Violations of the Usual Sequence of Drug Initiation: Prevalence and Associations With the Development of Dependence in the New Zealand Mental Health Survey*

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ABSTRACT. Objective: For 3 decades, studies have reported that the usual sequence of drug initiation is licit drugs, then cannabis, and then other illicit drugs. This article describes the prevalence of violations of this sequence, the predictors of violations, and the relationship between violations and the onset of alcohol or drug dependence. **Method:** The New Zealand Mental Health Survey is a nationally representative sample with 12,992 face-to-face interviews carried out in 2003-2004. The response rate was 73.3%. The World Health Organization Composite International Diagnostic Interview (CIDI 3.0) was used in the survey. Reports of the age at first use were obtained for alcohol and drugs but not for smoking. **Results:** Violations of the usual sequence of drug initiation were uncommon in the population (2.6%). Use of other illicit drugs

before cannabis was the main violation, found in 2.3% of alcohol users, 3.0% of cannabis users, 8.6% of cocaine users, and 16.7% of those who had used other illicit drugs. Use of other illicit drugs before cannabis was more predominant in younger cohorts and those with more early-onset internalizing disorders. Violations had little association with the development of dependence in users when other important predictors such as age at onset of use and the number of illicit drugs used were taken into account. Internalizing disorders and early-onset bipolar disorder also predicted dependence. **Conclusions:** In New Zealand, violations of the gateway sequence are not common and they are not markers of progression to dependence. (*J. Stud Alcohol Drugs* 69: 789-795, 2008)

NUMEROUS STUDIES OF THE SEQUENCE of drug use initiation have shown that tobacco and alcohol are the first drugs used, followed by cannabis, and then by other drugs (Ellickson et al., 1992; Morral et al., 2002). Much attention has been focused on Kandel's "gateway" hypothesis, which proposes that the observed sequence from licit drugs (alcohol and tobacco) to cannabis to other illicit drugs is a causal one, with use at each stage increasing the proportion of users going on to the next stage (Kandel and Faust, 1975; Kandel et al., 1992; Yamaguchi and Kandel, 1984). In the decades since the first articles on the gateway hypothesis appeared, there have been marked changes in drug markets (Degenhardt et al., 2000; Johnson and Gerstein, 1998), yet

the gateway sequence has still been observed in most studies (Ellickson et al., 1992; Fergusson et al., 2006; Fergusson and Horwood, 2000), even though the mechanism has not been determined (Fergusson et al., 2006).

Many studies of the gateway hypothesis have been longitudinal, as is appropriate to investigate the issue of causality. Nonetheless, because these studies have involved cohorts born in a single year (Fergusson et al., 2006; Fergusson and Horwood, 2000) or a narrow range of years (Ellickson et al., 1992; Kandel et al., 1992), they have been unable to compare birth cohorts to see the consequences of the changes in drug availability in the past 50 years. Also, few longitudinal studies are large enough to look at those people who violate the usual sequence of drug use.

Sequence violations have been found to be more common in studies of disadvantaged or deviant groups than in the unselected samples referenced here. Mackesy-Amity et al. (1997) found that 67% of serious drug users did not report the usual sequence of alcohol, marijuana, and then other drugs. Golub and Johnson (1994) found that, in about half of the serious drug users they studied, cannabis was the first drug, with some not progressing to use of alcohol. Unusual drug pathways have also been reported for homeless youth (Ginzler et al., 2003) and delinquent boys (Young et al., 1995). These findings suggest that people whose sequence of drug initiation deviates from the usual course may be at higher risk of developing dependence.

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Associations between sequence violations and the development of dependence have been investigated in a recent article from the National Comorbidity Survey Replication (Degenhardt et al., 2008b), an adequately large community sample of the United States. Overall, only 5% of the population reported any sequence violation, with most of these being the use of other illicit drugs before cannabis. Violations were not strongly associated with the risk of dependence.

The New Zealand Mental Health Survey (Oakley Browne et al., 2006; Wells et al., 2006b) provides an opportunity to investigate sequence violations in another large community sample in a country with sufficient use of alcohol and drugs to detect violations. Comparison of the studies of drug use in these two countries (Degenhardt et al., 2007c; Wells et al., in press) shows similar lifetime use of alcohol (New Zealand = 94.6%, United States = 92.0%) and cannabis (New Zealand = 41.6%, United States = 42.7%) but much less use ever of cocaine in New Zealand (4.2%; United States = 16.4%). In New Zealand, the median age at onset for those younger than 65 years of age was lowest for alcohol, followed by cannabis, and it was highest for cocaine.

This article investigates sequence violations in the initiation of drug use on the basis of data from the New Zealand Mental Health Survey. The aims are to (1) document the extent of various types of violation of the sequence of drug initiation, both as population prevalences and as prevalences among users of particular drugs; (2) predict each type of violation from sociodemographic characteristics and early-onset mental disorders; and (3) investigate whether violation of the usual sequence for a drug predicts the onset of dependence, taking account of sociodemographic characteristics, early-onset mental disorder, age at onset of use, and time since onset.

Method

The New Zealand Mental Health Survey was a face-to-face survey carried out in 2003-2004 (Wells et al., 2006a,b). Permission was granted by all 14 regional health ethics committees and written informed consent was obtained from all participants.

Sample

A multistage probability sample was taken. The primary sampling units were 1,320 small census units called meshblocks, which were systematically sampled throughout the whole country. Meshblocks mostly contain 40-70 households. Households were selected within each meshblock, and then one person age 16 years or older was selected per household, using a Kish grid (Kish, 1965). The response rate was 73.3%, resulting in a sample size of 12,992.

Measurement of the age at initiation of drug use

All participants were asked if they had ever used any of these substances: alcohol; cannabis; cocaine; prescription drugs (not used as prescribed or used without prescription); opioids; or any other drugs such as glue, LSD (lysergic acid diethylamide), and peyote. If they answered positively, they were asked to give the age at which they first used the substance. Participants were asked if they were or had ever been smokers, but they were not asked at what age they first used tobacco.

Definitions of violations of the usual sequence of drug initiation

Three types of violation of the usual sequence of drug initiation were defined as follows: (1) first use of cannabis before alcohol and never being a smoker; (2) first use of another illicit drug (cocaine, prescription drugs, opioids, glue, LSD, or other illicit drugs) before alcohol and never being a smoker; and (3) first use of another illicit drug before cannabis.

These three types of violation are not mutually exclusive. A violation was counted even if the drug expected later in the sequence was never used. Because the age at onset for first use of tobacco was not obtained, the more stringent requirement of never being a smoker had to be used to assess a violation, instead of considering only the relative ages of first use.

Violations were investigated for each of four overlapping groups of drug users: alcohol, cannabis, cocaine, and other illicit drugs.

Diagnostic assessment

Lifetime diagnoses of internalizing, externalizing, and substance-use disorders according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR; American Psychiatric Association, 2000), were based on responses to the World Health Organization Composite International Diagnostic Interview (CIDI 3.0), a fully structured lay interview presented from a laptop computer (Kessler and Üstün, 2004).

Internalizing disorders included specific phobia, social phobia, panic disorder, agoraphobia, generalized anxiety disorder, major depressive disorder or dysthymic disorder, and posttraumatic stress disorder. A count of the number of these disorders before age 16 was calculated (range: 0-7).

The only externalizing disorder assessed was bipolar disorder. A broad definition was used including bipolar I, bipolar II, and subthreshold such as hypomania without a major depressive episode (Kessler et al., 2006). Onset was determined from the first episode of mania or hypomania. Onset before age 16 counted as early onset (a 0/1 variable).

For substance-use disorders, alcohol disorder was assessed separately from drug disorder. For alcohol dependence and drug dependence, there was gating for entry to dependence; only those reporting ever having at least one abuse symptom were routed on to the dependence questions.

Statistical analysis

All analyses used weights because of differences in the probability of selection of households and the probability of selection within a household (only one person per household); nonresponse; and poststratification by age, gender, and ethnicity to the 2001 Census of Population and Dwellings (www.stats.govt.nz/census/2001-census-data/default.htm). Analyses were carried out in SUDAAN Version 9 using Taylor series linearization methods to take account of weighting and the complex survey design (Research Triangle Institute, 2004).

After estimation of the proportion of users of each drug who reported each type of violation of the usual sequence of drug initiation, prediction of violation was carried out using joint logistic regression models including age at interview (birth cohort), gender, number of early-onset internalizing disorders, and early-onset externalizing disorder (before age 16). To have at least 10 events per predictor (Harrell et al., 1996), logistic regression models were fitted only for those violations with more than 60 violators.

The onset of dependence among drug users was modeled using discrete-time survival models. For each drug, data were converted from individual records into a person-years format and analyzed by logistic regression (Efron, 1988), again including all predictors in each model. This discrete-survival procedure permits the use of time-dependent covariates: years since the onset of use, whether alcohol had ever been used, and the number of other drugs that had ever been used. Fixed covariates were age at interview (birth cohort), gender, age at onset of drug use, and the presence or absence of violations. The odds ratios (ORs) reported are for the first onset of dependence in a year.

Results

The prevalence of violations in the population is presented in Table 1. Violations were quite uncommon, with only 2.6%

of the participants having any violation. The least common violation was the use of illicit drugs (other than cannabis) before alcohol and without becoming a smoker (0.1%). The use of cannabis before alcohol and without becoming a smoker was slightly more common in younger age groups ($\chi^2 = 24.9$, 3 df, $p < .0001$), as expected from the increasing availability of cannabis. Other drugs must also have become more available, because their use before cannabis was also a little more common in younger age groups ($\chi^2 = 8.3$, 3 df, $p = .04$).

A sensitivity analysis was carried out to see the possible impact of not knowing the age at onset of tobacco use. Table 1 provides conservative estimates of the first two violations (illicit before licit) by requiring that individuals had never been smokers. Ignoring smoking provides upper limits for these violation prevalences. The upper limit estimate obtained by ignoring smoking was 1.9% overall for the prevalence of cannabis use before alcohol use; this was clearly age related (16-24 years = 3.8%, 24-44 years = 2.7%, 45-64 years = 0.8%, ≥ 65 years = $<0.1\%$). The upper limit estimate for the use of other illicit drugs before alcohol was very low (0.4% overall and 0.3%, 0.7%, 0.2%, and 0.2% for 16-24 years, 24-44 years, 45-64 years, and ≥ 65 years, respectively). Thus, even these unrealistic upper limits, which would have all smokers starting smoking after use of cannabis or other illicit drugs, still show it is uncommon to use illicit drugs before licit drugs in New Zealand.

A particular violation could be rare in the population but nonetheless much more common among users of a particular drug or drug group. Therefore, Table 2 presents the violations for each group of drug users. Because most participants had used alcohol, the results for alcohol users are very similar to those in Table 1 for the population. Only 3.8% of cannabis users had any violation. In New Zealand, cocaine comes late in the sequence of drug use; use of cocaine seldom accounted for use of other illicit drugs before cannabis (not shown in Table 2). Among users of illicit drugs other than cannabis or cocaine, there was some use of other illicit drugs before use of cannabis (16.7%). About half of this group had not proceeded to use cannabis by the time of interview (only 160 of the cannabis users had used other

TABLE 1. Prevalence of each gateway violation (V), by age cohort and overall ($N = 12,992$)

Gateway violation	Age 16-24 ($n = 1,535$)		Age 25-44 ($n = 5,304$)		Age 45-64 ($n = 3,909$)		Age ≥ 65 ($n = 2,244$)		Total ($n = 12,992$)	
	% (SE)	n	% (SE)	n	% (SE)	n	% (SE)	n	% (SE)	n
Cannabis before alcohol, no smoking, V1	0.6 (0.2)	12	0.5 (0.1)	25	0.2 (0.1)	6	0.0 (0.0)	≤ 5	0.4 (0.1)	43
Other illicit drugs before alcohol, no smoking, V2	0.2 (0.1)	≤ 5	0.1 (0.0)	12	0.0 (0.0)	≤ 5	0.0 (0.0)	≤ 5	0.1 (0.0)	22
Other illicit drugs before cannabis, V3	2.3 (0.5)	31	2.7 (0.3)	165	1.9 (0.2)	88	1.6 (0.4)	37	2.2 (0.2)	321
Any of these violations, V1, V2, or V3	2.8 (0.5)	42	3.2 (0.3)	190	2.0 (0.3)	94	1.6 (0.4)	37	2.6 (0.2)	363

TABLE 2. Prevalence of each gateway violation among each drug user group, by age cohort and overall ($N = 12,992$)

User group/gateway violation	Age 16-24		Age 25-44		Age 45-64		Age ≥ 65		Total	
	% (SE)	<i>n</i>	% (SE)	<i>n</i>	% (SE)	<i>n</i>	% (SE)	<i>n</i>	% (SE)	<i>n</i>
Among alcohol users ($n = 12,033$)										
Cannabis before both: V1 ^a	0.5 (0.2)	10	0.5 (0.1)	22	0.2 (0.1)	≤ 5	0.0 (0.0)	≤ 5	0.3 (0.1)	37
Other illicit drugs before both: V2 ^a	0.2 (0.1)	≤ 5	0.1 (0.0)	7	0.0 (0.0)	≤ 5	0.0 (0.0)	≤ 5	0.1 (0.0)	13
Other illicit drugs before cannabis: V3	2.5 (0.5)	31	2.8 (0.3)	161	1.9 (0.3)	86	1.7 (0.4)	35	2.3 (0.2)	313
Any of these	2.9 (0.6)	40	3.3 (0.3)	183	2.1 (0.3)	91	1.7 (0.4)	35	2.7 (0.2)	349
Among cannabis users ($n = 5,292$)										
Cannabis before both: V1 ^a	1.2 (0.5)	12	0.9 (0.2)	25	0.5 (0.2)	6	0.0 (0.0)	0	0.9 (0.2)	43
Other illicit drugs before both: V2 ^a	0.3 (0.3)	≤ 5	0.1 (0.0)	≤ 5	0.0 (0.0)	≤ 5	0.0 (0.0)	≤ 5	0.1 (0.1)	6
Other illicit drugs before cannabis: V3	3.0 (0.8)	16	3.0 (0.4)	102	2.9 (0.6)	38	5.2 (2.6)	≤ 5	3.0 (0.3)	160
Any of these	3.9 (0.8)	27	3.9 (0.4)	127	3.4 (0.6)	44	5.2 (2.6)	≤ 5	3.8 (0.3)	202
Among cocaine users ($n = 520$)										
Cannabis before both: V1 ^a	0.1 (0.1)	≤ 5	0.4 (0.3)	≤ 5	1.9 (1.8)	≤ 5	0.0 (0.0)	0	0.7 (0.5)	≤ 5
Other illicit drugs before both: V2 ^a	0.0 (0.0)	≤ 5	0.2 (0.2)	≤ 5	0.0 (0.0)	≤ 5	0.0 (0.0)	0	0.1 (0.1)	≤ 5
Other illicit drugs before cannabis: V3	5.9 (4.5)	≤ 5	9.8 (2.0)	34	6.3 (2.4)	9	100.0 (0.0)	≤ 5	8.6 (1.5)	49
Any of these	6.0 (4.5)	≤ 5	10.2 (2.0)	36	8.2 (3.0)	10	100.0 (0.0)	≤ 5	9.3 (1.6)	53
Among other illicit drugs users ($n = 1,714$)										
Cannabis before both: V1 ^a	0.8 (0.7)	≤ 5	0.5 (0.2)	6	0.7 (0.7)	≤ 5	0.0 (0.0)	≤ 5	0.6 (0.2)	9
Other illicit drugs before both: V2 ^a	0.9 (0.7)	≤ 5	0.5 (0.2)	12	0.3 (0.2)	≤ 5	2.9 (2.3)	≤ 5	0.6 (0.2)	22
Other illicit drugs before cannabis: V3	12.5 (2.5)	31	14.2 (1.4)	165	20.8 (2.7)	88	96.3 (3.7)	37	16.7 (1.2)	321
Any of these	12.5 (2.5)	32	14.7 (1.4)	171	21.5 (2.6)	89	96.3 (3.7)	37	17.1 (1.2)	329

^a"Before both" means "before alcohol and never having been a smoker."

illicit drugs first, whereas 321 reported use of other illicit drugs before cannabis).

Those who had used any illicit drug before using alcohol and tobacco predominantly used cannabis, especially those in the youngest age group (Table 3).

The only gateway violation common enough to model was the use of other illicit drugs before cannabis or without going on to use cannabis (Violation 3). Age cohort, gender, and early-onset bipolar disorder did not predict this violation, but it was more common among those with more early-onset internalizing disorders (OR = 1.4 for each additional disorder; Table 4).

Subsequent analyses investigate whether gateway violations were associated with the onset of dependence among users (Table 5). The models included other likely predictors of onset of dependence.

The ORs found for the prediction of alcohol dependence among alcohol users were similar to those for the prediction of drug dependence for each group of drug users. Older participants, who were therefore from earlier birth cohorts, were less likely to progress from use to dependence, particularly if they were age 65 years or older. Female users were approxi-

mately half as likely as men to develop dependence. The risk of dependence was higher among those in whom the more early-onset internalizing disorders had been experienced (OR = 1.5-1.8), and it was more than threefold higher in those with early-onset bipolar disorder, the only externalizing disorder measured. The later the first use of alcohol was, the lower the risk of alcohol dependence (OR = 0.4); the same pattern was seen to an even more marked extent for drug use and drug dependence (OR = 0.1-0.1). Furthermore, the risk was lower for each year following first use that a person had not developed dependence, although this reduction (OR = 0.7-0.9) was less than that for delay in first use. Among

TABLE 4. A model predicting who used other illicit drugs before cannabis ($N = 12,992$)

Variable	Other illicit drugs before cannabis, V3
Age cohort	
16-24, OR (95% CI)	1.3 (0.7-2.6)
25-44, OR (95% CI)	1.6 (1.0-2.5)
45-64, OR (95% CI)	1.1 (0.7-1.9)
≥ 65 , OR (95% CI)	1.0 (-)
χ^2 , 3 df	6.1, $p = .11$
Gender	
Female, OR (95% CI)	1.1 (0.9-1.5)
Male, OR (95% CI)	1.0 (-)
χ^2 , 1 df	0.7, $p = .39$
No. of disorders	
Early internalizing, ^a OR (95% CI)	1.4 (1.2-1.6)
Early externalizing, bipolar, ^b OR (95% CI)	0.9 (0.3-2.6)
χ^2 , 2 df	22.0, $p < .0001$

Notes: V = violation. ^aA count of the number of internalizing disorders with onset before 16 years of age out of specific phobia, social phobia, panic disorder, agoraphobia, generalized anxiety disorder, major depressive disorder or dysthymic disorder, and posttraumatic stress disorder (0-7); ^ba 0/1 variable indicating whether there was onset of bipolar disorder before 16 years of age.

TABLE 3. Drugs used among those who used any illicit drugs before alcohol and without being a smoker, by age cohort and overall

Age cohort	<i>n</i>	Cannabis % (SE)	Cocaine % (SE)	Other illicit drugs % (SE)
16-24	14	95.5 (3.5)	0.0 (0.0)	25.4 (17.6)
25-44	34	88.2 (5.8)	2.2 (2.2)	13.8 (6.1)
45-64	10	85.3 (10.9)	0.0 (0.0)	14.7 (10.9)
≥ 65	≤ 5	— ^a	— ^a	— ^a
Total	61	88.0 (4.6)	1.3 (1.3)	18.4 (6.2)

^aToo few observations to estimate.

TABLE 5. Risk factors for the first onset of alcohol or drug dependence in each group of drug users (discrete survival models with all predictors)

Variable	Among alcohol users (<i>N</i> = 12,033) Alcohol dependence	Among cannabis users (<i>n</i> = 5,292) Drug dependence	Among other illicit drug users (<i>n</i> = 1,714) Drug dependence
Age cohort, baseline ≥ 65			
16-24, OR (95% CI)	3.3 (1.7-6.4)	24.0 (7.3-79.2)	18.1 (2.3-143.4)
25-44, OR (95% CI)	1.6 (0.8-3.0)	17.5 (5.8-52.9)	14.9 (2.3-98.3)
45-64, OR (95% CI)	1.6 (0.8-3.0)	11.1 (3.4-36.0)	8.3 (1.1-62.8)
χ^2 , 3 df	28.0, <i>p</i> < .0001	29.4, <i>p</i> < .0001	13.3, <i>p</i> = .004
Gender			
Female, OR (95% CI)	0.4 (0.3-0.6)	0.5 (0.4-0.7)	0.6 (0.4-0.9)
χ^2 , 1 df	42.4, <i>p</i> < .0001	16.6, <i>p</i> < .0001	6.6, <i>p</i> = .01
Use			
Alcohol, ^a OR (95% CI)	—	3.9 (1.1-13.7)	2.6 (0.4-15.9)
χ^2 , 1 df	—	4.7, <i>p</i> = .03	1.1, <i>p</i> = .30
Age at onset			
Relevant drug, ^b OR (95% CI)	0.4 (0.3-0.6)	0.1 (0.1-0.2)	0.1 (0.1-0.3)
χ^2 , 1 df	25.9, <i>p</i> < .0001	61.2, <i>p</i> < .0001	36.7, <i>p</i> < .0001
No. of years since			
Age at 1st use, ^{a,b} OR (95% CI)	0.9 (0.9-0.9)	0.8 (0.7-0.8)	0.7 (0.7-0.8)
χ^2 , 1 df	160.2, <i>p</i> < .0001	137.2, <i>p</i> < .0001	83.1, <i>p</i> < .0001
Violation			
Cannabis before both, ^c OR (95% CI)	0.6 (0.1-3.2)	0.1 (0.0-0.3)	0.3 (0.0-2.3)
Other illicit drugs before both, ^c OR (95% CI)	0.8 (0.1-6.7)	15.2 (2.4-96.6)	2.1 (0.1-31.6)
Other illicit drugs before cannabis, OR (95% CI)	1.5 (0.9-2.5)	0.4 (0.2-0.8)	0.5 (0.2-1.4)
χ^2 , 3 df	2.4, <i>p</i> = .50	32.2, <i>p</i> < .0001	4.3, <i>p</i> = .23
No. of illicit drugs used ^a			
4, OR (95% CI)	11.3 (5.5-23.4)	45.9 (23.9-88.2)	51.0 (6.0-431.7)
3, OR (95% CI)	10.8 (6.5-17.9)	23.1 (14.6-36.4)	22.9 (2.9-182.6)
2, OR (95% CI)	7.7 (5.3-11.0)	7.3 (4.8-11.2)	7.0 (1.0-49.5)
1, OR (95% CI)	4.5 (3.4-6.0)	1.0 (—)	1.0 (—)
0, OR (95% CI)	1.0 (—)	—	—
χ^2 , 4 df	156.7, <i>p</i> < .0001	234.9, <i>p</i> < .0001	54.2, <i>p</i> < .0001
No. of disorders			
Early internalizing, ^d OR (95% CI)	1.8 (1.6-1.9)	1.6 (1.4-1.8)	1.5 (1.2-1.7)
Early bipolar, ^e OR (95% CI)	3.1 (2.2-4.4)	3.4 (2.1-5.5)	3.6 (2.1-6.2)
χ^2 , 2 df	248.6, <i>p</i> < .0001	70.0, <i>p</i> < .0001	37.0, <i>p</i> < .0001

^aA time-dependent variable; ^bthe relevant drug is the drug or drug group listed in the column heading; ^c“before both” means “before alcohol and never having been a smoker”; ^da count of the number of internalizing disorders with onset before 16 years of age out of specific phobia, social phobia, panic disorder, agoraphobia, generalized anxiety disorder, major depressive disorder or dysthymic disorder, and posttraumatic stress disorder (0-7); ^ea 0/1 variable indicating whether there was onset of bipolar disorder before 16 years of age.

alcohol users, violations were unrelated to the development of alcohol dependence; similarly, for other illicit drug users, violations were unrelated to the development of drug dependence. In contrast, among cannabis users, those who had used cannabis before alcohol or had used other illicit drugs before cannabis were significantly less likely to develop drug dependence, whereas use of other illicit drugs before alcohol was associated with higher risk (although this was imprecisely determined and based on very few cases). There is a clear relationship between the number of illicit drugs (or drug groups) used and the development of both alcohol dependence and drug dependence. No results are shown for cocaine users; estimates for the number of illicit drugs were extreme because almost no one was in the baseline category (one illicit drug).

Among cannabis users, the apparent preventive effect of using another illicit drug before cannabis (OR = 0.4) is more than countered by the increased risk associated with using another drug (OR = 7.3 for one more drug, 45.9 for three other drugs). Therefore, the net effect of using one other drug, for instance, and using it before the first use of cannabis would be a threefold increase in the risk of dependence (OR = 2.9) compared with not using that drug.

Discussion

This study shows that, in New Zealand, most users of alcohol, cannabis, and other illicit drugs follow an initiation sequence of alcohol, cannabis, and then other drugs. Even in the youngest age group, fewer than 4% had used an illicit

drug before alcohol, and the drug was usually cannabis. Because of the unavailability of illicit drugs, particularly cannabis, before the 1970s, older people were less likely to have any violations; this illustrates the impact of drug markets on the sequence of drug initiation.

Does violation of the usual sequence of drug initiation matter? The answer is no for the development of alcohol dependence among alcohol users, taking account of other correlates of dependence. Among cannabis users, the apparent preventive effect of using other illicit drugs before cannabis is illusory, as the use of another drug increases the risk of drug dependence, producing a net increase in risk.

The more illicit drugs have ever been used, the higher the risk of alcohol dependence and drug dependence, even taking account of other correlates. However, the extent of use of each drug is not known. Those who use multiple illicit drugs may use more frequently and in larger amounts, and this higher consumption may be the main causal factor. The strong cannabis gateway effects reported by Fergusson et al. (2006), even after controlling for many covariates and unseen fixed effects, were in relation to the extent of use of cannabis, not just whether it was ever used. Nonetheless, genetic studies continue to find support for both correlated liabilities and gateway models (Agrawal et al., 2006). Furthermore, the simulations of Morral et al. (2002) show how apparent gateway effects can be obtained from a nonspecific random propensity to use drugs, which is correlated with opportunity to use drugs and with use of drugs given opportunity.

Results from the National Comorbidity Study Replication in the United States (Degenhardt et al., 2008b) are similar to these results from New Zealand, apart from some differences in the prediction of the onset of dependence. In New Zealand, use of other illicit drugs before cannabis was associated with a decrease in the risk of dependence (OR = 0.4; 95% confidence interval [CI]: 0.2-0.8), whereas in the United States, no such decrease was seen (OR = 1.2; CI: 0.7-2.0). These differences may be the results of the different drug markets in the two countries, such as the use of so-called party drugs, particularly herbal highs. These drugs contain mostly benzylpiperazine (BZP), which has been legal in New Zealand until 2008, although purchase was restricted to those ages 18 or older, whereas BZP has not been legal in the United States.

One concern about the findings on progression to dependence is the likely impact of the gating in the interview whereby at least one symptom of abuse ever was required for entry into the dependence sections (this gating no longer exists in the current CIDI 3.0). Hasin and Grant (2004) showed that alcohol dependence could occur in the absence of abuse. Applying their figures to the lifetime gating in the CIDI indicates that 13.9% of those with lifetime alcohol dependence would have been missed because of gating. (The 34% missed that was quoted by Grant et al. [2007] is not relevant because it concerns current symptoms of abuse in

those with current dependence.) Degenhardt et al. (2007a,b, 2008a) have used data from the U.S. National Epidemiologic Survey on Alcohol and Related Conditions, a survey without gating, to assess the impact for dependence estimates. They did find that imposing gating lowered the 12-month prevalence estimate for alcohol dependence (3.8% down to 2.5%; Degenhardt et al., 2007a) but had little impact on the prevalence for cannabis dependence (Degenhardt et al., 2007b) or cocaine dependence (Degenhardt et al., 2008a), nor were associations with correlates affected. Therefore, although the prevalence of alcohol dependence in New Zealand may be slightly underestimated, it seems unlikely that models of progression from use to dependence will be biased.

The advantage of this survey is that it is large, nationally representative, and covers a range of ages, and hence birth cohorts, over the period when New Zealand changed from a society in which not much other than alcohol and tobacco was available (before the 1970s) to a society in which cannabis is very widely available and a number of other drugs can also be obtained.

There are some major limitations to this study. The first is that the reports of age at onset for use and for symptoms of dependence are retrospective; this is the downside of being able to include such a wide age range in this cross-sectional survey. The second limitation is that assessment of drug dependence is not specific to a particular drug or drug group. Nonetheless, this assessment fits with the DSM-IV definition of dependence, which includes not only subjects who meet criteria for a particular drug but also those with polydrug use (including alcohol), whereby every criterion is met but with different drugs contributing different criteria (American Psychiatric Association, 2000). Also, not requiring each symptom to be attributed to a particular drug makes it easier for users of multiple drugs to respond. The third limitation relates to the possible underdiagnosis of dependence because of "gating," as previously discussed. The fourth limitation is that violations were uncommon, which limited the precision of estimates of their association with progression to dependence. The age at onset of tobacco use was not reported, just whether someone was or ever had been a smoker. Finally, reporting of nonmedical use of prescription drugs or use of other drugs was for use of any drug within those drug groups; therefore no distinction could be made, for instance, between use of glue and use of ecstasy.

In conclusion, violations of the expected gateway sequence of drug use were uncommon in New Zealand, although they were more likely in more recent birth cohorts; when violations did occur, they were not markers of progression to dependence. The number of illicit drugs used was a strong predictor of progression, as was early onset of use. The number of early-onset internalizing disorders was associated with a modest increase in the risk of dependence. Given the prevalence of these disorders, intervention to assist with both the disorder and substance use seems warranted,

as well as broader early interventions to alleviate living situations such as poverty; dysfunctional families; and trauma such as physical abuse, sexual abuse, or violence in the home. The threefold increase in risk of dependence in those with early-onset bipolar disorder indicates the need for early identification and treatment (pharmacological and psychological) for these young people.

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