposure to nicotine results in metabolic changes in the offspring that are consistent with obesity and type 2 diabetes. Authors proposed that observed metabolic changes may be a consequence of the initial insult to the beta cell during fetal life and that this animal model has many characteristics of diabetes in humans.

Table A3.1-3 Continued

Study	Species/exposure	Measures	Outcome/findings	Comments
Gao et al. (2005)	• Offspring of Wistar rats were given nicotine or saline during pregnancy and lactation.	• Postnatal growth in offspring from weaning to 26 weeks	• Exposure to nicotine resulted in increased postnatal body weight and fat pad weight and an increased amount of perivascular adipose tissue (PVAT) in the offspring. • Phenylephrine-induced contraction without PVAT was not different between saline- and nicotine-exposed rats.	Prenatal nicotine exposure increased adiposity and caused an alteration in the modulatory function of PVAT on vascular relaxation response.
O'Dell et al. (2006)	• Male Wistar rats • Osmotic minipumps delivered saline or nicotine (0-4.7 mg/kg/day free base or 3.2 mg/kg/day free base) from ~P29 to P36 for adolescents and from ~P36 to P44 for adults to compare somatic and affective withdrawal. • Withdrawal was precipitated in both groups with mecamylamine.	• Somatic and affective withdrawal from chronic nicotine	• Adults displayed elevated ICSS thresholds during precipitated withdrawal, while adolescents showed no change. • Adults also displayed a dose-dependent increase in somatic withdrawal symptoms, while mecamylamine precipitated significant withdrawal in adolescents only at the highest dose (3.0 mg/kg, i.p.).	Overall, adolescents showed decreased sensitivity to the somatic and negative affective symptoms of nicotine withdrawal versus adults. These effects are not likely because of metabolic differences because blood nicotine levels were similar. The mechanism may be immature cholinergic and/or dopaminergic neurotransmission in the VTA.
Shram et al. (2006)	• Male Wistar rats • 10-day CPP with saline or nicotine (0.2, 0.4, or 0.8 mg/kg free base, s.c.) conditioning followed by testing on P38 or P70–P73 • 4-day CTA with saccharin and nicotine (0, 0.2, 0.4, or 0.8 mg/kg free base, s.c.) pairings followed by access to water or saccharin on P35 or P70–P73	• Rewarding and aversive properties of nicotine • CPP and CTA	• Adolescent rats displayed CPP for 0.8 mg/kg nicotine, while adults did not display CPP for any dose. • In CTA, nicotine pairings in adults attenuated saccharin consumption at the 0.4-mg/kg dose and trends for attenuation at 0.2 and 0.8 mg/kg. • Adolescents did not show any change in saccharin intake.	Periadolescent rats were less sensitive to the aversive effects of nicotine; results suggest that reward-aversion balance may shift toward reward in adolescents. Two possible substrates proposed: immature mesolimbic dopamine system and immature cholinergic system.

Table A3.1-3 Continued

Study	Species/exposure	Measures	Outcome/findings	Comments
Smith et al. (2006)	• Male and female Long- Evans rats • Osmotic minipumps delivered saline or nicotine (1 or 2 mg/kg/day free base) from P28 to P42 or P85 to P99. • Testing was done 1 month after treatment.	• Emotional responding in adulthood	• High- and low-dose-exposed adolescents spent less time in the center of the open-field arena. • Low-dose exposure to nicotine enhanced fear conditioning. However, extinction of freezing behavior was impaired after low-dose exposure. • Adult exposed rats overall displayed greater freezing in cued-fear conditioning than adolescent exposed animals, regardless of treatment. • No gender-related differences were seen.	Adolescent nicotine produced lasting increases in anxiety-like behavior and enhanced fear learning with impaired extinction. This may be because of increased α4 nAChR mRNA levels in PFC.
Brielmaier et al. (2007)	• Male Sprague-Dawley rats • Single-trial place conditioning began on P28 or P77 with saline or nicotine (0.5 mg/kg free base, s.c.), and testing occurred 2 days later.	• Rewarding effects of nicotine • CPP	• Adolescents developed a significant place preference for a single nicotine exposure, while adults did not.	Age-related differences in sensitivity to nicotine were likely attributable to continuing maturation of cholinergic or mesocorticolimbic dopamine systems.
Britton et al. (2007)	• Pregnant Sprague-Dawley rats • Osmotic minipumps delivered saline or nicotine (2 mg/kg/day free base) from gestational day 7 to pup weaning on P21.	• nAChR signaling in adolescence • Effects of perinatal nicotine exposure were measured using nicotine-stimulated 86Rb+ efflux assay in the frontal cortex, hippocampus, striatum, and thalamus.	• Cholinergic signaling via nAChRs was assessed in adolescent (P28, P35, and P49) and adult (P69) offspring. • In controls, nicotine-stimulated 86Rb+ peaked at mid-adolescence (P35 and/or P49) in all regions. • Perinatal nicotine eliminated the peak.	nAChR function, especially of the α4β2 subtype, peaked during adolescence. This may be attributable to higher expression, or differences in desensitization and recovery from desensitization. Perinatal nicotine prevented normal developmental trajectory of nAChR function, possibly attributable to decreased receptor expression or binding. This contrasts with clinical work showing greater sensitivity to nicotine in adolescence.

Table A3.1-3 Continued

Study	Species/exposure	Measures	Outcome/findings	Comments
Chen et al. (2007)	• Lewis rats, P43–P45 to P55–P57; 10-day, prolonged access (23 hours/day) i.v. self-administration of saline or nicotine (0, 7.5, 15, 30, or 60 µg/kg/infusion, free base)	• Reinforcing effects of i.v. nicotine • Intravenous self-administration with prolonged access	• Male and female adolescents acquired self-administration of nicotine at 15 and 30 µg/kg doses but did not acquire the behavior at 7.5 µg/kg dose. • Age comparison in females at 30 µg/kg dose showed that adolescents self-administered significantly more nicotine and acquired the behavior more rapidly than adults.	Observed no gender-based differences in sensitivity to nicotine dose in adolescent rats, with both genders showing an inverted U-shaped dose–response relationship, although rates of self-administration were still high at the higher doses. Adult females showed slower acquisition and decreased intake than adolescent females. Age differences may be attributable to enhanced metabolism, learning, or drug-induced corticosterone release in adolescents.
Kota et al. (2007)	• Adolescent (P28–P36) and adult (P75–P84) ICR mice • CPP (0.05–1 mg/kg, s.c. injections of nicotine or saline) • Withdrawal (osmotic minipumps delivered saline or nicotine [48 mg/kg/day]) for 7 days; on day 8, minipumps were removed to assess spontaneous withdrawal, or withdrawal was precipitated with 2.0 mg/kg, s.c. mecamylamine. • Anxiety-like and somatic withdrawal symptoms were scored.	• nAChR signaling in adolescence and adulthood • CPP, nicotine-stimulated 86Rb+ efflux, spontaneous and precipitated withdrawal	• Adolescents had increased sensitivity (versus adults) to rewarding effects of low nicotine doses (0.05 and 0.1 mg/kg) in a CPP paradigm. • In both spontaneous and precipitated withdrawal, adolescents showed fewer somatic and affective symptoms than adults. • nAChR function was potentiated in adolescents, who showed a leftward shift of the nicotine dose–response curve in the 86Rb+ efflux assay.	Adolescents were more sensitive to the rewarding effects of nicotine, but they exhibited fewer withdrawal symptoms than adults during precipitated and spontaneous withdrawal. A possible mechanism is increased function of nAChRs, also found here. Increased nAChR expression may also play a role, but it was not tested herein.

Table A3.1-3 Continued

Study	Species/exposure	Measures	Outcome/findings	Comments
McQuown et al. (2007)	• Male and female Sprague-Dawley rats (P28–P32 or P86–P90) • Rats were pretreated with nicotine (60 µg/kg/day, i.v.) for 4 days; with sucrose or cocaine (200 or 500 µg/kg/infusion, i.v.) self-administration the following 5 days.	• Reinforcing effects of other drugs of abuse • Acquisition of cocaine self-administration	• Adolescents had greater cocaine intake on all days of self-administration than adults. • Sucrose self-administration was unaffected by pretreatment.	Low-dose, semichronic nicotine exposure in early adolescence enhanced the reinforcing properties of cocaine but not sucrose. This difference is potentially attributable to immaturity of corticolimbic dopamine systems. This result suggests a "gateway" effect of adolescent nicotine on drug rewards but not natural rewards.
Shram et al. (2007)	• Male Wistar rats • Rats received acute injections of saline or nicotine (0.4 or 0.8 mg/kg, s.c.) on P35 or P67–P70.	• Nicotine-induced neural activation	• Adolescents had higher basal *cFos* levels in paraventricular nucleus of the thalamus, medial septum, and ventral tegmental area, while adults had higher *cFos* in pedunculopontine tegmental nucleus. • Nicotine-induced *cFos* in multiple subcortical regions, with adolescents showing greater induction in BNST, PVN of the thalamus, VTA, and NAc-shell.	Regions important for reward processing, such as the VTA, NAc-shell, and BNST, were more sensitive to nicotine-induced *cFos* increases in adolescent rats than in adult rats. Immature cholinergic and dopaminergic systems or different nicotine pharmacokinetics likely underlie age-dependent responses to acute nicotine.
Bergstrom et al. (2008)	• Long-Evans rats • Osmotic minipumps delivered saline or nicotine (2 mg/kg/day) from P29 to P43 or P80 to P93. • Tissue was collected 5 weeks later for Golgi-Cox staining.	• Synaptic remodeling • Layer V pyramidal neurons	• Nicotine exposure during adulthood increased basilar dendritic length and branch number in simple neurons. • Adolescent nicotine exposure led to a modest increase in basilar dendritic length in complex neurons.	Both adolescent and adult nicotine exposure altered pyramidal neuron structure but in distinct morphologic subtypes depending on age.

Table A3.1-3 Continued

Study	Species/exposure	Measures	Outcome/findings	Comments
Doura et al. (2008)	• Sprague-Dawley rats • Osmotic minipumps delivered saline or nicotine (6 mg/kg/day free base) for 14 days starting on P29 or in adulthood (~P70–P90) • Tissue collected on day 14.	• nAChR expression • Quantitative autoradiography for measurement of α7 α4β2* and α6* nAChRs using [^{125}I]αBtx, [^{125}I]A-85380, and [^{125}I]α-Ctx MII binding, respectively	• In saline-treated adolescents, binding at α4β2 nAChRs was uniformly higher across the 38 regions analyzed than in saline-treated adults, with a 50% mean increase. • Nicotine-induced upregulation of α4β2* nAChRs was less profound in adolescents. • Saline-treated adolescents had higher binding at α7, while nicotine treatment induced less upregulation than in adults. • α6 binding was largely similar across ages in saline-treated animals, but adolescents showed downregulation after nicotine, while adults showed no change in α6 binding.	α4β2* and α7 nAChRs showed a developmental peak during adolescence and a decreased sensitivity to nicotine-induced upregulation. This age difference in saline-treated animals may be explained by normal synaptic pruning in adolescence. α6* nAChRs, on the other hand, do not show a similar developmental arc and nicotine-induced downregulation that is not seen in adults. This may be attributable to unique subunit compositions in α6* nAChRs in adolescents.
Torres et al. (2008)	• Male Wistar rats • 10-day CPP with saline, nicotine (0–1.8 mg/kg free base, s.c.), or damphetamine (0–2.0 mg/kg salt, s.c.) conditioning followed by testing on P42 or P74. Adult rats were drug-naïve or pre-exposed to nicotine via osmotic minipumps delivering 4.7 mg/kg/day from P28 to P42.	• Rewarding and aversive properties of nicotine • CPP	• Naïve rats developed preference for nicotine in an inverted U-shape dose response, although adolescents developed preference for a wider range of doses than adults. • Adults developed preference for 0.2 mg/kg nicotine only. • In pre-exposed adults, no preference developed for the 0.2 mg/kg dose, but aversion to the 1.2 mg/kg dose did not develop. • Adolescents also showed diminished aversion to high doses (1.2 or 1.8 mg/kg). Conditioning with d-amphetamine showed no age differences in development of CPP.	Adolescents were more sensitive to the rewarding properties and less sensitive to the aversive properties of nicotine, but they showed no age differences in sensitivity to the effects of d-amphetamine. Pre-exposure to nicotine during adolescence blocked CPP in adulthood without causing tolerance and decreased aversion to high nicotine doses.

Table A3.1-3 Continued

Study	Species/exposure	Measures	Outcome/findings	Comments
Counotte et al. (2009)	• Male Wistar rats • Thrice-daily saline or nicotine (0.4 mg/kg, s.c.) from P34 to P43 or P60 to P69 • Behavioral testing occurred 5 weeks later.	• Attention/cognition • 5-CSRTT or delayed-reward task	• In 5-CSRTT, adolescent nicotine had detrimental effects on accuracy (i.e., reduction in correct detection) and increased impulsivity and time-out responses. • There were no effects of treatment on the delayed-reward task.	Adolescent exposure to nicotine produced lasting deficits in visuospatial attention and increased impulsive action but not impulsive choice. The mechanism may be hyperresponsiveness of dopaminergic terminals in medial PFC or alterations of serotonergic signaling.
Iñiguez et al. (2009)	• Male Sprague-Dawley rats (P30) • Two injections of nicotine (0.32 mg/kg, s.c.) on P30 • Behavioral testing on P85	• Mood • FST (sensitivity to aversive stimuli)	• During FST in adulthood, nicotine exposure produced higher immobility and lower swimming counts than in vehicle-treated rats.	Single nicotine exposure during adolescence enhanced sensitivity to aversive stimuli in adulthood. Chronic nicotine's ability to produce persistent depressive-like symptoms was blocked by acute nicotine or antidepressant treatment.
Counotte et al. (2011)	• Wistar rats (P34–P43 or P60–P69 during drug treatment) • Thrice-daily saline or nicotine (0.4 mg/kg, s.c.) for 10 days • Behavioral testing 5 weeks later	• Attention, cognition • 5-CSRTT	• Measured 5-CSRTT and synaptic protein expression and function in adulthood. • More impulsivity, impaired attention, and downregulation of mGluR2 in PFC of adolescent-treated rats only.	Adolescent, but not postadolescent, nicotine treatment led to diminished attention span and greater impulsivity as adults. Deficits were associated with reduction of presynaptic mGluR2 expression and function in PFC; group II mGluR2 agonist rescues deficits.

Table A3.1-3 Continued

Study	Species/exposure	Measures	Outcome/findings	Comments
Dao et al. (2011)	• Male Sprague-Dawley rats • Rats were treated with nicotine (60 µg/kg/day, i.v.) for 1 or 4 days starting at P28 or P86.	• Nicotine-induced neural activation	• Acute nicotine increased *cFos* in the NAc-shell and BLA of adolescents but not adults. • Subchronic nicotine induced significant *cFos* expression in the BLA of both ages but a greater increase in the NAcshell of adolescents. • Basal *cFos* differences were seen in PFC, NAc core, and dorsal striatum that were unaffected by acute or subchronic nicotine.	Acute or subchronic nicotine during adolescence had more profound activational effects in regions mediating reward and executive function than in adulthood. This may help to explain age-related behavioral differences seen in responses to nicotine, such as increased cocaine self-administration and quinpirole-induced locomotion.
Goriounova and Mansvelder (2012)	• Male Wistar rats • Thrice-daily injections of saline or nicotine (0.4 mg/kg free base, s.c.) from P34 to P43 or P60 to P69 • Tissue collected for electrophysiology 1–4 days or 5 weeks after treatment.	• Spike-timing-dependent plasticity in the PFC	• In adolescent control cells, induction of tLTP resulted in increased synaptic strength of 130% ± 15% for 45 minutes in the medial PFC. • This increase was not seen after acute bath application of nicotine. • Four days after adolescent nicotine exposure, tLTP induction resulted in less potentiation than in saline-treated animals. • Five weeks after nicotine treatment, exposed adults showed greater potentiation after a single action potential tLTP induction protocol than saline-treated adults, but no change in potentiation to a 5 AP tLTP induction protocol. • Nicotine treatment in adulthood had no effect on spike-timing-dependent plasticity.	Adolescent nicotine exposure produced lasting alterations in excitatory synapses and a resulting increase in tLTP. In the short term, reduced tLTP induction may be attributable to nicotine-induced increases in mGluR2 levels, while persistent reductions in inhibitory mGluR2 signaling from nicotine allowed for increased tLTP in adults.

Table A3.1-3 Continued

Study	Species/exposure	Measures	Outcome/findings	Comments
Portugal et al. (2012)	• Male C57BL/6J mice • Mice received acute nicotine (0, 0.045, 0.09, or 0.18 mg/kg free base, i.p., 5 minutes before training) or chronic nicotine via osmotic minipumps (0, 3.0, 6.3, or 12 mg/kg free base) for 12 days starting at P23, P38, or P53. • Testing occurred 24 hours later (chronic nicotine); 24 hours after pump removal (withdrawal); or 30 days after pump removal (prior chronic nicotine).	• Learning and memory	• Acute nicotine enhanced contextual fear conditioning in all ages, although this occurred across a broader range of doses in preadolescents. • Withdrawal impaired contextual fear conditioning in all ages, but at different doses. • Additional testing found that adolescent mice withdrawing from 1.1 mg/kg/day also showed impairments. • Prior exposure to nicotine during preadolescence or adolescence impaired contextual fear conditioning in adulthood, but adult nicotine had no effect. • No changes in cued-fear conditioning were seen with any age or treatment.	Adolescents were especially sensitive to nicotine withdrawal-induced deficits in hippocampal-dependent contextual fear conditioning, showing impairments across a wide range of doses. The mechanism may be lack of drug-induced upregulation of high-affinity nAChR binding in the hippocampus, decreases in total hippocampal CREB, or differences in nAChR desensitization.
Natividad et al. (2013)	• Wistar rats • Drug-naïve adolescents and adults or adolescent nicotine-exposed adults began prolonged access (23 hours/day) i.v. self-administration of saline or increasing nicotine (0.03, 0.06, or 0.09 mg/kg/0.1 mL infusion) at P43–P45 or P75 in a 4 days-on and 3 days-off extinction paradigm. • Exposed adolescents had minipumps deliver nicotine (4.7 mg/kg/day) for 14 days.	• Reinforcing effects of nicotine • Intravenous self-administration with prolonged access and periods of forced abstinence	• Adolescents had the highest levels of nicotine intake at all doses, an increase in responding after each period of forced abstinence, and the highest responding during extinction. • Pre-exposed adults had the second-highest nicotine intake, followed by naïve adults. • Adolescents also showed high nonreinforced responses relative to other groups.	Adolescents seemed to be particularly sensitive to the reinforcing or motivational properties of nicotine, and exposure during this period produced lasting increases in nicotine reward. High nonreinforced responding in adolescents may reflect increased impulsivity, motivation, or drug-induced activity.

Table A3.1-3 Continued

Study	Species/exposure	Measures	Outcome/findings	Comments
Pickens et al. (2013)	• Male and female Long- Evans rats • Daily saline or nicotine (1 mg/kg, i.p.) injections from P25 to P59 • 35-day drug-free period before 7 weeks of SMC testing	• Attention/cognition • SMC task	• Regardless of treatment, females learned chunk-boundary and violation elements more slowly than males. • Nicotine exposure impaired chunk-boundary element learning in males only, but it impaired violation elements in females. • Extra training abolished drug-induced impairments in learning.	Adolescent nicotine exposure produced lasting impairments in stimulus–response discrimination, but not abstract rule learning, in a gender-dependent manner. The mechanism may be impairment of hippocampal-dependent memory systems or drug-induced alterations in nAChR expression or function in hippocampal circuits.
Dickson et al. (2014)	• C57BL/6J mice • Osmotic minipumps delivered saline or nicotine (24 mg/kg/day free base) from P28 to P56. • 5-day cocaine self-administration (1.0 mg/kg, i.v.) from P73 to P77 before dose–response analysis with 0.18–1.8 mg/kg cocaine	• Reinforcing effects of other drugs of abuse • Acquisition of cocaine self-administration	• All animals acquired cocaine self-administration behavior at the 1.0 mg/kg dose. • Adolescent nicotine exposure had no effect. • In a dose–response analysis, adolescent nicotine exposure significantly increased cocaine intake at all but the highest 1.8 mg/kg dose, compared with unexposed adults.	Greater cocaine intake in exposed animals during dose–response may be attributable to nicotine-induced hyperactivity, in contrast to McQuown and colleagues (2007), where adolescent nicotine enhanced self-administered i.v. cocaine. This difference may be attributable to species or the time between nicotine exposure and the start of self-administration, with altered dopamine dynamics during nicotine withdrawal promoting cocaine self-administration.

Table A3.1-3 Continued

Study	Species/exposure	Measures	Outcome/findings	Comments
Mojica et al. (2014)	• Sprague-Dawley rats (P28–P32 or P86–P90) • Rats were pretreated with nicotine (60 µg/kg/day, i.v.) for 4 days; sucrose or cocaine (500 µg/kg/infusion, i.v.) self-administration for at least 12 days, followed by extinction and cocaine- or sucrose-primed reinstatement.	• Reinforcing effects of other drugs of abuse • Acquisition of cocaine self-administration	• Nicotine pretreatment in adolescence enhanced acquisition of cocaine self-administration, but it decreased reinforced/nonreinforced discrimination in adults. • Adolescent exposure also accelerated extinction of cocaine seeking, with no effect on drug-primed reinstatement. • There was a slight enhancement of sucrose self-administration in adolescent-exposed animals, but no change in extinction or reinstatement of sucrose seeking.	Brief, low-dose nicotine exposure in early adolescence produced lasting enhancements of drug-related learning. The mechanism may be altered dopaminergic signaling in the dorsal striatum in response to nicotine.
Pipkin et al. (2014)	• Sprague-Dawley rats • Daily injections of saline or nicotine (0.16 or 0.64 mg/kg, s.c.) from P35 to P50 followed by a switch to saline or continuation of same nicotine dose for remainder of study. • Methamphetamine (0.05 mg/kg, i.v.) self-administration began ~1 week later.	• Reinforcing effects of other drugs of abuse • Acquisition and reinstatement of methamphetamine self-administration	• 0.16 mg/kg nicotine during the pre-exposure and onward produced increased responding for methamphetamine at FR1. • At FR3, both groups receiving 0.16 mg/kg nicotine (pre-exposure only or throughout) had higher methamphetamine intake than saline- or high-dose nicotine-treated animals. • Reinstatement to methamphetamine seeking after 14 days of extinction was not affected by prior nicotine exposure.	Nicotine exposure during adolescence led to greater drug intake in adulthood, but no change in methamphetamine seeking. The mechanism for enhancement may be attributable to an additive effect of nicotine and methamphetamine on mesolimbic dopamine activity.

Table A3.1-3 Continued

Study	Species/exposure	Measures	Outcome/findings	Comments
Ehlinger et al. (2016)	• Sprague-Dawley rats • Saline or nicotine (0.05 mg/kg, s.c.) was co-administered with vehicle or the D1R antagonist SCH-23390 (0.05 mg/kg, s.c. 20 minutes before nicotine) every other day from P28 to P42. • Tissue was collected for Golgi-Cox staining 1 or 21 days after treatment.	• Synaptic remodeling • Nucleus accumbens MSNs	• Nicotine induced significant and persistent remodeling of dendrites on nucleus accumbens MSNs (i.e., increases in dendritic length and bifurcations suggesting new branch formation) that was blocked by a dopamine D1R antagonist. • Nicotine also produced a transient, D1R-independent increase in spine density.	Maturation of nucleus accumbens MSN dendrites can be altered by exposure to nicotine, and drug-induced remodeling was persistent at least into early adulthood (P63). The mechanism may be enhanced activation of the cAMP-PKA pathway downstream of D1Rs. No direct age comparison was done.

Note: **α4β2** = alpha 4 beta 2-nicotinic acetylcholine receptor subtype; **α7** = alpha 7 nicotinic acetylcholine receptor subtype; **α6** = alpha 6 nicotinic acetylcholine receptor subtype; **arc** = activity-regulated cytoskeleton-associated protein; **[^{125}I]α-Btx binding** = measurement of binding at α7 nAChRs using the antagonist alpha-bungarotoxin; **[^{125}I]αCtxMII binding** = measurement of binding at α6 nAChRs using the antagonist alpha-conotoxin MII; **[^{125}I]A-85380 binding** = measurement of binding at a4b2 nAChRs using the agonist A-85380; **5AP tLTP protocol** = 5 action potential timing-dependent long-term potentiation protocol; **5-CSRTT** = 5-choice serial reaction time task; **BLA** = basolateral amygdala; **BNST** = bed nucleus of the stria terminalis; ***cFos*** = protooncogene and immediate early gene used as a marker of neuronal activity; **cAMPPKA** = cyclic AMP-protein kinase A, signaling cascade; **CPP** = conditioned place preference; **CREB** = cAMP response element-binding protein; **CRF** = corticotropin-releasing factor; **CTA** = conditioned taste aversion; **d** = days; **D1R** = dopamine D1 receptor; **FR** = fixed ratio; **FST** = forced swim test; **g** = grams; **ICR mice** = Institute for Cancer Research strain of mice; **ICSS** = intracranial self-stimulation; **i.p.** = intraperitoneal; **i.v.** = intravenous; **kg** = kilogram; **mg** = milligram; **mGluR2** = metabotropic glutamate receptor 2; **mL** = milliliter; **µg** = microgram; **mRNA** = messenger ribonucleic acid; **MSN** = medium spiny neuron; **nAChR** = nicotinic acetylcholine receptor; **NAcshell** = nucleus accumbens shell; ***NGFI-B*** = nerve growth factor-induced gene-B; **PFC** = prefrontal cortex; **P85 (and similar)** = postnatal day number; **PVN =** paraventricular nucleus of the thalamus; **86Rb+ efflux assay =** measure of nicotinic acetylcholine receptor function via rubidium-86 ion efflux; **VTA =** ventral tegmental area; **s.c.** = subcutaneous; **SMC** = serial multiple choice.

Table A3.1-4 Human studies on the effects of nicotine exposure on fetal brain development

A. Sudden infant death syndrome and potentially related risk factors

Study	Population	Outcomes examined	Findings
Richardson et al. (2009)	• 25 full-term, healthy infants: 12 born to women who smoked 3–20 cigarettes/day and 13 born to women who did not smoke	The study compared measures of arousal in infants of smokers and nonsmokers. Infants were assessed using daytime polysomnography at 2–4 weeks, 2–3 months, and 5–6 months of age. Arousal was induced by pulsatile air-jet stimulation to the nostrils (trigeminal stimulation) during active and quiet sleep in supine and prone positions. Physiological and electroencephalogram changes were assessed, and arousal experiences were classified as subcortical activation or cortical arousal. Chi-square tests were used to conduct statistical comparisons.	In tobacco-exposed infants, total arousability and progression from subcortical activation to cortical arousal were depressed at 2–4 weeks and 5–6 months of age. A dose-dependent relationship between cortical activation proportions and urinary cotinine levels was found for supine and prone positions at 2–3 months of age. Sleep position was strongly associated with arousal process, regardless of tobacco exposure (infants exhibited higher cortical arousal proportions when prone than when supine).
Gunnerbeck et al. (2011)	• 609,551 live births to Nordic mothers recorded in the Swedish Medical Birth Register • 7,599 maternal snus users and 58,319 smokers	Neonatal outcomes were determined from hospitalization ICD-10 codes P28.2 (cyanotic attacks of newborn); P28.3 (primary sleep apnea of newborn); and P28.4 (other apnea of newborn). Tobacco exposure data were collected at first antenatal visit. Associations between tobacco exposure and newborn apnea were examined and adjusted for maternal age, height, parity, education, infant gender, gestational age, being small for gestational age, and method of child delivery. Dual users of both cigarettes and snus were not included.	Maternal snus use was significantly associated with infant apnea. Maternal smoking was not significantly associated with infant apnea after adjusting for gestational age, being small for gestational age, method of child delivery, and other variables.
Spindel & McEvoy (2016)	• Literature Review	Examination of pulmonary effects of (a) in utero nicotine exposure and (b) in utero tobacco product exposure, and subsequent comparison of the health impacts of these exposures.	Nicotine appears to mediate most of the pulmonary effects of maternal smoking during pregnancy as evident by the similarity of effects and underlying mechanisms of action. The effects of maternal smoking on lung development are mediated by nicotinic receptors, changes in airway geometry, effects on airway epithelial cell proliferation, and oxidative mechanisms. Similarly, animal models show that the effects of prenatal nicotine exposure are also mediated by these same mechanisms. Therefore, both descriptive and mechanistic data support the likelihood that e-cigarettes affect lung development.

Table A3.1-4 Continued

B. Altered corpus callosum

Study	Design/population	Outcomes examined	Findings
Jacobsen et al. (2007a)	• 33 adolescents with prenatal exposure to tobacco (25 were current smokers at the time of the study and 8 were never smokers); 34 adolescents with no prenatal exposure to tobacco (14 were current smokers at the time of the study and 20 were never smokers) • Participants did not have any other substance abuse or psychiatric disorders.	This study analyzed nonsmokers and smokers who were abstinent for 1 week before the assessment. Outcomes included general intelligence, reading achievement, scores on word recognition tasks, motor speed, depression, and inattention. Magnetic resonance imaging and fractional anisotropy were used to examine white matter microstructure. Prenatal tobacco exposure was ascertained through parental interviews.	Smokers with prenatal exposure to tobacco reported more symptoms of nicotine dependence and depression than smokers without such prenatal exposure. Prenatal exposure to tobacco was associated with disruption of white matter microstructure, especially in the anterior and cortical regions of the internal capsule. Findings were significant after controlling for potential confounders: baseline symptoms of depression, gender, alcohol use, cannabis use, and prenatal exposure to alcohol use.
Paus et al. (2008)	• Case-control study • 300 adolescents, 12–18 years of age: 146 exposed to maternal cigarette smoking during pregnancy and 154 matched, unexposed controls • Subjects were matched on school and maternal education. • Subjects were excluded if they were exposed to alcohol during pregnancy.	This study examined the possible effects of maternal smoking during pregnancy on the size and structural properties of the corpus callosum. The size of the corpus callosum and magnetization-transfer ratios were assessed using magnetic resonance imaging in exposed and unexposed participants. Prenatal exposure to tobacco was ascertained retrospectively through interviews with mothers. T-tests and analysis of variance were used to assess associations between exposure to tobacco and size of the corpus callosum. Multiple regression analysis was used to adjust for household income and breastfeeding.	In females, the corpus callosum, especially the posterior part, was smaller in those who were exposed to tobacco prenatally than in those who were not exposed. No effects were seen in males. Prenatal exposure to tobacco (or not) did not result in any differences in the myelination index for either gender.

Table A3.1-4 Continued

C. Auditory processing defects

Study	Design/population	Outcomes examined	Findings
Kristjansson et al. (1989)	• 79 children, 4–7 years of age: 52 children of women who smoked during pregnancy and 27 children of women who were nonsmokers • Sample was selected from a larger cohort study in Ottawa (Ontario, Canada) of 700 women who were interviewed during pregnancy and whose offspring were given neurologic and behavioral tests at regular intervals.	Children were given a visual vigilance task and an auditory vigilance task. Activity levels during testing were monitored. Testers were blind to exposure status. Information on maternal use of tobacco was collected during pregnancy. Associations between maternal use of tobacco and children's activity scores and auditory and visual omission errors were analyzed using hierarchical linear regression. Data on maternal use of marijuana and alcohol, education, family income, and exposure to tobacco during childhood were included in adjusted analyses.	Prenatal smoking was associated with increased activity scores (scores increased as maternal smoking increased). Prenatal smoking was not associated with auditory or visual omission errors or visual commission but was associated with auditory commission.
McCartney et al. (1994)	• Longitudinal drug study (the Ottawa Prenatal Prospective Study) • 110 offspring, 6–11 years of age	This study assessed the potential effects of prenatal exposure to maternal tobacco use on central auditory processing. SCAN, a central auditory processing task, was administered blindly by testers to obtain information about parental tobacco use. Maternal cigarette use during pregnancy was assessed during interviews conducted throughout pregnancy. Exposure to secondhand smoke during pregnancy and yearly thereafter was assessed using a questionnaire; exposure to secondhand smoke during pregnancy was also assessed from urine cotinine. Multivariate analysis was conducted, and results were adjusted for family income; parental education; maternal age; parity; weight; gestational weight gain; caffeine, marijuana, and alcohol use; protein and calorie intake during pregnancy; child's birth weight, gender, and home environment; and family history of hearing problems.	Maternal smoking during pregnancy was linearly associated with poorer performance on a central auditory processing task, particularly the Competing Words subtest. Results remained significant after adjusting for other drug use, demographic variables, and exposure to secondhand smoke during pregnancy and postnatally.

Table A3.1-4 C Continued

Study	Design/population	Outcomes examined	Findings
Franco et al. (1999)	• 26 newborns from Belgium: 13 were born to women who smoked more than nine cigarettes per day during pregnancy, and 13 were born to women who did not smoke during pregnancy. • 42 infants, approximately 12 weeks of age: 21 infants of women who smoked, and 21 infants of women who did not smoke.	White noise of increasing intensity was administered during rapid-eye-movement sleep. Levels of arousal and awakening thresholds during 9-hour, night-monitoring sessions were evaluated using a scalp electroencephalogram, electro-oculogram, electrocardiogram, thoracic and abdominal respiratory movements, and airflow by thermistors. An actigram recorded gross body movements. Oxygen saturation was recorded using a transcutaneous sensor. Outcomes in newborns and infants exposed and not exposed to tobacco were compared using Wilcoxon nonmatched pairs, signed-rank test, and χ^2 test.	More intense auditory stimuli were needed in newborns and infants of smokers than in newborns and infants of nonsmokers. Behavioral awakening occurred less frequently in newborns of smokers than in those of nonsmokers. Results were not explained by differences in exposure to maternal alcohol, drug, and sedative use; previous sleep deprivation; body position during sleep; environmental light; temperature; or background noise.
Leech et al. (1999)	• Longitudinal study • 608 mother/child pairs • Children, 6 years of age, who were participating in the Maternal Health Practices and Child Development Project • Mothers of lower socioeconomic status were recruited from a prenatal clinic; more than 50% were African American.	This study of 6-year-olds assessed the relationships between (a) prenatal exposure to alcohol, marijuana, tobacco, and cocaine and (b) attention and impulsivity, as measured by a continuous performance task. Child demographic factors were also included in the assessment.	Prenatal exposure to tobacco, marijuana, and cocaine was predictive of inattention and impulsivity in the continuous performance task. Tobacco use during the second and third trimesters and cocaine use during the first trimester predicted increased omission errors. Marijuana use during the second trimester predicted increased commission errors and fewer omission errors. Lower omission errors were also associated with younger child age, maternal work or school status, higher maternal hostility scores, and lower scores on the Stanford-Binet Intelligence Scale.
Cowperthwaite et al. (2007)	• 38 fetuses of mothers who smoked, and 20 fetuses of mothers who did not smoke • Mothers were from antenatal clinics in southern Canada.	Fetuses were assessed for 1 hour or more after mothers smoked. Assessments included spontaneous fetal heart rate and body movements and were conducted with and without maternal speaking. Outcomes in tobacco-exposed and unexposed fetuses were compared.	Spontaneous behaviors did not differ between tobacco-exposed and unexposed fetuses. Fetuses less than 37 weeks of gestation in mothers who smoked had a delayed onset of response to maternal voice compared with fetuses in mothers who did not smoke.

Table A3.1-4 C Continued

Study	Design/population	Outcomes examined	Findings
Jacobsen et al. (2007a)	• 181 adolescent smokers and nonsmokers with and without prenatal exposure to maternal smoking, 13–18 years of age, were recruited from a local community.	This study assessed three kinds of attention: auditory, visual selective, and visual divided. A subset of 63 subjects also underwent functional magnetic resonance imaging while performing auditory, visual selective, and visual divided attention tasks. Outcomes in adolescents exposed and not exposed to tobacco were compared. Regression models were used to adjust for potential confounders.	Prenatal exposure to tobacco smoke was associated with depressed mood at the time of the assessment, decreased accuracy, and slower lexical discrimination during auditory attention relative to visual selective and visual divided-attention conditions. Compared with females, males with prenatal exposure had a greater reduction in performance accuracy during auditory conditions relative to visual conditions. Results from magnetic resonance imaging indicated that subjects with prenatal exposure had greater activation of the right superior temporal gyrus during the auditory conditions and increased activation of the left and right lingual gyrus relative to subjects with no exposure to tobacco. Prenatal exposure to tobacco smoke was associated with visual attention performance accuracy. Results did not change after controlling for prenatal exposure to alcohol, cannabis, and cocaine. Female nonsmokers with no prenatal exposure to maternal smoking had the most accurate performance in both auditory and visual modalities; female smokers with prenatal exposure to tobacco performed the least accurately; those with prenatal or adolescent exposure performed intermediately.
Key et al. (2007)	• 16 healthy newborn infants: 8 born to mothers who smoked and 8 born to mothers who did not smoke • Infants were matched on gender, gestational age, and birth weight at 48 or less hours old.	Event-related potentials in response to speech stimuli were measured to assess speech-processing ability. Outcomes in infants exposed and not exposed to tobacco were compared.	Infants of smokers demonstrated abnormal changes in hemispheric symmetry for speech processing. Compared with infants of nonsmokers, infants of smokers discriminated among fewer syllables, began the discrimination process 150 milliseconds later, and differentiated among fewer stimuli.

Table A3.1-4 C Continued

Study	Design/population	Outcomes examined	Findings
Korres et al. (2007)	• 200 newborns undergoing screening for hearing impairment: 100 were born to women who smoked and 100 to women who did not smoke. • All newborns were at low risk for hearing loss.	TEOAEs were measured to assess hearing loss. Mothers were interviewed about cigarette use during each trimester of pregnancy; only nonsmokers and "habitual" smokers were enrolled. Cigarette use was categorized in increments of five, starting with less than five cigarettes/day. Outcomes in newborns exposed and not exposed to tobacco were compared using the t-test for unpaired data.	The mean response and mean amplitude at 4,000 Hz of TEOAEs were significantly lower in newborns exposed to tobacco smoke than in those who were not exposed, supporting the conclusion that exposure to tobacco in utero had a modest but detrimental effect on the function of outer hair cells. There was no dose–response relationship, and all exposure groups appeared to be equally affected.
Kable et al. (2009)	• 172 mother–infant pairs were recruited after delivery from two hospitals in Atlanta, Georgia.	Mother–infant pairs were recruited at delivery and followed longitudinally. Auditory brainstem-evoked responses were used to assess differences in sensory processing of auditory stimuli at 6 months of age. Planned polynomial contrasts were conducted to assess dose–response relationships for linear, quadratic, and cubic relationships. Findings were on the basis of tobacco use by mothers during pregnancy: smoked less than a half pack of cigarettes per day, a half pack to a full pack per day, or more than one pack per day.	Maternal smoking level was negatively associated with response latency, even after controlling for confounders: participant age, perinatal complications, and maternal alcohol use.
Peck et al. (2010)	• 40 mother–newborn pairs were drawn from a cohort of 110 pregnant women from a predominantly lower socioeconomic-status population receiving prenatal care in Oklahoma City, Oklahoma.	Auditory brainstem-evoked responses were recorded in neonates to assess neuroelectrical activity of the auditory nerve following a sound stimulus. Maternal smoking status was determined at the first prenatal visit by self-reports and urine cotinine levels. Cox proportional hazards models were used to develop hazard ratios to compare rates of response in infants exposed and not exposed to tobacco. Several potential confounders were examined.	Newborns of mothers with the highest cotinine concentrations responded at a rate four times that of nonsmoking mothers. Findings were not affected by postmenstrual age at testing, maternal age, maternal race, infant gender, education, household income, birth weight, or creatinine concentration. Associations with more moderate cotinine levels were not observed.
Durante et al. (2011)	• Cross-sectional study of neonates in São Paulo, Brazil • Study group: 98 neonates born to mothers who smoked during pregnancy • Control group: 320 neonates born to mothers who did not smoke • Sample size = 418	TEOAEs were studied to determine the effect of maternal smoking during pregnancy on cochlear functioning. Neonates were placed in a common crib. A probe with a soft rubber tip was inserted into the external auditory meatus to record TEOAEs.	Maternal smoking during pregnancy had a negative effect on cochlear function, as determined by otoacoustic emissions testing.

Table A3.1-4 C Continued

Study	Design/population	Outcomes examined	Findings
Durante et al. (2013)	• Cotinine levels were measured in youth (8–10 years of age). • Sample size = 145	This study analyzed the effect of tobacco smoke exposure during childhood on cochlear physiology by measuring the TEOAE response levels. Comparisons were made of TEOAEs among youth exposed to secondhand smoke and those not exposed.	Youth exposed to secondhand smoke showed lower response levels to auditory testing, mainly on frequencies of 2.8 kHz on the right and left ears and 2.0 kHz on the left ear, and lower signal noise response levels, mainly on the 1.0 kHz and 1.4 kHz frequencies, when compared with controls that were not exposed to secondhand smoke.
Katbamna et al. (2013)	• 14 mother–infant pairs: 7 smokers and 7 nonsmokers • Infants were full term, and mothers were mainly from urban areas, with low- to middle-income levels and uncomplicated pregnancies.	This study sought to determine relationships between prenatal smoke exposure-induced changes in hearing responses and changes in placental gene expression. Cochlear echo response amplitudes and auditory brainstem response wave latencies were examined. Gene microarray was used to identify upregulated and downregulated placental gene expression. Functional gene clusters with the highest enrichment scores were identified.	Cochlear echo response amplitudes and auditory brainstem response wave latencies were reduced in newborns of mothers who smoked. Changes in newborn cochlear and auditory brainstem functions were correlated with changes in placental gene expression of a cluster of genes that modulate cochlear hair motility. The role of these genes in the placenta was associated with active contractile function in the anchoring villi during maternal–fetal perfusion matching. The closure and relaxation of the cluster of genes in placental anchoring villi contraction may play a similar role in the cochlea during sensory neurotransduction.
Kisilevsky et al. (2014)	• Longitudinal study of auditory information processing in fetuses • Sample size = 167	This study measured auditory information processing in fetuses through 15 months of age using the Mullen Scales of Early Learning and MacArthur-Bates Communicative Development Inventory subscales.	Findings suggest that fetal growth restriction affects the development of auditory system functioning and indicate that it may be possible to identify individual fetuses and newborns at risk for language deficits and to intervene early, when the foundation for language is being laid.

Table A3.1-4 Continued

D. Appetitive behaviors: Smoking uptake, nicotine dependence

Study	Design/population	Outcomes examined	Findings
Kandel et al. (1994)	• 192 adolescent girls followed from grades 10 and 11 and their first-born offspring, as selected from the NYS cohort • 797 female youth from the NLSY cohort and their first-born offspring	Women who were enrolled in the NYS cohort were followed for 19 years, and their offspring were interviewed at 9–17 years of age. Women from the NLSY (a nationally representative sample) were enrolled as youth and interviewed annually; their offspring were interviewed at 10–18 years of age. Women and their offspring were interviewed about past drug use. Information about maternal smoking and other drug use during the pregnancy with the study's offspring was ascertained retrospectively. Associations between prenatal tobacco exposure and offspring smoking and persistence of smoking were assessed. Logistic regression was used to control for maternal age, education, and smoking behaviors.	The NYS analysis revealed a significant association between maternal smoking during pregnancy and smoking by their offspring 13 years later; the association was stronger for daughters than for sons. Controlling for alcohol and marijuana use during pregnancy did not change the findings. The association between maternal smoking and persistence of smoking in offspring was stronger for daughters than for sons. Maternal current smoking was examined as a potential confounder, but maternal smoking during pregnancy was the strongest risk factor for daughters' smoking. In the NLSY analysis, maternal smoking during pregnancy was associated with the offspring's current and persistent smoking (but not ever smoking), especially for daughters.
Griesler et al. (1998)	• 187 mothers and their first-born offspring from the NYS cohort; mothers were recruited from public high schools in the state of New York.	Mothers were followed from 15–16 years of age to 34–35 years of age. Offspring were interviewed at 3–13 years of age and again at 9–17 years of age. Ever and past-year smoking were assessed in adolescent offspring. Prenatal smoking was ascertained retrospectively from interviews; maternal smoking in the first year after child delivery was also assessed. Maternal reports were used to assess child behavioral problems using scales from Schaefer and colleagues (1977) and Furstenberg and colleagues (1987). Outcomes in offspring exposed and not exposed to tobacco were compared.	Maternal smoking of at least one pack of cigarettes per day during pregnancy was associated with problem behaviors in offspring, especially in daughters. In daughters, there was a significant association between maternal smoking of at least one pack of cigarettes per day during pregnancy and current smoking in adolescence, even after adjusting for maternal current smoking, early child behavior problems, and maternal monitoring. In survival models, elevated child behavior problems were significantly associated with onset of smoking in girls, and maternal smoking during pregnancy was not significant.
Kandel and Udry (1999)	• 240 mother–daughter pairs from the Child Health and Development Study were followed from pregnancy.	Daughters' smoking during adolescence and adulthood was assessed through interviews conducted with the daughters when they were 15–17 years of age and 27–30 years of age. Maternal tobacco use during pregnancy was assessed by maternal self-reports and blood samples during pregnancy. Outcomes for daughters exposed and not exposed to tobacco were compared; results were adjusted for potential confounders.	Maternal prenatal cotinine level was not significantly associated with daughters' adolescent smoking, but mother's self-reported smoking was significantly associated with that outcome. Maternal prenatal cotinine and testosterone levels were positively correlated; maternal testosterone was significantly associated with daughters' adolescent smoking.

Table A3.1-4 D Continued

Study	Design/population	Outcomes examined	Findings
Buka et al. (2003)	• 1,248 offspring from two samples of the Collaborative Perinatal Project, a multisite cohort study of more than 50,000 women, who were recruited during pregnancy from 1959 to 1966, and their offspring. • Offspring were followed from birth to 29 years of age.	Maternal smoking during pregnancy was assessed at each prenatal visit, offspring smoking behavior and nicotine dependence were obtained by interviews, per the Diagnostic Interview Schedule. Maternal smoking was categorized as none, smoked less than one pack of cigarettes per day, and smoked at least one pack of cigarettes per day. Associations between exposure and outcomes were assessed using logistic regression to generate adjusted ORs.	Offspring of women who smoked at least one pack of cigarettes per day during pregnancy were more likely to meet DSM-III criteria for lifetime tobacco dependence than offspring of women who did not smoke during pregnancy. The odds of progressing from smoking to nicotine dependence were almost twice as high in offspring whose mothers smoked heavily during pregnancy. These findings remained significant after adjusting for gender and age, maternal socioeconomic status, and age at pregnancy. Odds of marijuana dependence were not significantly elevated among offspring of smokers.
Lieb et al. (2003)	• Prospective longitudinal cohort study • 938 adolescents, 14–17 years of age, from Munich, Germany, participating in the Early Developmental Stages of Psychopathology study • Followed for 4 years	Smoking and nicotine dependence were assessed using the Munich Composite International Diagnostic Interview. Outcomes in adolescents exposed and not exposed to tobacco were compared.	Children of mothers who smoked during pregnancy had a higher lifetime prevalence of nicotine dependence than children who were not exposed to tobacco during their mother's pregnancy. Differences were not observed between sons and daughters.
Oncken et al. (2004)	• 298 adult tobacco users seeking smoking cessation treatment who were able to report whether they were exposed in utero to tobacco	This study examined the potential associations between maternal smoking and their offspring's smoking initiation, progression of cigarette use, and current nicotine dependence. Participants were asked if their mothers smoked during pregnancy. Univariate analysis was used to conduct statistical comparisons.	Females exposed to tobacco in utero transitioned from initial to daily smoking more rapidly than females without in utero exposure to tobacco; the opposite was true for males. Measures of current use and dependence, including Fagerström Test for Nicotine Dependence, prior withdrawal, and number of past-year quit attempts, were associated with in utero exposure, gender, or interactions of exposure and gender.

Table A3.1-4 D Continued

Study	Design/population	Outcomes examined	Findings
Cornelius et al. (2005)	• Prospective birth cohort study • 567 mothers and their offspring were randomly selected from an urban hospital-based prenatal clinic in Pittsburgh, Pennsylvania. • Followed to 14 years of age	This study examined smoking by offspring at 14 years of age, amount smoked, and age at onset of smoking. Maternal tobacco use during pregnancy was assessed during each trimester of pregnancy. Smoking among offspring was ascertained from interviews, using questions adapted from the Health Behavior Questionnaire, and from cotinine concentration in urine. Associations between maternal smoking and offspring's ever smoking were assessed with logistic regression. Cox proportional hazards was used to identify risk factors for age at onset of smoking.	Prenatal exposure to tobacco in the third trimester of pregnancy significantly predicted ever smoking in offspring, amount smoked, and age at onset of smoking. Results remained significant after adjusting for maternal and child psychological characteristics. Results were not significant, however, after adjusting for maternal current smoking and peer smoking.
Roberts et al. (2005)	• Data from the 1958 National Child Development Study and the 1970 British Birth Survey	This study examined associations between maternal smoking during pregnancy and smoking among offspring in adolescence and adulthood. Smoking among offspring at 16 and 30 or 33 years of age was assessed through questionnaires. Maternal smoking during pregnancy was assessed from a questionnaire administered at the end of pregnancy; smoking was defined as smoking one or more cigarettes per day. Multivariate logistic regression was used to control for potential confounders, including gender of offspring, birth cohort, maternal age at birth of offspring, and maternal and paternal smoking at 16-year follow-up.	Multigroup analyses revealed that among offspring whose mothers smoked during pregnancy, females were 15% more likely than males to smoke cigarettes by 16 years of age. Smoking at 16 years of age in female offspring of mothers who smoked during pregnancy doubled the likelihood of smoking at the 30- and 33-year follow-ups.
Al Mamun et al. (2006)	• Longitudinal cohort study • 3,058 mothers and offspring enrolled in the Mater-University of Queensland Study of Pregnancy in Brisbane, Australia • Offspring followed to 21 years of age	Mothers were asked to record their tobacco use when they were at 18 weeks' gestation; 3–5 days after child delivery; and at the 6-month, 5-year, and 14-year follow-ups. Smoking behaviors of offspring were compared on the basis of their mother's tobacco use during pregnancy (never smoked, smoked before or after but not during pregnancy, or smoked during pregnancy) using regression models and controlling for confounders.	Smoking by offspring as young adults (early- or late-onset smoking) was significantly associated with maternal smoking during pregnancy compared with no maternal smoking, but not with maternal smoking during other times. Results remained significant after adjusting for potential confounders, including maternal age at birth of offspring, gender of offspring, family income, and maternal education.

Table A3.1-4 D Continued

Study	Design/population	Outcomes examined	Findings
Munafò et al. (2006)	• Offspring of women enrolled in the National Child Development Study, a cohort of the British population • Followed from birth to adulthood	This study examined associations between maternal smoking during late pregnancy and the likelihood of smoking among offspring in adolescence and adulthood. Smoking among offspring was assessed from questionnaires administered at 16, 23, and 33 years of age. Maternal smoking after the fourth month of pregnancy was assessed from maternal self-reports at the end of pregnancy. The zero-inflated negative-binomial model was used to analyze daily cigarette counts; the count proportion was fit with negative binomial regression models, and smoking status was fit with a logistic regression model. Results were controlled for paternal socioeconomic status, maternal smoking before pregnancy, and parental smoking status at the 16-year follow-up.	Maternal smoking in late pregnancy was associated with increased likelihood of male offspring being nonsmokers at the 16-, 23-, and 33-year follow-ups. There was no association observed for female offspring.
Kandel et al. (2007)	• Longitudinal study • 353 students in grades 6–10 in public schools in Chicago • One parent (usually the mother) • Followed for 2 years	Household interviews were conducted three times during the study period. Time to nicotine dependence criteria, per DSM-IV, and full dependence syndrome were assessed. Maternal smoking during pregnancy was assessed through parental interviews. Other potential risk factors were also assessed, including race, gender, one or both parents ever being nicotine-dependent, positive diagnostic screen for conduct disorder, pleasant experience with first use of tobacco, marijuana use before tobacco use, alcohol use before tobacco use, peer smoking, depressive symptoms, positive screen for anxiety disorder, academic performance, and pubertal stage.	Maternal smoking during pregnancy was not associated with time to nicotine dependence criteria, per DSM-IV, or time to full dependence syndrome.

Table A3.1-4 D Continued

Study	Design/population	Outcomes examined	Findings
Weiss et al. (2008)	• Cohort study of long-term smokers • Sample size = 2,827 • Long-term smokers in Utah and Wisconsin and by the NHLBI Lung Health Study	This study compared nicotine addiction, assessed via Fagerström Test, using a candidate-gene approach with neuronal nAChR subunit genes. The panel included common coding variants and haplotypes detected in eight α and three β nAChR subunit genes in European Americans.	Susceptibility and protective haplotypes at the *CHRNA5-A3-B4* locus were associated with nicotine dependence severity ($p=2.0\times10^{-5}$; odds ratio=1.82; 95% CI, 1.39–2.39) in subjects who began daily smoking at or before 16 years of age. A substantial shift in susceptibility versus protective diplotype frequency (AA vs. BC=17%, AA vs. CC=27%) was observed in smokers who began using by age 16. This genetic effect was not observed in subjects who began daily nicotine use after the age of 16. These results establish a strong mechanistic link among early nicotine exposure, common *CHRNA5-A3-B4* haplotypes, and adult nicotine addiction in three independent populations of European origin.
O'Callaghan et al. (2009)	• 2,571 mothers and offspring enrolled in the Mater-University of Queensland Study of Pregnancy in Brisbane, Australia	The potential effects of maternal smoking during pregnancy on offspring nicotine dependence were examined using data from a longitudinal cohort whose offspring were followed to 21 years of age. Offspring completed the Composite International Diagnostic Interview (Auto) to assess nicotine dependence and withdrawal according to DSM-IV criteria. Tobacco use by mothers during pregnancy was assessed during prenatal care (never smoked, smoked before or after but not during pregnancy, or smoked during pregnancy). Logistic regression was used to control for potential confounders.	Smoking during pregnancy was significantly associated with offspring nicotine dependence and withdrawal at 21 years of age in a comparison with offspring of women who never smoked. This finding remained after adjusting for a variety of potential confounders, including maternal age at birth of offspring, education, duration of breastfeeding, parental communication, and internalizing or externalizing behavior problems.

Table A3.1-4 D Continued

Study	Design/population	Outcomes examined	Findings
Tehranifar et al. (2009)	• 262 offspring of women enrolled in New York City's National Collaborative Perinatal Project, a multisite cohort study of more than 50,000 women who were recruited during pregnancy from 1959 to 1966, and their offspring • Offspring were followed prospectively until 7 years of age, then enrolled in an adult follow-up study at approximately 41 years of age.	This study examined the relationship between exposure to secondhand smoke over the life course and adult smoking status. Offspring smoking status, number of years of smoking, age at smoking initiation, average daily consumption of tobacco, and age at cessation were assessed at adult follow-up. Maternal smoking during pregnancy was assessed during enrollment of mothers during pregnancy. Exposure to secondhand smoke in childhood and adulthood was assessed by self-reports of smokers in the home.	Current and former smokers were more likely than never smokers to have been exposed to prenatal tobacco and adult household tobacco. Results remained significant after adjusting for socioeconomic status.
Agrawal et al. (2010)	• 1,741 offspring of fathers who were twins participating in the U.S. Vietnam Era Twin Registry and their female spouses	Offspring of study participants were interviewed at 12 and 34 years of age and were assessed for remediation, conduct problems, ADHD, low scholastic achievement, and regular smoking. Prenatal tobacco exposure was assessed retrospectively by interview. Associations between maternal smoking during pregnancy and outcomes were assessed using regression analysis and Kaplan-Meier curves for survivor function. Participants were tested for initiation of smoking and regular smoking. Potential confounders were examined, including ethnicity and education of parents and parental drug and alcohol dependence.	Maternal smoking at any time during pregnancy was associated with low scholastic achievement, earlier age of initiation and onset of regular smoking, and ADHD in offspring. The association with ADHD in offspring was attributable to confounders (maternal ADHD, maternal conduct disorder, and low paternal education).
Sullivan et al. (2011)	• Systematic review • 57 studies of mothers' prenatal smoking status in offspring using sex- and gender-based analyses were included.	This study examined whether maternal smoking during pregnancy influences smoking among female offspring more so than among male offspring. Ten studies used sex-based analyses and 51 used gender-based analyses; 4 used both and were counted in both groups.	Mother's prenatal and postnatal smoking status influenced smoking among female offspring more so than among male offspring. Four of 10 studies found evidence of female-specific effects of maternal prenatal smoking; 1 study found evidence of male-specific effects; 2 studies found evidence of effects on both males and females; and 3 studies found no association for either gender.

Table A3.1-4 D Continued

Study	Design/population	Outcomes examined	Findings
D'Onofrio et al. (2012)	• Two separate samples from the United States and Sweden • Sample 1: A representative sample of 6,094 adolescent offspring of the women in the NLSY (1979) • Sample 2: All (1,187,360) offspring born in Sweden from 1983 to 1995	Outcomes included self-reports from adolescents about their use of cigarettes and other substances, age at onset of cigarette and substance use before or after 14 years of age, and convictions and hospitalizations for alcohol—or drug-related problems. Collection of maternal tobacco use, covariates, and outcomes among offspring varied by study. Cox proportional hazards survival analysis was used for all outcomes, which were right-censored; logistic regression models were used for dichotomous outcomes.	Maternal smoking during pregnancy was associated with adolescent alcohol use, cigarette use, marijuana use, substance-related driving convictions, narcotic convictions, and drug-related hospitalizations. In an analysis of differentially exposed siblings using data from Sweden, the associations were attenuated and no longer statistically significant.
Rydell et al. (2012)	• 3,020 Swedish youth, 11–18 years of age, in the Children's Smoking and Environment in Stockholm County Study (the BROMS)	This study examined potential associations between maternal smoking during pregnancy and adolescent tobacco uptake, nicotine dependence, and withdrawal symptoms. Adolescent outcomes were assessed through self-administered questionnaires of the youth. Parental questionnaires were used to retrospectively assess prenatal exposure to tobacco. Cox regression was employed to analyze the onset of tobacco use. Logistic regression was used to study cravings, withdrawal symptoms, and tobacco consumption at 17 years of age. Results were adjusted for potential confounders, including parental education and postnatal tobacco use.	Girls with prenatal exposure to tobacco had two to three times the odds of experiencing a high number of withdrawal symptoms, craving for tobacco, and heavy tobacco use (five or more cigarettes smoked or snus dips per day), but not onset of use. No significant associations were observed among boys.
Weden and Miles (2012)	• 6,349 participants, 14–25 years of age, from the Children and Young Adults of the NLSY	Intergenerational transmission of smoking was assessed. A panel survey of all offspring of women in a population-representative cohort was used; children born to participating women were followed longitudinally. Youth smoking trajectories were constructed using mixture latent trajectory analysis.	The classes of smoking trajectory were early onset, early experiment, late onset, and nonsmoker. Analysis of the three smoking trajectories indicated that in all cases, youth whose mothers smoked during pregnancy were more likely to develop the trajectory than to become nonsmokers.

Table A3.1-4 D Continued

Study	Design/population	Outcomes examined	Findings
Stroud et al. (2014)	• 1,086 mother–offspring pairs enrolled in the Collaborative Perinatal Project, a multisite cohort study of more than 50,000 women who were recruited during pregnancy from 1959 to 1966, and their offspring	This study examined the association between maternal smoking during pregnancy, offspring nicotine dependence, and the potential mediating roles of prenatal glucocorticoid and androgens. Lifetime nicotine dependence among offspring was assessed by interviews during 40 years of follow-up and was based on DSM-IV criteria. Maternal smoking during pregnancy was assessed during prenatal visits. Bivariate associations were estimated with polychoric, polyserial, and Pearson correlations. A causal steps approach was used to examine potential mediators using multivariate logistic regression analysis. Potential confounders were examined, including gravidity and parity, maternal age at child delivery, race and ethnicity, socioeconomic status, maternal use of other drugs, and maternal history of treatment for mental illness.	Cotinine-validated maternal tobacco use during pregnancy was significantly associated with nicotine dependence in daughters. Results remained significant after adjusting for potential confounders, including maternal demographic and obstetrical factors, alcohol and drug use, and maternal mental disorders.
Taylor et al. (2014)	• 6,484 offspring, 14–16 years of age, of participants in the Avon Longitudinal Study of Parents and Children	Study included comparisons of associations between (a) maternal and partner smoking during pregnancy and (b) smoking initiation among offspring, using partner smoking as a negative control and a Mendelian randomization analysis (n = 1,020) using a genetic variant in mothers of European ancestry only. Parental smoking during pregnancy was assessed during pregnancy; status of smoking among offspring was assessed at 14–16 years of age by questionnaire (nonsmoker, experimenter, late-onset regular smoker, and early-onset regular smoker). Multinomial logistic regression was used to assess associations between parental smoking and outcomes among offspring, and results were adjusted for potential confounders.	Maternal and partner smoking were associated with the smoking status of offspring, even after adjusting for confounders, but there was no clear dose–response relationship with the level of parental smoking. Maternal *rs1051730* genotype (associated with heavy smoking) was not associated with smoking among offspring.

Table A3.1-4 D Continued

Study	Design/population	Outcomes examined	Findings
Shenassa et al. (2015)	• 1,783 adult offspring of women who were enrolled in the Providence and Boston sites of the Collaborative Perinatal Project (a multisite cohort study of more than 50,000 women who were recruited during pregnancy from 1959 to 1966, and their offspring) and also enrolled in the New England Family Study	This study examined maternal smoking during pregnancy and risk of nicotine dependence among offspring. Follow-up studies of offspring were conducted using multistage sampling, which oversampled families with multiple siblings and siblings discordant for maternal smoking during pregnancy. Maternal smoking during pregnancy was assessed during prenatal study visits. Smoking among offspring was assessed by the Life Interview of Smoking Trajectory Questionnaire. Lifetime nicotine dependence was based on DSM-IV criteria and assessed using the Composite International Diagnostic Interview. Logistic regression models were used to explore independent associations between maternal smoking during pregnancy and offspring smoking, nicotine dependence, and marijuana use.	Maternal smoking during pregnancy was significantly associated with progression from weekly smoking to nicotine dependence but not weekly smoking or progression to marijuana dependence. Within-family and between-family analyses supported an effect of maternal smoking during pregnancy on progression to nicotine dependence.

E. Appetitive behaviors: Use of other substances

Study	Design/population	Outcomes examined	Findings
Fergusson et al. (1998)	• Birth cohort of 1,265 children born in Christchurch, New Zealand • Followed to 18 years of age	Outcomes were assessed at 16–18 years of age and included conduct disorder, major depression, anxiety, and substance use. Outcomes were compared between adolescents exposed and not exposed to tobacco in utero.	Exposure to tobacco in utero was significantly associated with psychiatric symptoms for conduct disorder, depression, substance abuse, and alcohol abuse. The association with conduct disorder remained significant after adjusting for potential confounders, including lower socioeconomic status, impaired child-rearing behaviors, and parental and family problems. Effects were more pronounced among males than among females.

Table A3.1-4 E Continued

Study	Design/population	Outcomes examined	Findings
Weissman et al. (1999)	• 50 offspring of mothers who smoked during pregnancy and 97 offspring of mothers who did not smoke during pregnancy • Offspring were followed for 10 years.	This study examined associations between maternal smoking during pregnancy and ADHD, conduct disorder, and substance abuse among offspring. Psychiatric diagnostic assessments were conducted by interview with parents and offspring using the Schedule for Affective Disorders and Schizophrenia—Lifetime Version. Maternal smoking during pregnancy was assessed retrospectively by interview. Proportional hazards regression models were used to examine associations between offspring's exposure to tobacco and psychopathology. Results were adjusted for demographic factors, parental psychopathological conditions, pregnancy risk factors, and family parenting risk factors.	Maternal tobacco use during pregnancy was significantly associated with prepubertal onset of conduct disorder in boys, and adolescent onset of drug dependence in girls. These findings were not explained by maternal substance use during pregnancy, parental psychiatric diagnosis, family risk factors, prenatal and early-developmental history of offspring, postnatal maternal smoking, or smoking among offspring.
Porath and Fried (2005)	• 152 adolescents, 16–21 years of age, born of mothers who participated during pregnancy in the Ottawa Prenatal Prospective Cohort Study	This study examined associations between maternal cigarette smoking and marijuana use during pregnancy and risk of initiation and regular use of substances by offspring. Outcomes included initiation and daily or regular use of tobacco and marijuana. Maternal tobacco use was ascertained during pregnancy. Logistic regression was used to compare outcomes in exposure groups while controlling for potential confounders, including parity, gender, maternal use of alcohol and caffeine during pregnancy, family income, parental education, postnatal exposure to secondhand smoke, exposure to marijuana smoke, and age of offspring at time of testing.	Offspring of mothers who smoked cigarettes during pregnancy had increased risks for initiation of cigarette smoking during adolescence. Findings were more pronounced for males than females, and they remained significant after adjusting for confounders.

Table A3.1-4 E Continued

Study	Design/population	Outcomes examined	Findings
Nomura et al. (2011)	• 1,625 offspring of women who were enrolled in the Providence (Rhode Island) and Boston (Massachusetts) sites of the Collaborative Perinatal Project (a multisite cohort study of more than 50,000 women who were recruited during pregnancy from 1959 to 1966 and their offspring) and also enrolled in the New England Family Study • Offspring were followed from birth to 40 years of age and older.	This study examined the association between maternal smoking during pregnancy and lifetime risk of alcohol use disorder in offspring. Lifetime risk of alcohol use disorder was assessed using DSM-IV criteria. Maternal smoking status was assessed during prenatal visits. Survival analysis techniques were used to examine differences between proportions of subjects free from alcohol use disorders. Potential mediating factors were explored, including low birth weight, neurologic abnormalities, poor academic functioning, and behavioral dysregulation.	Offspring of mothers who smoked 20 or more cigarettes per day during pregnancy had greater risk of alcohol use disorder than offspring of mothers who did not smoke during pregnancy. No excess risk was noted in offspring of mothers who smoked fewer than 20 cigarettes per day during pregnancy. Maternal smoking during pregnancy was associated with neurobehavioral problems in infancy and childhood, which, in turn, were associated with increased risk for alcohol use disorder in adulthood.
Huang et al. (2013)	• Six- to 9-week-old male mice, kept in plastic cages on a 12-hour day/night cycle in groups of five with ad libitum food and water	This study examined whether the metaplastic effect of nicotine on cocaine also applies in the amygdala. The study examined whether exposure to nicotine prior to exposure to cocaine enhances LTP in the amygdala. Short-term (1 day) and long-term (7 days) exposure to nicotine prior to cocaine exposure was examined.	Pretreatment with nicotine (i.e., exposure to nicotine prior to cocaine exposure) enhanced LTP in response to cocaine in the amygdala in both groups (short and long). The association is unidirectional in that pretreatment with cocaine followed by exposure to nicotine does not elicit the same response in the amygdala. After 40 days of nicotine cessation, the LTP response can no longer be generated.

Table A3.1-4 Continued

F. Appetitive behaviors: Overweight and obesity

Study	Design/population	Outcomes examined	Findings
Gilman et al. (2008)	• 52,919 offspring from the Collaborative Perinatal Project, a multisite cohort study of more than 50,000 women who were recruited during pregnancy from 1959 to 1966 and their offspring	This study assessed maternal tobacco use during pregnancy and 14 developmental outcomes in offspring (e.g., obesity, intelligence, academic achievement, conduct problems, and asthma). Cognition was assessed in offspring at 4 years of age (Stanford-Binet Intelligence Scale) and 7 years of age (Wechsler Intelligence Scale for Children). Academic performance was assessed at 7 years of age (Wide Range Achievement Test). Neurologic "soft signs" were assessed by physician examination. Behavioral observations were made at 7 years of age through psychological assessments; conduct problems were determined on the basis of consistency and stability across samples. Body mass index was recorded at 7 years of age. Maternal smoking during pregnancy was assessed during prenatal visits. Generalized estimating equations and linear and logistic regression analyses were used; matched analyses among siblings were conducted.	Maternal smoking was associated with overweight at birth and with childhood overweight in unadjusted and adjusted models. Associations between maternal smoking and 12 other outcomes that were significant in unadjusted analyses were no longer significant after adjusting for potential confounders, including race and ethnicity, parental ages, household crowding, parental history of psychiatric and substance use disorders, maternal employment, and socioeconomic status.
Oken et al. (2008)	• Systematic review and meta-analysis • 84,563 children enrolled in 14 observational studies	This study examined associations between maternal smoking during pregnancy and childhood overweight.	Children whose mothers smoked during pregnancy were at greater risk for overweight at 3–33 years of age compared with children whose mothers did not smoke during pregnancy, even when adjusted ORs were used. Meta-analysis generated a pooled adjusted OR of 1.50 (95% CI, 1.36–1.65).
Iliadou et al. (2010)	• Population-based cohort study • 124,203 singleton males born to Nordic women in Sweden • Males followed to 18 years of age	This study examined associations between maternal smoking during pregnancy and childhood overweight and obesity in young adult Swedish males born of mothers who did and did not smoke during pregnancy. Associations among siblings were also examined, controlling for common genes and shared environment.	The risk of overweight was higher in sons of mothers who smoked during pregnancy than in sons of mothers who did not smoke during pregnancy. However, after stratifying for maternal smoking across two subsequent male pregnancies, the risk in the second pregnancy was higher only if the mother smoked during both male pregnancies, suggesting that increased risk is explained by familial factors.

Table A3.1-4 F Continued

Study	Design/population	Outcomes examined	Findings
Ino (2010)	• Systematic review and meta-analysis • 17 studies, ranging from 252 to 34,866 participants	This study examined associations between maternal smoking during pregnancy and childhood obesity in offspring.	All studies showed a positive association between maternal smoking during pregnancy and childhood obesity. Meta-analysis using data from 16 studies of offspring, 3–33 years of age, generated a pooled adjusted OR of 1.64 (95% CI, 1.42–1.90). Results were significant after adjusting for publication bias. Maternal obesity, low socioeconomic status, low birth weight, and absence of breastfeeding did not appear to confound results.
Lotfipour et al. (2010)	• 423 adolescents from the Saguenay Youth Study in Quebec, Canada	This study examined associations between prenatal exposure to maternal cigarette smoking and outcomes in offspring. Cigarette smoking and substance use by offspring were assessed by questionnaire, and the volume of dopamine-rich regions of the striatum was measured with T1-weighted magnetic resonance imaging. The study also assessed potential interactions between prenatal exposure to maternal cigarette smoking and a polymorphism in the offspring in the α6 nAChR gene and the outcomes of interest. Offspring exposed and not exposed to maternal cigarette smoking were matched for maternal education.	Significant interactions exist between prenatal exposure to maternal cigarette smoking and the α6 nAChR SNP in the offspring in predicting adolescent lifetime smoking and substance use. The α6 nAChR subunit could modify these effects.
Weng et al. (2012)	• Systematic review and meta-analysis • Prospective studies of children followed from birth to at least 2 years of age, seven of which examined maternal smoking and childhood overweight	This study examined risk factors, including maternal smoking during pregnancy, for childhood overweight identifiable during infancy.	Maternal smoking during pregnancy was associated with childhood overweight in all seven of the studies where this was examined. Meta-analysis using data from these seven studies generated a pooled adjusted OR of 1.47 (95% CI, 1.36–1.73).
Behl et al. (2013)	• 83 studies of children 1 year of age or older	This review of epidemiologic studies examined maternal smoking during pregnancy and obesity in offspring.	Evidence (based on human and animal research) supports the conclusion that maternal smoking increases risk of obesity or overweight in offspring, but contributions from unmeasured residual confounding cannot be ruled out. Data were insufficient to assess contributions of exposure to secondhand smoke after child delivery.

Table A3.1-4 F Continued

Study	Design/population	Outcomes examined	Findings
La Merril et al. (2015)	• Prospective study of daughters, 44–54 years of age • Sample size = 1,801	This study aimed to identify whether parental tobacco smoking during gestation was associated with risk of diabetes mellitus.	Prenatal maternal smoking had a stronger association with daughters' diabetes mellitus risk than did prenatal paternal smoking. Estimates of the effect of parental smoking were unchanged when further adjusted by daughters' birth weight or current body mass index.
Harrod et al. (2015)	• Mother–offspring pairs were analyzed in the longitudinal Healthy Start study. • Sample size = 670	This study examined associations between exposure to prenatal smoking and early-life changes in fat mass (FM), fat-free mass (FFM), and anthropometrics.	Exposure to prenatal smoking was significantly associated with reduced neonatal FM ($p = 0.007$) and FFM ($p = 0.02$). Overall, exposure to prenatal smoking was significantly associated with rapid postnatal growth, which may increase the offspring's risk of metabolic diseases.
Mourtakos et al. (2015)	• A random sample of 5,125 children was extracted from a national database and matched with their mothers.	This study investigated the association between gestational weight gain, maternal age, and lifestyle habits (e.g., physical activity, smoking, alcohol consumption) during pregnancy and body mass index of the offspring at the age of 8.	Maternal behaviors, including smoking status during pregnancy, were significantly associated with obesity in the offspring at the age of 8.
Bao et al. (2016)	• Self-reported survey • Sample size = 15,665 singleton pregnancies from 10,152 women	This study examined fetal exposure to parental smoking and gestational diabetes in daughters.	Maternal heavy smoking (≥25 cigarettes/day) during pregnancy was associated with higher risk of gestational diabetes in the daughter.

Table A3.1-4

G. Appetitive behaviors: Altered size and sensitivity of brain reward systems

Study	Design/population	Outcomes examined	Findings
Toro et al. (2008)	• 314 adolescents: 155 exposed and 159 not exposed to tobacco smoke in utero	This study examined the effects of maternal smoking during pregnancy on several outcomes in offspring: thickness of the cerebral cortex; general intelligence (using the Wechsler Intelligence Scale for Children); and positive youth development. Maternal smoking during pregnancy was assessed retrospectively through a maternal interview. Thickness of the cerebral cortex was measured using magnetic resonance imaging. Analyses of cortical thickness were performed using mean values for each of 33 regions and employing thickness values determined at each of 163,842 vertices. Positive youth development was assessed using the five Cs model (competence, confidence, character, social connection, and caring or compassion). Age was included as a covariate in each analysis. Adolescents exposed and not exposed in utero to tobacco smoke were matched on maternal education.	Prenatal exposure to maternal smoking was associated with thinner orbitofrontal, middle frontal, and parahippocampal cortices, especially in females. Based on these findings, the score for "caring" was examined specifically; there was a significant negative correlation between the thickness measurements of the orbitofrontal cortex and scores for "caring" in females who were exposed in utero to maternal smoking.
Lotfipour et al. (2009)	• 597 adolescents (275 sibships), 12–18 years of age, from the Saguenay Youth Study in Quebec, Canada	This study assessed the potential involvement of the orbitofrontal cortex in mediating the relationship between maternal smoking during pregnancy and substance use in offspring. Substance use by offspring was assessed through a questionnaire, and thickness of the orbitofrontal cortex was measured with T1-weighted magnetic resonance imaging. Behavioral data were analyzed using hierarchical linear modeling. Potential confounders were explored, including breastfeeding status and parent-based predictors of substance use. Cortical thickness was analyzed in 314 adolescents; associations between genotype, behavior, and cortical thickness were examined using linear models that included potential interactions. Adolescents exposed and not exposed to maternal smoking during pregnancy were matched on maternal education.	Prenatal exposure to tobacco was significantly associated with substance use in offspring. Results did not change after controlling for potential confounders, including birth weight, breastfeeding status, maternal alcohol use during pregnancy, and parental history of antisocial behavior. Among exposed adolescents, the likelihood of drug experimentation was associated with the degree of thinning in the orbitofrontal cortex.

Table A3.1-4 G Continued

Study	Design/population	Outcomes examined	Findings
Haghighi et al. (2013)	• 378 adolescents, 13–19 years of age, from the Saguenay Youth Study in Quebec, Canada	This study assessed associations between prenatal exposure to maternal cigarette smoking and enhanced fat intake and risk of obesity in offspring. Exposure to maternal smoking was defined as smoking more than one cigarette per day in the second trimester of pregnancy vs. no exposure at any time during the 12 months preceding and throughout pregnancy. Subtle variations in brain regions involved with reward processing were studied with magnetic resonance imaging; regions included the amygdala, nucleus accumbens, and orbitofrontal cortex. Offspring exposed and not exposed to maternal smoking during pregnancy were matched for maternal education. Regression models adjusted for gender, age, and height.	Prenatal exposure to maternal smoking was significantly associated with higher total body fat and fat intake, as well as lower volume of the amygdala. Amygdala volume correlated inversely with fat intake.
Müller et al. (2013)	• A subgroup of 177 healthy adolescents, 13–15 years of age, with prenatal exposure to maternal tobacco use, and 177 matched controls not exposed to maternal tobacco use were recruited for the IMAGEN study—a European multicenter study of impulsivity, reinforcement sensitivity, and emotional reactivity in adolescents.	This study examined the effects of maternal tobacco use during pregnancy on offspring's brain response during reward processing. Response to reward in the ventral striatum was assessed with functional magnetic resonance imaging. Adolescents exposed to prenatal maternal tobacco use and those not exposed were matched for gender, maternal education level, and imaging site.	Prenatal exposure to maternal tobacco use was associated with a weaker response in the ventral striatum during reward anticipation among those exposed than in unexposed controls. There were no differences in responsivity of the ventral striatum to the receipt of a reward.

Table A3.1-4 Continued

H. Attention and cognition, behavioral disorders

Study	Design/population	Outcomes examined	Findings
Linnet et al. (2003)	• Systematic review • 24 studies of maternal tobacco use during pregnancy • Offspring were 4–36 years of age.	This study examined behavioral outcomes in offspring related to ADHD in childhood and prenatal exposure to nicotine, alcohol, and caffeine, and psychosocial stress. Only studies using validated diagnostic or screening instruments for ADHD and ADHD symptoms were included. No meta-analysis was performed.	A greater risk of ADHD-related disorders was observed in children whose mothers smoked during pregnancy. Many studies had methodologic shortcomings, such as recall bias, limited assessments of exposure, low statistical power, or insufficient control for confounders.
Langley et al. (2005)	• 13 studies reviewed • Participants were 5–12 years of age.	This review examined 13 population-based epidemiologic studies of ADHD-related behaviors and maternal smoking during pregnancy. A pooled OR for case control studies (n = 5) was calculated.	The majority of studies (n = 11) identified maternal smoking during pregnancy as a risk factor for ADHD behaviors; the pooled OR for case control studies was 2.39 (95% CI, 1.61–3.52). Methodologic limitations included misclassification of exposure and an inability to control for all relevant confounders and genetic factors.
D'Onofrio et al. (2008)	• Nationally representative sample of 6,283 mothers, who were enrolled at 14–21 years of age in the NLSY, and their offspring, who were 4–10 years of age	This study assessed associations between maternal smoking during pregnancy and conduct problems, oppositional defiance problems, and attention deficit/hyperactivity problems in offspring. Offspring were compared with siblings who differed in their prenatal exposure to tobacco. Smoking during the most recent pregnancy was assessed by interviews at each wave of the study.	There was no effect of maternal smoking during pregnancy on conduct problems or oppositional defiance problems in the offspring. There was a modest association with attention deficit/hyperactivity problems that was attenuated by methodologic and statistical controls.
Bennett et al. (2009)	• 18 children, 12 years of age, 7 with prenatal exposure to tobacco, and 11 not exposed prenatally	The brain function of children exposed and not exposed to tobacco prenatally was assessed during a go/no-go response inhibition task using event-related functional magnetic resonance imaging. Outcomes for exposed and not exposed children were compared, and results were controlled for prenatal exposure to alcohol, neonatal medical problems, environmental risks, IQ, current exposure to secondhand smoke, and handedness.	Children exposed to tobacco prenatally showed greater activation in a relatively large and diverse set of regions of the brain, including left frontal, right occipital, and bilateral temporal and parietal regions. Unexposed children showed activation in the cerebellum, which is important for attention and motor preparation. Tobacco-exposed children showed inefficient recruitment of regions required for response inhibition.

Table A3.1-4 H Continued

Study	Design/population	Outcomes examined	Findings
Thapar et al. (2009)	• 815 families of offspring conceived through assisted reproductive technologies and born to either related or genetically unrelated women • Women were recruited through fertility clinics in the United Kingdom and the United States.	This study examined associations between maternal smoking during pregnancy and ADHD in offspring among related and unrelated mother–offspring pairs. Offspring were assessed at 4–11 years of age through parental questionnaires and antenatal records. Multiple regression analysis was used to control for maternal alcohol use, multiple-birth status, birth weight, gestational age, parental ADHD symptoms, family income, and age and gender of offspring.	The associations between maternal smoking during pregnancy and ADHD symptoms in offspring were much stronger for related pairs than unrelated pairs, but this was not the case for maternal smoking and birth weight, where associations were similar for related and unrelated pairs.
Boutwell and Beaver (2010)	• An estimated 3,300 U.S. children from the Early Childhood Longitudinal Study, Birth Cohort • Children were followed from 9 months to 4 years of age.	Behavioral, cognitive, and emotional development were assessed using the Preschool and Kindergarten Behavior Scales—Second Edition. Maternal smoking was assessed from the birth certificate and categorized as "yes" or "no." Data on potential confounders included maternal antisocial behaviors, substance abuse (alcohol and other drugs), depression, and education attainment; the child's race and gender, rearing environment, complications of labor and delivery, and Apgar scores; and paternal antisocial behavior, substance abuse, and depression. Propensity score-matching analysis was performed using 14 covariates.	Before matching on propensity scores, subjects differed on 11 of 14 covariates. Prior to being placed in matched groups, children of mothers who smoked during pregnancy exhibited higher levels of externalizing problem behaviors than children of mothers who did not smoke during pregnancy. After placement in matched groups, prenatal exposure to tobacco no longer predicted externalizing behavior problems.

Table A3.1-4 H Continued

Study	Design/population	Outcomes examined	Findings
Wakschlag et al. (2010)	• Pregnancy cohort study • 139 adolescent offspring from the Maternal Infant Smoking Study of East Boston	The study tested whether a functional polymorphism in the gene encoding the enzyme monoamine oxidase A (*MAOA*) interacts with prenatal exposure to tobacco to predict outcomes in offspring. Outcomes included antisocial behavior (conduct disorder symptoms and hostile attribution bias). Maternal tobacco exposure (active smoking and exposure to secondhand smoke) was assessed via questionnaire and serum cotinine levels during pregnancy. Covariates included family income, age of offspring, prenatal maternal alcohol use, parental antisocial behavior, and harsh parenting. Linear mixed models were used to examine conduct disorder symptoms, and linear models were used to examine hostile attribution score. Permutation methods were used to test for gene–prenatal tobacco exposure interactions.	Boys with low-activity *MAOA 5' uVNTR* genotype who were exposed to tobacco prenatally were at increased risk for conduct disorder symptoms. Girls with high-activity *MAOA uVNTR* genotype who were exposed to tobacco prenatally were at increased risk for conduct disorder symptoms and hostile attribution bias.
Lavigne et al. (2011)	• Convenience sample of 679 children, 4 years of age, who were recruited from primary care practices throughout Cook County, Illinois, and from public schools with preschool programs in Chicago	Internalizing and externalizing behavioral problems and negative temperament were assessed using several modalities: DISC-YC, CSI ADHD scales, DISC-YC generalized anxiety scale and CSI generalized anxiety scale (for anxiety symptoms); and DISC-YC major depression scale, CSI major depression scale, and CSI dysthymia scale (for depressive symptoms). For ADHD, the inattentive (ADHD-I) and hyperactive (ADHD-H) subtypes were examined separately, as was the combined type (ADHD-C), using the Children's Behavior Questionnaire negative affectivity scale. Mothers were interviewed about their smoking status during pregnancy. Outcomes in children exposed and not exposed to tobacco through maternal smoking during pregnancy were compared using analysis of variance and linear regression; results were adjusted for socioeconomic status, life stress, family conflict, maternal depression, maternal support/scaffolding, mother–child attachment, and child negative affect and effortful control. Smoking status during pregnancy was assessed through interviews with the expectant mothers.	Smoking during pregnancy was associated with ADHD in an unadjusted analysis, but not after correcting for multiple comparisons. Smoking during pregnancy was not associated with ADHD-H or ADHD-C. Smoking during pregnancy was not associated with symptoms of oppositional defiant disorder, anxiety, or depression in offspring.

Table A3.1-4 H Continued

Study	Design/population	Outcomes examined	Findings
Wakschlag et al. (2011)	• Pregnancy cohort study • 211 adolescent offspring (30 sibling pairs) from the Maternal Infant Smoking Study of East Boston	This study examined potential associations between prenatal exposure to maternal tobacco use and disruptive behavior outcomes (aggression dimension, noncompliance dimension, temper loss dimension, and low concern dimension) in offspring. Exposure to tobacco through the mother (via active smoking and exposure to secondhand smoke) was assessed through a questionnaire and serum cotinine levels during pregnancy. Covariates included offspring's exposure to secondhand smoke and age, parental antisocial behavior, and family adversity. Multilevel repeated-measures models were used to examine effects of exposure while controlling for age and gender of offspring, parental antisocial behavior, family adversity, and current exposure to secondhand smoke.	Prenatal exposure to maternal tobacco use was significantly associated with noncompliance and aggression dimensions, even after adjusting for potential confounders. There were no significant associations with temper loss or low concern for others. Maternal responsive engagement did not moderate the effects of the exposure on the average estimate of disruptive behavior, but there was a significant interaction between paternal responsive engagement and prenatal tobacco exposure for an average estimate of disruptive behavior.
Langley et al. (2012)	• 8,324 offspring from the Avon Longitudinal Study of Parents and Children in the United Kingdom • Offspring were followed from gestation to late adolescence.	ADHD symptoms among offspring were assessed at 91 months of age through parental completion of the Development and Wellness Being Assessment. Maternal smoking status was assessed at 18 and 32 weeks of gestation (paternal smoking at 18 weeks). Associations between maternal smoking during pregnancy and paternal smoking and ADHD in offspring were assessed using regression analysis to explore causal vs. household-level confounding. Potential confounders included gender of offspring, ethnicity, singleton/twin status, maternal alcohol use during pregnancy, education, and parental occupation.	ADHD symptoms among offspring were associated with maternal smoking during pregnancy and paternal smoking. Paternal exposure was associated independent of maternal exposure, suggesting genetic or household-level confounding rather than a causal relationship.
Latimer et al. (2012)	• 47 studies of prenatal exposure to maternal smoking present antenatally and in the first 4 years of life	This review examined studies on ADHD; oppositional defiant disorder; conduct disorder; and deficits in attention, motor control and perception, and reactive attachment disorder.	Eight high-quality, large, population-based cohort studies, in which potential confounding was well controlled, found a link between prenatal maternal smoking and increased risk of ADHD in offspring.

Table A3.1-4 H Continued

Study	Design/population	Outcomes examined	Findings
McCrory and Layte (2012)	• 7,505 children, 9 years of age, participating in the Growing Up in Ireland study	Children's behavioral problems were assessed using the Strengths and Difficulties Questionnaire across instruments for parents and teachers. Classification of maternal smoking during pregnancy was obtained retrospectively at the time of child assessment from parental interview. Propensity score matching was used to create exposed and unexposed groups, which did not differ in their propensity to smoke with respect to 16 characteristics.	After matching, children exposed to maternal smoking during pregnancy were significantly more likely to score in the problematic range on the Strengths and Difficulties Questionnaire total difficulties index. Maternal smoking during pregnancy was more strongly associated with externalizing than internalizing behaviors.
Gaysina et al. (2013)	• Examined three studies: – Christchurch Health and Development Study, a longitudinal cohort study of adopted and biological children; 1,088 children reared by genetically related mothers and 36 children reared by genetically unrelated adoptive mothers – Early Growth and Development Study, a longitudinal study of adoption at birth; 310 children reared by genetically unrelated adoptive mothers – Cardiff IVF Study, an adoption-at-conception study among genetically related families and genetically unrelated families; 636 children reared by genetically related mothers and 206 by genetically unrelated mothers	Outcomes included child conduct problems at 4–10 years of age using the Rutter and Conners behavioral scales, the Child Behavior Checklist, the Children's Behavior Questionnaire, and the Strengths and Difficulties Questionnaire. Regression analysis was used to test for dose–response relationships between maternal smoking during pregnancy and conduct problems in children. The potential confounders examined included the child's gender, ethnicity, birth weight, and breastfeeding status; maternal age at birth of child and education; family socioeconomic status; family breakdown; placement age; and parenting practices.	Among children reared by genetically related mothers and genetically unrelated mothers adopted at birth, a significant association was observed between maternal smoking during pregnancy and conduct problems in children. Children whose mothers smoked at least 10 cigarettes per day during pregnancy had the highest mean scores of conduct problems. In fully adjusted models, associations between maternal smoking during pregnancy and conduct problems in children were attenuated but remained significant for genetically related mother–child pairs and in genetically unrelated mother–child pairs in the Early Growth and Development Study, but they were not significant in the Christchurch Health and Development Study. Meta-analysis confirmed an association between maternal smoking during pregnancy and offspring conduct problems in genetically related mother–child pairs.

Table A3.1-4 H Continued

Study	Design/population	Outcomes examined	Findings
O'Brien (2013)	• Pregnancy cohort study • 176 offspring, 11–18 years of age, from the Maternal Infant Smoking Study of East Boston	The study examined potential interactions between prenatal exposure to maternal tobacco use and two functional genetic markers in the dopamine system to predict externalizing behaviors in offspring. Transporter gene *DAT1* and dopamine receptor gene *DRD4* were used to predict a latent composite of externalizing behavior by gender. Maternal tobacco exposure was assessed via questionnaire and serum cotinine levels during pregnancy; trimester-specific exposure was not included in the analysis. Behavioral outcomes included ADHD, oppositional defiance disorder, conduct disorder, substance use (nicotine, alcohol, and marijuana); and scales from the C-DISC-IV and the Antisocial Behavior Checklist. Multigroup regression analysis was conducted; covariates included maternal age, youth age, prenatal maternal alcohol and drug use, maternal and paternal antisocial behavior and harsh parenting, maternal employment, education, and total household income.	The interaction between *DAT1* (but not *DRD4*) and prenatal exposure to maternal tobacco use during pregnancy was significant in boys. *DAT1* genetic susceptibility did not increase risk of externalizing behaviors in the absence of exposure to tobacco. The final model predicted 23% of the variance for girls and 60% of the variance for boys for externalizing behavior. Risk genotypes (*DAT1*) can modify the effects of prenatal exposure to tobacco in boys.
Jasinska et al. (2014)	• Review of existing literature of human neuroimaging research on nicotine and tobacco.	This study examined current literature on several topics including: receptor-level PET and SPECT studies specific to nAChRs and upregulation of nAChRs inducted by chronic smoking; interaction of nicotine with the mesocorticolimbic dopamine system; functional activity and connectivity; and fMRI studies detailing the behavioral/cognitive effects of nicotine and large-scale brain networks.	This review summarized the literature that discusses the addictive properties and cognition-enhancing effects of nicotine; highlighted the clinical significance of the elucidation of neurobiological mechanisms of nicotine; and presented an overview of the use of PET, SPECT, and fMRI neuroimaging methods used to study nicotine in vivo, including the effects of nicotine on nAChRs and the dopamine system.
Kuja-Halkola et al. (2014)	• 2,754,626 children born in Sweden	Data were obtained from several nationwide Swedish registries. Traditional and within-family analyses examined associations between maternal smoking during pregnancy and outcomes in offspring, including low academic achievement, general cognitive ability, and externalizing behaviors. Data on maternal smoking during pregnancy was collected during the first prenatal care visit. Outcomes for exposed and unexposed offspring were compared using linear and logistic regression; potential confounders included maternal age, birth year, and gender of offspring.	Through traditional analysis, maternal smoking during pregnancy was significantly associated with all outcomes. However, none of the associations remained significant after within-family analysis of discordant-exposed offspring. In quantitative genetic models, genetic factors explained the majority of the associations.

Table A3.1-4 H Continued

Notes: **ADHD** = attention deficit hyperactivity disorder; **CI** = confidence interval; **C-DISC-IV** = Diagnostic Interview for Children–Version 4; **CSI** = Child Symptom Inventory; **DISC-YC** = Diagnostic Interview Schedule for Children-Parent Scale-Young Child; **DSM-IV** = Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; **fMRI** = functional magnetic resonance imaging; **ICD10** = International Statistical Classification of Diseases and Related Health Problems, 10th revision; **LTP** = long-term synaptic protentiation; **nAChR** = nicotinic acetylcholine receptor; **NLSY** = National Longitudinal Survey of Youth; **NYS** = New York State Follow-Up; **OR** = odds ratio; **PET** = positron emission tomography; **SCAN** = Screening test for Auditory Processing Disorders; **SNP** = single-nucleotide polymorphism; **SPECT** = single photon emission computed tomography; **TEOAEs** = transient evoked otoacoustic emissions.

Table A3.1-5 Preclinical/animal studies on fetal nicotine exposure

Study	Species/exposure	Measures	Findings	Comments
Navarro et al. (1988)	• Pregnant Sprague-Dawley rats • Osmotic minipumps delivered saline or nicotine (6 mg/kg/day) from gestational days 4 to 20 or twice-daily injections of saline or nicotine (3 mg/kg/day, s.c.) from gestational days 4 to 20.	• Catecholaminergic system function	• Tissue was collected at various time points postnatally (P2, P5, P10, P15, P22, P30, P35, and P45) for assessment of catecholamine levels and utilization rates. • Minipump delivery of nicotine produced an overall reduction in NE and DA levels and use in the cerebral cortex immediately after birth that dissipated between postnatal weeks 2 and 4 but became apparent again in young adulthood for NE levels only. • There were no changes in cerebral NE synaptosomal uptake, but TH activity was decreased; in the midbrain and brainstem, lower NE levels and use were apparent in young adulthood only but without changes in TH or synaptosomal uptake. • Reduced NE and DA content was also seen in the kidneys and lungs, but repeated s.c. injections had a stimulatory effect on neurotransmitter levels and utilization rates.	—
Sorenson et al. (1991)	• Sprague-Dawley rats • Rats received nicotine (0 or ~6 mg/kg/day) in drinking water starting 15 days before mating and throughout gestation.	• Attention, cognition—radial eight-arm maze task	• Adolescent offspring (P45–P65) were tested in a radial eight-arm maze task. • Nicotine exposure impaired learning in both genders in the eight-arm maze.	Nicotine exposure during gestation impairs acquisition of an attentional learning task without changing levels of motivation, suggesting lower impulse control.

Table A3.1-5 Continued

Study	Species/exposure	Measures	Findings	Comments
Richardson and Tizabi (1994)	• Pregnant Sprague-Dawley rats • Osmotic minipumps delivered saline or nicotine (6 mg/kg/day) from gestational days 4 to 20.	• Catecholaminergic system function	• Early-adolescent offspring (P19–P21) were tested for hyperactivity and for DA and D_2 receptor levels. • Gestational nicotine produced dose-dependent hyperactivity, as measured by open-field locomotion in a subset of offspring. • In these hyperactive offspring, DA levels were decreased in the VTA and striatum, but DA levels increased in the substantia nigra. • DA and D_2 receptor levels also were reduced in the striatum. • There were no changes in DA or D_2 receptor levels in the PFC or NAc.	In adult animals, nicotine-induced locomotion is attributable to activation of the mesolimbic DA pathway. These data, however, suggest that the nigrostriatal DA pathway contributes to hyperactivity in offspring of nicotine-exposed dams via increased striatal DA release.
Slotkin et al. (1995)	• Pregnant Sprague-Dawley rats • Osmotic minipumps delivered saline or nicotine (0.7 or 2.1 mg/kg/day free base) from gestational days 5 to 22.	• Response to hypoxia	• 1-day-old pups were placed in hypoxic conditions (5% O_2 balanced with N_2). • Survival, adrenal catecholamine release, and release of norepinephrine in the brain were assessed. • 15% of the animals exposed to the high dose of prenatal nicotine died. • Basal adrenal catecholamine release was unaffected by nicotine treatment, but normal norepinephrine release in response to hypoxia was absent in nicotine-exposed animals without changes in noradrenergic receptor binding.	Prenatal nicotine exposure leads to the loss of neonatal hypoxia tolerance. Two mechanisms likely contribute: cardiovascular, mediated by adrenal catecholamines; and respiratory, mediated by release of norepinephrine in the central nervous system. Prenatal nicotine exposure led to the complete loss of the adrenomedullary release in response to hypoxia.

Table A3.1-5 Continued

Study	Species/exposure	Measures	Findings	Comments
Fewell and Smith (1998)	• Pregnant Sprague-Dawley rats • Osmotic minipumps delivered saline or nicotine (6 mg/kg/day free base) from gestational days 6 to P5 or P6.	• Response to hypoxia	• On P5 or P6, pups were exposed to a single period of hypoxia (97% N_2–3% CO_2), and time to last gasp was recorded; or they were exposed to repeated hypoxic events and their ability to autoresuscitate from primary apnea was measured. • Prenatal nicotine exposure had no effect on time to last gasp, but it significantly impaired the ability for autoresuscitation from primary apnea (18 ± 1 recovered periods in vehicle-exposed pups vs. 12 ± 2 recovered periods in nicotine-exposed pups). • Autoresuscitation failure was attributable to A-V dissociation following early cardiac resuscitation.	Nicotine exposure during gestation impairs newborns' ability to autoresuscitate from primary apnea during repeated hypoxic events, like what may happen during repeated episodes of sleep apnea. The mechanism may be altered non-neurogenic catecholamine release.

Table A3.1-5 Continued

Study	Species/exposure	Measures	Findings	Comments
Slotkin (1998)	—	• Review on disruption of neuron replication, differentiation, and function following gestational nicotine.	—	Review article highlighting animal models of the effects of gestational nicotine on fetal neuron development and function. Emphasized findings are that prenatal nicotine increases biomarkers of cell damage and decreases cell number in fetal brain, likely through a persistent increase in constitutive *cFos* expression that activates apoptosis. Nicotine also decreases DNA synthesis and negatively affects adrenomedullary function. nAChR upregulation and resulting hypoactive cholinergic systems after nicotine exposure also likely contribute to behavioral abnormalities in exposed offspring. The relationship between these changes and negative consequences in offspring like SIDS or behavioral deficits is discussed. The greater impact of tobacco/nicotine on fetal development compared to cocaine is also discussed.
Muneoka et al. (1999)	• Pregnant Sprague-Dawley rats • Daily injections of saline or nicotine (3 or 6 mg/kg, s.c.) from gestational days 7 to 20 • Tissue collected from male pups at 8–9 weeks	• Catecholaminergic system function	• HPLC-ECD was used to measure DA, NE, serotonin, and their metabolites in the cortex, hippocampus, striatum, hypothalamus, and cerebellum. • Exposed offspring trended toward lower DA in the cortex, but they had significantly lower DOPAC content in the cortex only. • No differences seen in NE, serotonin, HVA, or 5-HIAA.	High-dose nicotine during gestation reduces total cortical dopaminergic activity via reduced innervation. Authors suggest that this DA dysfunction may contribute to offsprings' vulnerability to drug abuse and psychiatric disorders.

Table A3.1-5 Continued

Study	Species/exposure	Measures	Findings	Comments
Aramakis et al. (2000)	• Male and female Sprague-Dawley pups were injected twice daily with saline or nicotine (1 or 2 mg/kg, s.c.) from P1 to P7–8, P8 to P11–14, or P20 to P23–25, and slices were prepared the next morning. • A fourth group received saline or nicotine (2 mg/kg, s.c.) from P8 to P16, and slices were prepared 7–10 days later.	• Development of excitatory neurotransmission in the auditory cortex during a critical period	• Whole-cell recordings were used to measure glutamate EPSPs and intrinsic membrane properties of layer II–IV pyramidal neurons. • Nicotine exposure during postnatal weeks 1 or 4 had no effect on synaptic function. Exposure during postnatal week 2 produced lasting changes in EPSPs, with longer durations, multiple peaks, and enhanced NMDAR components, without changing number or binding of α7 nAChRs. • Prior exposure to nicotine also blunted normal nicotine-enhanced NMDAR EPSPs. • Membrane properties related to spike generation, but not passive membrane characteristics, were also altered by nicotine during postnatal week 2.	Normal maturation of nAChR regulation of glutamatergic neurotransmission in the auditory cortex is disrupted by nicotine exposure during the second, but not first or fourth, postnatal week. This disruption is lasting and selective to NMDAR-mediated neurotransmission and is not associated with changes in α7 nAChR number or binding. The second postnatal week may represent a critical period of nAChR development in the auditory cortex that can be disrupted by nicotine.
Klein et al. (2003)	• Pregnant C57Bl/6J mice • Mice received 2% SAC alone or with nicotine (50 µg/mL) in drinking water from gestational day 9 to weaning of pups on P21.	• Response to drug rewards in later developmental stages—oral nicotine self-administration	• Male and female offspring were tested during periadolescence (P35–42) for oral self-administration of nicotine. • Animals had unlimited access to SAC-only and sweetened nicotine solution (50 µg/mL nicotine) in home cages in a two-bottle choice test, with bottles switched daily to prevent place preference. • Exposed offspring consumed significantly more nicotine-containing solution than did unexposed offspring. • Further analyses found that exposed males had increased preference for nicotine over SAC (64.6% vs. 23.2%, respectively), while females did not (35% vs. 37.8%, respectively).	Perinatal nicotine exposure produces gender-dependent increases in nicotine preference during the periadolescent period, with only males showing greater nicotine preference. This gender difference may be attributable to prenatal nicotine-induced nAChR upregulation occurring in males but not in females.

Table A3.1-5 Continued

Study	Species/exposure	Measures	Findings	Comments
Pauly et al. (2004)	• C57Bl/6 mice • Mice received 2% SAC alone or with nicotine (200 µg/mL free base) in drinking water starting 30 days before mating and until gestational day 18.	• Hyperactivity in later developmental stages—open-field test	• Offspring exposed to prenatal SAC or nicotine were tested for basal locomotor activity at P20, P40, and P60, followed the next day by nicotine-induced (0 or 1.0 mg/kg, i.p.) hypothermia testing. • Female-exposed offspring displayed hyperactivity at P20 but no treatment differences at P40 or P60. • Male-exposed offspring were hyperactive at P40 and P60 and displayed significant stereotypy compared with unexposed male offspring. • Females, but not males, showed a blunted hypothermic response to a nicotine challenge at P60.	Gestational nicotine gender-dependently influences hyperactivity and acute pharmacologic responses to nicotine during adolescence and early adulthood. Higher stereotypy in exposed male offspring may be attributable to nicotine-induced increases in dopaminergic activity.
Levin et al. (2006)	• Pregnant Sprague-Dawley rats • Osmotic minipumps delivered water or nicotine (6 mg/kg/day free base) from gestational days 4 to 21.	• Response to drug rewards in later developmental stages—nicotine self-administration with forced abstinence	• Female offspring underwent standard i.v. self-administration of nicotine (0.03 mg/kg/infusion free base) for 4 weeks starting at P40–46. • A 7-day drug-free period followed the 4 weeks of self-administration before self-administration was tested for 5 days starting at P82. • Initial acquisition of nicotine self-administration was unaffected by prior nicotine exposure, but self-administration was significantly increased in exposed animals after forced abstinence.	Prenatal nicotine produced a significant increase in i.v. nicotine self-administration during adulthood that became apparent only after a period of forced abstinence from nicotine. It should be noted that offspring were single-housed after weaning. Isolation rearing can alter a multitude of behaviors, including enhanced psychostimulant self-administration (Hall et al. 1998).

Table A3.1-5 Continued

Study	Species/exposure	Measures	Findings	Comments
Liang et al. (2006)	• Sprague-Dawley rats • Twice-daily injections of saline or nicotine (0.7 mg/kg free base, s.c.) from P8 to P12, when expression of nAChRs peaks in the primary auditory cortex	• Auditory processing—nAChR regulation of signaling processing in primary cortex and auditory learning	• Adults (>P60) underwent auditory-cued active avoidance and in vivo auditory physiology testing. • Perinatal nicotine significantly decreased avoidance behavior without affecting tone orienting or motor function. • Acute nicotine exposure (0.7 mg/kg, s.c.) in control rats enhanced sensitivity to sound of neural responses in layers III and IV of A1 that was attenuated by the nonspecific nAChR antagonist mecamylamine. • Exposed animals did not show this enhancement of auditory responses after acute nicotine.	nAChRs in the primary auditory cortex normally function to enhance sensitivity and responsiveness to auditory stimuli, but exposure to nicotine during postnatal week 2 impairs auditory learning. These deficits are not associated with changes in nAChR binding.
Pentel et al. (2006)	• Pregnant Holtzman Sprague-Dawley rats (with or without prior nicotine-vaccine exposure) received computer-controlled saline or nicotine (2 mg/kg/day free base, i.v.) from gestational days 1 to 20. • On gestational day 20, a final dose of radiolabeled nicotine (0.05 mg/kg, i.v.) was delivered, and fetal blood/tissue was collected 25 minutes later.	• Activation of placental nAChRs by maternal nicotine	• Gestational nicotine exposure produced significant increases in brainwide nAChR binding in the fetal brain and spinal cord, as measured by 125I-epibatadine binding. • Nicotine exposure also decreased *cFos* induction in the fetal caudate, adrenal glands, and lungs, but not the hippocampus. • The nicotine vaccine did not affect fetal receptor binding or *cFos* expression.	Using a dosing regimen that models human smoking, gestational nicotine upregulates nAChR density throughout the fetal brain and spinal cord. Maternal vaccination against nicotine reduces nicotine distribution in the fetal brain, but it had no influence on nAChR density or neuronal activity.

Table A3.1-5 Continued

Study	Species/exposure	Measures	Findings	Comments
Dwyer et al. (2008)	—	• Review on the role of nAChRs in regulating early brain plasticity	—	Review article highlighting the profound and diverse contribution of nAChRs in regulating the proper maturation of neural circuitry, from influencing cell survival and patterned spontaneous activity to regulation of developmental switches in GABAergic signaling. Includes a commentary on animal models of gestational nicotine exposure and summarizes clinical and preclinical work on the effects of gestational nicotine exposure, with a focus on SIDS, behavioral disorders, and auditory processing deficits.
Franke et al. (2008)	• Pregnant Sprague-Dawley rats • Osmotic minipumps delivered saline or nicotine (3 mg/kg/day free base) from gestational days 4 to 22. • Cocaine exposure for *cFos* analysis was done on postnatal day 32.	• Response to natural or drug rewards in later developmental stages—sucrose or cocaine self-administration • Neural activation in response to cocaine	• Adolescent rats (P32–43) exposed to prenatal nicotine showed an overall decrease in motivation to consume sucrose compared with nonexposed animals. • Both exposed and nonexposed animals acquired cocaine self-administration, but nonexposed animals worked more for the lower 200 µg/kg/infusion dose, while exposed animals worked more for the high 500 µg/kg/infusion dose.	Prenatal nicotine exposure has complex effects on responding to natural and drug rewards in adolescent offspring, with lower motivation for natural rewards and greater motivation for higher doses of cocaine, as compared with unexposed offspring. This may reflect decreased aversion in exposed offspring and is corroborated by less stereotypy to high doses.

Table A3.1-5 Continued

Study	Species/exposure	Measures	Findings	Comments
Chistyakov et al. (2010)	• Pregnant outbred Swiss mice • Mice received SAC alone or with nicotine (200 µg/mL free base) from 2 weeks before mating up to weaning of pups at P21.	• Response to drug rewards in later developmental stages—nicotine self-administration	• Adolescent male mice (6 weeks old) self-administered saline or nicotine (0.028, 0.056, 0.084, or 0.112 µg/infusion, free base) for one 30-minute test. • Exposed mice had significantly higher nicotine self-administration of 0.028 and 0.056 µg/infusion and similar levels of self-administration of the 0.084 µg/infusion dose than unexposed mice. • Spontaneous locomotor activity was tested at weeks 3, 4, 5, 7, and 10, but nicotine exposure had no effect in novel or familiar environments. • [3H]epibatidine-binding sites were unaffected by prenatal nicotine in the cortex and hippocampus at weeks 3 and 6.	The reinforcing effects of nicotine are sensitized in adolescent offspring of nicotine-exposed mothers without influencing locomotor behavior or nAChR binding in the cortex or hippocampus. As a result, exposed offspring self-administer more nicotine at low doses than unexposed offspring do.

Table A3.1-5 Continued

Study	Species/exposure	Measures	Findings	Comments
Cao et al. (2011)	• Pregnant Sprague-Dawley rats • Osmotic minipumps delivered saline or nicotine (3 mg/kg/day free base) from gestational days 4 to 18.	• Expression of genes involved in neuronal signaling and addiction	• Expression of 29 CAM genes associated with drug addiction was measured by qRT-PCR in exposed and unexposed female offspring (P35). • Nicotine exposure modified various CAM genes of the neurexin, immunoglobulin, cadherin, and adhesion-GPCR superfamilies, as well as their intracellular signaling pathways in the CPu, NAc, amygdala, and PFC. • Most of the affected CAM genes were downregulated, but Postn was upregulated in the NAc and PFC. • The CPu was particularly sensitive to modification by prenatal nicotine, with 17 genes showing altered expression. • Rho small GTPase-related pathways were modified by nicotine exposure in all four brain regions, while MAPK-related pathways were altered only in the PFC and amygdala. • GPCR-related signaling pathways, Notch and Wnt/Frizzled pathways, and growth factor-signaling pathways were also influenced by nicotine exposure in the NAc, PFC, and amygdala.	Gestational nicotine influences the expression of CAMs in a region-specific manner. In striatal regions, CAMs related to glutamate synapse structure and function were downregulated, with the CPu showing the greatest vulnerability. CAMs related to GABAergic synapse formation were altered in the PFC. Myelination-related CAMs were downregulated in both the PFC and CPu, suggesting that neuron–glia interactions are also affected by gestational nicotine. In the amygdala, CAMs important for emotional learning and memory were affected by nicotine exposure. Overall, prenatal nicotine likely reduces excitatory synapses in the ventral striatum while also compromising glutamatergic signaling in the dorsal striatum.

Table A3.1-5 Continued

Study	Species/exposure	Measures	Findings	Comments
Wei et al. (2011)	• Pregnant Sprague-Dawley rats • Osmotic minipumps delivered saline or nicotine (3 mg/kg/day free base) from gestational days 4 to 22.	• Expression of genes involved in neuronal signaling and addiction	• Female offspring (P35) of exposed or unexposed dams were used to assess cell survival/death, development/plasticity, immune response, and cellular metabolism-related pathways in the PFC, caudate putamen, NAc, PVN, and the amygdala. • The most robust changes occurred in cell death/survival pathways, with 24 biological pathways related to cell death/survival modulated by gestational nicotine in a region-dependent manner. • These pathways were further classified into three categories: growth factor, death receptor, and kinase cascade. • In the NAc, growth factor, kinase, and transcription factor expression were upregulated by prenatal nicotine, while growth factors, death receptors, and caspases were upregulated in the striatum by nicotine exposure. • Death receptor and caspase expression were decreased in the PFC.	Nicotine modulates both growth factor and death-receptor pathways by affecting the expression of their genes. The NAc showed an enhancement of cell survival pathways following nicotine exposure, while both cell death and survival pathways were increased in the structurally related striatum. Therefore, the balance of these pathways may determine the final effect of nicotine on cell survival.
Horst et al. (2012)	• Pregnant C57BL/6J mice • Mice were given nicotine (200 µg/mL) or vehicle (0.2% tartaric acid) in sweetened (2% SAC) drinking water throughout pregnancy and until pups were weaned at P21. • Exposed offspring were behavior tested in adulthood and compared to drug-naïve β2 nAChR KO animals.	• Auditory processing—auditory discrimination task	• Perinatal nicotine or lack of β2 subunit disrupted learning of auditory discrimination task attributable to increased probability of false-alarm responses.	Perinatal nicotine impairs auditory processing in an appetitive task. Impairments are long-lasting, as testing was done months after end of drug exposure. Some potential mechanisms: nicotine during critical developmental periods: (1) interferes with β2 nAChR subunit expression or function that is necessary for normal auditory learning, and/or (2) disrupts function of thalamocortical neurons.

Table A3.1-5 Continued

Study	Species/exposure	Measures	Findings	Comments
Lacy et al. (2012)	• Pregnant Sprague-Dawley rats • Rats received intermittent injections of saline or nicotine (0.05 mg/kg/injection) three times a day from gestational days 8 to 21.	• Response to natural rewards in later developmental stages—sucrose self-administration	• Adult offspring of both genders were tested for habituation of spontaneous locomotor activity and for operant responding to a natural reward. • Prior nicotine exposure had no effect on habituation to spontaneous locomotor activity. • For operant experiments, offspring acquired FR3 responding for 26% sucrose (w/v) before testing on varying concentrations (0%, 3%, 10%, 30%, and 56%, Latin-square design) on an FR3 and PR schedule. • Nicotine had no effect on acquisition of sucrose responding. • Both exposed and nonexposed offspring showed an inverted U-shaped response curve, with peak responding for 10% sucrose. • PR responding was significantly higher in nicotine-exposed rats than in nonexposed rats.	Nicotine exposure during gestation increases motivation for sucrose without altering sensitivity to varying concentrations of sucrose, weight, or spontaneous locomotor activity. These data suggest that prenatal exposure to low doses of nicotine results in long-term increases in motivation for natural rewards, which may help explain correlations between maternal smoking and adolescent obesity.
Schneider et al. (2012)	• Pregnant Wistar rats • Rats received nicotine (0.06 mg/mL) in drinking water 3 weeks before mating and throughout gestation. • Behavioral testing in male/female offspring P25–P50	• Attention, five-choice serial reaction time task (5-CSRTT), locomotor behavior, and delay-discounting	• Exposed offspring showed hyperactivity in a familiar environment; behavioral disinhibition in 5-CSRTT (i.e., more anticipatory responses, fewer omission errors, and shorter latency to errors); but no change in choice impulsivity.	Prenatal nicotine results in hyperactivity and greater impulsivity, which resemble some symptoms of ADHD. Previous work showed increased impulsivity in adult offspring with prenatal nicotine exposure, but symptoms of most psychiatric disorders emerge during adolescence.

Table A3.1-5 Continued

Study	Species/exposure	Measures	Findings	Comments
Zhu et al. (2012)	• Pregnant C57BL/6 mice • Mice were given 2% SAC or nicotine (0, 0.05, 0.1, or 0.2 mg/mL) plus 2% SAC in drinking water 3 weeks before mating and throughout pregnancy. • High offspring mortality in the 0.2 mg/kg nicotine group precluded testing, and so this dose was not used further.	• Catecholaminergic system function	• P42 and P60 offspring were tested for hyperactivity, regional brain volume, radial thickness, and DA turnover. • Offspring exposed to 0.1 mg/kg nicotine had significantly higher locomotor behavior in an open field than offspring exposed to SAC only or to 0.05 mg/kg nicotine. • Spontaneous hyperactivity in the dark period and beginning of the light period was also seen in nicotine-exposed offspring. • Oral, but not intraperitoneal, methylphenidate (0.75 mg/kg) transiently decreased hyperactivity in nicotine-exposed offspring in comparison to control levels. • Nicotine exposure significantly increased DA content but decreased (~100%) DA turnover (i.e., DOPAC/DA) in the PFC, and it had no effect on serotonin content or turnover. • Striatal DA turnover was also decreased (~50%) by prenatal nicotine. • Turnover was normalized by methylphenidate (0.75 mg/kg, p.o.). • Decreased cingulate cortex volume and radial thickness were also a consequence of prenatal nicotine.	Gestational nicotine produces behavioral, neuroanatomical, and neurochemical changes in mice that parallel the human ADHD phenotype. These changes are limited to the dopaminergic system, and hyperactivity and DA turnover are normalized by oral methylphenidate treatment.

Table A3.1-5 Continued

Study	Species/exposure	Measures	Findings	Comments
Cao et al. (2013)	• Pregnant Sprague-Dawley rats • Osmotic minipumps delivered nicotine (3 mg/kg/day free base) from gestational days 4 to 18. • PFC, NAc, and CPu were collected from pups at P20–21, P35–36, or P59–60.	• White matter structure	• Exposed adolescent (P35–36) males had increased myelination in PFC, CPu, and NAc, while females had decreased myelination in PFC, no change in CPu, and some genes upregulated in NAc. • Levels normalized by adulthood for males but not for females.	Prenatal nicotine age-, gender-, and region-dependently alters myelination. Juvenile and adolescent gender differences may be attributable to gonadal hormone stimulation of oligodendrocyte development and subsequent myelination. Lasting changes in females may suggest greater sensitivity to the effects of gestational nicotine.
Chang et al. (2013)	• Pregnant Sprague-Dawley rats • Osmotic minipumps delivered nicotine (0.075 or 1.5 mg/kg/day) for 14 days. • Nicotine delivery started on gestational day 8.	• Consummatory behavior—oral intake of alcohol, nicotine, and high-fat diet	• Oral consumption of ethanol, nicotine, and a high-fat diet were tested in adolescent offspring (P40–60). • Prenatal nicotine exposure increased consumption of 0.02% nicotine solution, 2% ethanol solution, and a 50% fat content chow without altering normal food and water intake.	Low-dose nicotine exposure during gestation increases consummatory behavior during adolescence that may lead to obesity. The mechanism is likely induction of orexigenic peptide systems in the hypothalamus and central amygdala.
Gorini et al. (2013)	• Pregnant Sprague-Dawley rats • Osmotic minipumps delivered saline or nicotine (6 mg/kg/day free base) for 28 days, starting from gestational day 3.	• Brainstem function	• Tissue from pups (ages P3–7) of both genders was used for assessment of TCR. • Nicotine-exposed pups had significantly greater TCR than unexposed pups (average decrease in heart rate of 71 ± 12.4 bpm vs. 35 ± 2.6 bpm). • Nicotine exposure also increased trigeminally evoked glutamate neurotransmission by 64.2% ± 7.2% compared with unexposed pups. • Serotonin 5-HT_{1A} and 5-$HT_{2A/C}$ antagonists attenuated increases in EPSCs.	Prenatal nicotine enhances TCR and facilitates glutamatergic input to cardiac vagal nerves upon trigeminal afferent stimulation. This enhancement is attributable to increases in serotonergic signaling in the brainstem via 5-HT_{1A} and 5-$HT_{2A/C}$ receptors. Exaggerated TCR and greater glutamatergic neurotransmission to cardiac vagal neurons likely produce increased bradycardia, drops in blood pressure, and apnea that lead to SIDS.

Table A3.1-5 Continued

Study	Species/exposure	Measures	Findings	Comments
Morgan et al. (2013)	• Pregnant Sprague-Dawley rats • Rats received thrice-daily injections of saline or nicotine (0.15 mg/kg/day, i.v.) from gestational days 8 to 20.	• Orexin/hypocretin expression and function	• Expression of orexin and MCH neurons in the LH and orexin projections from LH to VTA was measured in adult offspring (P130) of exposed and unexposed dams. • Prenatal nicotine exposure increased the number of orexin neurons in the LH without affecting the expression of MCH neurons. • Almost all VTA dopaminergic neurons received contacts from orexin fibers. • Prenatal nicotine significantly increased the number of orexin-positive appositions onto DA cells.	Gestational nicotine produces long-lasting increases in the number of LH orexin neurons and orexin-dopaminergic connections in the VTA. These data suggest that a greater orexin-mediated influence on motivation may mediate some of the behavioral effects seen in nicotine-exposed offspring. The mechanism may be that prenatal nicotine interferes with normal postnatal pruning, resulting in more LH orexin neurons, possibly through drug-induced increases in brain-derived neurotrophic factor.
Mychasiuk et al. (2013)	• Pregnant Long-Evans rats • Daily injections of saline or nicotine (0.3 mg/kg, s.c.) after mating and until pups were born	• Neuronal morphology—Golgi-Cox analysis of dendritic length, dendritic branching, and spine density	• Golgi-Cox analysis was done in adult offspring (P100). • Exposed males had greater dendritic complexity, while females had less dendritic complexity in PFC and NAc. • In the orbital frontal cortex, all offspring had greater spine density, and males had more dendritic branching.	Prenatal nicotine induces long-lasting changes in neuronal morphology in regions critical for executive function and reward behavior. Authors suggest this may be a mechanism for gestational nicotine exposure's increasing vulnerability to nicotine addiction later in life.
Bailey et al. (2014)	• Pregnant WT or α5 nAChR subunit KO mice • Mice received nicotine (200 µg/mL) in sweetened (+2% SAC) water throughout gestation and until weaning at P21. • Tissue collected at postnatal week 3 or in adulthood.	• Neurochemical changes (acetylcholine) • Whole-cell recording and immunohistochemistry of layer VI mPFC neurons	• Exposed young and adult WT mice had greater apical dendritic complexity and decreased nAChR signaling. • This pattern was also seen in unexposed α5 KO mice. • Exposed KO mice showed normalized morphology but were more sensitive to acute nicotine, showing greater reduction in nAChR signaling.	Prenatal nicotine leads to persistent changes in apical dendrite morphology and physiology that are dependent, in part, on the α5 nAChR subunit. This implies that prenatal nicotine can alter dendritic morphology in layer VI mPFC neurons important for attention, although behavioral effects were not tested here.

Table A3.1-5 Continued

Study	Species/exposure	Measures	Findings	Comments
Lacy et al. (2014)	• Pregnant Sprague-Dawley rats • Rats received intermittent injections of saline or nicotine (0.05 mg/kg/injection) three times a day from gestational days 8 to 21.	• Response to drug rewards in later developmental stages—methamphetamine self-administration	• Adult offspring (P70) were tested for methamphetamine self-administration on FR (0.05 mg/kg/infusion, i.v.) and PR (0.005, 0.025, and 0.05 mg/kg/infusion, i.v.) schedules. • Both genders acquired methamphetamine self-administration on an FR schedule regardless of prenatal nicotine exposure, but females acquired the behavior more rapidly. • In PR responding, nicotine-exposed offspring of both genders had higher break points at all doses and had significantly higher intake at the 0.025 and 0.05 mg/kg doses.	Gestational nicotine produces lasting increases in motivation for methamphetamine without influencing acquisition of methamphetamine self-administration.
McNair and Kohlmeier (2015)	• Pregnant mice (from the Naval Medical Research Institute) • Mice received 2% SAC alone or with nicotine (300 µg/mL free base) in drinking water throughout gestation.	• Glutamatergic signaling in brain reward circuitry—calcium imaging	• Calcium imaging was used to measure glutamatergic neurotransmission in the laterodorsal tegmental nucleus of offspring, P7–22. • Nicotine exposure led to decreased AMPA receptor-mediated calcium responses and a second-to-first response ratio >1 after a second application of AMPA. • In control animals, the second-to-first response ratio with AMPA stimulation was <1. • Responses to repeated NMDA also showed a significant increase in nicotine-exposed offspring compared with unexposed offspring, without differences in calcium responses to a single NMDA application.	Gestational nicotine can reduce both AMPAR- and NMDAR-mediated glutamatergic neurotransmission in the laterodorsal tegmental nucleus, a brain region critical for assigning motivational salience. Decreased AMPA-mediated calcium responses are likely attributable to changes in receptor quantity, subunit composition, and/or calcium permeability.

Table A3.1-5 Continued

Study	Species/exposure	Measures	Findings	Comments
Zhu et al. (2014)	• C57Bl/6 mice • Mice received 2% SAC alone or with nicotine (0.1 mg/mL) in drinking water starting 3 weeks before mating and throughout pregnancy. • F1 females from PNE and SAC groups were bred with WT, drug-naïve males at 6–8 weeks of age to generate the F2 generation. • Females of the F2 generation were bred with WT, drug-naïve males at 6–8 weeks of age to produce the F3 generation. • A parallel set of experiments had F1 males from PNE and SAC groups mate with WT, drug-naïve females to produce the F2 generation.	• Hyperactivity in later developmental stages—multigenerational effects of nicotine exposure and amelioration by methylphenidate	• Spontaneous locomotor activity was assessed in 6- to 7-week-old F2 and F3 male and female mice. • F2 male and female mice derived from F1 PNE females and F3 male and female mice derived from F2 PNE females displayed significant increases in locomotor activity compared with SAC counterparts. • Oral methylphenidate (0.75 mg/kg) decreased locomotor activity in F2 and F3 PNE mice. • Locomotor activity of F2 mice derived from male F1 PNE mice was not significantly different from their SAC counterparts.	Nicotine-induced hyperactivity can be transmitted through the maternal line to affect offspring of both genders, and oral methylphenidate at clinically relevant doses can attenuate hyperactivity in these mice. These data suggest that the hypodopaminergic state present in F1 females was likely transmitted to the F2 and F3 generations. The mechanism for this change is likely epigenetic and may be limited to epigenetic changes of mitochondrial genes. See Leslie (2013) for further discussion on the implications of these epigenetic changes.

Note: **A1** = primary auditory cortex; **ADHD** = attention deficit hyperactivity disorder; **AMPA** = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; **AMPAR** = AMPA receptor; **A-V** = atrial-ventricular; **bpm =** beats per minute; **CAM** = cell-adhesion molecule; ***cFos*** **=** protooncogene and immediate early gene used as a marker of neuronal activity; **5-CSRTT** = 5-choice serial reaction time task; **CO_2** = carbon dioxide; **CPu =** caudate putamen; **DA** = dopamine; **D1R** = dopamine D1 receptor; **DOPAC**= 3,4dihydroxyphenylacetic acid, metabolite of dopamine; **EPSCs** = excitatory postsynaptic currents; **EPSPs** = excitatory postsynaptic potentials; **F1** = first filial generation (and similar); **FR** = fixed ratio; **G20 =** gestational day 20 (and similar); **GABAergic =** any cell, especially any neuron, that releases gamma-aminobutyric acid (GABA); **GPCR** = Gprotein-coupled-receptor; GTPases (singular **GTPase**) are a large family of hydrolase enzymes that can bind and hydrolyze guanosine triphosphate (GTP); **5-HIAA** = 5-hydroxyindole acetic acid, the primary metabolite of serotonin; **HPLC-ECD =** high-performance liquid chromatography electrochemical detection; **$5HT_{1AR}$** = serotonin (5-hydroxytryptamine) receptor 1A; **$5\text{-}HT_{2A/C}$ =** serotonin (5-hydroxytryptamine) receptor 2 A/C; **HVA =** homovanillic acid, a metabolite of dopamine; **i.p.** =intraperitoneal; **i.v.** = intravenous; **kg** = kilogram; **KO** = knockout; **LH** = lateral hypothalamus; **MAPK** = mitogen-activated protein kinase; **MCH** = melaninconcentrating hormone; **mg** = milligram; **min** = minute; **µg** = microgram; **mL** = milliliter; **mPFC** = medial prefrontal cortex; **N_2** = nitrogen; **NAc** = nucleus accumbens; **nAChRs =** nicotinic acetylcholine receptors; **NE =** norepinephrine; **NMDAR =** *N*-methyl-D-aspartate receptor; **O_2 =** oxygen; **P3** (and similar) = postnatal day 3; **PFC** = prefrontal cortex; **PNE** = prenatal nicotine exposure; **p.o.** = per os (by mouth); **Postn** = periostin, osteoblast-specific factor; **PR** = progressive ratio; **PVN** = paraventricular nucleus of the thalamus; **qRT-PCR** = quantitative real-time polymerase chain reaction; **SAC** = saccharin; **s.c.** = subcutaneous; **SIDS** = sudden infant death syndrome; **TCR** = trigeminocardiac reflex; **TH** = tyrosine hydroxylase; **VTA** = ventral tegmental area; **Wnt** = Wingless-Type MMTV Integration Site Family, member 1, intracellular signaling factors; **WT** = wild type; **w/v** = weight/volume.

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