Published in final edited form as:
Drug Alcohol Depend. 2010 April 1; 108(1-2): 49–55. doi:10.1016/j.drugalcdep.2009.11.016.

Mechanisms underlying the lifetime co-occurrence of tobacco and cannabis use in adolescent and young adult twins

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Abstract

Using twins assessed during adolescence (Virginia Twin Study of Adolescent Behavioral Development: 8–17 years) and followed up in early adulthood (Young Adult Follow-Up, 18–27 years), we tested 13 genetically informative models of co-occurrence, adapted for the inclusion of covariates. Models were fit, in Mx, to data at both assessments allowing for a comparison of the mechanisms that underlie the lifetime co-occurrence of cannabis and tobacco use in adolescence and early adulthood. Both cannabis and tobacco use were influenced by additive genetic (38–81%) and non-shared environmental factors with the possible role of non-shared environment in the adolescent assessment only. Causation models, where liability to use cannabis exerted a causal influence on the liability to use tobacco fit the adolescent data best, while the reverse causation model (tobacco causes cannabis) fit the early adult data best. Both causation models (cannabis to tobacco and tobacco to cannabis) and the correlated liabilities model fit data from the adolescent and young adult assessments well. Genetic correlations (0.59–0.74) were moderate. Therefore, the relationship between cannabis and tobacco use is fairly similar during adolescence and early adulthood with reciprocal influences across the two psychoactive substances. However, our study could not exclude the possibility that 'gateways' and 'reverse gateways', particularly within a genetic context, exist, such that predisposition to using one substance (cannabis or tobacco) modifies predisposition to using the other. Given the high addictive potential of nicotine and the ubiquitous nature of cannabis use, this is a public health concern worthy of considerable attention.

Keywords

genetic; cannabis; tobacco; twin; Neale-Kendler; comorbidity

1. INTRODUCTION

Over 70% of those aged 12 years and older, in the United States, report a lifetime history of tobacco use, primarily cigarettes (Substance Abuse and Mental Health Services Administration

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(SAMHSA), 2005). Globally, the rates of youth tobacco use vary greatly, being highest in Central and Eastern Europe, India and some of the Pacific Islands (Mackay et al., 2006). Lifetime use of cannabis, the most common illicit psychoactive substance in developed nations, shows marked variations in prevalence across countries, 40% in the United States and New Zealand being highest in the world in this age group (Degenhardt et al., 2008). While there is epidemiological evidence in favor of a robust association between tobacco and cannabis use (Degenhardt et al., 2001; Kandel et al., 1993; Korhonen et al., 2008; Lynskey et al., 1998; Mathers et al., 2006; Patton et al., 2006), the potential genetic underpinnings of their co-occurence are largely unknown. Adolescent twin studies have demonstrated that both tobacco (heritability ranging from 0.45–0.84)(Maes et al., 1999; McGue et al., 2000; Rose et al., 2009) and cannabis use (heritability ranging from 0.40–0.65) (Agrawal et al., 2006; Rhee et al., 2003) are heritable and there is some suggestion that common genetic factors mould the lifetime co-occurrence of tobacco and cannabis use (Young et al., 2006). However, common genetic influences are but one of several mechanisms by which the relationship between tobacco and cannabis can be explained.

There are two important considerations related to the genetic and environmental underpinnings of substance use. First, the etiology of substance use changes significantly across developmental stages. For instance, McGue et al (McGue et al., 2000) report substance shared environmental influences on both cannabis and tobacco use (Fowler et al., 2007; Maes et al., 1999; Rhee et al., 2003) during adolescence while adult samples often find that heritable factors explain twin similarity in substance use (Agrawal et al., 2006; Heath et al., 1993; Kendler et al., 1999; Kendler et al., 2003a; Kendler et al., 2008; Lynskey et al., 2002; Maes et al., 2004). Kendler and colleagues also show decay in the relative role of shared environment with increasing respondent age (Kendler et al., 2008). A second related consideration is that the mechanisms that induce the observed correlations between tobacco and cannabis use may also vary across development. In the case of alcohol and illicit drug dependence, Rhee et al. (Rhee et al., 2006) found that in adolescents, a model where a single liability underlying both alcohol and illicit drug dependence fit significantly better than the traditional correlated risks model, which has been shown to be a reasonable fit to data on adult twins (Kendler et al., 2003b; Kendler et al., 2007).

We are not aware of any systematic hypothesis-testing for the relationship between tobacco and cannabis use. In the present study, we use data from the Virginia Twin Study of Adolescent Behavioral Development (VTSABD, ages 8–17 years) and the Young Adult Follow-up (YAFU, aged 18–27 years) to contrast 13 genetically informative mechanisms, established for twin data by Neale and Kendler (Neale et al., 1995) and subsequently modified to allow for covariates by Rhee et al. (2007) that may govern the association between cannabis and tobacco use in a longitudinal sample that assessed twin pairs during childhood/adolescence and young adulthood.

2. METHODS AND MATERIALS

2.1 Sample

Data for this study are drawn from the VTSABD (Eaves et al., 1997; Hewitt et al., 1997; Silberg et al., 1996; Simonoff et al., 1997), a longitudinal study of 1412 juvenile twin pairs, and the YAFU (Silberg et al., 2007), a follow-up to the VTSABD, which re-interviewed 2289 twins at 18 years or older. The sampling design, ascertainment strategy and recruitment have been extensively described in related publications. In brief, the VTSABD used a cohort – sequential design to recruit twins aged 8–17 years using statewide recruitment via the Virginia school systems. During the first wave of data collection, 74.5% of the 1894 eligible families completed assessments. Twins (and families) were then invited to participate in 3 additional waves of data collection, provided they were still enrolled in school and under 18 years of age. Of the families

that continued to meet the age and residence requirements, 80–81% completed waves 2 (N=1990) and wave 3 (N=1148) with a substantially smaller subset being eligible and completing wave 4 (N=360). At each wave, twins were interviewed using an extensive psychiatric assessment instrument that included the Child and Adolescent Psychiatric Assessment (CAPA) (Angold et al., 1995).

Upon turning 18 years of age, 2,824 eligible twins from VTSABD were re-contacted and invited to participate in a follow-up study. Semi-structured telephone interviews based on the Structured Clinical Interview of DSM (SCID, Spitzer et al. 1990) were conducted with participants with a response rate of 80.8%.

2.2 Measures

Both the Child CAPA and the semi-structured YAFU interviews queried the twins about their lifetime and current history of tobacco and cannabis use. In the CAPA, the Alcohol section included questions on whether the participant had ever smoked cigarettes and whether they had ever tried marijuana (hashish, pot, grass, weed). In the YAFU interview, participants were asked whether they had ever smoked cigarettes or used tobacco products regularly and whether they had ever used cannabis (marijuana, hashish, THC, other).

Across the VTSABD and YAFU, cannabis use was coded dichotomously to reflect a lifetime history of ever using cannabis. For tobacco use, a dichotomous measure of ever smoking even one cigarette was coded for the VTSABD, while in the older twins from the YAFU, the dichotomous tobacco measure reflected self-reported ‘regular’ use. Regular tobacco use, per se, was not assessed in the VTSABD and lifetime use (even once) was not included in the YAFU. For the VTSABD, data on more than one wave of interviews was available for a majority of the twins – twins were coded as cannabis or tobacco users if they responded positively at any one interview. While we did have quantitative assessments of cigarettes smoked per day in the YAFU, the twins were largely light smokers and to ensure adequate power, we restricted our analyses to ever smoking in the juvenile twins and regular smoking in the young adult twins.

2.3 Genetic Comorbidity/Co-occurrence Models

Thirteen genetically informative models that explain the co-occurrence of cannabis and tobacco use were tested in the juvenile and young adult twin pairs. Originally proposed by Klein and Riso (Klein et al., 1994) to describe psychiatric models of comorbidity/co-occurrence, these models were adapted under assumptions of multifactorial theory to a genetically informative framework by Neale & Kendler (Neale et al., 1995), and subsequently, by Rhee and colleagues (Rhee et al., 2007), with the latter allowing for the inclusion of measured covariates. Each model uses twin similarity to decompose variance into additive genetic (A), shared environmental (C) and individual-specific environmental (E) factors. As in the classical twin model, A is correlated 1.0 and 0.5 in members of MZ and DZ pairs respectively, and under the equal environments assumption, C is correlated 1.0 in members of MZ and DZ pairs. The E factors include measurement error and are uncorrelated across members of a twin pair. A, C and E influence an unmeasured uni-dimensional liability that underlies each trait (e.g. cannabis use and tobacco use). By allowing the relationship between A, C and E, and other parameters, such as thresholds of each trait, proportions of individuals reporting one versus both traits, and other features to vary, Neale & Kendler (1995) describe the following 13 mechanisms of comorbidity/co-occurrence which included chance, alternate forms, random and extreme multiformity, three independent disorders as well as correlated and causal liabilities. Brief descriptions of these models may be found in related publications (Agrawal et al., 2007; Neale et al., 1995; Rhee et al., 2006; Rhee et al., 2007) and in Table 2.

We use the adaptation of the Neale-Kendler models developed by Rhee et al., (2007) as we allowed for thresholds of both cannabis and tobacco use to be modified by sex (allowing us to include opposite-sex pairs, under an assumption of absence of sex differences) and age (coded dichotomously, to avoid assumptions of linearity, in VTSABD as under 13 years or older, and in YAFU as 22 years or older, representing the bottom and top quartiles respectively). The first series of models were fit under the assumption that A, C and E influencing tobacco and cannabis use in both male and female twins are equal and that there are no sex differences in the etiology of co-occurring tobacco and cannabis use. In a second series of models, we specifically examined whether the mechanisms underlying co-occurring tobacco and cannabis use differed by sex.

All models were fit using the statistical software package Mx (Neale, 2004). Briefly, the pattern of twin 1 and twin 2's responses for tobacco and cannabis use are used to classify them into one of 16 types of twin pairs. For instance, if both twins neither use tobacco nor cannabis then their pattern is 0000 (or type 1). However, if twin 1 uses tobacco and twin 2 uses cannabis, then their pattern is 1001 (or type 9). Table 1 lists the 16 observed patterns of data and the number of MZ and DZ pairs available from the VTSABD and YAFU for these analyses. In addition to a variable indicating type of twin pair (1–16), raw data on each covariate (sex and age) are included in the raw data file.

The major families of comorbidity/co-occurrence models are not nested – for instance, the random multiformity model is not nested within the correlated liability model, and therefore, we used Akaike's Information Criterion (Akaike H, 1987), an index of both fit and parsimony (Williams et al., 1994), as the fit index for model selection.

3. RESULTS

3.1 Association between cannabis and tobacco use

When they were assessed at childhood/adolescence, the sample (VTSABD) consisted of 1412 pairs of twins aged 8–17 years. Of the boys, 35.1% and 13.9% reported tobacco and cannabis use respectively with the odds of cannabis use in boys with tobacco use being 20.6 [95% C.I. 12.8–33.8]. In girls as well, the association between tobacco and cannabis use was high [O.R. 50.5, 95% C.I. 25.7–89.1], with 24.9 and 10.7% of the girls reporting tobacco and cannabis use respectively. In the young adult (YAFU) sample, 53.9% of the men and 42.6% of the women reported regular tobacco use while 59.8 and 51.3% of the men and women reporting lifetime cannabis use with the odds of cannabis use in regular tobacco users being 7.8 [95% C.I. 6.4–9.5 in juvenile sample, 6.1–9.3 in young adult sample] in both men and women.

3.2 Co-occurrence models in the VTSABD

The best-fitting family of models for the twins during their childhood/adolescence assessment (8–17 years) was those that allowed for causal paths between the liability to tobacco and cannabis use. Of these (reciprocal causation, tobacco cause cannabis, cannabis cause tobacco), the model where the liability to cannabis use was allowed to assert a causal influence on the individual's liability to use tobacco, fit the data best (Table 2), however the model where tobacco use influenced cannabis use fit reasonably well (difference in AIC between the models was 7). The extreme multiformity of cannabis model, where individuals whose risk for cannabis use exceeded a second threshold were at increased risk for tobacco use, fit the data as well as the tobacco causes cannabis use model. The most commonly tested model within genetically informative studies of co-occurring substance use, the correlated liabilities model fit third best, suggesting a fairly high genetic (Rg=0.75), shared environmental (Rc=0.91) and non-shared environmental (Re=0.71) overlap between cannabis and tobacco use (Table 3). The fit of the correlated liabilities model was within 2.7 AIC units of the reciprocal causation model.

3.3 Co-occurrence models in the YAFU

Similar to their VTSABD assessment, in their young adult assessment where the twins were aged 18–27 years, the family of causation models fit the data best. The relationship between regular smoking and cannabis use was best described by a model where liability to the former had a causal influence on the latter – a reverse direction to the model that fit the juvenile twin data best (Table 2). The second best fit was provided by the correlated liabilities model with fairly high extent of genetic and environmental overlap (Table 4) between regular smoking and cannabis use. The fit of the correlated liabilities model was 11.2 AIC units greater than the fit for the tobacco causes cannabis use model and only 7 AIC units lower than the other causation models – reciprocal causation and cannabis causes tobacco use. Intriguingly, the third best fit was provided by the 3 independent disorders model – the premise of this model is that the co-occurrence of regular smoking and cannabis use represents a behavior that is etiologically unique from using either substance by itself.

3.4 Genetic and environmental influences on tobacco and cannabis use

In the sample based on the childhood/adolescent assessment, twin similarity for both cannabis and tobacco use was explained by genetic, shared and non-shared environmental influences (Table 2). Using our best-fitting model, we tested for the statistical significance of genetic and shared environmental influences on tobacco and cannabis use – neither genetic (Tobacco: $\Delta\chi^2$ = 3.9 for df=1; Cannabis: $\Delta\chi^2$ =21.6 for df=1) nor shared environmental (Tobacco: $\Delta\chi^2$ = 12.6 for df=1; Cannabis: $\Delta\chi^2$=18.4 for df=1) factors could be constrained to zero without a statistically significant loss of model fit.

In the sample based on the young adult assessment, variation in regular tobacco use was entirely due to genetic and non-shared environmental factors while genetic, shared and non-shared environmental factors influences liability to cannabis use. From the best-fitting tobacco causes cannabis use model, genetic influences on tobacco and cannabis could not be constrained to zero ($\Delta\chi^2$= 62.7 for df=2), however, shared environmental influences on cannabis use could be constrained to zero without a significant deterioration in model fit ($\Delta\chi^2$= 2.2 for df=1).

3.5 Sex differences in 3 best-fitting twin models

We fitted the 3 best-fitting models emerging from the VTSABD and YAFU analyses separately to data on same-sex male and female MZ and DZ pairs.

In the VTSABD data, model-fit in male and female twins closely resembled each other. In both sexes, Cannabis causes Tobacco use was the best-fitting model (AIC_M=1284.2, AIC_F=1217.8), correlated liabilities fit second best (AIC_M=1292.8, AIC_F=1251.3) and the extreme multiformity of cannabis model provided the third best-fit (AIC_M=1314.8, AIC_F=1258.6). The role of additive (Males: $a^2_{tobacco}$=0.45, a $^2_{cannabis}$=0.44; Females: $a^2_{tobacco}$=0.43, $a^2_{cannabis}$=0.42) and shared environmental factors (Males: $c^2_{tobacco}$=0.41, $c^2_{cannabis}$=0.34; Females: $c^2_{tobacco}$=0.37, $c^2_{cannabis}$=0.30) were similar across sexes as were other parameters, such as the cannabis causes tobacco use path and the genetic and environmental correlations across cannabis and tobacco use. Thresholds varied considerably across sexes.

Similar to the VTSABD, in the YAFU assessments, with the exception of threshold variations, there was no evidence for variations between young adult male and female twins. In both sexes, the tobacco causes cannabis use model fit best (AIC_M=1486.7, AIC_F=2951.3). In men, correlated liabilities and three independent disorders fit second and third best respectively (AIC_M=1490.6 & 1496.7) while in the women, these two models had approximately equal fit (AIC_F=2957.0 & 2956.8). Both tobacco (Males: $a^2_{tobacco}$=0.79; Females: $a^2_{tobacco}$=0.77) and cannabis (Males: $a^2_{tobacco}$=0.76; Females: $a^2_{tobacco}$=0.75) were influenced by genetic and

individual-specific environmental factors to a similar extent, also with comparable estimates on other model parameters.

4. DISCUSSION

In 1975, Kandel (Kandel, 1975) proposed that underlying patterns of licit and illicit drug use was a gateway effect, which was characterized by sequence (i.e. a gateway drug is always initiated before other drugs), association (i.e. use of a gateway drug independently increases risk for use of other drugs) and causation (i.e. use of a gateway drug asserts a causal influence on use of other drugs) (Kandel, 2003). Research by her (Chen et al., 1995; Kandel et al., 1993; Kandel, 2002; Kandel et al., 1985; Kandel et al., 1992) and other investigators (Adler et al., 1981; Chen et al., 1995; Hawkins et al., 2002; Yamaguchi et al., 1984) subsequently posited that while cannabis may serve as 'gateway' to other illicit drug use, tobacco use served as a 'gateway' to cannabis use. Tobacco is often initiated prior to cannabis (Kandel et al., 1975; Kandel et al., 1993; Patton et al., 2006) and tobacco users are at considerably increased risk for using cannabis during their lifetime. However, Patton and colleagues (Patton et al., 2005) demonstrated that in a sub-group of adolescent Australians, cannabis use predicted onset of tobacco use – with non-tobacco using cannabis users at an eight-fold increased risk of onset of tobacco use by age 21. This effect of cannabis use on smoking behavior has since been noted across multiple studies (Agrawal et al., 2008b; Timberlake et al., 2007), although not as frequently for initiation.

The relationship between these two substances is further complicated by the genetic and environmental factors that influence liability to use tobacco and cannabis. While a shared etiology, primarily governed by common genetic influences, contributes to the covariation between tobacco and cannabis use (Han et al., 1999; Young et al., 2006), no study to date has tested all the competing models of co-occurrence of these two substances, particularly allowing for comparisons between adolescence and young adulthood. The latter is a prominent limitation of the genetic literature - first, as twin studies reveal that the etiology of substance use itself changes during development (Eaves et al., 1997; McGue et al., 2008; Rose, 1998; Scarr, 1992; Silberg et al., 2007) and second, as the mechanisms underlying the relationship between different substances may also change over time.

Most genetic studies examine the role of common genetic and environmental factors on tobacco and cannabis use, and we too find the correlated liabilities model to provide a reasonable fit to our data, with significant overlap in the latent genetic risk factors influencing the use of tobacco and cannabis. However, our best-fitting model in the juvenile and young adult twins was a causal model, which is closely related to the correlated liabilities model but assumes that there is a direct phenotypic relationship between cannabis and tobacco use that is not specifically due to genetic or environmental influences. This model was previously tested in a sample of adult twin women from Virginia (Neale et al., 2006) – in that study, tobacco use exerted a positive causal influence on cannabis use, but cannabis users were at decreased risk for initiation of tobacco use. Our findings in the adult sample mirror the study by Neale and colleagues (Neale et al., 2006) with both studies suggesting a link between the liability to smoke cigarettes and the liability to cannabis use.

Interpretation of the direction of causation in this series of twin studies warrants some caution. While it might be the case that 'reverse gateway' effects are in action in the VTSABD, there was no empirical evidence from our data to suggest that the predominant sequence of drug use was one where cannabis use preceded onset of cigarette smoking. About 8% of the twins reported a lower age of cannabis versus cigarette initiation, 20% reported the same age at initiation for both, and cigarette smoking followed by cannabis use was the predominant pattern with 31% reporting onset of cannabis use within 1–2 years of starting to smoke cigarettes. An

additional caveat for such analyses is the limited power afforded, particularly in adolescent twin samples, to distinguish between closely related models of co-occurrence. Furthermore, the usage of ever smoking even one cigarette versus smoking 'regularly' in the VTSABD and YAFU respectively, may have contributed to our results, and may reflect changing effects of cannabis involvement on various stages of tobacco involvement.

Several hypotheses may be proposed in explanation of our findings. First, cannabis and tobacco have a common route of administration with a recent study showing that the increased likelihood of cannabis use in tobacco users is largely restricted to those who use smoked forms of tobacco (Agrawal et al., 2008a). A second related mechanism involves the use of tobacco in cannabis-containing joints and, particularly the use of blunts (rolling cannabis and tobacco together) (Golub et al., 2005; Kelly, 2005) may explain the phenotypic effects of cannabis use on tobacco use. Third, genes encoding receptors, such as Cannabinoid Receptor 1 (*CNR1*) which is associated with both cannabis-related problems (Agrawal et al., 2008c; Hopfer et al., 2006) and with tobacco smoking initiation and nicotine dependence (Chen et al., 2008), may be involved. Fourth, a recent animal study shows that chronic nicotine exposure may modify sensitivity to other substances (Vihavainen et al., 2008). Finally, initiation of cannabis use and tobacco involvement may be linked by common environmental risk and protective factors, such as delinquent peers (Oetting et al., 1986).

Some limitations of this study are noteworthy. First, ours is a sample of Caucasian twins from Virginia and our findings may not extend to other ethnic populations, particularly those where cannabis use is tolerated, due to inherent differences in substance use practices across cultures. Second, assessments of regular tobacco use in the juvenile twins and of tobacco use, distinct from regular use in the young adult twins, were not available. A third related limitation is the subjective interpretability of regular smoking in the YAFU – participants were given no assistance in defining regular smoking and hence some subjects may not truly meet the threshold for common definitions of regular smoking. Fourth, power is a significant concern when fitting the Neale-Kendler models. Simulations have previously shown that power to discriminate between closely related models (e.g. reciprocal causation, tobacco causes cannabis, cannabis causes tobacco) is often limited (Rhee et al., 2004; Rhee et al., 2007). Fifth, while the current analyses do not exploit the longitudinal design of these data (partly, because it is infeasible to test comorbidity/co-occurrence models within a longitudinal framework), by homing in on a few key mechanisms, we set the stage for longitudinal analysis. Finally, the current data do not allow us to tease apart the various hypothesized mechanisms (e.g. aero-respiratory adaptation, blunt use) underlying the association between tobacco and cannabis use.

Notwithstanding these limitations, our results imply that while in early adolescence, cannabis use may increase risk for tobacco use, particularly in high-risk individuals, due to the high addictive potential of nicotine, cigarette smoking rapidly escalates in tobacco users and subsequently, during young adulthood, regular cigarette smoking exerts a direct influence on cannabis use, thus inducing a vicious cycle between these two, highly popular, psychoactive substances. This poses an enormous public health challenge that requires urgent attention.

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Table 1

Twin pairs available for analysis of 16 potential patterns of twin-cotwin endorsement of tobacco and cannabis use across VTSABD and YAFU

Data	Type	Description	MZM		MZF		DZM		DZF		DZO	
			VTSABD	YAFU	VTSABD	YAFU	VTSABD	YAFU	VTSABD	YAFU	VTSABD	YAFU
0000	1	No TOB & No CAN	167	59	275	112	95	17	127	31	149	25
0100	2	T1 CAN	0	13	0	12	1	3	1	4	3	14
0001	3	T2 CAN	3	8	1	14	2	5	1	10	4	6
1000	4	T1 TOB	27	9	21	4	18	8	11	5	34	12
0010	5	T2 TOB	24	1	32	8	13	5	13	8	26	10
1100	6	T1 CAN + TOB	3	7	3	6	3	11	4	11	9	16
0011	7	T2 CAN + TOB	4	7	4	12	5	9	4	13	9	18
0101	8	T1 CAN & T2 CAN	2	23	1	28	0	9	0	10	0	10
1001	9	T1 TOB & T2 CAN	1	1	0	1	1	0	1	3	0	2
0110	10	T1 CAN & T2 TOB	0	0	2	2	0	0	1	3	0	1
1101	11	T1 TOB + CAN & T2 CAN	2	9	1	11	0	4	0	7	1	12
0111	12	T1 CAN & T2 TOB + CAN	0	12	1	21	1	10	1	9	0	16
1010	13	T1 TOB & T2 TOB	29	11	30	12	15	2	8	2	20	7
1110	14	T1 TOB + CAN & T2 TOB	10	6	5	6	6	3	3	4	9	7
1011	15	T1 TOB & T2 TOB + CAN	10	6	5	6	4	9	5	6	9	7
1111	16	T1 TOB + CAN & T2 TOB + CAN	19	69	29	76	15	39	9	27	17	44
TOTAL			311	241	410	331	179	134	189	153	290	207

Column 1 represents types of twin pairs. Each number, 0 or 1, represents use by each twin of cannabis and tobacco. The sequence is Twin 1 tobacco, Twin 1 cannabis, Twin 2 tobacco, Twin 2 cannabis. Thus, 0110 represents those twin pairs where Twin 1 used cannabis and Twin 2 used tobacco. T1 and T2, in column 3, refer to Twin 1 and Twin 2; TOB=tobacco use, THC = cannabis use.

Table 2

Fit indices for the 13 Neale-Kendler models of co-occurring cannabis and tobacco use fitted to data on MZ and DZ twins from the VTSABD and YAFU.

MODEL	−2 Loglikelihood		# parameters	AIC	
	VTSABD	YAFU		VTSABD	YAFU
Chance *Cannabis and Tobacco use co-occur by chance alone.*	6350.4	6779.0	10	3612.4	4667.0
Alternate Forms *Common liability for both drugs with a proportion using cannabis and another proportion using tobacco.*	6086.2	6605.9	7	3342.2	4487.9
Random multiformity of Tobacco and Cannabis *Individual liability for each drug with a subset of tobacco users also at increased risk of tobacco use and vice versa.*	6004.6	6441.9	12	3270.6	4333.9
Random multiformity of Tobacco *Individual liability for each drug with a subset of tobacco users at increased risk for cannabis use.*	6091.0	6465.6	11	3355.0	4355.6
Random multiformity of Cannabis *Individual liability for each drug with a subset of cannabis users at increased risk for tobacco use.*	6005.3	6488.2	11	3269.3	4378.2
Extreme multiformity of Tobacco and Cannabis *Individual liability for each drug with a subset of "high risk" tobacco users also at increased risk of tobacco use and vice versa.*	5949.6	6460.7	14	3223.6	4360.7
Extreme multiformity of Tobacco *Individual liability for each drug with a subset of "high risk" tobacco users at increased risk for cannabis use.*	5964.6	6482.5	13	3232.6	4376.5
Extreme multiformity of Cannabis *Individual liability for each drug with a subset of "high risk" cannabis users at increased risk for tobacco use*	5941.2	6492.7	13	3209.2	4386.7
Correlated Liabilities *Liability to cannabis and tobacco use attributable to correlated genetic and environmental factors.*	5949.7	6401.9	13	3217.7	4295.9
Reciprocal Influence of Liabilities *Liability to tobacco use has causal influence on liability to cannabis use and vice versa.*	5949.0	6410.6	12	3215.0	4302.6
Tobacco causes Cannabis use *Liability to tobacco use has causal influence on liability to cannabis use.*	5945.4	6394.7	11	3209.4	4284.7
Cannabis causes Tobacco use *Liability to cannabis use has causal influence on liability to tobacco use.*	5938.4	6413.0	11	3202.4	4303.0
Three independent disorders *Co-occurring cannabis and tobacco use reflects a unique condition with an independent liability.*	5968.1	6411.2	15	3240.1	4309.2

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Table 3

Parameter estimates from the 3 best-fitting models for the 8–17 year old juvenile twins from the VTSABD.

	Cannabis causes Tobacco Use	Correlated Liabilities	Extreme Multiformity of Cannabis
$a^2_{tobacco}$	0.38	0.55	0.60
$c^2_{tobacco}$	0.24	0.22	0.00
$a^2_{cannabis}$	0.48	0.45	0.79
$c^2_{cannabis}$	0.41	0.30	0.00
Rg	-	0.74	-
Rc	-	0.89	-
Re	-	0.66	-
Cannabis →Tobacco	0.71[#]	-	-
$t1_{tobacco}$	0.23	0.20	0.43
Sex on Tobacco	0.24	0.30	0.32
Age on Tobacco	1.13	1.11	0.97
$t1_{cannabis}$	0.96	0.95	0.95
Sex on Cannabis	0.13	0.20	0.14
Age on Cannabis	1.40	1.21	5.2
$t2_{tobacco}$	∞	∞	∞
Sex on Tobacco	-	-	-
Age on Tobacco	-	-	-
$t2_{cannabis}$	∞	∞	0.14
Sex on Cannabis	-	-	−0.05
Age on Cannabis	-	-	−10.35

[#]The Tobacco → Cannabis path was 0.96 in the Tobacco Causes Cannabis use model.

Drug Alcohol Depend. Author manuscript; available in PMC 2011 April 1.

Table 4

Parameter estimates from the 3 best-fitting models for the 18–27 year old young adult twins from the YAFU

	Tobacco causes Cannabis Use	Correlated Liabilities	Three Independent Disorders
$a^2_{tobacco}$	0.81	0.76	0.81
$c^2_{tobacco}$	0.00	0.00	0.00
$a^2_{cannabis}$	0.57	0.59	0.45
$c^2_{cannabis}$	0.26	0.20	0.36
$a^2_{tobacco + cannabis}$	-	-	0.73
$c^2_{tobacco + cannabis}$	-	-	0.14
Rg	-	0.59	-
Rc	-	-	-
Re	-	0.73	-
Reg. Tobacco → Cannabis	0.91[#]	-	-
$t1_{tobacco}$	−0.18	−0.21	0.55
Sex on Tobacco	0.32	0.33	0.26
Age on Tobacco	0.08	0.13	0.04
$t1_{cannabis}$	−0.28	−0.32	0.39
Sex on Cannabis	0.23	0.24	0.09
Age on Cannabis	0.04	0.08	−0.05
$t1_{tobacco + cannabis}$	-	-	0.26
Sex on Tobacco + Cannabis	-	-	0.26
Age on Tobacco + Cannabis	-	-	0.11

[#]The Cannabis → Reg. Tobacco path was 0.81 in the Cannabis causes Tobacco use model.