HHS Public Access

Author manuscript

*Am J Drug Alcohol Abuse*. Author manuscript; available in PMC 2017 June 30.

Published in final edited form as:

*Am J Drug Alcohol Abuse*. 2017 March ; 43(2): 171–185. doi:10.1080/00952990.2016.1209512.

# Mechanisms and genetic factors underlying co-use of nicotine and alcohol or other drugs of abuse

**Sarah J. Cross, BA**[a], **Shahrdad Lotfipour, PhD**[b,c], and **Frances M. Leslie, PhD**[a,c]

[a]Department of Anatomy & Neurobiology, School of Medicine, University of California, Irvine, CA, USA

[b]Department of Emergency Medicine, School of Medicine, University of California, Irvine, CA, USA

[c]Department of Pharmacology, School of Medicine, University of California, Irvine, CA, USA

## Abstract

Concurrent use of tobacco and alcohol or psychostimulants represents a major public health concern, with use of one substance influencing consumption of the other. Co-abuse of these drugs leads to substantial negative health outcomes, reduced cessation, and high economic costs, but the underlying mechanisms are poorly understood. Epidemiological data suggest that tobacco use during adolescence plays a particularly significant role. Adolescence is a sensitive period of development marked by major neurobiological maturation of brain regions critical for reward processing, learning and memory, and executive function. Nicotine exposure during this time produces a unique and long-lasting vulnerability to subsequent substance use, likely via actions at cholinergic, dopaminergic, and serotonergic systems. In this review, we discuss recent clinical and preclinical data examining the genetic factors and mechanisms underlying co-use of nicotine and alcohol or cocaine and amphetamines. We evaluate the critical role of nicotinic acetylcholine receptors throughout, and emphasize the dearth of preclinical studies assessing concurrent drug exposure. We stress important age and sex differences in drug responses, and highlight a brief, low-dose nicotine exposure paradigm that may better model early use of tobacco products. The escalating use of e-cigarettes among youth necessitates a closer look at the consequences of early adolescent nicotine exposure on subsequent alcohol and drug abuse.

### Keywords

Adolescence; amphetamine; co-dependence; cocaine; e-cigarettes; ethanol; nicotinic acetylcholine receptors; tobacco

**CONTACT** Sarah J. Cross, BA, crosssj@uci.edu, Department of Anatomy & Neurobiology, University of California, Irvine, 367 Med Surge II, Irvine, CA 92697, USA.

Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/iada.

**Declaration of interest**

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

**ORCID**

Sarah J. Cross http://dx.orcid/0000-0002-6246-3815

## Introduction

Nicotine, via tobacco and increasingly from electronic nicotine delivery systems, is often used in conjunction with alcohol or other abused drugs. The majority of alcoholics smoke (1,2) and non-alcoholic drinkers are more likely to smoke than non-drinkers (3). Tobacco use also occurs in ~90% of cocaine and methamphetamine users (4–6). The combined use of tobacco with other abused substances is associated with substantial negative health outcomes. These include reduced cessation (7–9) and increased risk of cancer, heart disease, and mood disorders (10–14).

Epidemiological data suggest that tobacco in particular can act as a “gateway” to further substance use (15–18), and recent preclinical work lends support to this hypothesis (18–21). However, much of the preclinical research on nicotine interactions with other drugs fails to take into account the age of exposure, despite strong age-dependent associations in epidemiological studies. Initiation of substance use typically occurs during adolescence, with tobacco and alcohol use beginning in early teen years before subsequent progression to illicit drugs (16,22,23). Indeed, almost 90% of adult smokers started before the age of 18 (24). Important sex differences in tobacco use and trajectories (25) are also frequently ignored, with adolescent females being more likely to start smoking and less likely to quit than adolescent males (26,27).

Adolescence is marked by major reorganization of limbic brain regions that are important for learning, memory, and reward processing and characteristic behaviors of increased risk-taking, novelty seeking, and peer associations (28–31). It is conserved across mammalian species, with many of the same physiological and behavioral changes occurring in both humans and rodents (28,30,32). This developmental period is conservatively estimated to last from 12 to 18 years in humans and postnatal (P) days 28–42 in rodents (28), although the boundaries may extend beyond these ages (33–36). The dopamine system, which is critically involved in the rewarding properties of abused drugs (37,38), undergoes substantial remodeling during adolescence (31,39). Nicotinic acetylcholine receptors (nAChRs), which are ligand-gated ion channels consisting of pentameric combinations of $\alpha 2 - \alpha 7$ and $\beta 2 - \beta 4$ subunits, are also critically involved in the dynamic maturation of adolescent brain (40–42). Nicotine exposure during this time can produce unique and long-lasting behavioral and neurochemical changes, including modifications of cholinergic, dopaminergic, serotonergic, and endorphin systems (31,42–46), which may lead to further drug use.

In this review, we discuss the neurobiological and genetic factors underlying concurrent use of nicotine and alcohol or psychostimulants. We highlight important sex differences in concurrent use and argue that adolescent exposure to nicotine, via tobacco or e-cigarettes, is an essential component in the high rates of subsequent drug co-abuse.

## Concurrent use of nicotine and alcohol

### Human studies

Approximately 6.2 million people report alcohol use and tobacco dependence in the United States (US) during a single year (2). The economic costs associated with tobacco and

alcohol use total nearly 500 billion dollars per year in the US (47). It is increasingly clear that both substances influence consumption of the other, likely due to common genetic and molecular sites of action. Dependent smokers are approximately 10 times more likely to be alcoholics than non-smokers (48), and 70–80% of alcoholics smoke (2). Even young adults who only smoke occasionally are very likely to drink and, when drinking and smoking occur together, significantly greater amounts of alcohol are consumed (49,50). An increasing number of reports demonstrate associations between e-cigarette use and alcohol use and misuse among adolescents (51–54), although one study did not see any effect of e-cigarette consumption on alcohol use (55). Cessation and relapse are also negatively impacted by co-use. Current alcohol use disorder is associated with lower likelihood of smoking cessation and increased relapse to smoking (56), and nicotine dependence is associated with decreased odds of alcohol cessation in alcoholics (57–59). Additionally, female smokers have significantly higher alcohol craving in a treatment setting than nonsmokers (60). Experimental studies in humans have shown that nicotine increases the rewarding value of alcohol (61,62), and vice versa (63,64). Epidemiologic data also show that early adolescent onset smokers are at the greatest risk of excessive alcohol consumption and severe alcohol abuse disorders (49,65,66). Furthermore, an assessment of 12th grader patterns of use, from 1976 to 2010, has shown that the association of tobacco and alcohol co-use has increased over time, even though overall drug use has declined (67). These findings suggest that the behavior of co-users is increasingly attributable to factors that concomitantly influence both smoking and drinking.

Genetic mechanisms may contribute to tobacco and alcohol co-use. There is substantial overlap in a variety of genes that contribute to alcohol or tobacco use alone (68–70), but a full discussion is beyond the scope of this review. Instead, our focus is on known genetic underpinnings of co-use. Twin studies have shown that a substantial proportion of alcohol and nicotine co-dependence results from genetic influences, with more modest environmental contributions (71,72). Subsequent studies have tried to identify specific genetic associations between smoking and drinking. An area on chromosome 2 has been identified as a possible common genetic vulnerability locus for smoking and alcohol co-dependence (73). Genetic studies have also shown that nAChR genes are associated with both tobacco and alcohol addictions. In particular, recent evidence highlights the importance of the human gene cluster CHRNA5/A3/B4, which encodes α3, β4, and α5 nAChR subunits, respectively, in mediating these disorders (74–77). However, although genetic variations in the α5 nAChR subunit have been shown to influence risk for both alcohol and tobacco dependence, different single nucleotide polymorphisms (SNPs) of the gene are responsible (76). SNPs in other nAChR subunit genes have also been implicated in drug co-use, with CHRNB2 linked to initial subjective responses to both alcohol and tobacco (78), and the CHRNA6 - CHRNB3 gene complex linked to both smoking and heavy alcohol consumption (79,80). SNPs in the CHRNA5/A3/B4 gene cluster have been shown to be significant predictors of early initiation of tobacco or alcohol use (81–84) as well as associated with the frequency of adolescent binge drinking (85).

Consistent with a possible role of nAChRs in alcohol use disorders, there have been reports of clinical efficacy of varenicline, which is a partial agonist at α4β2 nAChRs and a full agonist at the α7 nAChR (86). A recent meta-analysis of clinical trials found that varenicline

reduces alcohol craving and total alcohol consumption in patients with alcohol use disorders (87). Drug effects are mild, however, and are more evident in less heavy drinkers (88,89).

## Animal studies

**Genetic models—**Genetic rodent models have helped provide evidence for the mechanisms mediating the associated addictions in humans and provided insight into possible therapeutic interventions. Our focus here is on genetic contributions to nicotine and alcohol consumption since it is most relevant to human drug use, but we also briefly discuss some other responses to ethanol. One approach involves the selective breeding of rats or mice for different responses to alcohol. For example, both rats and mice selectively bred for high sensitivity to alcohol's locomotor-stimulating or sedative effects have been found to be more sensitive to nicotine than low sensitivity animals (90–93). In another study, nicotine self-administration was examined in rats selectively bred for high (P) or low (NP) alcohol intake (94). Not only did P rats self-administer more nicotine than NP rats but, following extinction, they also exhibited greater cue- or drug-induced reinstatement of responding. Studies on mice selectively bred for differing sensitivity to the sedative effects of alcohol have linked alcohol effects on Y-maze activity to a region in mouse chromosome 2 that contains CHRNA4, the gene that encodes the α4 nAChR subunit (95). Subsequent biochemical analyses have confirmed that an A/T polymorphism at amino acid position 529 in the second intracellular loop of the α4 subunit protein influences the initial sensitivity of α4β2 nAChRs to alcohol exposure (96).

Use of transgenic mouse models with selective gene mutations has further confirmed a role for nAChR subunits in some alcohol-induced behaviors. The deletion of β2-containing nAChRs modifies anxiolytic and withdrawal behaviors to alcohol (97,98), but has no effect on alcohol drinking behavior (98) or alcohol preference (99). Deletion of the α7 nAChR subunit results in significant reduction of alcohol intake in female mice as compared to wild-type mice, with no effect in males (100). Knockout mice lacking the α7 nAChR subunit also have increased sensitivity to the hypothermic, sedative, and locomotor-stimulating effects of ethanol (101). Transgenic over-expression of α3, β4, and α5 nAChR subunit genes, which increases nicotine consumption, decreases alcohol intake in a two-bottle preference test (102). Although elimination of the α5 nAChR subunit does not modulate ethanol consumption in knockout mice, it results in slower recovery from ethanol-induced sleep (103).

Whereas gene deletion of α6 and β3 nAChR subunits, both highly expressed in midbrain dopamine neurons (104,105), does not influence alcohol consumption (106), a role for α6 nAChR subunits in alcohol reward has been demonstrated using transgenic mice (α6L9'S) expressing mutant, hypersensitive α6 nAChR subunits (107). Female α6L9'S mice show significantly elevated alcohol intake at low concentrations of alcohol in a two-bottle choice procedure, whereas α6L9'S of both sexes show significantly elevated alcohol intake in a drinking in the dark procedure and exhibit low dose alcohol-induced place preference not seen in control mice. Alcohol has been shown to activate dopamine neurons within the midbrain posterior ventral tegmental area (pVTA) that express higher levels of α4, α6 and β3 nAChR subunit genes than non-activated neurons (108). The role of α4 subunits in

alcohol reward has been further demonstrated by using two transgenic lines with either a deletion of the α4 subunit gene or an insertion of a hyperactive polymorphism (Leu9'Ala). Alcohol potentiates the electrophysiological response to acetylcholine in midbrain dopamine neurons in wild-type mice, an effect that is absent in α4 knockout mice (109). Furthermore, ethanol intake and preference are decreased in α4 knockout mice (108,110), whereas Leu9'Ala mice exhibit enhanced conditioned place preference (109). Infusion of varenicline into the pVTA has demonstrated the particular importance of α4 subunits in this brain region for alcohol reward. Whereas varenicline into the pVTA mildly decreased alcohol consumption in wild-type controls, it had no effect on animals with the α4 nAChR gene deletion. Conversely, low doses of varenicline that were ineffective in wild-type controls greatly reduced alcohol intake in Leu9'Ala hypersensitive mice. Together, these data show that α4-containing nAChRs are a critical element in varenicline reduction of alcohol consumption. In contrast, gene deletion studies have shown that β2 and α7 nAChR subunits have no role in varenicline actions (100).

**Behavioral pharmacology—**Pharmacological studies have also demonstrated a role for nAChRs in modulating ethanol reward and reinforcement, although they sometimes contrast with genetic rodent studies. Mecamylamine, a nonspecific nAChR antagonist, dose-dependently reduces ethanol consumption, blocks ethanol-induced conditioned place preference and inhibits ethanol activation of VTA dopamine neurons (111,112). Antagonism of α3β2-, β3-, and/or α6-containing nAChRs with α-conotoxin MII decreases ethanol-induced locomotion and dopamine overflow, as well as ethanol consumption and preference (113–115), although the α-conotoxin-PIA analogue that is selective for α6 nAChRs does not alter ethanol's locomotor or neurochemical effects (113). Blockade of α4β2 nAChRs with DHβE or α7 nAChRs with MLA has no effect on ethanol intake (111,115,116), but partial agonists of β4-containing nAChRs reduce ethanol consumption and seeking in rats (111,116).

As in humans, there are positive relationships between nicotine exposure and alcohol intake or self-administration in rodents (117–122), although this can depend on length and timing of exposure, strain, and route of administration. The opposite relationship, with alcohol influencing nicotine intake, has not been as thoroughly tested using animal models. Single systemic injections of nicotine have no effect on alcohol intake, while repeated exposure enhances both oral ethanol intake and self-administration (117–120). Nicotine pretreatment 3–4 hours prior to alcohol self-administration increases alcohol intake, whereas nicotine given immediately prior to the session has no effect or suppresses responding (121,122). The increased alcohol drinking 3–4 hours after nicotine exposure is accompanied by greater GABAergic inhibition of VTA neurons, resulting in decreased dopamine cell firing and lower nucleus accumbens (NAc) dopamine release that may increase the motivation for ethanol (122). Effects of extended nicotine pretreatment are eliminated by blocking stress hormone receptors, thus implicating corticosterone release in both behavioral and electrophysiological interactions. Concurrent nicotine and alcohol exposure, on the other hand, can have additive or synergistic effects within the mesolimbic dopamine system that may enhance their acute rewarding effects. Indeed, intravenous co-administration of nicotine and ethanol produces an additive increase in NAc dopamine (122), and systemic nicotine

plus intra-accumbens ethanol increases dopamine levels more than either drug alone (123,124). These studies serve to highlight potentially important differences in mechanism and pharmacology resulting from sequential versus concurrent drug exposure.

Recent preclinical studies have administered nicotine and alcohol together, with mixed results. While neither chronic exposure to nicotine or ethanol alone influences basal levels of glutamate in the medial prefrontal cortex of female rats, concurrent exposure produces long-lasting increases in basal glutamate without affecting clearance. This effect is accompanied by a heightened sensitivity to the rewarding effects of nicotine self-administered into the NAc-shell (125). Lê et al. (126) showed that concurrent intravenous nicotine and oral ethanol self-administration had no effect on alcohol intake and decreased nicotine intake. However, they suggest that this was due to patterns of within-session responding, where alcohol intake was highest in the first 20 minutes of the session but nicotine intake was steady across the entire session, preventing the nicotine-induced enhancement seen in other studies (117–119). Alcohol preferring rats will self-administer combined ethanol and nicotine directly into the pVTA at concentrations that do not support individual self-administration (127), while combinations of oral nicotine and ethanol are self-administered at levels similar to ethanol alone (121). Furthermore, microinfusion of nicotine into the pVTA of these rats will enhance ethanol self-administration, an effect that is blocked by antagonists for both nAChRs and 5-HT3 receptors (128).

Despite evidence that varenicline decreases alcohol intake (100,108,129), the effects on co-self-administration of nicotine and alcohol are not as clear (130,131). However, withdrawal from chronic concurrent exposure, which is more prolonged than withdrawal from either drug alone, can be attenuated by continued treatment with just one of the drugs (132). Furthermore, acute exposure to nicotine after chronic alcohol exposure, or vice versa, results in an attenuation of somatic withdrawal that is reversed by mecamylamine injections into the medial habenula or interpeduncular nucleus (132).

**Adolescence—**Whereas many preclinical studies use adult male animals, initiation of alcohol and tobacco use typically occurs during adolescence, with patterns of use differing between men and women (25,133). Brief pretreatment of male rats during early adolescence (P28–31) with low doses of nicotine enhances subsequent acquisition of alcohol self-administration (21). Periadolescent nicotine (P35–44) also enhances ethanol consumption in female mice (134), although one study reported no effect of adolescent nicotine exposure in rats on ethanol intake in adulthood (135). The discrepancy may be due to different age of testing for ethanol consumption or continuous versus intermittent exposure paradigms. Route of administration and metabolism rates may also influence behavioral responses. Adolescent rodents tend to have lower plasma cotinine or nicotine levels than adults with subcutaneous or intravenous drug administration (136,137), but are not different from adults following oral nicotine (138). Thus, depending on the route of administration, nicotine doses may need to be adjusted for adolescents to better match what adults are exposed to. Ethanol metabolism also seems to be faster in adolescents following oral intake (139), but potential age differences in metabolism have not been studied for intravenous ethanol. It should be noted that, although humans consume alcohol orally, intravenous exposure can be a valid

method for assessing age differences in ethanol's pharmacological effects because it bypasses chemosensory properties of taste and smell that might influence intake (140).

Individual differences may also underlie such discrepancies, since a prior study has shown that adolescent rats with high behavioral reactivity in a novel environment that are exposed to nicotine develop conditioned place preference to ethanol as adults, whereas low behavioral activity animals do not (141). In addition, concurrent acetaldehyde, the primary metabolite of ethanol, increases initial acquisition of nicotine self-administration in adolescent male rats (142). Whereas males exhibited a decrease in responding to nicotine-acetaldehyde combinations with age, females did not (143). More recent work demonstrates that adolescent males find concurrent intravenous nicotine and alcohol significantly more reinforcing than either drug alone. This enhanced reinforcement of co-administered drugs is not evident in adult males or females of either age, and seems to result from a functionally immature kappa opioid receptor system (44). Although research using adult animals has highlighted timing of drug exposure (i.e., whether nicotine is given as a pretreatment or concurrently with alcohol) as an important factor in behavioral and neurochemical responses to nicotine and alcohol, more work needs to be done in adolescents.

Flavor attributes of nicotine and alcohol may also contribute to co-use in adolescence. There is a positive relationship between acceptance of the negative chemosensory qualities of both drugs (i.e., bitter taste and aversive odor) and consumption (144,145), and recent work demonstrates that prenatal alcohol exposure decreases aversion to the taste and smell of nicotine (146) and alcohol (147,148) in adolescent rats. Similar changes in aversion to nicotine and alcohol may also occur following acute co-administration during adolescence, but this has not been studied.

Adolescent drug exposure also induces unique sex differences in markers of cholinergic function. While male adolescents display greater choline acetyltransferase (ChAT) activity after exposure to nicotine alone, ChAT activity is decreased in females (149). Ethanol co-exposure normalizes levels in both sexes. Since decreases in ChAT activity can mean a loss of cholinergic innervation (150), ethanol may have blocked compensatory axonal sprouting in males, while exerting a protective effect against nicotine-induced ChAT decreases in females. These findings may help explain sex differences in vulnerability to co-use in humans.

## Concurrent use of nicotine and psychostimulants

### Human studies

Concurrent use of nicotine/tobacco products with psychostimulants is a matter of clinical concern (6). Growing evidence demonstrates that cocaine and other psychostimulants interact with nicotine/tobacco use to influence brain, behavior and the overall health (4,151,152). Currently, over 1.5 million individuals use cocaine and 595,000 use methamphetamine in the US, with the majority starting prior to 18 years of age (153). The majority of cocaine (75%) and methamphetamine (87%) users are known to smoke (4,154), with use almost always occurring after smoking initiation (5,155). Cocaine or amphetamine use can increase the urge to smoke (151) and tobacco consumption (156). Individuals who

quit smoking also have a higher likelihood of remaining abstinent to illicit stimulants, particularly for cocaine dependence (157).

In contrast to nicotine and alcohol co-use, there is a paucity of genetic studies examining possible common genetic mechanisms underlying concurrent use of nicotine/tobacco products and psychostimulants. At the time of writing, only two studies have examined the genetic role of nAChRs in psychostimulant dependence, but both found a significant association of cocaine dependence with a nonsynonymous coding polymorphism, rs16969968, of the CHRNA5 gene (158,159). However, the association was in the reverse direction to that seen for nicotine dependence, with the polymorphism conferring a protective effect against cocaine dependence. In a more recent study of two ethnic populations with co-dependence to nicotine, alcohol and cocaine, significant roles and interaction effects were observed for SNPs in the genes encoding the two 5-HT3 receptors, HTR3A and HTR3B, and the serotonin transporter, SLC6A4 (160). These findings implicate a role for the serotonin system in the etiology of all three substance-use disorders.

Whereas this finding of a common genetic underpinning of all three substance use disorders may reflect a common liability for drug use (161,162), an alternative hypothesis is that early adolescent use of tobacco sensitizes the reward centers of the brain to other abused drugs (18). This “gateway” theory is largely the product of epidemiological observation of a strict temporal sequence of drug use initiation (15,23,163–165). However, there is also clinical evidence that adolescent tobacco use is strongly associated with positive initial response to cocaine in young adults and subsequent continued use (166). Furthermore, preclinical studies outlined below lend support for the gateway concept.

## Animal studies

**Genetic and pharmacological studies—**As with alcohol, psychostimulant responses are often enhanced by nicotine exposure. Chronic pretreatment with nicotine enhances cocaine reward-related behaviors, including locomotor sensitization, place preference and self-administration (167–171). In contrast, nicotine pretreatment can decrease (172) or have no effect (173) on self-administration of methamphetamine. Associated psychostimulant-induced increases in dopamine neurotransmission are also altered by nicotine. Indeed, combinations of nicotine and cocaine or amphetamine have additive or synergistic effects on dopamine release in the nucleus accumbens (174–176). Cocaine and amphetamines also interact strongly with the cholinergic system. Endogenous acetylcholine levels are increased following cocaine exposure (177), and cholinergic inputs to the VTA from the laterodorsal tegmental nucleus are necessary for the development and expression of cocaine place preference (178). Conversely, the non-selective nAChR antagonist, mecamylamine, inhibits cocaine-induced place preference and self-administration (179,180).

Both genetic and pharmacological approaches are useful in assessing the identity of relevant nAChRs. Whereas deletion of the α4 nAChR subunit does not alter cocaine reward (181,182), there is substantial evidence for a role of α6β2-containing nAChRs. Mice lacking β2 nAChR subunits show reduced cocaine place preference (180), whereas those lacking α6 subunits do not exhibit cocaine reward at any dose tested (182). In this latter study, the involvement of α6β2-containing nAChRs was confirmed pharmacologically by the blockade

of cocaine reward with the intracerebral administration of the selective nAChR antagonist α-conotoxin MII. Other nAChR-regulated brain circuits may also be involved in cocaine reward, since the high affinity α3β4 nAChR functional antagonists, AT-1001 and AT-1012, can also attenuate cocaine place preference (183). A less selective α3β4 nAChR antagonist, 18-methoxycoronaridine, has also been shown to inhibit the self-administration of both cocaine and methamphetamine (184,185).

**Adolescence—**A critical limitation of many behavioral studies is the use of adult animals, even though adolescence is a period of vulnerability to the effects of nicotine and other drugs of abuse. In order to model early adolescent smoking, one group has delivered nicotine to rats intravenously once daily for four days at a dose (60 μg/kg) that produces nicotine blood levels equivalent to that of 1–2 cigarettes (19–21,45,137). This brief, low-dose nicotine exposure in early adolescence produces unique, age-specific effects not seen in adult rats. These effects include enhancement of cocaine-induced locomotor sensitization, and enhanced acquisition of cocaine and methamphetamine self-administration. Nicotine effects are long-lasting, still evident ten days after the last drug administration, and are only evident when treatment is during early (P28–31) but not later (P37–40) adolescence. Whereas presynaptic markers of dopamine function are largely unaltered by this nicotine pretreatment, serotonin function is markedly influenced, and the observed behavioral alterations result from 5HT-1A receptor-mediated increases in dopamine D2 receptor function (21,46). A recent study in mice has also demonstrated long-lasting effects of early adolescent (P28–34) nicotine treatment on psychostimulant reward in adulthood, with nicotine-exposed animals displaying enhanced cocaine and amphetamine conditioned place preference. The same nicotine exposure during late adolescence (P47–59) or adulthood had no effect on subsequent psychostimulant reward (186).

Other studies that have treated adolescent animals for longer periods, at higher doses, and/or with continuous infusion, have produced mixed findings. Adolescent nicotine treatment did not influence acquisition of cocaine self-administration in adult rodents (187,188), and either did not change (188) or decreased conditioned place preference (189). However, the overall cocaine intake was higher in nicotine-pretreated mice than controls (187). Brief nicotine pretreatment of rats during early adolescence increases subsequent locomotor response to amphetamine, both during later adolescence and in adulthood (190). Furthermore, low dose, but not high dose, nicotine pretreatment during adolescence increases subsequent self-administration of methamphetamine in adults (191). The discrepancies across these studies may reflect strain or species differences, as well as differing nicotine treatment protocols and age of assessment of psychostimulant effects. However, they serve to illustrate how critically important it is to have appropriate animal models that reflect human use patterns.

## Guidance for future research, clinical practice, and policymaking

Epidemiological data have consistently shown that developmental tobacco or nicotine exposure can act as a gateway to subsequent substance abuse. As clinical studies are often unable to prove cause and effect (192), animal studies offer the ability to assess underlying neurobiological and neurochemical mechanisms. Indeed, both clinical and preclinical research has provided significant support for the “gateway” effect of nicotine and tobacco.

Even brief exposure to nicotine during early adolescence can produce long-lasting increases in sensitivity to the rewarding effects of alcohol, cocaine, and methamphetamine (19–21). The cholinergic and serotonergic systems, in particular, are likely mediators of co-use of these substances (Figure 1).

There are strong associations between the use of nicotine, alcohol, and other illicit substances throughout the lifespan, and the growing use of e-cigarettes among youth (193–195) represents a major public health concern. Recent evidence suggests that, although the use of traditional cigarettes is declining (196) and the majority of e-cigarette users in 8th and 10th grades do not abuse other substances, a unique class of polysubstance user emerges in 12th grade (197). Others have suggested that e-cigarette use increases the risk for alcohol use, and is therefore a public health risk for minors (52,198). Flavorings, such as bubble gum, mint, or fruit, are frequently added to e-cigarettes and may encourage use among teenagers. Data assessing how flavored e-cigarettes might influence subsequent risk of alcohol or psychostimulant abuse are not available yet, but recent work shows that adolescents who smoke mentholated cigarettes are more likely to binge drink than peers who smoke non-mentholated cigarettes (199). It is clear that longitudinal clinical studies will be required to evaluate whether e-cigarettes do pose a higher risk of subsequent substance abuse, but preclinical studies with nicotine alone suggest that this will be the case. Gaps in the pre-clinical assessment of co-occurring substance-use disorders still remain, however. The majority of the current animal research examines adult males only, ignoring important age and sex differences observed in both human and animal populations. For example, women have less success with cessation from tobacco products (27,200), escalate to heavy drinking faster, and develop alcohol-related brain damage more rapidly than males (201–203). Women also likely transition to dependence on psychostimulants faster and enter treatment earlier than men (204,205). In preclinical research, female rodents are more sensitive to the rewarding effects of nicotine (206) and have higher ethanol intake than male rodents (207,208). Acquisition of cocaine self-administration is also more rapid in females (205,209), and they exhibit higher motivation for cocaine under progressive ratio testing (210). However, few studies have examined the contribution of sex to nicotine and alcohol or psychostimulant co-use. Thus, future research should include both age and sex comparisons. Ultimately, doing so will assist in the development of more effective policies governing nicotine and tobacco, as well as the development of efficacious therapies tailored toward each unique population.

## Acknowledgments

**Funding**

This work was supported by NIH grant DA 040440, Tobacco-Related Disease Research Program project grants 21RT-0136 and 22RT-0103, and the National Alliance for Research on Schizophrenia and Depression Young Investigator Grant 21517.

## References

1. Batel P, Pessione F, Maître C, Rueff B. Relationship between alcohol and tobacco dependencies among alcoholics who smoke. Addiction. 1995; 90:977–980. [PubMed: 7663320]

2. Falk DE, Yi H-y, Hiller-Sturmhöfel S. An epidemiologic analysis of co-occurring alcohol and tobacco use and disorders: findings from the National Epidemiologic Survey on Alcohol and Related Conditions. Alcohol Res Health. 2006; 29:162–171. [PubMed: 17373404]

3. Kandel D, Chen K, Warner LA, Kessler RC, Grant B. Prevalence and demographic correlates of symptoms of last year dependence on alcohol, nicotine, marijuana and cocaine in the U.S. population. Drug Alcohol Depend. 1997; 44:11–29. [PubMed: 9031816]

4. Budney AJ, Higgins ST, Hughes JR, Bickel WK. Nicotine and caffeine use in cocaine-dependent individuals. J Subst Abuse. 1993; 5:117–130. [PubMed: 8400835]

5. Gorelick DA, Simmons MS, Carriero N, Tashkin DP. Characteristics of smoked drug use among cocaine smokers. Am J Addict. 1997; 6:237–245. [PubMed: 9256990]

6. Weinberger AH, Sofuoglu M. The impact of cigarette smoking on stimulant addiction. Am J Drug Alcohol Abuse. 2009; 35:12–17. [PubMed: 19152200]

7. Humfleet G, Muñoz R, Sees K, Reus V, Hall S. History of alcohol or drug problems, current use of alcohol or marijuana, and success in quitting smoking. Addict Behav. 1999; 24:149–154. [PubMed: 10189984]

8. McKee SA, Krishnan-Sarin S, Shi J, Mase T, O'Malley SS. Modeling the effect of alcohol on smoking lapse behavior. Psychopharmacology (Berl). 2006; 189:201–210. [PubMed: 17013640]

9. Kahler CW, Borland R, Hyland A, McKee SA, Thompson ME, Cummings KM. Alcohol consumption and quitting smoking in the International Tobacco Control (ITC) Four Country Survey. Drug Alcohol Depend. 2009; 100:214–220. [PubMed: 19056188]

10. Blot WJ, McLaughlin JK, Winn DM, Austin DF, Greenberg RS, Preston-Martin S, Bernstein L, Schoenberg JB, Stemhagen A, Fraumeni JF. Smoking and drinking in relation to oral and pharyngeal cancer. Cancer Res. 1988; 48:3282–3287. [PubMed: 3365707]

11. Acott AA, Theus SA, Marchant-Miros KE, Mancino AT. Association of tobacco and alcohol use with earlier development of colorectal cancer: should we modify screening guidelines? Am J Surg. 2008; 196:915–918. [PubMed: 19095109]

12. Le Strat Y, Ramoz N, Gorwood P. In alcohol-dependent drinkers, what does the presence of nicotine dependence tell us about psychiatric and addictive disorders comorbidity? Alcohol Alcohol. 2010; 45:167–172. [PubMed: 20089545]

13. Rueda M, Robertson Y, Acott A, Rueda S, Keikhoff A, Guerrero W, Mancino AT. Association of tobacco and alcohol use with earlier development of colorectal pathology: should screening guidelines be modified to include these risk factors? Am J Surg. 2012; 204:963–967. [PubMed: 23040696]

14. Dal Maso L, Torelli N, Biancotto E, Di Maso M, Gini A, Franchin G, Levi F, La Vecchia C, Serraino D, Polesel J. Combined effect of tobacco smoking and alcohol drinking in the risk of head and neck cancers: a re-analysis of case-control studies using bi-dimensional spline models. Eur J Epidemiol. 2015; 31:385–393. [PubMed: 25855002]

15. Kandel DB, Yamaguchi K, Chen K. Stages of progression in drug involvement from adolescence to adulthood: further evidence for the gateway theory. J Stud Alcohol. 1992; 53:447–457. [PubMed: 1405637]

16. Lai S, Lai H, Page JB, McCoy CB. The association between cigarette smoking and drug abuse in the United States. J Addict Dis. 2000; 19:11–24.

17. Degenhardt L, Dierker L, Chiu WT, Medina-Mora ME, Neumark Y, Sampson N, Alonso J, Angermeyer M, Anthony JC, Bruffaerts R, de Girolamo G, de Graaf R, Gureje O, Karam AN, Kostyuchenko S, Lee S, Lépine J-P, Levinson D, Nakamura Y, Posada-Villa J, Stein D, Wells JE, Kessler RC. Evaluating the drug use "gateway" theory using cross-national data: consistency and associations of the order of initiation of drug use among participants in the WHO World Mental Health Surveys. Drug Alcohol Depend. 2010; 108:84–97. [PubMed: 20060657]

18. Kandel D, Kandel E. The Gateway Hypothesis of substance abuse: developmental, biological and societal perspectives. Acta Paediatr. 2015; 104:130–137. [PubMed: 25377988]

19. McQuown SC, Belluzzi JD, Leslie FM. Low dose nicotine treatment during early adolescence increases subsequent cocaine reward. Neurotoxicol Teratol. 2007; 29:66–73. [PubMed: 17174067]

20. McQuown SC, Dao JM, Belluzzi JD, Leslie FM. Age-dependent effects of low-dose nicotine treatment on cocaine-induced behavioral plasticity in rats. Psychopharmacology (Berl). 2009; 207:143–152. [PubMed: 19727678]
21. Dao JM, McQuown SC, Loughlin SE, Belluzzi JD, Leslie FM. Nicotine alters limbic function in adolescent rat by a 5-HT1A receptor mechanism. Neuropsychopharmacology. 2011; 36:1319–1331. [PubMed: 21412223]
22. Hanna EZ, Yi HY, Dufour MC, Whitmore CC. The relationship of early-onset regular smoking to alcohol use, depression, illicit drug use, and other risky behaviors during early adolescence: results from the youth supplement to the third national health and nutrition examination survey. J Subst Abuse. 2001; 13:265–282. [PubMed: 11693451]
23. Biederman J, Monuteaux MC, Mick E, Wilens TE, Fontanella JA, Poetzl KM, Kirk T, Masse J, Faraone SV. Is cigarette smoking a gateway to alcohol and illicit drug use disorders? A study of youths with and without attention deficit hyperactivity disorder. Biol Psychiatry. 2006; 59:258–264. [PubMed: 16154546]
24. Substance Abuse and Mental Health Services Administration. Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings. Rockville, MD, USA: Substance Abuse & Mental Health Services Administration; 2011. HHS Publication No. (SMA) 11-4658
25. Chen P, Jacobson KC. Developmental trajectories of substance use from early adolescence to young adulthood: gender and racial/ethnic differences. J Adolesc Health. 2012; 50:154–163. [PubMed: 22265111]
26. Anderson C, Burns DM. Patterns of adolescent smoking initiation rates by ethnicity and sex. Tob Control. 2000; 9:II4–II8. [PubMed: 10841585]
27. Perkins KA. Smoking Cessation in Women. CNS Drugs. 2001; 15:391–411. [PubMed: 11475944]
28. Spear LP. The adolescent brain and age-related behavioral manifestations. Neurosci Biobehav Rev. 2000; 24:417–463. [PubMed: 10817843]
29. O'Donnell P. Adolescent maturation of cortical dopamine. Neurotox Res. 2010; 18:306–312. [PubMed: 20151241]
30. Spear LP. Adolescent neurodevelopment. J Adolesc Health. 2013; 52:S7–13. [PubMed: 23332574]
31. Yuan M, Cross SJ, Loughlin SE, Leslie FM. Nicotine and the adolescent brain. J Physiol (Lond). 2015; 593:3397–3412. [PubMed: 26018031]
32. Spear LP. Assessment of adolescent neurotoxicity: rationale and methodological considerations. Neurotoxicol Teratol. 2007; 29:1–9. [PubMed: 17222532]
33. Laviola G, Macrì S, Morley-Fletcher S, Adriani W. Risk-taking behavior in adolescent mice: psychobiological determinants and early epigenetic influence. Neurosci Biobehav Rev. 2003; 27:19–31. [PubMed: 12732220]
34. Sturman DA, Moghaddam B. The neurobiology of adolescence: changes in brain architecture, functional dynamics, and behavioral tendencies. Neurosci Biobehav Rev. 2011; 35:1704–1712. [PubMed: 21527288]
35. Hollenstein T, Lougheed JP. Beyond storm and stress: typicality, transactions, timing, and temperament to account for adolescent change. Am Psychol. 2013; 68:444–454. [PubMed: 23915399]
36. Burke AR, Miczek KA. Stress in adolescence and drugs of abuse in rodent models: role of dopamine, CRF, and HPA axis. Psychopharmacology (Berl). 2014; 231:1557–1580. [PubMed: 24370534]
37. Koob GF, Volkow ND. Neurocircuitry of addiction. Neuropsychopharmacology. 2010; 35:217–238. [PubMed: 19710631]
38. Ikemoto S, Bonci A. Neurocircuitry of drug reward. Neuropharmacology. 2014; 76:329–341. [PubMed: 23664810]
39. Dwyer JB, Leslie FM. Adolescent maturation of dopamine D1 and D2 receptor function and interactions in rodents. In PLoS ONE. 2016; 11:e0146966.
40. Kota D, Martin BR, Robinson SE, Damaj MI. Nicotine dependence and reward differ between adolescent and adult male mice. J Pharmacol Exp Ther. 2007; 322:399–407. [PubMed: 17446302]

41. Doura MB, Gold AB, Keller AB, Perry DC. Adult and periadolescent rats differ in expression of nicotinic cholinergic receptor subtypes and in the response of these subtypes to chronic nicotine exposure. Brain Res. 2008; 1215:40–52. [PubMed: 18474362]
42. Dwyer JB, McQuown SC, Leslie FM. The dynamic effects of nicotine on the developing brain. Pharmacol Ther. 2009; 122:125–139. [PubMed: 19268688]
43. Azam L, Chen Y, Leslie FM. Developmental regulation of nicotinic acetylcholine receptors within midbrain dopamine neurons. Neuroscience. 2007; 144:1347–1360. [PubMed: 17197101]
44. Lárraga, A. Age- and sex-dependent behaviors induced by alcohol and nicotine [dissertation]. 2013.
45. Mojica CY, Belluzzi JD, Leslie FM. Age-dependent alterations in reward-seeking behavior after brief nicotine exposure. Psychopharmacology (Berl). 2014; 231:1763–1773. [PubMed: 24030468]
46. Mojica CY, Dao JM, Yuan M, Loughlin SE, Leslie FM. Nicotine modulation of adolescent dopamine receptor signaling and hypothalamic peptide response. Neuropharmacology. 2014; 77:285–293. [PubMed: 24157491]
47. National Institute on Drug Abuse. Trends and statistics. Available from: https://www.drugabuse.gov/related-topics/trends-statistics [last accessed 2 Aug 2016]
48. DiFranza JR, Guerrera MP. Alcoholism and smoking. J Stud Alcohol. 1990; 51:130–135. [PubMed: 2308350]
49. Weitzman ER, Chen Y-Y. The co-occurrence of smoking and drinking among young adults in college: national survey results from the United States. Drug Alcohol Depend. 2005; 80:377–386. [PubMed: 16009507]
50. Campbell ML, Bozec LJ, McGrath D, Barrett SP. Alcohol and tobacco co-use in nondaily smokers: an inevitable phenomenon? Drug Alcohol Rev. 2012; 31:447–450. [PubMed: 21615810]
51. Cohn A, Villanti A, Richardson A, Rath JM, Williams V, Stanton C, Mermelstein R. The association between alcohol, marijuana use, and new and emerging tobacco products in a young adult population. Addict Behav. 2015; 48:79–88. [PubMed: 26042613]
52. Kristjansson AL, Sigfusdottir ID. E-cigarette use and relations to tobacco and alcohol use among adolescents. BMC Med. 2015; 13:103. [PubMed: 25929616]
53. Surís J-C, Berchtold A, Akre C. Reasons to use e-cigarettes and associations with other substances among adolescents in Switzerland. Drug Alcohol Depend. 2015; 153:140–144. [PubMed: 26077606]
54. Jiang N, Wang MP, Ho SY, Leung LT, Lam TH. Electronic cigarette use among adolescents: a cross-sectional study in Hong Kong. BMC Public Health. 2016; 16:202. [PubMed: 26932396]
55. Camenga DR, Kong G, Cavallo DA, Liss A, Hyland A, Delmerico J, Cummings KM, Krishnan-Sarin S. Alternate tobacco product and drug use among adolescents who use electronic cigarettes, cigarettes only, and never smokers. J Adolesc Health. 2014; 55:588–591. [PubMed: 25085648]
56. Weinberger AH, Pilver CE, Hoff RA, Mazure CM, McKee SA. Changes in smoking for adults with and without alcohol and drug use disorders: Longitudinal evaluation in the US population. Am J Drug Alcohol Abuse. 2013; 39:186–193. [PubMed: 23721534]
57. McKee SA, Weinberger AH. How can we use our knowledge of alcohol-tobacco interactions to reduce alcohol use? Annu Rev Clin Psychol. 2013; 9:649–674. [PubMed: 23157448]
58. Chiappetta V, García-Rodríguez O, Jin CJ, Secades-Villa R, Blanco C. Predictors of quit attempts and successful quit attempts among individuals with alcohol use disorders in a nationally representative sample. Drug Alcohol Depend. 2014; 141:138–144. [PubMed: 24948080]
59. Weinberger AH, Platt J, Jiang B, Goodwin RD. Cigarette smoking and risk of alcohol use relapse among adults in recovery from alcohol use disorders. Alcohol Clin Exp Res. 2015; 39:1989–1996. [PubMed: 26365044]
60. Hitschfeld MJ, Schneekloth TD, Ebbert JO, Hall-Flavin DK, Karpyak VM, Abulseoud OA, Patten CA, Geske JR, Frye MA. Female smokers have the highest alcohol craving in a residential alcoholism treatment cohort. Drug Alcohol Depend. 2015; 150:179–182. [PubMed: 25746235]
61. Kouri EM, McCarthy EM, Faust AH, Lukas SE. Pretreatment with transdermal nicotine enhances some of ethanol's acute effects in men. Drug Alcohol Depend. 2004; 75:55–65. [PubMed: 15225889]

62. Rose JE, Brauer LH, Behm FM, Cramblett M, Calkins K, Lawhon D. Psychopharmacological interactions between nicotine and ethanol. Nicotine Tob Res. 2004; 6:133–144. [PubMed: 14982697]

63. Glautier S, Clements K, White JAW, Taylor C, Stolerman IP. Alcohol and the reward value of cigarette smoking. Behav Pharmacol. 1996; 7:144–154. [PubMed: 11224406]

64. King AC, Epstein AM. Alcohol dose-dependent increases in smoking urge in light smokers. Alcohol Clin Exp Res. 2005; 29:547–552. [PubMed: 15834219]

65. Grant BF. Age at smoking onset and its association with alcohol consumption and DSM-IV alcohol abuse and dependence: results from the National Longitudinal Alcohol Epidemiologic Survey. J Subst Abuse. 1998; 10:59–73. [PubMed: 9720007]

66. Riala K, Hakko H, Isohanni M, Järvelin M-R, Räsänen P. Teenage smoking and substance use as predictors of severe alcohol problems in late adolescence and in young adulthood. J Adolesc Health. 2004; 35:245–254. [PubMed: 15313508]

67. Daw J, Nowotny KM, Boardman JD. Changing patterns of tobacco and alcohol co-use by gender in the United States, 1976–2010. Demogr Res. 2013; 28:637–648. [PubMed: 25493070]

68. Tanner J-A, Chenoweth MJ, Tyndale RF. Pharmacogenetics of nicotine and associated smoking behaviors. Curr Top Behav Neurosci. 2015; 23:37–86. [PubMed: 25655887]

69. Noble EP. Addiction and its reward process through polymorphisms of the D2 dopamine receptor gene: a review. Eur Psychiatry. 2000; 15:79–89.

70. Enoch M-A. Genetic influences on response to alcohol and response to pharmacotherapies for alcoholism. Pharmacol Biochem Behav. 2014; 123:17–24. [PubMed: 24220019]

71. Swan GE, Carmelli D, Cardon LR. Heavy consumption of cigarettes, alcohol and coffee in male twins. J Stud Alcohol. 1997; 58:182–190. [PubMed: 9065896]

72. True WR, Xian H, Scherrer JF, Madden PA, Bucholz KK, Heath AC, Eisen SA, Lyons MJ, Goldberg J, Tsuang M. Common genetic vulnerability for nicotine and alcohol dependence in men. Arch Gen Psychiatry. 1999; 56:655–661. [PubMed: 10401514]

73. Bierut LJ, Rice JP, Goate A, Hinrichs AL, Saccone NL, Foroud T, Edenberg HJ, Cloninger CR, Begleiter H, Conneally PM, Crowe RR, Hesselbrock V, Li T-K, Nurnberger JI, Porjesz B, Schuckit MA, Reich T. A genomic scan for habitual smoking in families of alcoholics: common and specific genetic factors in substance dependence. Am J Med Genet A. 2004; 124A:19–27. [PubMed: 14679582]

74. Spitz MR, Amos CI, Dong Q, Lin J, Wu X. The CHRNA5-A3 region on chromosome 15q24-25.1 is a risk factor both for nicotine dependence and for lung cancer. J Natl Cancer Inst. 2008; 100:1552–1556. [PubMed: 18957677]

75. Bierut LJ. Nicotine dependence and genetic variation in the nicotinic receptors. Drug Alcohol Depend. 2009; 104:S64–S69. [PubMed: 19596527]

76. Wang JC, Grucza R, Cruchaga C, Hinrichs AL, Bertelsen S, Budde JP, Fox L, Goldstein E, Reyes O, Saccone N, Saccone S, Xuei X, Bucholz K, Kuperman S, Nurnberger J, Rice JP, Schuckit M, Tischfield J, Hesselbrock V, Porjesz B, Edenberg HJ, Bierut LJ, Goate AM. Genetic variation in the CHRNA5 gene affects mRNA levels and is associated with risk for alcohol dependence. Mol Psychiatry. 2009; 14:501–510. [PubMed: 18414406]

77. Li MD, Xu Q, Lou X-Y, Payne TJ, Niu T, Ma JZ. Association and interaction analysis of variants in CHRNA5/CHRNA3/CHRNB4 gene cluster with nicotine dependence in African and European Americans. Am J Med Genet B Neuropsychiatr Genet. 2010; 153B:745–756. [PubMed: 19859904]

78. Ehringer MA, Clegg HV, Collins AC, Corley RP, Crowley T, Hewitt JK, Hopfer CJ, Krauter K, Lessem J, Rhee SH, Schlaepfer I, Smolen A, Stallings MC, Young SE, Zeiger JS. Association of the neuronal nicotinic receptor beta2 subunit gene (CHRNB2) with subjective responses to alcohol and nicotine. Am J Med Genet B Neuropsychiatr Genet. 2007; 144B:596–604. [PubMed: 17226798]

79. Hoft NR, Corley RP, McQueen MB, Huizinga D, Menard S, Ehringer MA. SNPs in CHRNA6 and CHRNB3 are associated with alcohol consumption in a nationally representative sample. Genes Brain Behav. 2009; 8:631–637. [PubMed: 19500157]

80. Hoft NR, Corley RP, McQueen MB, Schlaepfer IR, Huizinga D, Ehringer MA. Genetic association of the CHRNA6 and CHRNB3 genes with tobacco dependence in a nationally representative sample. Neuropsychopharmacology. 2009; 34:698–706. [PubMed: 18704094]
81. Schlaepfer IR, Hoft NR, Collins AC, Corley RP, Hewitt JK, Hopfer CJ, Lessem JM, McQueen MB, Rhee SH, Ehringer MA. The CHRNA5/A3/B4 gene cluster variability as an important determinant of early alcohol and tobacco initiation in young adults. Biol Psychiatry. 2008; 63:1039–1046. [PubMed: 18163978]
82. Weiss RB, Baker TB, Cannon DS, von Niederhausern A, Dunn DM, Matsunami N, Singh NA, Baird L, Coon H, McMahon WM, Piper ME, Fiore MC, Scholand MB, Connett JE, Kanner RE, Gahring LC, Rogers SW, Hoidal JR, Leppert MF. A candidate gene approach identifies the CHRNA5-A3-B4 region as a risk factor for age-dependent nicotine addiction. PLoS Genet. 2008; 4:e1000125. [PubMed: 18618000]
83. Kapoor M, Wang J-C, Bertelsen S, Bucholz K, Budde JP, Hinrichs A, Agrawal A, Brooks A, Chorlian D, Dick D, Hesselbrock V, Foroud T, Kramer J, Kuperman S, Manz N, Nurnberger J, Porjesz B, Rice J, Tischfield J, Xuei X, Schuckit M, Edenberg HJ, Bierut LJ, Goate AM. Variants located upstream of CHRNB4 on chromosome 15q25.1 are associated with age at onset of daily smoking and habitual smoking. PLoS ONE. 2012; 7:e33513. [PubMed: 22438940]
84. Lubke GH, Stephens SH, Lessem JM, Hewitt JK, Ehringer MA. The CHRNA5/A3/B4 gene cluster and tobacco, alcohol, cannabis, inhalants and other substance use initiation: replication and new findings using mixture analyses. Behav Genet. 2012; 42:636–646. [PubMed: 22382757]
85. Coon H, Piasecki TM, Cook EH, Dunn D, Mermelstein RJ, Weiss RB, Cannon DS. Association of the CHRNA4 neuronal nicotinic receptor subunit gene with frequency of binge drinking in young adults. Alcohol Clin Exp Res. 2014; 38:930–937. [PubMed: 24428733]
86. Mihalak KB, Carroll FI, Luetje CW. Varenicline is a partial agonist at alpha4beta2 and a full agonist at alpha7 neuronal nicotinic receptors. Mol Pharmacol. 2006; 70:801–805. [PubMed: 16766716]
87. Erwin BL, Slaton RM. Varenicline in the treatment of alcohol use disorders. Ann Pharmacother. 2014; 48:1445–1455. [PubMed: 25095786]
88. de Bejczy A, Löf E, Walther L, Guterstam J, Hammarberg A, Asanovska G, Franck J, Isaksson A, Söderpalm B. Varenicline for treatment of alcohol dependence: a randomized, placebo-controlled trial. Alcohol Clin Exp Res. 2015; 39:2189–2199. [PubMed: 26414337]
89. Falk DE, Castle IJP, Ryan M, Fertig J, Litten RZ. Moderators of varenicline treatment effects in a double-blind, placebo-controlled trial for alcohol dependence: an exploratory analysis. J Addict Med. 2015; 9:296–303. [PubMed: 26083958]
90. de Fiebre CM, Marks MJ, Collins AC. Ethanol-nicotine interactions in long-sleep and short-sleep mice. Alcohol. 1990; 7:249–257. [PubMed: 2331320]
91. de Fiebre CM, Romm E, Collins JT, Draski LJ, Deitrich RA, Collins AC. Responses to cholinergic agonists of rats selectively bred for differential sensitivity to ethanol. Alcohol Clin Exp Res. 1991; 15:270–276. [PubMed: 2058804]
92. de Fiebre NC, Dawson R, de Fiebre CM. The selectively bred high alcohol sensitivity (HAS) and low alcohol sensitivity (LAS) rats differ in sensitivity to nicotine. Alcohol Clin Exp Res. 2002; 266:765–772.
93. Bergstrom HC, Palmer AA, Wood RD, Burkhart-Kasch S, McKinnon CS, Phillips TJ. Reverse selection for differential response to the locomotor stimulant effects of ethanol provides evidence for pleiotropic genetic influence on locomotor response to other drugs of abuse. Alcohol Clin Exp Res. 2003; 27:1535–1547. [PubMed: 14574223]
94. Lê AD, Li Z, Funk D, Shram M, Li TK, Shaham Y. Increased vulnerability to nicotine self-administration and relapse in alcohol-naive offspring of rats selectively bred for high alcohol intake. J Neurosci. 2006; 26:1872–1879. [PubMed: 16467536]
95. Tritto T, Marley RJ, Bastidas D, Stitzel JA, Collins AC. Potential regulation of nicotine and ethanol actions by alpha4-containing nicotinic receptors. Alcohol. 2001; 24:69–78. [PubMed: 11522425]
96. Butt CM, Hutton SR, Stitzel JA, Balogh SA, Owens JC, Collins AC. A polymorphism in the alpha4 nicotinic receptor gene (Chrna4) modulates enhancement of nicotinic receptor function by ethanol. Alcohol Clin Exp Res. 2003; 27:733–742. [PubMed: 12766617]

97. Butt CM, King NM, Stitzel JA, Collins AC. Interaction of the nicotinic cholinergic system with ethanol withdrawal. J Pharmacol Exp Ther. 2004; 308:591–599. [PubMed: 14610221]

98. Dawson A, Miles MF, Damaj MI. The β2 nicotinic acetylcholine receptor subunit differentially influences ethanol behavioral effects in the mouse. Alcohol. 2013; 47:85–94. [PubMed: 23419392]

99. Butt CM, King NM, Hutton SR, Collins AC, Stitzel JA. Modulation of nicotine but not ethanol preference by the mouse Chrna4 A529T polymorphism. Behav Neurosci. 2005; 119:26–37. [PubMed: 15727510]

100. Kamens HM, Andersen J, Picciotto MR. Modulation of ethanol consumption by genetic and pharmacological manipulation of nicotinic acetylcholine receptors in mice. Psychopharmacology (Berl). 2010; 208:613–626. [PubMed: 20072781]

101. Bowers BJ, McClure-Begley TD, Keller JJ, Paylor R, Collins AC, Wehner JM. Deletion of the alpha7 nicotinic receptor subunit gene results in increased sensitivity to several behavioral effects produced by alcohol. Alcohol Clin Exp Res. 2005; 29:295–302. [PubMed: 15770102]

102. Gallego X, Ruiz-Medina J, Valverde O, Molas S, Robles N, Sabrià J, Crabbe JC, Dierssen M. Transgenic over expression of nicotinic receptor alpha 5, alpha 3, and beta 4 subunit genes reduces ethanol intake in mice. Alcohol. 2012; 46:205–215. [PubMed: 22459873]

103. Santos N, Chatterjee S, Henry A, Holgate J, Bartlett SE. The α5 neuronal nicotinic acetylcholine receptor subunit plays an important role in the sedative effects of ethanol but does not modulate consumption in mice. Alcohol Clin Exp Res. 2013; 37:655–662. [PubMed: 23164049]

104. Azam L, Winzer-Serhan UH, Chen Y, Leslie FM. Expression of neuronal nicotinic acetylcholine receptor subunit mRNAs within midbrain dopamine neurons. J Comp Neurol. 2002; 444:260–274. [PubMed: 11840479]

105. Leslie FM, Mojica CY, Reynaga DD. Nicotinic receptors in addiction pathways. Mol Pharmacol. 2013; 83:753–758. [PubMed: 23247824]

106. Kamens HM, Hoft NR, Cox RJ, Miyamoto JH, Ehringer MA. The α6 nicotinic acetylcholine receptor subunit influences ethanol-induced sedation. Alcohol. 2012; 46:463–471. [PubMed: 22572056]

107. Powers MS, Broderick HJ, Drenan RM, Chester JA. Nicotinic acetylcholine receptors containing α6 subunits contribute to alcohol reward-related behaviours. Genes Brain Behav. 2013; 12:543–553. [PubMed: 23594044]

108. Hendrickson LM, Zhao-Shea R, Pang X, Gardner PD, Tapper AR. Activation of alpha4* nAChRs is necessary and sufficient for varenicline-induced reduction of alcohol consumption. J Neurosci. 2010; 30:10169–10176. [PubMed: 20668200]

109. Liu L, Hendrickson LM, Guildford MJ, Zhao-Shea R, Gardner PD, Tapper AR. Nicotinic acetylcholine receptors containing the α4 subunit modulate alcohol reward. Biol Psychiatry. 2013; 73:738–746. [PubMed: 23141806]

110. Hendrickson LM, Gardner P, Tapper AR. Nicotinic acetylcholine receptors containing the α4 subunit are critical for the nicotine-induced reduction of acute voluntary ethanol consumption. Channels (Austin). 2011; 5:124–127. [PubMed: 21239887]

111. Hendrickson LM, Zhao-Shea R, Tapper AR. Modulation of ethanol drinking-in-the-dark by mecamylamine and nicotinic acetylcholine receptor agonists in C57BL/6J mice. Psychopharmacology (Berl). 2009; 204:563–572. [PubMed: 19247637]

112. Bhutada P, Mundhada Y, Ghodki Y, Dixit P, Umathe S, Jain K. Acquisition, expression, and reinstatement of ethanol-induced conditioned place preference in mice: effects of exposure to stress and modulation by mecamylamine. J Psychopharmacol (Oxford). 2012; 26:315–323. [PubMed: 22182742]

113. Jerlhag E, Grøtli M, Luthman K, Svensson L, Engel JA. Role of the subunit composition of central nicotinic acetylcholine receptors for the stimulatory and dopamine-enhancing effects of ethanol. Alcohol Alcohol. 2006; 41:486–493. [PubMed: 16799162]

114. Larsson A, Jerlhag E, Svensson L, Söderpalm B, Engel JA. Is an alpha-conotoxin MII-sensitive mechanism involved in the neurochemical, stimulatory, and rewarding effects of ethanol? Alcohol. 2004; 34:239–250. [PubMed: 15902919]

115. Kuzmin A, Jerlhag E, Liljequist S, Engel J. Effects of subunit selective nACh receptors on operant ethanol self-administration and relapse-like ethanol-drinking behavior. Psychopharmacology (Berl). 2009; 203:99–108. [PubMed: 18987848]

116. Chatterjee S, Steensland P, Simms JA, Holgate J, Coe JW, Hurst RS, Shaffer CL, Lowe J, Rollema H, Bartlett SE. Partial agonists of the α3β4* neuronal nicotinic acetylcholine receptor reduce ethanol consumption and seeking in rats. Neuropsychopharmacology. 2011; 36:603–615. [PubMed: 21048701]

117. Lê AD, Corrigall WA, Harding JW, Juzytsch W, Li TK. Involvement of nicotinic receptors in alcohol self-administration. Alcohol Clin Exp Res. 2000; 24:155–163. [PubMed: 10698366]

118. Lê AD, Wang A, Harding S, Juzytsch W, Shaham Y. Nicotine increases alcohol self-administration and reinstates alcohol seeking in rats. Psychopharmacology (Berl). 2003; 168:216–221. [PubMed: 12536264]

119. Olausson P, Ericson M, Löf E, Engel JA, Söderpalm B. Nicotine-induced behavioral disinhibition and ethanol preference correlate after repeated nicotine treatment. Eur J Pharmacol. 2001; 417:117–123. [PubMed: 11301066]

120. Bito-Onon JJ, Simms JA, Chatterjee S, Holgate J, Bartlett SE. Varenicline, a partial agonist at neuronal nicotinic acetylcholine receptors, reduces nicotine-induced increases in 20% ethanol operant self-administration in Sprague-Dawley rats. Addict Biol. 2011; 16:440–449. [PubMed: 21392178]

121. Hauser SR, Getachew B, Oster SM, Dhaher R, Ding Z-M, Bell RL, McBride WJ, Rodd ZA. Nicotine modulates alcohol-seeking and relapse by alcohol-preferring (P) rats in a time-dependent manner. Alcohol Clin Exp Res. 2012; 36:43–54. [PubMed: 21689122]

122. Doyon WM, Dong Y, Ostroumov A, Thomas AM, Zhang TA, Dani JA. Nicotine decreases ethanol-induced dopamine signaling and increases self-administration via stress hormones. Neuron. 2013; 79:530–540. [PubMed: 23871233]

123. Tizabi Y, Copeland RL, Louis VA, Taylor RE. Effects of combined systemic alcohol and central nicotine administration into ventral tegmental area on dopamine release in the nucleus accumbens. Alcohol Clin Exp Res. 2002; 26:394–399. [PubMed: 11923594]

124. Tizabi Y, Bai L, Copeland RL, Taylor RE. Combined effects of systemic alcohol and nicotine on dopamine release in the nucleus accumbens shell. Alcohol Alcohol. 2007; 42:413–416. [PubMed: 17686828]

125. Deehan GA, Hauser SR, Waeiss RA, Knight CP, Toalston JE, Truitt WA, McBride WJ, Rodd ZA. Coadministration of ethanol and nicotine: the enduring alterations in the rewarding properties of nicotine and glutamate activity within the mesocorticolimbic system of female alcohol-preferring (P) rats. Psychopharmacology (Berl). 2015; 232:4293–4302. [PubMed: 26306917]

126. Lê AD, Lo S, Harding S, Juzytsch W, Marinelli PW, Funk D. Coadministration of intravenous nicotine and oral alcohol in rats. Psychopharmacology (Berl). 2010; 208:475–486. [PubMed: 20013113]

127. Truitt WA, Hauser SR, Deehan GA, Toalston JE, Wilden JA, Bell RL, McBride WJ, Rodd ZA. Ethanol and nicotine interaction within the posterior ventral tegmental area in male and female alcohol-preferring rats: evidence of synergy and differential gene activation in the nucleus accumbens shell. Psychopharmacology (Berl). 2015; 232:639–649. [PubMed: 25155311]

128. Hauser SR, Deehan GA, Toalston JE, Bell RL, McBride WJ, Rodd ZA. Enhanced alcohol-seeking behavior by nicotine in the posterior ventral tegmental area of female alcohol-preferring (P) rats: modulation by serotonin-3 and nicotinic cholinergic receptors. Psychopharmacology (Berl). 2014; 231:3745–3755. [PubMed: 24599396]

129. Cippitelli A, Brunori G, Gaiolini KA, Zaveri NT, Toll L. Pharmacological stress is required for the anti-alcohol effect of the α3β4* nAChR partial agonist AT-1001. Neuropharmacology. 2015; 93:229–236. [PubMed: 25689019]

130. Funk D, Lo S, Coen K, Lê AD. Effects of varenicline on operant self-administration of alcohol and/or nicotine in a rat model of co-abuse. Behav Brain Res. 2015; 296:157–162. [PubMed: 26365457]

131. Scuppa G, Cippitelli A, Toll L, Ciccocioppo R, Ubaldi M. Varenicline decreases nicotine but not alcohol self-administration in genetically selected Marchigian Sardinian alcohol-preferring (msP) rats. Drug Alcohol Depend. 2015; 156:126–132. [PubMed: 26383997]

132. Perez E, Quijano-Cardé N, De Biasi M. Nicotinic mechanisms modulate ethanol withdrawal and modify time course and symptoms severity of simultaneous withdrawal from alcohol and nicotine. Neuropsychopharmacology. 2015; 40:2327–2336. [PubMed: 25790020]

133. Kuhn C. Emergence of sex differences in the development of substance use and abuse during adolescence. Pharmacol Ther. 2015; 153:55–78. [PubMed: 26049025]

134. Locker AR, Marks MJ, Kamens HM, Klein LC. Exposure to nicotine increases nicotinic acetylcholine receptor density in the reward pathway and binge ethanol consumption in C57BL/6J adolescent female mice. Brain Res Bull. 2015; 123:13–22. [PubMed: 26428091]

135. Smith AM, Kelly RB, Chen W-JA. Chronic continuous nicotine exposure during periadolescence does not increase ethanol intake during adulthood in rats. Alcohol Clin Exp Res. 2002; 26:976–979. [PubMed: 12170106]

136. O'Dell LE, Bruijnzeel AW, Smith RT, Parsons LH, Merves ML, Goldberger BA, Richardson HN, Koob GF, Markou A. Diminished nicotine withdrawal in adolescent rats: implications for vulnerability to addiction. Psychopharmacology (Berl). 2006; 186:612–619. [PubMed: 16598454]

137. Cao J, Belluzzi JD, Loughlin SE, Keyler DE, Pentel PR, Leslie FM. Acetaldehyde, a major constituent of tobacco smoke, enhances behavioral, endocrine, and neuronal responses to nicotine in adolescent and adult rats. Neuropsychopharmacology. 2007; 32:2025–2035. [PubMed: 17287824]

138. Adriani W, Macrì S, Pacifici R, Laviola G. Peculiar vulnerability to nicotine oral self-administration in mice during early adolescence. Neuropsychopharmacology. 2002; 27:212–224. [PubMed: 12093595]

139. Hefner K, Holmes A. An investigation of the behavioral actions of ethanol across adolescence in mice. Psychopharmacology (Berl). 2007; 191:311–322. [PubMed: 17206494]

140. Green AS, Grahame NJ. Ethanol drinking in rodents: is free-choice drinking related to the reinforcing effects of ethanol? Alcohol. 2008; 42:1–11. [PubMed: 18164576]

141. Philpot RM, Engberg ME, Wecker L. Ethanol conditioned place preference and alterations in ΔFosB following adolescent nicotine administration differ in rats exhibiting high or low behavioral reactivity to a novel environment. Behav Brain Res. 2014; 262:101–108. [PubMed: 24412683]

142. Belluzzi JD, Wang R, Leslie FM. Acetaldehyde enhances acquisition of nicotine self-administration in adolescent rats. Neuropsychopharmacology. 2005; 30:705–712. [PubMed: 15496937]

143. Park MK, Belluzzi JD, Han S-H, Cao J, Leslie FM. Age, sex and early environment contribute to individual differences in nicotine/acetaldehyde-induced behavioral and endocrine responses in rats. Pharmacol Biochem Behav. 2007; 86:297–305. [PubMed: 17141304]

144. Bachmanov AA, Kiefer SW, Molina JC, Tordoff MG, Duffy VB, Bartoshuk LM, Mennella JA. Chemosensory factors influencing alcohol perception, preferences, and consumption. Alcohol Clin Exp Res. 2003; 27:220–231. [PubMed: 12605071]

145. Pritchard WS, Robinson JH, Guy TD, Davis RA, Stiles MF. Assessing the sensory role of nicotine in cigarette smoking. Psychopharmacology (Berl). 1996; 127:55–62. [PubMed: 8880944]

146. Mantella NM, Youngentob SL. Prenatal alcohol exposure increases postnatal acceptability of nicotine odor and taste in adolescent rats. PLoS ONE. 2014; 9:e102255. [PubMed: 25029285]

147. Youngentob SL, Glendinning JI. Fetal ethanol exposure increases ethanol intake by making it smell and taste better. Proc Natl Acad Sci U S A. 2009; 106:5359–5364. [PubMed: 19273846]

148. Glendinning JI, Simons YM, Youngentob L, Youngentob SL. Fetal ethanol exposure attenuates aversive oral effects of TrpV1, but not TrpA1 agonists in rats. Exp Biol Med (Maywood). 2012; 237:236–240. [PubMed: 22378825]

149. Ribeiro-Carvalho A, Lima CS, Filgueiras CC, Manhães AC, Abreu-Villaça Y. Nicotine and ethanol interact during adolescence: effects on the central cholinergic systems. Brain Res. 2008; 1232:48–60. [PubMed: 18692029]

150. Trauth JA, McCook EC, Seidler FJ, Slotkin TA. Modeling adolescent nicotine exposure: effects on cholinergic systems in rat brain regions. Brain Res. 2000; 873:18–25. [PubMed: 10915806]

151. Brewer AJ, Mahoney JJ, Nerumalla CS, Newton TF, De La Garza R. The influence of smoking cigarettes on the high and desire for cocaine among active cocaine users. Pharmacol Biochem Behav. 2013; 106:132–136. [PubMed: 23541494]

152. O'Neill J. Interaction of methamphetamine abuse, tobacco abuse, and gender in the brain. Am J Drug Alcohol Abuse. 2015; 41:269–271. [PubMed: 26120900]

153. National Institute on Drug Abuse. DrugFacts: Nationwide trends. Available from: https://www.drugabuse.gov/publications/drugfacts/nationwide-trends [last accessed 2 Aug 2016]

154. Grant KM, Kelley SS, Agrawal S, Meza JL, Meyer JR, Romberger DJ. Methamphetamine use in rural Midwesterners. Am J Addict. 2007; 16:79–84. [PubMed: 17453608]

155. Russell K, Dryden DM, Liang Y, Friesen C, O'Gorman K, Durec T, Wild TC, Klassen TP. Risk factors for methamphetamine use in youth: a systematic review. BMC Pediatr. 2008; 8:48. [PubMed: 18957076]

156. Tidey JW, O'Neill SC, Higgins ST. d-amphetamine increases choice of cigarette smoking over monetary reinforcement. Psychopharmacology (Berl). 2000; 153:85–92. [PubMed: 11255931]

157. Winhusen TM, Kropp F, Theobald J, Lewis DF. Achieving smoking abstinence is associated with decreased cocaine use in cocaine-dependent patients receiving smoking-cessation treatment. Drug Alcohol Depend. 2014; 134:391–395. [PubMed: 24128381]

158. Grucza RA, Wang JC, Stitzel JA, Hinrichs AL, Saccone SF, Saccone NL, Bucholz KK, Cloninger CR, Neuman RJ, Budde JP, Fox L, Bertelsen S, Kramer J, Hesselbrock V, Tischfield J, Nurnberger JI, Almasy L, Porjesz B, Kuperman S, Schuckit MA, Edenberg HJ, Rice JP, Goate AM, Bierut LJ. A risk allele for nicotine dependence in CHRNA5 is a protective allele for cocaine dependence. Biol Psychiatry. 2008; 64:922–929. [PubMed: 18519132]

159. Sherva R, Kranzler HR, Yu Y, Logue MW, Poling J, Arias AJ, Anton RF, Oslin D, Farrer LA, Gelernter J. Variation in nicotinic acetylcholine receptor genes is associated with multiple substance dependence phenotypes. Neuropsychopharmacology. 2010; 35:1921–1931. [PubMed: 20485328]

160. Yang J, Li MD. Association and interaction analyses of 5-HT3 receptor and serotonin transporter genes with alcohol, cocaine, and nicotine dependence using the SAGE data. Hum Genet. 2014; 133:905–918. [PubMed: 24590108]

161. Palmer RHC, Button TM, Rhee SH, Corley RP, Young SE, Stallings MC, Hopfer CJ, Hewitt JK. Genetic etiology of the common liability to drug dependence: evidence of common and specific mechanisms for DSM-IV dependence symptoms. Drug Alcohol Depend. 2012; 123:S24–S32. [PubMed: 22243758]

162. Vanyukov MM, Tarter RE, Kirillova GP, Kirisci L, Reynolds MD, Kreek MJ, Conway KP, Maher BS, Iacono WG, Bierut L, Neale MC, Clark DB, Ridenour TA. Common liability to addiction and "gateway hypothesis": theoretical, empirical and evolutionary perspective. Drug Alcohol Depend. 2012; 123:S3–17. [PubMed: 22261179]

163. Lewinsohn PM, Rohde P, Brown RA. Level of current and past adolescent cigarette smoking as predictors of future substance use disorders in young adulthood. Addiction. 1999; 94:913–921. [PubMed: 10665079]

164. Brook JS, Balka EB, Ning Y, Brook DW. Trajectories of cigarette smoking among African Americans and Puerto Ricans from adolescence to young adulthood: associations with dependence on alcohol and illegal drugs. Am J Addict. 2007; 16:195–201. [PubMed: 17612823]

165. Wilens TE, Adamson J, Monuteaux MC, Faraone SV, Schillinger M, Westerberg D, Biederman J. Effect of prior stimulant treatment for attention-deficit/hyperactivity disorder on subsequent risk for cigarette smoking and alcohol and drug use disorders in adolescents. Arch Pediatr Adolesc Med. 2008; 162:916–921. [PubMed: 18838643]

166. Lambert NM, McLeod M, Schenk S. Subjective responses to initial experience with cocaine: an exploration of the incentive-sensitization theory of drug abuse. Addiction. 2006; 101:713–725. [PubMed: 16669905]

167. Horger BA, Giles MK, Schenk S. Preexposure to amphetamine and nicotine predisposes rats to self-administer a low dose of cocaine. Psychopharmacology (Berl). 1992; 107:271–276. [PubMed: 1615126]

168. Levine A, Huang Y, Drisaldi B, Griffin EA, Pollak DD, Xu S, Yin D, Schaffran C, Kandel DB, Kandel ER. Molecular mechanism for a gateway drug: epigenetic changes initiated by nicotine prime gene expression by cocaine. Sci Transl Med. 2011; 3:107ra109.

169. Mello NK, Newman JL. Discriminative and reinforcing stimulus effects of nicotine, cocaine, and cocaine + nicotine combinations in rhesus monkeys. Exp Clin Psychopharmacol. 2011; 19:203–214. [PubMed: 21480727]

170. Buffalari DM, Marfo NYA, Smith TT, Levin ME, Weaver MT, Thiels E, Sved AF, Donny EC. Nicotine enhances the expression of a sucrose or cocaine conditioned place preference in adult male rats. Pharmacol Biochem Behav. 2014; 124:320–325. [PubMed: 24967870]

171. Li H, Bu Q, Chen B, Shao X, Hu Z, Deng P, Lv L, Deng Y, Zhu R, Li Y, Zhang B, Hou J, Du C, Zhao Q, Fu D, Zhao Y, Cen X. Mechanisms of metabonomic for a gateway drug: nicotine priming enhances behavioral response to cocaine with modification in energy metabolism and neurotransmitter level. PLoS ONE. 2014; 9:e87040. [PubMed: 24489831]

172. Hiranita T, Nawata Y, Sakimura K, Anggadiredja K, Yamamoto T. Suppression of methamphetamine-seeking behavior by nicotinic agonists. Proc Natl Acad Sci U S A. 2006; 103:8523–8527. [PubMed: 16717181]

173. Neugebauer NM, Harrod SB, Bardo MT. Nicotine elicits methamphetamine-seeking in rats previously administered nicotine. Drug Alcohol Depend. 2010; 106:72–78. [PubMed: 19733448]

174. Zernig G, O'Laughlin IA, Fibiger HC. Nicotine and heroin augment cocaine-induced dopamine overflow in nucleus accumbens. Eur J Pharmacol. 1997; 337:1–10. [PubMed: 9389374]

175. Gerasimov MR, Franceschi M, Volkow ND, Rice O, Schiffer WK, Dewey SL. Synergistic interactions between nicotine and cocaine or methylphenidate depend on the dose of dopamine transporter inhibitor. Synapse. 2000; 38:432–437. [PubMed: 11044890]

176. Kim MN, Jutkiewicz EM, Zhang M, Gnegy ME. The sensitizing effect of acute nicotine on amphetamine-stimulated behavior and dopamine efflux requires activation of β2 subunit-containing nicotinic acetylcholine receptors and glutamate N-methyl-D-aspartate receptors. Neuropharmacology. 2011; 60:1126–1134. [PubMed: 20971124]

177. Mark GP, Hajnal A, Kinney AE, Keys AS. Self-administration of cocaine increases the release of acetylcholine to a greater extent than response-independent cocaine in the nucleus accumbens of rats. Psychopharmacology (Berl). 1999; 143:47–53. [PubMed: 10227079]

178. Shinohara F, Kihara Y, Ide S, Minami M, Kaneda K. Critical role of cholinergic transmission from the laterodorsal tegmental nucleus to the ventral tegmental area in cocaine-induced place preference. Neuropharmacology. 2014; 79:573–579. [PubMed: 24467849]

179. Levin ED, Mead T, Rezvani AH, Rose JE, Gallivan C, Gross R. The nicotinic antagonist mecamylamine preferentially inhibits cocaine vs. food self-administration in rats Physiol Behav. 2000; 71:565–570. [PubMed: 11239676]

180. Zachariou V, Caldarone BJ, Weathers-Lowin A, George TP, Elsworth JD, Roth RH, Changeux JP, Picciotto MR. Nicotine receptor inactivation decreases sensitivity to cocaine. Neuropsychopharmacology. 2001; 24:576–589. [PubMed: 11282258]

181. McGranahan TM, Patzlaff NE, Grady SR, Heinemann SF, Booker TK. α4β2 nicotinic acetylcholine receptors on dopaminergic neurons mediate nicotine reward and anxiety relief. J Neurosci. 2011; 31:10891–10902. [PubMed: 21795541]

182. Sanjakdar SS, Maldoon PP, Marks MJ, Brunzell DH, Maskos U, McIntosh JM, Bowers MS, Damaj MI. Differential roles of α6β2* and α4β2* neuronal nicotinic receptors in nicotine- and cocaine-conditioned reward in mice. Neuropsychopharmacology. 2015; 40:350–360. [PubMed: 25035086]

183. Khroyan TV, Yasuda D, Toll L, Polgar WE, Zaveri NT. High affinity α3β4 nicotinic acetylcholine receptor ligands AT-1001 and AT-1012 attenuate cocaine-induced conditioned place preference

and behavioral sensitization in mice. Biochem Pharmacol. 2015; 97:531–541. [PubMed: 26256075]

184. Glick SD, Kuehne ME, Raucci J, Wilson TE, Larson D, Keller RW, Carlson JN. Effects of iboga alkaloids on morphine and cocaine self-administration in rats: relationship to tremorigenic effects and to effects on dopamine release in nucleus accumbens and striatum. Brain Res. 1994; 657:14–22. [PubMed: 7820611]
185. Glick SD, Maisonneuve IM, Szumlinski KK. 18-Methoxycoronaridine (18-MC) and ibogaine: comparison of antiaddictive efficacy, toxicity, and mechanisms of action. Ann N Y Acad Sci. 2000; 914:369–386. [PubMed: 11085336]
186. Alajaji M, Lazenka MF, Kota D, Wise LE, Younis RM, Carroll FI, Levine A, Selley DE, Sim-Selley LJ, Damaj MI. Early adolescent nicotine exposure affects later-life cocaine reward in mice. In Neuropharmacology. 2016; 105:308–317.
187. Dickson PE, Miller MM, Rogers TD, Blaha CD, Mittleman G. Effects of adolescent nicotine exposure and withdrawal on intravenous cocaine self-administration during adulthood in male C57BL/6J mice. Addict Biol. 2014; 19:37–48. [PubMed: 22978678]
188. Pomfrey RL, Bostwick TA, Wetzell BB, Riley AL. Adolescent nicotine exposure fails to impact cocaine reward, aversion and self-administration in adult male rats. Pharmacol Biochem Behav. 2015; 137:30–37. [PubMed: 26255152]
189. Kelley BM, Rowan JD. Long-term, low-level adolescent nicotine exposure produces dose-dependent changes in cocaine sensitivity and reward in adult mice. Int J Dev Neurosci. 2004; 22:339–348. [PubMed: 15380833]
190. Santos GC, Marin MT, Cruz FC, Delucia R, Planeta CS. Amphetamine- and nicotine-induced cross-sensitization in adolescent rats persists until adulthood. Addict Biol. 2009; 14:270–275. [PubMed: 19523043]
191. Pipkin JA, Kaplan GJ, Plant CP, Eaton SE, Gil SM, Zavala AR, Crawford CA. Nicotine exposure beginning in adolescence enhances the acquisition of methamphetamine self-administration, but not methamphetamine-primed reinstatement in male rats. Drug Alcohol Depend. 2014; 142:341–344. [PubMed: 25042760]
192. Mathers M, Toumbourou JW, Catalano RF, Williams J, Patton GC. Consequences of youth tobacco use: a review of prospective behavioural studies. Addiction. 2006; 101:948–958. [PubMed: 16771887]
193. Dutra LM, Glantz SA. Electronic cigarettes and conventional cigarette use among U.S. adolescents: a cross-sectional study JAMA Pediatr. 2014; 168:610–617. [PubMed: 24604023]
194. Bunnell RE, Agaku IT, Arrazola RA, Apelberg BJ, Caraballo RS, Corey CG, Coleman BN, Dube SR, King BA. Intentions to smoke cigarettes among never-smoking US middle and high school electronic cigarette users: National Youth Tobacco Survey, 2011–2013. Nicotine Tob Res. 2015; 17:228–235. [PubMed: 25143298]
195. Wills TA, Knight R, Williams RJ, Pagano I, Sargent JD. Risk factors for exclusive e-cigarette use and dual e-cigarette use and tobacco use in adolescents. Pediatrics. 2015; 135:e43–e51. [PubMed: 25511118]
196. Farrelly MC, Loomis BR, Han B, Gfroerer J, Kuiper N, Couzens GL, Dube S, Caraballo RS. A comprehensive examination of the influence of state tobacco control programs and policies on youth smoking. Am J Public Health. 2013; 103:549–555. [PubMed: 23327252]
197. Miech RA, O'Malley PM, Johnston LD, Patrick ME. E-Cigarettes and the drug use patterns of adolescents. Nicotine Tob Res. 2015
198. Hughes K, Bellis MA, Hardcastle KA, McHale P, Bennett A, Ireland R, Pike K. Associations between e-cigarette access and smoking and drinking behaviours in teenagers. BMC Public Health. 2015; 15:244. [PubMed: 25886064]
199. Azagba S, Sharaf MF. Binge drinking and marijuana use among menthol and non-menthol adolescent smokers: findings from the youth smoking survey. Addict Behav. 2014; 39:740–743. [PubMed: 24369112]
200. Perkins KA, Donny E, Caggiula AR. Sex differences in nicotine effects and self-administration: review of human and animal evidence. Nicotine Tob Res. 1999; 1:301–315. [PubMed: 11072427]

201. Randall CL, Roberts JS, Del Boca FK, Carroll KM, Connors GJ, Mattson ME. Telescoping of landmark events associated with drinking: a gender comparison. J Stud Alcohol. 1999; 60:252–260. [PubMed: 10091964]

202. Zilberman M, Tavares H, el-Guebaly N. Gender similarities and differences: the prevalence and course of alcohol- and other substance-related disorders. J Addict Dis. 2003; 22:61–74.

203. Mann K, Ackermann K, Croissant B, Mundle G, Nakovics H, Diehl A. Neuroimaging of gender differences in alcohol dependence: are women more vulnerable? Alcohol Clin Exp Res. 2005; 29:896–901. [PubMed: 15897736]

204. Back SE, Brady KT, Jackson JL, Salstrom S, Zinzow H. Gender differences in stress reactivity among cocaine-dependent individuals. Psychopharmacology (Berl). 2005; 180:169–176. [PubMed: 15682303]

205. Becker JB, Hu M. Sex differences in drug abuse. Front Neuroendocrinol. 2008; 29:36–47. [PubMed: 17904621]

206. O'Dell LE, Torres OV. A mechanistic hypothesis of the factors that enhance vulnerability to nicotine use in females. Neuropharmacology. 2014; 76:566–580. [PubMed: 23684991]

207. Almeida OF, Shoaib M, Deicke J, Fischer D, Darwish MH, Patchev VK. Gender differences in ethanol preference and ingestion in rats. The role of the gonadal steroid environment. J Clin Invest. 1998; 101:2677–2685. [PubMed: 9637701]

208. McMurray MS, Williams SK, Jarrett TM, Cox ET, Fay EE, Overstreet DH, Walker CH, Johns JM. Gestational ethanol and nicotine exposure: effects on maternal behavior, oxytocin, and offspring ethanol intake in the rat. Neurotoxicol Teratol. 2008; 30:475–486. [PubMed: 18664381]

209. Lynch WJ. Sex differences in vulnerability to drug self-administration. Exp Clin Psychopharmacol. 2006; 14:34–41. [PubMed: 16503703]

210. Roberts DC, Bennett SA, Vickers GJ. The estrous cycle affects cocaine self-administration on a progressive ratio schedule in rats. Psychopharmacology (Berl). 1989; 98:408–411. [PubMed: 2501818]

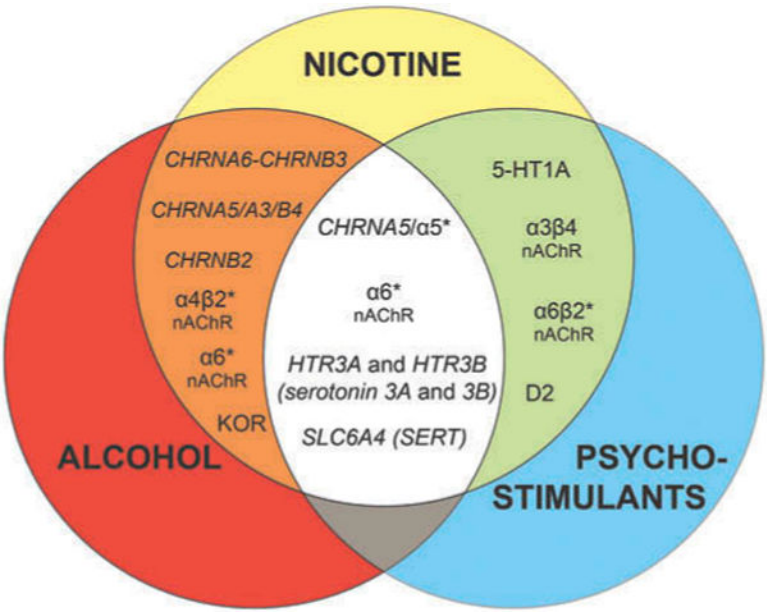


**Figure 1.**

Overlapping receptor systems involved in nicotine and alcohol or psychostimulant dependence. Genetic and pharmacological studies in both humans and rodents suggest that co-use of nicotine and alcohol or psychostimulants is mediated, in part, by activity at overlapping substrates. In particular, cholinergic and serotonergic systems underlie reward-related behaviors, including drug intake, preference, and dependence to all three drugs of abuse. Asterisks (*) indicate nAChRs containing other subunits. Italics indicate human genes. KOR = kappa opioid receptor.