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Multiple substance use among young males ☆

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Abstract

Neurobiological studies hypothesize a common final pathway of addictive behavior in the mesolimbic dopaminergic system. Nicotine has been shown to sensitize the reward pathway, thereby causing increased drug-seeking behavior. Since there is evidence to suggest that nicotine, alcohol and other psychoactive substances act on the same final pathway and seem to augment their effects in animal subjects, drug intake behavior of humans would likely be reflected in increased substance use of nicotine-dependent persons. We used biological markers of substance use as well as questionnaires to assess the levels of psychoactive substance use among 18-year-old males in a naturalistic cross-sectional setting. We found that increasing levels of nicotine dependence were related to higher levels of alcohol abuse and dependence. Furthermore, higher levels of nicotine dependence were associated with elevated levels of recent cannabinoid use.

MESH-Keywords: Tobacco Dependence; Illicit Drugs; Alcohol Abuse; Alcohol Dependence; Illicit Drug Testing; Adolescents; Epidemiology; HSI

1. Introduction

Epidemiological studies have shown that among youth, tobacco smoking and alcohol use, as well as the use of other psychoactive substances, are associated (Merrill et al., 1999; Degenhardt et al., 2001; Wagner and Anthony, 2002). In addition, adolescents' early experiences with alcohol and tobacco have been found to have an influence on the later development of their use of other substances (Sutherland and Willner, 1998; Höfler et al., 1999).

There is growing evidence that human adolescence is a period of increased biological vulnerability to the addictive effects of psychoactive substances. Chambers et al. (2003) suggested that a greater motivational drive in adolescence, together with an immature inhibitory control system, which is a part of the motivational neurocircuitry, could be responsible for impulsive actions and increased novelty-seeking and risk-taking behavior, including the experimental use of drugs. They further suggest that the direct pharmacological effects of psychoactive substances on the dopamine system may be increased during adolescence and lead to permanent neural changes.

Neurobiological studies have located the common basis of addictive behavior in the reward system of the mesolimbic pathways (Balfour and Ridley, 2000; Lingford-Hughes and Nutt, 2003; Nestler, 2005). Laboratory research has shown increased dopamine overflow in the nucleus accumbens after nicotine injections as well as nicotine sensitization of the mesolimbic dopamine system (Corrigall et al., 1994; Balfour et al., 1998; Iyaniwura et al., 2001). Additional findings suggest that other psychoactive substances also sensitize this part of the reward system. This sensitization may lead to drug-seeking behavior and increase the risk of addiction (Pontieri et al., 1996; Robinson and Berridge, 2001). In rodent models it has been shown that, in comparison to adults, adolescent rats and mice are hypersensitive to the reinforcing effects of nicotine (Levin et al., 2003; Adriani et al.,

☆ The procedures described in this work are in compliance with the Declaration of Helsinki on human subjects.

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2006) and less sensitive to nicotine withdrawal. This indicates an unfavorable tendency to pursue positive effects through nicotine use (O'dell et al., 2006). Other laboratory findings suggest that there is evidence for the common, reward system-stimulating properties of ethanol and nicotine (Kunin et al., 1999) and for the potentiating effects of multiple drugs on the reward system. Blomqvist et al. (1996) found that the voluntarily alcohol intake of rats increased after chronic nicotine and amphetamine exposition.

With these neurobiological findings in mind, we hypothesized that persons with high levels of nicotine dependence would also have higher levels of alcohol dependence and tend to use other psychoactive drugs as well. We administered questionnaires and analyzed biological markers of substance use of 1,902 18-year-old males. We examined the interactive effects between tobacco and alcohol dependence as well as the interactions between tobacco dependence and the recent use of cannabinoids, opiates, benzodiazepines, cocaine and amphetamines.

2. Methods

2.1. Research subjects

In Austria, 18-year-old males are required to undergo a medical examination to assess their health status and their psychological and physical ability to perform obligatory National Service. Examinations take place annually. The examination described in this report took place over a time period of ten weeks between March and May of 2002. A sample of 1,902 males was drawn from all 18-year-old Austrian males of an approximately 1,550,000 citizen area (Lower Austria). All 18-year-old males from each of the seven districts in this county were examined.

The districts were selected from three regions, each with different characteristics: (1) rural regions with economically important hard liquor and cider production (low average income, poor access to Vienna); (2) regions with poor access to Vienna, no agrarian alcohol production and low average income; (3) urbanized regions around the capitol of Vienna with viniculture and high average income. The total sample size was 3.8% of all Austrian 18-year-old males in the year 2002.

2.2. Participant study procedure

Approximately 60 persons were examined on each day of the study. Starting at 8.00 a.m., prior to the computer-assisted psychological assessment of the ability to perform service, the males were asked to complete a two-sided pencil-and-paper questionnaire. Approximately 25 males participated in each questionnaire session, which lasted about 10 minutes. Each participant sat at a separate table and the group session was assisted by a psychologist. The groups were assured that the survey was anonymous, that their data would be handled strictly confidentially, and that the responses would have no impact on their National Service assessment. Smoking was not permitted during the examination process, from 8.00 a.m. until the end of tests.

2.3. Biological markers of substance use

During the medical examination, as a matter of annual routine, blood samples were taken from each male and checked for γ-glutamyltransferase (γ –GT, GGT) and mean corpuscular volume (MCV) as markers of alcohol intake. Other parameters like GPT, GOT, glucose, cholesterol, billirubin, triglyceride and creatinine levels were also assessed but are not reported here. These parameters will be available for evaluation in further studies.

In addition to the assessment of self-reports of smoking, a smokerlyser (EC50 Smokerlyser; Bedfont Instruments; Kent, UK) was used to measure the level of carbon monoxide (CO) in exhaled air, higher levels being a standard marker of smoking. Smokers were defined as having CO levels of > 5 ppm, non-smokers as having CO levels of ≤ 5 ppm.

Urine samples were collected and analyzed for illicit drugs at the Clinical Institute of the Medical and Chemical Laboratory Diagnostics in Vienna. The young male subjects were screened for cannabinoids, opiates, cocaine, amphetamines and benzodiazepines. The urine specimens used in illicit drug testing were collected under supervised conditions. Qualitative in-vitro-immunoassays of 1,898 persons were performed with a clinical analyzer (Hitachi 912) and reagents were provided by Microgenics Inc. (CEDIA DAU, Fremont, CA, USA). In accordance with the recommendations of SAMSHA (Substance Abuse and Mental Health Services Administration, Wolff et al., 1999), the following cut-off values were used: 300 ng/ml for opiates, benzodiazepines and cocaine; 1000 ng/ml for amphetamines; and 100 ng/ml for cannabinoids.

2.4. Questionnaires on alcohol and tobacco dependence

As suggested for brief screenings by the Plinius Maior Society (1994), the CAGE questionnaire (Ewing, 1984) and two additional simple questions were used to assess alcohol-related symptoms and reasons for alcohol consumption: (1) 'Do you like the taste of alcohol?' and (2) 'Do you drink alcohol because of its effects? If so, which effect do you aim at?' Five answers were applicable: 'mood', 'to calm down', 'to forget', 'anxiety', 'other'. The use of the CAGE questionnaire in epidemiological surveys is supported by findings of good sensitivity to and specificity of alcohol dependence at a cut-off of >=2 (Chan et al., 1994; Liskow et al., 1995; Bradley et al., 2001; Saremi et al., 2001).

Two questions from the Fagerström Tolerance Questionnaire were used to assess tobacco use and dependence. Both questions (HSI, Heaviness of Smoking Index) have been found to be powerful predictors of nicotine dependence and were validated by plasma and saliva cotinine measurement as well as carbon monoxide (CO) levels (Heatherton et al., 1989, 1991): (1) 'How many cigarettes do you smoke per day?' – possible answers were 'non-smoker,' '10 or less,' '11–20,' '21–30,' and '31 or more' (scored as ns, 0, 1, 2 and 3); and (2) 'When do you smoke your first cigarette in the morning?' – answers: 'within 5 minutes,' '6–30 minutes,' '31–60 minutes,' and 'after more than 60 minutes' (scored between 3 and 0). In accordance with recent findings, a total HSI score of 4 or more is henceforth referred to as high nicotine dependence (Diaz et al., 2005;

Chabrol et al., 2005). An HSI score of 0 to 3 is referred to as mild nicotine dependence.

2.5. Statistical methods

Data analysis was conducted using SPSS 12.0 software (SPSS Inc., Chicago, IL, USA). Out of a total of 1,902, 32 questionnaires on tobacco use and 7 on alcohol consumption were excluded from statistical analysis due to incomplete or contradictory answers. Three of 1,891 MCV measurements were excluded from analysis due to invalid non-physiological values. Spearman correlation coefficients were calculated to assess associations between HSI categories and carbon monoxide levels. A chi-square test was used to compare the psychoactive substance use of smokers and non-smokers. Student's T-test was applied to analyze differences in biological markers between alcohol-abusing and alcohol-dependent subjects. An ANOVA was calculated to assess differences in psychoactive substance use between HSI categories and differences in biological markers of alcohol intake between CAGE categories. All tests were considered significant at the level of $p < 0.05$.

3. Results

3.1. Measures of alcohol use

The mean level and standard error (SE) of GGT among the examined persons was 12.2±0.17 U/l, ranging between 1 and 124 U/l. The 10th, 25th, 50th, 75th, and 90th percentile levels of GGT were 7, 8, 10, 14, and 19 U/l, respectively. Fifty-nine of 1,894 blood samples had GGT levels of ≥ 28 U/l. Sensitivity, when the CAGE cut-off of ≥ 1 was used as a standard, was 3%, specificity 97%.

The mean±SE MCV level of the entire sample was 87.9± 0.07 fl. The levels were 84, 86, 88, 90, and 91 fl, for the 10th, 25th, 50th, 75th, and 90th percentile, respectively. MCV values ranged between 59 fl and 98 fl. Three out of 1,891 MCV measurements were excluded from analysis due to invalid non-physiological values (8 fl, 14 fl, and 25 fl). Only one of 1,891 blood samples had a MCV of ≥ 98.0 fl. Sensitivity, when a CAGE cut-off of ≥ 1 was used as a standard, was 0.4%, specificity 99%. In total, 287 persons (15.1% CI: 13.5–16.8) had one or more, and 60 (3.2%, CI: 2.4–4.0) persons had two or more positive responses to CAGE questions. 70.5% of all examined males reported 'liking the taste of alcohol' and 29.1% (CI: 27.1–31.2) reported 'drinking alcohol because of its effects'. The conditions that participants most desired to modulate were 'mood' (27.8%, CI: 25.8–29.8) and 'anxiety' (2.4%, CI: 1.7–3.1). No significant differences were found between CAGE categories (0, 1, 2, 3, 4) in ANOVA for MCV $F(4, 1885)=0.555$, $p=0.696$ and GGT $F(4, 1888)=0.414$, $p=0.799$.

Table 1
Comparison of alcohol abuse and dependence, cannabinoids and opiate use between Smokers and Non-smokers defined by carbon monoxide levels (CO)

	Smoking status		χ^2	p
	CO ≤ 5 ppm (N=1029)	CO > 5 ppm (N=867)		
	n	n		
CAGE >=1	123	164	17.7	0.000*
CAGE >=2	25	35	4.0	0.047*
Cannabinoids	12	84	71.1	0.000*
Opiates	33	17	2.9	0.092

* significant in Chi-Square Test.

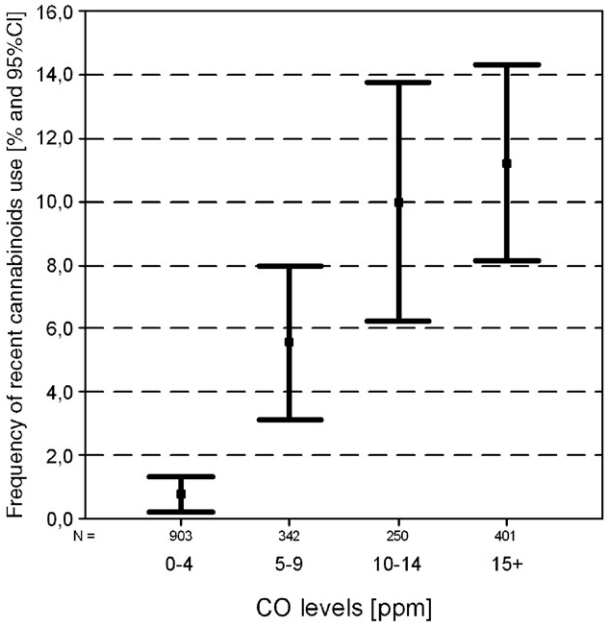

Fig. 1. Recent use of cannabinoids increases with carbon monoxide (CO) levels.

3.2. Measures of tobacco use

It was possible to analyze 1,896 valid CO measurements out of the 1,902 taken. About 54.3% of those examined had a CO level of under 5 ppm. The mean and SE CO levels of the sample were 8.2±0.18 ppm, ranging between 1 and 85 ppm. The 10th, 25th, 50th, 75th, and 90th percentile CO levels were 1 ppm, 2 ppm, 5 ppm, 13 ppm, and 20 ppm. The median CO level was 5 ppm.

Nine-hundred and eight males (48.6%, CI: 46.3–50.8) reported being non-smokers; 817 participants (43.7%, CI: 41.4–45.9) had a low HSI score of between 0 and 3 points and 145 (7.8%, CI: 6.54–8.97) had a high score of 4 to 6 points. The corresponding mean and SE of CO levels were 2.8±0.11 ppm (non-smokers), 12.6±0.25 ppm (HSI 0–3), and 16.9±0.63 ppm (HSI 4–6). The HSI categories significantly correlated in terms of carbon monoxide levels when Spearman's rank correlation test was applied ($r=0.748$ $p=0.000$).

3.3. Urine drug testing

Of all the persons examined, 145 (7.6%, CI: 6.4–8.8) had a positive urine-test for illicit drugs. 5.1% (CI: 4.1–6.0) had a positive urine test for cannabinoids. The second most prevalent illicit drug category was opiates with 2.7% (CI: 1.9–3.3). The prevalence of other illicit substances (cocaine, amphetamines and benzodiazepines) was under 0.5%.

Table 2
Nicotine dependence levels (HSI) and corresponding frequency (%) of alcohol abuse and dependence as well as recent cannabinoids and opiates use

		HSI categories							F	p
		0	1	2	3	4	5	6		
	n	220	130	233	234	90	38	16		
CAGE >=1	%	10,5	14,6	21,5	23,9	20	39,5	37,5	5,12	<0,0001*
	95%CI	(6,4;14,5)	(8,5;20,8)	(16,1;26,8)	(18,4;29,4)	(11,6;28,4)	(23,2;55,8)	(10,9;64,1)		
CAGE >=2	%	5,5	4,6	7,7	8,5	8,9	15,8	50,0	3,65	0,001*
	95%CI	(1,1;9,8)	(−0,6;9,8)	(2,7;12,7)	(3,3;13,8)	(0,2;17,6)	(−2,2;33,8)	(2,3;97,7)		
Cannabinoids	%	5,9	4,6	11,2	9,8	8,8	23,7	18,8	3,16	0,005*
	95%CI	(2,8;9)	(1,0;8,3)	(7,1;15,2)	(6;13,7)	(2,9;14,7)	(9,5;37,8)	(−2,7;40,2)		
Opiates	%	1,4	1,5	3,0	2,1	3,3	0	12,5	1,76	0,105
	95%CI	(−0,2;2,9)	(−0,6;3,7)	(0,8;5,2)	(0,3;4,0)	(−0,4;7)	(0;0)	(−5,7;30,7)		

* significant in ANOVA at 0,05 level.

3.4. Multiple drug use - Interactions

Table 1 shows the difference between smokers and non-smokers in terms of other substance use. Accordingly, persons with CO levels of > 5 ppm were significantly more often abusing alcohol (CAGE ≥ 1), or were alcohol-dependent (CAGE ≥ 2) than persons with a low CO level of ≤ 5 ppm. Also, persons with high CO levels had cannabinoids in their urine samples significantly more often than those with low CO levels. Interestingly, smokers and non-smokers as defined by CO levels showed no differences in opiate use.

The correlations between cannabinoid-positive urine tests and CO level categories are shown in Fig. 1. The corresponding mean percentage of positive urine tests for each CO category was 0.8%, 5.5%, 10.0%, and 11.2%, respectively. The differences between categories were significant in ANOVA $F(3,1895)=27.4$, $p=0.000$.

The categories of the HSI (Table 2) show different levels of alcohol abuse and dependence. Persons with low HSI scores are generally more likely to abuse alcohol or be alcohol dependent than those with low HSI scores. Alcohol abuse (CAGE ≥ 1) was found 3.6 times more often in those with the highest HSI score (6) than in those with a low HSI (0). This ratio was even greater (9.1) for alcohol dependence (CAGE ≥ 2). Similarly, the percentage of cannabinoid-positive urine specimens significantly increased with higher levels of nicotine dependence. The ratio between a high (6) and low (0) HSI score was 3.2 for cannabinoids. The differences between HSI categories in terms of opiate use were not significant.

4. Discussion

The aim of this study was to cast light on the association between nicotine dependence and other psychoactive substance use. We focused on a representative young male population, selected from regions with different characteristics of average income, level of rurality and local alcohol production. To assess psychoactive substance use, we used well-adapted questionnaires, standard markers of tobacco and alcohol use, and illicit drug tests.

The CAGE questionnaire has been previously used in epidemiological surveys and is supported by good sensitivity to and specificity of alcohol dependence at a cut-off of >=2 (Chan et al., 1994; Liskow et al., 1995; Bradley et al., 2001; Saremi et al., 2001). A cut-off of >=1 is considered to indicate alcohol abuse or problem drinking (Malet et al., 2005; Agabio et al., 2006). State markers of alcohol use (GGT, MCV) showed a strongly Gaussian distribution in the sample. However, the cut-off values of GGT (28 U/l) and MCV (98 fl), as suggested by the laboratory, do not seem to be useful as markers of alcohol abuse in a general population of 18-year-old males. Due to the low sensitivity of GGT and MCV, our study supports other findings of low usability of these markers for screening a young population (Savola et al., 2004). Therefore, we suggest reconsidering the cut-off values of standard alcohol markers for youth. Further studies may develop appropriate cut-off values for alcohol abuse and dependence in youth on the basis of our representative healthy population data.

Carbon monoxide measured in breath is used as a standard in determining tobacco dependence (Fagerström and Schneider, 1989). Our results confirm previous correlations found between carbon monoxide and HSI responses (Kozlowski et al., 1994). The HSI has recently been found to be a valid measure of nicotine dependence (Chabrol et al., 2005). Each of the HSI scores (0–6) represents a certain degree of nicotine dependence. Diaz et al. (2005) analyzed the specificity and sensitivity of the HSI questionnaire and defined an optimal cut-off of >=4 for high nicotine dependence with scores below 4 indicating low nicotine dependence.

To distinguish smokers from non-smokers, it has been suggested to use a CO cut-off of greater than 5 ppm for military staff (Low et al., 2004). We could show that smokers with CO levels of over 5 ppm are about two times more often alcohol dependent and abuse alcohol significantly more frequently, than non-smokers. Similarly, we found that recent use of cannabinoids is more frequent among smokers than non-smokers. We could also show that cannabinoid-positive urine tests gradually increase with CO levels in breath. Interestingly, no significant difference between smokers and non-smokers was found regarding opiate use. This result may be due to the statistically low number of opiate-positive urine tests in this sample.

Epidemiological findings have repeatedly shown that alcohol abuse and dependence are more common among smokers and nicotine-dependents (Sutherland and Willner, 1998; Merrill et al., 1999; John et al., 2003). These findings are supported by

our results derived from the combination of a biological marker of tobacco use (carbon monoxide) and the CAGE questionnaire. More frequent cannabinoid use among smokers has been shown in previous epidemiological studies (Merrill et al., 1999; Degenhardt et al., 2001; Richter et al., 2002), but the novelty of our findings lies in the fact that this association was confirmed not only by questionnaires but also by biological markers (carbon monoxide and cannabinoids in urine) in a naturalistic epidemiological setting.

Of course, a simple association of two parameters in research (e.g. cannabis use and other illicit drug use) is not enough to draw conclusions about causality. The complex phenomenon of the cause of psychoactive substance dependence has to be discussed in terms of genetic vulnerability as well as psychological and social factors.

However, to establish more precise causal relationships between two measures in etiologic studies, the use of causal contrast models has been suggested (Maldonado and Greenland, 2002). In our study, HSI-defined tobacco dependence was used as such a causal contrast. We could show that increasing levels of nicotine dependence are associated with gradually higher levels of alcohol abuse and dependence, as well as higher levels of recent cannabinoids use. A limitation of this association is the HSI's decreasing sensitivity with increasing scores and decreasing specificity with decreasing scores (Diaz et al., 2005). A causal contrast model was also used to examine the association between CO levels and cannabinoids in urine. Similarly, cannabinoids in urine gradually increased with CO levels.

These findings are supported by neurobiological studies that have shown the influence of nicotine on the dopaminergic rewarding pathways (Balfour et al., 1998; Iyaniwura et al., 2001; Brody et al., 2004) and the common effects of other psychoactive substances on the reward system (Blomqvist et al., 1996; Kunin et al., 1999). Some researchers hypothesize that the incentive sensitization of the reward system seems to modify the neurobiological substrate and therefore leads to increased drug craving (Robinson and Berridge, 2001). This may result in increased experimental drug use during a period of life in which individuals are biologically more vulnerable to addictive drug effects (Chambers et al., 2003). We conclude that with increasing nicotine dependence, which reflects the grade of vulnerability of the reward system, other psychoactive substances play an increasing role in the behavior of youth. Biederman et al. (2006) found youth with ADHD to be at a greater risk of progressing from tobacco use to the use of other psychoactive substances. They suggest that preexisting dopaminergic abnormalities associated with ADHD may have an influence on the rewarding properties and increase vulnerability to developing alcohol and drug use disorders after initial tobacco use. In an animal study, Adriani et al. (2006) confirmed that pre-exposure to nicotine during adolescence leads to increased vulnerability to later nicotine dependence. Thus, one may more accurately speak of a 'neurochemical gateway effect' (Kelley and Rowan, 2004) or 'pharmacological priming' (Collier, 2006) than of a 'gateway drug'.

Of course, besides dopamine, other transmitters like opioids, glutamate, cannabinoids, 5-HT, and deeper molecular structures including genes, are involved in the reward system (Balfour and Ridley, 2000; Lingford-Hughes and Nutt, 2003; Manzanares et al., 2005). Nonetheless, psychosocial influences of the environment in terms of family or peers, comorbidity with psychiatric disorders, and the influence of the availability and cost of psychoactive substances, are confounding factors in psychoactive substance use. Due to the large and representative sample we used, these factors may have had less impact on our results, but we do not know to what extent they may have altered them. A replication of this study accounting for such confounding factors is required in the future. There are also other limitations of this study: The questionnaires used herein were selected due to time restrictions because of their shortage, and although validated, they do not reflect the state of the art in epidemiological research on nicotine and alcohol prevalence. Other instruments such as FTND, AUDIT and MAST and structured interviews (CIDI or SCID) should be used in a future replication of the study.

In summary, our results may support previous findings of the potentiating and common effects of multiple substance use, but they do so, on the basis of both questionnaires and biological markers of psychoactive substance use, which represents a novel approach. We could cast light on the usability of common biological markers and replicate the association between tobacco, alcohol and cannabinoids by causal contrasts. We suggest that tobacco dependence is an important factor that increases vulnerability of youth to the addictive effects of alcohol and the use of cannabinoids. Further studies might focus on the genetic aspects of, and environmental influences affecting, psychoactive substance use. However, there is now already sufficient evidence of the rising worldwide problem of youth tobacco smoking (Centers for Disease Control and Prevention, 2006). Therefore, our primary aim should be to reduce youth smoking.

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