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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☆

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ABSTRACT

Background: It is unclear whether the normative sequence of drug use initiation, beginning with tobacco and alcohol, progressing to cannabis and then other illicit drugs, is due to causal effects of specific earlier drug use promoting progression, or to influences of other variables such as drug availability and attitudes. One way to investigate this is to see whether risk of later drug use in the sequence, conditional on use of drugs earlier in the sequence, changes according to time-space variation in use prevalence. We compared patterns and order of initiation of alcohol, tobacco, cannabis, and other illicit drug use across 17 countries with a wide range of drug use prevalence.
Method: Analyses used data from World Health Organization (WHO) World Mental Health (WMH) Surveys, a series of parallel community epidemiological surveys using the same instruments and field procedures carried out in 17 countries throughout the world.
Results: Initiation of "gateway" substances (i.e. alcohol, tobacco and cannabis) was differentially associated with subsequent onset of other illicit drug use based on background prevalence of gateway substance use. Cross-country differences in substance use prevalence also corresponded to differences in the likelihood of individuals reporting a non-normative sequence of substance initiation.

☆ Supplementary information for this article is available. Please see Appendix A for more information.

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Conclusion: These results suggest the "gateway" pattern at least partially reflects unmeasured common causes rather than causal effects of specific drugs on subsequent use of others. This implies that successful efforts to prevent use of specific "gateway" drugs may not in themselves lead to major reductions in the use of later drugs.

1. Introduction

Community epidemiological research, concentrated in North America and Oceania, has documented a common sequence of drug use initiation that begins with tobacco and alcohol use, followed by cannabis and then other illicit drugs. This pattern was originally described as the "gateway pattern", with use of an earlier drug in this sequence predicting progression to use of later ones (e.g. cannabis and other drugs) (Grau et al., 2007; Kandel et al., 1986, 1992; Kandel and Faust, 1975; Kandel, 1984; van Ours, 2003; Yamaguchi and Kandel, 1984).

Some commentators have argued that the gateway pattern is due to a causal effect of earlier substance use on use of later substances (Fergusson et al., 2006; Rebellon and Van Gundy, 2006). A variety of pathways have been proposed, some more reductionist than others. One suggestion for a gateway effect of cannabis use on subsequent opioid use, for example, is that cannabis alters the opioid system in the brain, leading to a change in hedonic processing that promotes subsequent opioid use (Ellgren et al., 2007). If true, such causal effects of earlier substances in the gateway sequence on subsequent use of later substances would suggest that efforts to prevent use of specific earlier drugs might help reduce initiation of the later ones. However, the gateway pattern observed in epidemiological data is also consistent with the existence of one or more unmeasured common causes, such as a risk-taking predisposition and latent propensity to use drugs as just one of a range of risk behaviours, rather than a causal effect of earlier gateway drugs (Morral et al., 2002). If common causes account for the gateway pattern, then we would not expect prevention of use of specific earlier drugs in the sequence to cause a reduction in use of later substances. Debate about these possibilities continues (Fergusson et al., 2006; Hall, 2006; Morral et al., 2002; Schenk, 2002).

One approach to investigating this issue that has not been pursued in the past is to examine data on time-space variation in use of drugs earlier and later in the gateway sequence. An analogous approach was presented by Weiss et al. (1988) in their evaluation of cocaine use among hospitalised drug users: cocaine use was strongly related to mood disorder in cohorts studied in 1980–1982, but when cocaine use was more common (1982–1986) the association between mood disorder and cocaine was reduced. Similarly, the association between nicotine dependence and psychiatric disorders has become stronger in more recent US cohorts as smoking has become less common; a pattern that is thought to be related to changes in social norms, such that nicotine dependence is a more powerful marker of "deviance" now than when smoking was much more normative in the past (Breslau et al., 2004). These studies suggest that the association between cocaine and tobacco use and mood disorders may not be a simple causal one; and perhaps that the prevalence of drug use might impact upon associations with other variables. Conversely, if associations between the use of a drug and other outcomes (such as psychiatric disorders or other drug use) were *causal*, we would expect changes in prevalence of one drug to have no impact on *associations* with later outcomes (e.g. cannabis use would remain similarly associated with other illicit drug use, but there would be lower levels of those later outcomes).

The Weiss et al. analysis is compelling: it could be taken to suggest that the pharmacological effects of cocaine were less important in predicting adverse outcomes than sociocultural meanings of use (i.e. a shift from being a rarely used drug, perhaps perceived as dangerous, with those using it high risk-takers; to later use by a considerably larger proportion of the population). This implies that some external (sociocultural) factors influenced changes in prevalence of use, with the difference in prevalence due to reasons that would not be expected to influence the outcomes under study (other than through exposure to cocaine).

This assumption is formalised in the econometric method of *instrumental variables* analysis, in which a causal determinant of a putative risk factor is found, which can be assumed not to have any direct causal effect on an outcome other than through the risk factor (Pearl, 2000). When such an instrument is found, it can be used to estimate the magnitude of the causal effect of the risk factor on the outcome in such a way as to separate out any bias due to reciprocal causation or unmeasured common causes. The classic case in economics was the use of information about forest fires in Northwest USA, and railroad strikes, to influence the price of lumber, which in turn influenced the number of new housing starts. This allowed the effects of economic stimulation on interest rates to be estimated, independent of the effects of the interest rate on economic stimulation (Angrist & Krueger, 2001).

Assuming that time-space variation in the prevalence of drug use results at least in part from instrumental variables, we can study the extent to which variation in use of early "gateway" drugs predicts subsequent change in use of later drugs in the gateway sequence. We know, for example, that US tobacco use dropped dramatically in the 1990s, due to a combination of public education campaigns and aggressive taxation policy, influences that would not be expected to have any direct effect on use of cannabis or other illicit drugs other than through the effect of reducing tobacco use. Was this reduction in tobacco use accompanied by the reduction in use of illicit drugs that would be predicted by the gateway theory? We are unaware of any direct analysis of epidemiological data aimed at answering that question.

We present this type of analysis here. Rather than focus on a single country in a single time period though, we present cross-national comparisons, combining information about between-country differences with information about within-country through-time variation, to examine broad patterns of association. No attempt is made to measure explicit instrumental variables. Instead, we work on the implicit assumption that the time-space variation in prevalence of earlier so-called gateway drugs (alcohol, tobacco and cannabis) reflects factors that would not be expected to influence use of later drugs directly. This makes the comparison of time-space variation useful for making preliminary inferences about the potential effects of interventions to specifically reduce use of drugs early in the "gateway" sequence upon use of drugs later in the sequence.

Cross-national data can provide some information on this issue, as the prevalence of licit and illicit drug use varies dramatically across countries and cultures. If the "gateway sequence" was consistent across diverse countries, this would provide support for a more strongly causal interpretation of the sequence. Alternatively, if there was variation in both levels and associations across countries, this would support the putative influence of other variables on the association. Some limited data exist on this issue. Specifically, two studies in New Zealand (Wells and McGee, 2008) and the United States (Degenhardt et al., 2009) found that violations

of the normative order of substance initiation, although uncommon, were more common among more recent cohorts, who also had a higher prevalence of drug use. They also found that "violating" this sequence was not associated with increased dependence risk. Rather, it was prior cumulative exposure to total drugs, and an earlier onset of initiation, that were significant predictors of transition to dependence. These results argue against the hypothesis that use of *specific* "gateway" drugs has a causal effect on subsequent initiation of use of later ones.

It would be useful to extend these results to a larger set of countries with a wider range of variation in drug use to consider the consistency of the order of initiation of drug use, and observe whether associations between use of one drug and initiation of another are consistently observed. The current paper presents the results of such an extension using the World Health Organization (WHO) World Mental Health (WMH) Surveys, a series of parallel community epidemiological surveys using the same instruments and field procedures that were carried out in 17 countries throughout the world. The aims of this study are to

(1) examine the prevalence of drug use by age 29 years across age cohort and country;
(2) consider if differences in prevalence are associated with differences in associations with drug use later in the "gateway" sequence;
(3) examine whether violations of the "gateway" sequence vary according to age cohort and country differences in prevalence of drug use earlier in the sequence;
(4) examine whether the specific order of initiation of drug use predicts later development of drug dependence.

2. Method

2.1. Sample

WMH surveys were carried out in 7 countries classified by the World Bank (World Bank, 2003) as developing (Colombia, Lebanon, Mexico, Nigeria, Peoples' Republic of China, South Africa, Ukraine) and 10 classified as developed (Belgium, France, Germany, Italy, Japan, Israel, Netherlands, New Zealand, Spain, and United States of America). The total sample size was 85,088, with individual country sample sizes ranging from 2372 (the Netherlands) to 12,992 (New Zealand). The weighted average response rate across countries was 69.9%, with country-specific response rates ranging from 45.9% (France) to 87.7% (Colombia). All surveys were based on probability household samples of adults that were either representative of particular regions of the country (in China, Colombia, Japan, and Mexico) or nationally representative (other countries). Table 1 presents sample characteristics for the WMHS.

All interviews were conducted face-to-face by trained lay interviewers. Each interview had two parts. All respondents completed Part I, which contained core mental disorders, while all Part I respondents who met criteria for any core mental disorder plus a probability sub-sample of approximately 25% of other Part I respondents were administered Part II. The Part II interview assessed correlates, service use, and disorders of secondary interest to the study. The assessment of substance use patterns was included in Part II. The Part II survey data were weighted to adjust for the over-sampling of people with mental disorders and for differential probabilities of selection within households, as well as to match samples to population socio-demographic distributions, making the weighted Part II samples representative of the populations from which they were selected.

Standardised interviewer-training procedures, WHO translation protocols for all study materials and quality control procedures for interviewer and data accuracy were consistently applied across all WMH countries in an effort to ensure cross-national comparability. These procedures are described in more detail elsewhere (Alonso et al., 2002; Kessler et al., 2004; Kessler and Üstün, 2004). Informed consent was obtained before beginning interviews in all countries. Procedures for obtaining informed consent and protecting human subjects were approved and monitored for compliance by the Institutional Review Boards of the organizations coordinating the surveys in each country.

2.2. Measures

Mental and substance disorders were assessed with Version 3.0 of the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI) (Kessler and Üstün, 2004), a fully structured lay-administered interview designed to generate research diagnoses of commonly occurring DSM-IV disorders (American Psychiatric Association [APA], 1994).

Participants were separately asked if they had ever used tobacco, alcohol, cannabis and other illicit drugs. A report of ever using a drug was followed with questions about age of first use ("How old were you the very *first* time you ever smoked even a puff of a cigarette, cigar, or pipe?"; "How old were you the very *first* time you ever drank an alcoholic beverage—including either beer, wine, a wine cooler, or hard liquor?"; How old were you the *first* time you used marijuana or hasish?"; "How old were you the *first* time you used cocaine?"; "How old were you the *first* time you used one or more of the drugs on page Y in your reference book such as heroin, opium, glue, LSD, peyote, or any other drug?"), age-of-onset (AOO) of first regular use, lifetime occurrence of symptoms of abuse/dependence, and AOO of abuse-dependence. Exceptions were that AOO of tobacco use, nicotine dependence and drug dependence were not assessed in Belgium, France, Germany, Italy, the Netherlands, and Spain; AOO of tobacco use and nicotine dependence were not assessed in Japan and New Zealand; nicotine dependence was not assessed in Israel and South Africa.

2.2.1. Order of onset and violations of the gateway progression. Different onset orders, as determined by retrospective age-of-onset reports were evaluated. Violations of the gateway progression were defined as:

Violation 1: First use of cannabis before both alcohol and tobacco.
Violation 2: First use of other illicit drugs (cocaine, heroin, opium, glue, LSD, peyote, or any other drug) before alcohol and tobacco.
Violation 3: First use of other illicit drugs (cocaine, heroin, opium, glue, LSD, peyote, or any other drug) before cannabis.

For countries that did not assess age-of-onset of tobacco use, in order to be a violation that included use of cannabis or other illicit drugs before "both alcohol and tobacco", respondents must have reported either never having used tobacco, with a later age-of-onset of alcohol use; or never having used both tobacco and alcohol prior to use of illicit drugs.

In order to examine whether a less stringent text of the gateway sequence may have produced different results, we examined use of cannabis before *either* alcohol or cannabis use (i.e. before the use of one of these drugs). Although violations of this sort were more common, the pattern of findings was similar (Supplementary Tables 1a, 2a, 3).[1]

2.3. Analysis methods

Cumulative prevalence of drug use and gateway violations by age 29 were estimated for each country and cohort, with standard errors derived using the Taylor series linearisation (TSL) methods implemented in SUDAAN to adjust for the effects of weighting and clustering on the precision of estimates. When p-values are reported or indicated, they are from Wald tests obtained from TSL design-based coefficient variance–covariance matrices ($\alpha = 0.05$; two-tailed). Regression models were then carried out to examine the significance of age cohort associations (defined by interview age 18–29, 30–44, 45–59, and ≥60) with drug use and with each of the three gateway violations within each country.

The associations of the onset of substances earlier in the gateway sequence with the subsequent first onset of the later drug in the sequence were estimated using discrete-time survival analysis with person-year as the unit of analysis within country and controlling for person-year and sex. Person-years were restricted to those ≤29 to make cross-cohort comparisons. Discrete-time survival models pooled across countries were run to include the interaction between use of each gateway drug category and the prevalence of gateway drug use within each country. Covariates included, gender, age cohort, and country. Odds ratios and 95% confidence intervals for the interaction term are presented, to evaluate whether the strength of the association between gateway drug use and initiation of subsequent drugs in the sequence differs according to background prevalence of use within each country.

3. Results

3.1. Cross-national and cohort differences in drug use

Drug use by age 29 years by age group at interview is presented in Table 2 for all 17 countries. South Africa had the lowest level of alcohol use, with 40.6% of the total sample reporting any use by age 29 years, followed by Lebanon (52.8%), Nigeria (55.6%) and Israel (55.7%). Tobacco use was relatively rare in South Africa (32.4%) and Nigeria (16.1%). Cannabis use was very low in Nigeria (2.8%), Japan

[1] Supplementary tables are available with the online version of this paper at doi.xxx/j.drugalcdep.xxx.

Table 1
WMH sample characteristics.

Country	Survey[a]	Sample characteristics[b]	Field dates	Age range	Sample size			Response rate[c]
					Part I	Part II	Part II and age ≤44[d]	
Belgium	ESEMeD	Stratified multistage clustered probability sample of individuals residing in households from the national register of Belgium residents. NR	2001–2002	18+	2419	1043	486	50.6
Colombia	NSMH	Stratified multistage clustered area probability sample of household residents in all urban areas of the country (approximately 73% of the total national population)	2003	18–65	4426	2381	1731	87.7
France	ESEMeD	Stratified multistage clustered sample of working telephone numbers merged with a reverse directory (for listed numbers). Initial recruitment was by telephone, with supplemental in-person recruitment in households with listed numbers. NR	2001–2002	18+	2894	1436	727	45.9
Germany	ESEMeD	Stratified multistage clustered probability sample of individuals from community resident registries. NR	2002–2003	18+	3555	1323	621	57.8
Israel	NHS	Stratified multistage clustered area probability sample of individuals from a national resident register. NR	2002–2004	21+	4859	–	–	72.6
Italy	ESEMeD	Stratified multistage clustered probability sample of individuals from municipality resident registries. NR	2001–2002	18+	4712	1779	853	71.3
Japan	WMHJ2002–2003	Un-clustered two-stage probability sample of individuals residing in households in four metropolitan areas (Fukiage, Kushikino, Nagasaki, Okayama)	2002–2003	20+	2436	887	282	56.4
Lebanon	LEBANON	Stratified multistage clustered area probability sample of household residents. NR	2002–2003	18+	2857	1031	595	70.0
Mexico	M-NCS	Stratified multistage clustered area probability sample of household residents in all urban areas of the country (approximately 75% of the total national population)	2001–2002	18–65	5782	2362	1736	76.6
Netherlands	ESEMeD	Stratified multistage clustered probability sample of individuals residing in households that are listed in municipal postal registries. NR	2002–2003	18+	2372	1094	516	56.4
New Zealand	NZMHS	Stratified multistage clustered area probability sample of household residents. NR	2004–2005	16+	12,992	7435	4242	73.3
Nigeria	NSMHW	Stratified multistage clustered area probability sample of households in 21 of the 36 states in the country, representing 57% of the national population. The surveys were conducted in Yoruba, Igbo, Hausa and Efik languages	2002–2003	18+	6752	2143	1203	79.3
PRC	B-WMH S-WMH	Stratified multistage clustered area probability sample of household residents in the Beijing and Shanghai metropolitan areas.	2002–3	18+	5201	1628	570	74.7
South Africa	SASH	Stratified multistage clustered area probability sample of household residents. NR	2003–2004	18+	4351	–	–	87.1
Spain	ESEMeD	Stratified multistage clustered area probability sample of household residents. NR	2001–2002	18+	5473	2121	960	78.6
Ukraine	CMDPSD	Stratified multistage clustered area probability sample of household residents. NR	2002	18+	4725	1720	541	78.3
United States	NCS-R	Stratified multistage clustered area probability sample of household residents. NR	2002–2003	18+	9282	5692	3197	70.9

[a] ESEMeD: The European Study of the Epidemiology of Mental Disorders; NSMH: The Colombian National Study of Mental Health; NHS: Israel National Health Survey; WMHJ2002–2003: World Mental Health Japan Survey; LEBANON: Lebanese Evaluation of the Burden of Ailments and Needs of the Nation; M-NCS: The Mexico National Comorbidity Survey; NZMHS: New Zealand Mental Health Survey; NSMHW: The Nigerian Survey of Mental Health and Wellbeing; B-WMH: The Beijing World Mental Health Survey; S-WMH: The Shanghai World Mental Health Survey; SASH: South Africa Health Survey; CMDPSD: Comorbid Mental Disorders during Periods of Social Disruption; NCS-R: The US National Comorbidity Survey Replication.

[b] Most WMH surveys are based on stratified multistage clustered area probability household samples in which samples of areas equivalent to counties or municipalities in the US were selected in the first stage followed by one or more subsequent stages of geographic sampling (e.g. towns within counties, blocks within towns, households within blocks) to arrive at a sample of households, in each of which a listing of household members was created and one or two people were selected from this listing to be interviewed. No substitution was allowed when the originally sampled household resident could not be interviewed. These household samples were selected from Census area data in all countries other than France (where telephone directories were used to select households) and the Netherlands (where postal registries were used to select households). Several WMH surveys (Belgium, Germany, Italy) used municipal resident registries to select respondents without listing households. The Japanese sample is the only totally un-clustered sample, with households randomly selected in each of the four sample areas and one random respondent selected in each sample household. Nine of the 15 surveys are based on nationally representative (NR) household samples, while two others are based on nationally representative household samples in urbanized areas (Colombia, Mexico).

[c] The response rate is calculated as the ratio of the number of households in which an interview was completed to the number of households originally sampled, excluding from the denominator households known not to be eligible either because of being vacant at the time of initial contact or because the residents were unable to speak the designated languages of the survey. The weighted average response rate is 69.9%

[d] All countries, with the exception of Nigeria, People's Republic of China, and Ukraine (which were age restricted to ≤39) were age restricted to ≤44.

Table 2
Prevalence of drug use by age 29 years, according to age group at interview. Data from the World Mental Health Surveys (n = 54,068).

	Age at interview															Age association χ^{2} [a,b]
	18–29[c]			30–44			45–59			≥60			Total[c]			
	%	SE	*n*	%	SE	*n*	%	SE	*n*	%	SE	*n*	%	SE	*n*	
Americas																
Colombia[d]																
Tobacco	49.1	2.0	702	43.2	1.8	759	56.4	2.3	539	56.3	4.2	138	48.4	1.0	2138	24.0**
Alcohol	96.1	0.7	1375	93.3	0.7	1612	87.5	1.5	861	83.8	2.4	200	92.5	0.4	4048	105.8**
Tobacco or alcohol	96.8	0.8	1385	93.9	0.7	1626	89.9	1.2	889	86.7	2.4	213	93.6	0.4	4113	83.1**
Cannabis	14.4	0.8	206	9.0	0.9	144	11.2	1.7	83	5.3	2.2	8	10.8	0.5	441	45.2**
Other illicit drugs[b]	7.2	0.8	103	4.5	0.6	68	1.7	0.5	21	1.0	0.7	2	4.4	0.3	194	35.9**
Mexico[d]																
Tobacco	64.4	1.5	1326	58.8	1.7	1215	55.5	2.2	579	52.9	3.6	181	59.6	1.0	3301	67.0**
Alcohol	91.5	0.9	1884	82.3	0.9	1773	76.8	1.5	826	73.8	2.9	248	83.9	0.5	4731	247.0**
Tobacco or alcohol	92.1	0.8	1897	85.6	0.9	1855	79.9	1.4	864	78.6	2.5	269	86.2	0.5	4885	186.7**
Cannabis	11.5	1.3	236	7.7	0.9	148	4.5	0.8	47	1.7	0.7	7	8.0	0.5	438	58.1**
Other illicit drugs[b,e]	9.6	1.2	197	2.9	0.5	61	1.0	0.4	11	0.0	0.0	0	4.5	0.4	269	79.4**
United States[a]																
Tobacco	74.4	2.5	1020	73.3	1.8	1399	75.1	1.7	1206	71.2	2.3	702	73.5	1.3	4327	17.6**
Alcohol	96.2	0.9	1318	93.4	0.9	1729	92.0	1.2	1425	81.7	2.0	800	91.0	0.9	5272	151.8**
Tobacco or alcohol	96.0	1.0	1316	94.8	0.9	1754	94.7	1.0	1463	87.0	1.7	853	93.3	0.8	5386	56.2**
Cannabis	57.6	2.0	789	57.6	1.9	1165	40.7	1.5	711	2.1	0.5	30	40.9	1.0	2695	341.8**
Other illicit drugs[b]	27.3	1.7	374	29.3	1.6	606	15.7	1.1	269	0.9	0.4	9	18.7	0.7	1258	170.9**
Europe																
Belgium[a]																
Tobacco[f]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Alcohol	88.4	5.2	121	93.9	1.5	319	96.0	1.1	278	82.0	4.6	220	90.4	1.8	938	18.8**
Tobacco[f] or alcohol	88.4	5.2	121	93.9	1.5	319	96.0	1.1	278	82.0	4.6	220	90.4	1.8	938	18.8**
Cannabis[e]	31.0	6.6	42	9.9	1.9	44	4.3	1.1	19	0.0	0.0	0	9.8	1.4	105	105.7**
Other illicit drugs[b]	10.2	3.5	14	2.6	1.0	16	0.6	0.3	5	0.7	0.5	3	3.0	0.8	38	46.8**
France[a]																
Tobacco[f]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Alcohol	94.5	2.0	218	94.2	1.8	470	93.2	1.8	363	81.3	3.4	274	90.8	1.2	1325	114.7**
Tobacco[f] or alcohol	94.5	2.0	218	94.2	1.8	470	93.2	1.8	363	81.3	3.4	274	90.8	1.2	1325	114.7**
Cannabis	52.9	4.8	122	19.5	2.3	133	7.7	2.2	30	0.1	0.1	1	17.9	1.6	286	186.4**
Other illicit drugs[b]	11.0	2.2	25	4.9	1.0	35	2.4	1.0	9	1.6	1.0	4	4.5	0.8	73	32.0**
Germany[a]																
Tobacco[f]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Alcohol	98.1	0.9	182	96.7	1.1	420	94.5	1.3	326	91.6	2.0	322	94.9	0.9	1250	79.6**
Tobacco[f] or alcohol	98.1	0.9	182	96.7	1.1	420	94.5	1.3	326	91.6	2.0	322	94.9	0.9	1250	79.6**
Cannabis	45.6	4.7	84	21.2	2.3	108	8.9	2.2	37	2.1	1.5	6	16.8	1.6	235	92.8**
Other illicit drugs[b]	14.6	3.2	27	3.5	0.9	22	1.3	0.5	9	0.1	0.1	1	3.6	0.7	59	53.2**
Italy[a]																
Tobacco[f]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Alcohol	79.6	3.8	262	72.0	2.9	383	75.8	2.1	358	64.4	2.8	299	72.3	1.8	1302	38.9**
Tobacco[f] or alcohol	79.6	3.8	262	72.0	2.9	383	75.8	2.1	358	64.4	2.8	299	72.3	1.8	1302	38.9**
Cannabis[e]	17.4	3.2	57	9.6	1.6	57	3.1	0.8	19	0.0	0.0	0	6.6	0.9	133	94.6**
Other illicit drugs[b,e]	1.1	0.5	3	1.9	0.9	11	1.1	0.5	7	0.0	0.0	0	1.0	0.3	21	4.3
Netherlands[a]																
Tobacco[f]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Alcohol	92.6	4.5	122	93.6	1.1	354	95.6	1.3	317	84.0	3.2	210	92.0	1.3	1003	42.1**
Tobacco[f] or alcohol	92.6	4.5	122	93.6	1.1	354	95.6	1.3	317	84.0	3.2	210	92.0	1.3	1003	42.1**
Cannabis	38.9	8.7	51	27.3	3.3	114	13.0	2.6	51	0.1	0.1	1	18.4	1.1	217	72.8**
Other illicit drugs[b,e]	15.5	5.5	20	4.2	0.9	24	3.1	1.5	13	0.0	0.0	0	4.1	0.8	57	19.9**
Spain[a]																
Tobacco[f]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Alcohol	93.4	1.8	311	91.0	1.5	558	87.1	2.0	373	71.5	2.7	505	85.7	1.1	1747	70.6**
Tobacco[f] or alcohol	93.4	1.8	311	91.0	1.5	558	87.1	2.0	373	71.5	2.7	505	85.7	1.1	1747	70.6**
Cannabis[e]	38.0	4.7	126	21.7	2.9	150	7.1	1.8	30	0.0	0.0	0	15.7	1.3	306	123.5**
Other illicit drugs[b]	11.5	2.7	38	7.9	2.1	55	0.7	0.3	4	0.2	0.2	1	4.9	0.8	98	53.5**
Ukraine[a]																
Tobacco	81.1	2.9	242	69.9	3.3	269	58.6	3.3	215	32.4	2.7	183	59.5	1.8	909	180.4**
Alcohol	99.7	0.3	298	98.6	0.6	406	97.2	1.0	384	84.5	2.1	523	94.7	0.7	1611	273.1**
Tobacco or alcohol	99.4	0.6	297	98.7	0.6	407	97.6	1.1	388	84.6	2.1	524	94.8	0.7	1616	233.5**
Cannabis	15.2	2.8	45	8.3	1.8	32	1.2	0.7	6	0.8	0.5	3	6.0	0.9	86	46.7**
Other illicit drugs[b,e]	2.6	0.7	7	1.0	0.4	8	0.1	0.1	1	0.0	0.0	0	0.9	0.2	16	27.8**

Table 2 (*Continued*)

	Age at interview															Age association $\chi^{2\,a,b}$
	18–29[c]			30–44			45–59			≥60			Total[c]			
	%	SE	*n*	%	SE	*n*	%	SE	*n*	%	SE	*n*	%	SE	*n*	
Middle East and Africa																
Israel[d,g]																
Tobacco	49.7	0.6	537	46.2	1.4	672	49.2	1.4	628	36.8	1.4	408	46.0	0.3	2245	84.0**
Alcohol	67.3	0.6	728	57.2	1.3	842	52.4	1.4	678	43.3	1.5	479	55.7	0.3	2727	273.3**
Tobacco or alcohol	74.9	0.6	810	69.2	1.3	1003	68.3	1.3	870	57.3	1.4	634	68.0	0.3	3317	182.4**
Cannabis	24.3	0.4	262	13.3	0.9	198	6.1	0.7	79	1.0	0.3	11	11.0	0.2	550	241.0**
Other illicit drugs[b,e]	4.4	0.3	47	2.3	0.4	36	0.7	0.2	10	0.0	0.0	0	1.8	0.1	93	67.9**
Lebanon[a]																
Tobacco	75.3	6.4	176	65.4	4.0	259	67.0	4.7	167	48.9	5.4	97	64.1	2.5	699	12.7**
Alcohol	52.8	5.4	124	51.9	4.1	191	60.8	4.1	133	39.4	6.2	82	52.8	3.0	530	17.4**
Tobacco or alcohol	80.8	4.7	189	76.2	3.3	294	82.8	3.3	194	56.9	5.7	116	75.4	2.2	793	22.7**
Cannabis	8.2	2.7	19	4.2	1.6	15	4.4	2.2	10	1.3	0.6	4	5.1	1.0	48	24.0**
Other illicit drugs[b]	0.8	0.6	1	0.0	0.0	0	2.0	1.5	4	0.0	0.0	0	0.8	0.4	5	–#
Nigeria[a]																
Tobacco	9.0	1.9	62	18.1	1.8	142	20.6	2.1	80	25.2	2.6	114	16.1	1.1	398	16.6**
Alcohol	62.1	3.0	432	52.3	2.6	387	50.8	3.6	182	52.6	3.4	217	55.6	1.7	1218	23.4**
Tobacco or alcohol	63.1	3.2	439	55.9	2.5	406	53.9	3.4	195	60.3	3.4	252	58.5	1.8	1292	15.6**
Cannabis	3.1	1.4	21	3.6	0.7	36	2.9	1.0	11	0.8	0.5	3	2.8	0.6	71	5.0
Other illicit drugs[b]	0.4	0.2	2	0.3	0.2	4	0.3	0.3	1	0.2	0.2	1	0.3	0.1	8	–#
South Africa[d]																
Tobacco	33.2	1.6	532	32.0	1.7	426	31.2	2.1	253	31.8	3.1	112	32.4	1.0	1323	17.4**
Alcohol	45.5	2.1	729	41.1	1.6	550	34.5	2.0	261	31.1	2.8	109	40.6	1.2	1649	80.1**
Tobacco or alcohol	52.0	2.1	833	48.6	1.9	671	44.4	1.9	353	43.4	3.0	160	48.8	1.1	2017	55.3**
Cannabis	12.7	1.2	203	7.7	1.0	88	4.9	1.3	34	4.3	2.0	11	8.5	0.6	336	66.7**
Other illicit drugs[b]	3.0	0.7	48	2.7	0.6	22	0.3	0.2	2	1.1	0.9	2	2.2	0.4	74	11.7**
Asia																
People's Republic of China[a]																
Tobacco	49.3	4.2	124	58.3	3.0	340	48.1	3.8	246	38.4	4.2	105	51.3	2.1	815	26.0**
Alcohol	78.7	4.4	199	64.3	2.5	384	61.0	3.3	308	35.2	4.5	91	62.0	1.7	982	67.2**
Tobacco or alcohol	84.0	3.6	212	75.2	2.9	451	68.2	3.2	343	53.1	4.8	141	72.3	1.9	1147	53.7**
Cannabis	1.4	1.4	3	0.4	0.3	3	0.0	0.0	0	0.2	0.2	1	0.3	0.1	7	–#
Other illicit drugs[b]	0.6	0.6	1	0.0	0.0	0	0.0	0.0	0	0.2	0.2	1	0.2	0.2	2	–#
Japan[a]																
Tobacco[f]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Alcohol	97.2	1.9	91	95.4	1.9	177	91.8	2.8	269	67.6	3.7	216	85.3	1.8	753	41.4**
Tobacco[f] or alcohol	97.2	1.9	91	95.4	1.9	177	91.8	2.8	269	67.6	3.7	216	85.3	1.8	753	41.4**
Cannabis[e]	4.5	2.6	4	3.1	1.6	6	0.8	0.8	1	0.0	0.0	0	1.6	0.5	11	8.1**
Other illicit drugs[b]	4.8	3.6	4	4.2	2.0	6	1.1	0.8	4	1.4	1.3	2	2.4	0.8	16	3.6
Oceania																
New Zealand[d]																
Tobacco[f]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Alcohol	95.4	0.7	2241	95.1	0.4	3951	95.3	0.5	2931	89.1	0.8	2597	94.1	0.3	11,720	278.2**
Tobacco[f] or alcohol	95.4	0.7	2241	95.1	0.4	3951	95.3	0.5	2931	89.1	0.8	2597	94.1	0.3	11,720	278.2**
Cannabis	63.0	1.4	1480	54.8	1.0	2361	32.9	1.0	1002	2.0	0.4	55	40.1	0.7	4898	1028.1**
Other illicit drugs[b]	23.6	1.6	554	14.1	0.7	617	7.9	0.6	245	0.6	0.2	17	11.3	0.5	1433	352.6**

Chi-square tests examined associations between the prevalence of drug use by age 29 and age at the time of interview.
(–) Prevalence results were not obtained and therefore the chi-square test was not performed.
(#) The chi-square test was not performed because *n* for total is small ($n \leq 10$).
[a] Part II sample only.
[b] Other illicit drugs included cocaine and other drugs. Prescription drugs are not included in the definition of other illicit drugs.
[c] Projected cumulative estimates for prevalence of respondents less than 29 years of age at interview.
[d] Part I sample only.
[e] Since *n* is zero or small for some cells, they were collapsed so that the chi-square test could be executed.
[f] Age of tobacco use was not assessed.
[g] Israel sampled participants age 21–29 rather than 18–29.
** Significant at the 0.05 level, two-sided test.

(1.6%), and the People's Republic of China (0.3%). Despite relatively low rates of alcohol and tobacco use, South Africa showed moderate prevalence of cannabis use (8.5%) relative to the remaining countries (cross-country median 9.8%). In Japan, the use of other illicit drugs by age 29 years was *more* prevalent than cannabis (Table 2). Age cohort differences in drug use were common: most countries showed increases in prevalence of use of all drugs among younger cohorts.

3.2. Cross-national and age cohort differences in associations between order of initiation of drug use and later other drug use

With few exceptions, substances earlier in the "gateway" sequence predicted drug use later in the sequence (Table 3). However, the strength of these associations differed across countries. For example, cannabis use was less strongly associated with later illicit drug use (cocaine and other illicit drugs) among young adults

Table 3
Association between the initiation of a drug and the later use of other drugs by 29 years, according to country and age cohort.

	Age at interview										Age association $\chi^{2\,a}$
	18–29		30–44		45–59		≥60		Total		
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	
Americas											
Colombia[b]											
Tobacco or alcohol use and later cannabis use	34.8*	(12.7–95.3)	25.0*	(7.6–82.3)	20.6*	(4.1–104.7)	–	–	29.0*	(14.2–59.1)	113.2**
Tobacco or alcohol use and later other illicit drug use[a]	12.3*	(4.3–35.6)	63.9*	(15.9–256.5)	–	–	–	–	24.7*	(10.9–56.0)	20.9**
Cannabis use and later other illicit drug use[a]	56.5*	(20.1–158.7)	86.6*	(20.9–359.6)	34.6*	(6.9–173.7)	38.5	(0.3–4652.6)	64.3*	(30.0–138.0)	2.2
Mexico[b]											
Tobacco or alcohol use and later cannabis use	31.1*	(10.0–97.2)	91.8*	(36.4–231.9)	–	–	–	–	66.3*	(28.7–152.8)	187.1**
Tobacco or alcohol use and later other illicit drug use[a]	26.5*	(7.0–100.6)	25.7*	(7.6–86.4)	–	–	–	–	38.1*	(14.0–104.0)	85.0**
Cannabis use and later other illicit drug use[a]	32.6*	(16.2–65.6)	42.7*	(14.1–129.6)	–	–	–	–	40.9*	(21.7–77.3)	467.7**
United States[c]											
Tobacco or alcohol use and later cannabis use	63.2*	(28.4–140.4)	58.0*	(28.6–117.8)	48.8*	(30.0–79.3)	30.5*	(4.0–233.0)	62.0*	(42.0–91.6)	2.4
Tobacco or alcohol use and later other illicit drug use[a]	34.8*	(18.7–65.0)	58.0*	(29.4–114.4)	25.9*	(11.3–59.4)	–	–	45.1*	(30.8–66.0)	21.0**
Cannabis use and later other illicit drug use[a]	107.1*	(57.9–198.1)	80.5*	(42.1–153.9)	169.1*	(65.2–438.4)	253.0*	(29.3–2187.3)	137.1*	(94.8–198.3)	5.0
Europe											
Belgium[c]											
Tobacco[d] or alcohol use and later cannabis use	19.3*	(4.3–86.6)	66.8*	(9.5–470.3)	–	–	–	–	53.1*	(18.5–152.2)	818.2**
Tobacco[d] or alcohol use and later other illicit drug use[a]	–	–	14.7*	(0.9–236.7)	–	–	–	–	48.9*	(8.2–293.1)	–
Cannabis use and later other illicit drug use[a]	1542.6*	(52.1–45714.2)	357.1*	(23.2–5488.0)	96.0*	(10.5–873.8)	1.0*	(1.0–1.0)	871.9*	(182.0–4177.5)	0.7
France[c]											
Tobacco[d] or alcohol use and later cannabis use	46.8*	(8.2–266.2)	181.8*	(61.6–537.2)	83.7*	(9.4–741.7)	–	–	126.9*	(31.6–509.5)	1.2
Tobacco[d] or alcohol use and later other illicit drug use[a]	77.3*	(15.1–396.2)	29.9*	(3.6–248.6)	–	–	2.7*	(1.1–6.1)	36.2*	(10.6–123.4)	53.4**
Cannabis use and later other illicit drug use[a]	58.1*	(4.3–776.6)	87.2*	(23.5–323.5)	–	–	–	–	80.3*	(25.8–250.5)	167.8**
Germany[c]											
Tobacco[d] or alcohol use and later cannabis use	108.1*	(20.5–569.8)	65.9*	(19.4–223.7)	23.6*	(2.4–229.8)	–	–	115.9*	(36.4–369.6)	16.6**
Tobacco[d] or alcohol use and later other illicit drug use[a]	215.3*	(18.5–2502.3)	–	–	–	–	6.1*	(2.5–15.0)	–	–	26.6**
Cannabis use and later other illicit drug use[a]	416.2*	(22.2–7817.4)	35.7*	(4.2–302.6)	174.7*	(6.4–4743.4)	–	–	294.0*	(39.4–2195.6)	40.9**
Italy[c]											
Tobacco[d] or alcohol use and later cannabis use	22.3*	(5.5–89.8)	–	–	1.6	(0.4–7.5)	–	–	34.9*	(13.9–87.9)	2033.7**
Tobacco[d] or alcohol use and later other illicit drug use[a]	25.9*	(2.5–270.1)	–	–	0.4	(0.0–5.3)	–	–	11.5	(0.7–188.1)	231.4**
Cannabis use and later other illicit drug use[a]	158.3*	(4.9–5096.6)	325.2*	(3.6–29595.5)	729.8*	(235.8–2258.4)	–	–	268.6*	(43.3–1664.2)	3.7

Table 3 (*Continued*)

	Age at interview										Age association χ^{2} [a]
	18–29		30–44		45–59		≥60		Total		
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	
Netherlands[c]											
Tobacco[d] or alcohol use and later cannabis use	22.4*	(1.5–337.6)	469.4*	(48.2–4574.6)	511.6*	(82.4–3175.2)	–	–	156.9*	(29.6–830.2)	3.5
Tobacco[d] or alcohol use and later other illicit drug use[a]	–	–	–	–	–	–	–	–	–	–	–
Cannabis use and later other illicit drug use[a]	7.4*	(1.8–30.4)	1805.9*	(174.9–18642.3)	2015.4*	(24.9–1.6E5)	–	–	62.5*	(9.6–406.5)	139.8**
Spain[c]											
Tobacco[d] or alcohol use and later cannabis use	212.3*	(60.5–745.2)	113.9*	(37.8–342.7)	–	–	–	–	224.8*	(101.3–498.7)	966.2**
Tobacco[d] or alcohol use and later other illicit drug use[a]	77.7*	(24.2–249.0)	20.3*	(6.0–69.3)	–	–	–	–	47.5*	(19.9–113.5)	84.6**
Cannabis use and later other illicit drug use[a]	160.1*	(36.8–695.9)	572.7*	(136.9–2394.9)	–	–	–	–	626.0*	(221.8–1766.6)	32.6**
Ukraine[c]											
Tobacco or alcohol use and later cannabis use	–	–	36.4*	(3.0–441.4)	–	–	–	–	150.6*	(16.8–1351.1)	–
Tobacco or alcohol use and later other illicit drug use[a]	–	–	–	–	–	–	–	–	–	–	–
Cannabis use and later other illicit drug use[a]	79.4*	(14.8–425.9)	73.1*	(3.1–1746.5)	–	–	–	–	179.7*	(37.8–855.5)	112.1**
Middle East and Africa											
Israel[b,e]											
Tobacco or alcohol use and later cannabis use	182.5*	(55.9–595.8)	47.9*	(22.1–103.9)	60.9*	(16.7–222.6)	14.6*	(2.7–79.4)	97.6*	(57.4–166.0)	10.2**
Tobacco or alcohol use and later other illicit drug use[a]	–	–	–	–	–	–	–	–	–	–	–
Cannabis use and later other illicit drug use[a]	3650.6*	(209.0–63756.4)	258.5*	(57.0–1172.4)	–	–	–	–	1479.7*	(388.2–5640.3)	861.0**
Lebanon[c]											
Tobacco or alcohol use and later cannabis use	–	–	–	–	–	–	–	–	–	–	–
Tobacco or alcohol use and later other illicit drug use[a]	–	–	–	–	–	–	–	–	–	–	–
Cannabis use and later other illicit drug use[a]	–	–	–	–	–	–	–	–	–	–	–
Nigeria[c]											
Tobacco or alcohol use and later cannabis use	15.5*	(3.0–80.5)	–	–	–	–	–	–	–	–	–
Tobacco or alcohol use and later other illicit drug use[a]	0.9	(0.1–7.6)	0.7	(0.0–20.2)	–	–	–	–	1.7	(0.3–11.3)	24.7**
Cannabis use and later other illicit drug use[a]	8.9	(0.5–163.0)	3.5	(0.2–64.4)	–	–	–	–	22.2*	(2.2–226.6)	81.3**
South Africa[b]											
Tobacco or alcohol use and later cannabis use	60.6*	(25.5–144.3)	26.4*	(8.0–87.1)	37.5*	(2.5–554.1)	11.4	(0.8–164.5)	46.4*	(25.2–85.6)	5.5
Tobacco or alcohol use and later other illicit drug use[a]	17.4*	(5.5–54.7)	3.5	(0.3–40.4)	–	–	–	–	10.9*	(3.4–34.7)	58.7**
Cannabis use and later other illicit drug use[a]	39.0*	(12.0–127.2)	27.3*	(2.7–280.3)	–	–	–	–	34.1*	(11.0–106.2)	110.9**

Table 3 (*Continued*)

	Age at interview										Age association χ^{2} [a]
	18–29		30–44		45–59		≥60		Total		
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	
Asia											
People's Republic of China[c]											
Tobacco or alcohol use and later cannabis use	–	–	–	–	–	–	–	–	–	–	–
Tobacco or alcohol use and later other illicit drug use[a]	–	–	–	–	–	–	–	–	–	–	–
Cannabis use and later other illicit drug use[a]	–	–	–	–	–	–	–	–	–	–	–
Japan[c]											
Tobacco[d] or alcohol use and later cannabis use	–	–	–	–	–	–	–	–	3.2	(0.1–112.1)	–
Tobacco[d] or alcohol use and later other illicit drug use[a]	0.2	(0.0–10.7)	0.1	(0.0–3.2)	0.0*	(0.0–0.6)	–	–	0.2	(0.0–2.5)	15.3**
Cannabis use and later other illicit drug use[a]	67.5	(0.7–6974.1)	593.1*	(19.7–17884.6)	–	–	–	–	455.4*	(37.5–5522.9)	60.9**
Oceania											
New Zealand[b]											
Tobacco[d] or alcohol use and later cannabis use	29.5*	(22.4–38.9)	48.8*	(37.1–64.3)	48.0*	(29.4–78.4)	–	–	57.9*	(47.2–71.0)	3.0
Tobacco[d] or alcohol use and later other illicit drug use[a]	110.8*	(53.2–230.7)	29.6*	(18.1–48.6)	129.7*	(40.1–419.5)	2.2	(0.6–8.0)	66.6*	(46.2–96.2)	35.5**
Cannabis use and later other illicit drug use[a]	117.0*	(56.8–241.1)	44.2*	(28.0–69.9)	315.7*	(118.6–840.8)	20.3*	(4.6–88.6)	118.0*	(83.3–167.2)	32.0**

Results are based on discrete-time survival models with person-year as the unit of analyses. Person-year and sex are used as a control.
(–) Analysis was omitted due to zero or too few outcomes that model could not converge.
[a] Other illicit drugs include cocaine and other drugs. Prescription drugs are not included in the definition of other illicit drugs.
[b] Part I sample only.
[c] Part II sample only.
[d] Age of tobacco used was not accessed.
[e] Israel sampled participants age 21–29 rather than 18–29.
* OR significant at the 0.05 level, two-sided test.
** Significant at the 0.05 level, two-sided test.

Table 4
Percent of those using other illicit drugs[a] by age 29 years who had NOT already used cannabis before beginning other illicit drug[a] use, by country and age at interview.

	Age at interview						Age association χ^2 [b]
	18–29[b]			Total[b]			
	%	SE	*n*	%	SE	*n*	
Americas							
Colombia[c]	42.2	4.9	27	33.4	4.8	52	15.6**
Mexico[c,d]	58.3	9.6	77	48.4	6.4	106	63.9**
United States[e]	12.6	2.2	45	11.4	1.2	126	17.3**
Europe							
Belgium[e]	8.7	6.6	1	16.7	6.6	9	–#
France[e]	21.7	10.0	6	33.5	6.1	23	4.9
Germany[e]	7.8	4.5	2	17.4	7.4	9	–#
Italy[e]	27.0	20.8	1	21.8	10.5	6	–#
Netherlands[e,d]	40.7	19.1	10	20.7	9.6	15	59.8**
Spain[e,d]	12.3	4.2	6	10.0	2.9	13	7.0**
Ukraine[e]	32.1	8.3	5	34.5	11.0	8	–#
Middle East and Africa							
Israel[c,f]	2.4	0.2	1	5.8	0.3	5	–#
Lebanon[e]	–	–	0	–	–	0	–#
Nigeria[e]	93.1	2.7	3	77.8	17.4	7	–#
South Africa[c]	51.1	10.2	16	59.2	9.7	33	7.8
Asia							
People's Republic of China[e]	–	–	1	–	–	2	–#
Japan[e]	77.3	52.4	2	83.2	10.9	13	2.0
Oceania							
New Zealand[c]	7.0	1.7	30	12.7	1.3	164	28.6

(–) Small or zero numbers, so estimate not reported.
(#) The chi-square test was not performed because *n* for total is small ($n \leq 10$).
[a] Other illicit drugs included cocaine and other drugs. Prescription drugs are not included in the definition of other illicit drugs.
[b] Projected estimates.
[c] Part I sample only.
[d] Since *n* is zero or small for some cells, they were collapsed so that the chi-square test could be executed.
[e] Part II sample only.
[f] Israel sampled participants age 21–29 rather than 18–29.
** Significant at the 0.05 level, two-sided test.

(18–29 years) in the Netherlands than it was in Belgium, Spain and the United States.

Discrete-time survival models pooled across countries revealed a significant interaction between the initiation of alcohol/tobacco and *prevalence* of alcohol/tobacco use predicting the subsequent initiation of other illicit drugs (OR = 32.7, CI 8.3–129.0), suggesting that alcohol/tobacco initiation was associated more strongly with the subsequent onset of other illicit drug use in countries/cohorts with *higher* rates of alcohol/tobacco use. Conversely, cannabis initiation was more strongly associated with the subsequent onset of other illicit drug use in countries/cohorts with *lower* rates of cannabis use (OR = 0.3, CI 0.2–0.6). There was no significant interaction effect of the onset of alcohol/tobacco and the prevalence of alcohol/tobacco use in a country upon later cannabis initiation.

3.3. Cross-national and cross-cohort differences in violations to the gateway sequence

Estimated prevalence of violations to the gateway sequence among drug users in each of the 17 countries is presented in Table 4 (and Supplementary Tables 1 and 2). Cannabis users in South Africa, a country with the lowest rates of both alcohol and tobacco use, showed the highest rate of violating the typical gateway sequence, with 16.3% never using both alcohol and tobacco as of the age of first cannabis use. This rate was one and one third to more than 10 times higher than that seen among cannabis users in countries where alcohol and/or tobacco use was prevalent (Supplementary Tables 1 and 1a). Among other illicit drug users, Japan had the highest rate of violating the gateway sequence, with 52.5% failing to use both alcohol and tobacco as of the onset of other illicit drug use (Supplementary Tables 2 and 2a). Nigeria had the second highest rate, with 51.8% failing to have used both alcohol and tobacco as of the onset of other illicit drug use. In comparison, within countries where rates of alcohol and/or tobacco were highest, the use of other illicit drugs before both alcohol and tobacco was rare (Germany 0.6%, New Zealand 0.2% and Ukraine 0.0%; Supplementary Tables 2 and 2a).

Cannabis was rarely used before other illicit drugs by most other illicit substance users in countries where cannabis use was rare (Japan 83.2%, Nigeria 77.8%, Table 4). In countries where rates of cannabis use were highest, violations to the gateway sequence were uncommon (U.S. 11.4%, New Zealand, 12.7%).

Further analyses were conducted to consider whether violations to the "gateway" sequence of initiation predicted the later onset of dependence among users of each drug type (Table 5, Supplementary Table 3). Discrete-time survival models pooled across all countries (controlling for country in models) revealed that violations to the "gateway" sequence of initiation largely did *not* predict the onset of any drug dependence in a given year. Rather, it was the number of drugs used, and an earlier onset of exposure to drugs *overall*, that predicted transition to dependence (Table 5, Supplementary Table 3a). Early onset mental disorders (both internalising and externalising) were also important predictors of the development of dependence.

4. Discussion

The present paper examined the extent and ordering of licit and illicit drug use across 17 disparate countries worldwide. This comparison, using surveys conducted with representative samples of

Table 5
Multivariable predictors of onset of dependence by drug type. Pooled analyses from the WHO World Mental Health Surveys.

	Alcohol dependence among alcohol users		Tobacco dependence[a] among tobacco users		Drug dependence[b] among cannabis users		Drug dependence[b] among cocaine users		Drug dependence[b] among other illicit drug# users	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Female	0.4*	(0.3–0.5)	1.0	(0.9–1.1)	0.7*	(0.5–0.8)	0.9	(0.6–1.3)	0.8	(0.6–1.0)
Age at interview										
18–29	2.0*	(1.5–2.7)	2.2*	(1.8–2.6)	1.2	(0.4–4.0)	0.8	(0.1–5.2)	1.2	(0.2–6.6)
30–44	1.2	(0.9–1.6)	1.1	(0.9–1.3)	1.0	(0.3–3.3)	0.7	(0.1–4.7)	1.0	(0.2–5.8)
45–59	1.4*	(1.0–1.8)	1.1	(1.0–1.4)	0.8	(0.2–2.9)	0.6	(0.1–4.2)	0.9	(0.1–5.0)
60+	1.0	–	1.0	–	1.0	–	1.0	–	1.0	–
No. of internalising disorders by 15 years[c]	1.7*	(1.6–1.8)	1.3*	(1.2–1.3)	1.6*	(1.4–1.7)	1.5*	(1.3–1.7)	1.5*	(1.3–1.6)
No. of externalising disorder by 15 years[d]	1.7*	(1.5–1.9)	1.2*	(1.1–1.4)	1.4*	(1.2–1.7)	1.4*	(1.1–1.7)	1.4*	(1.2–1.7)
Age-of-onset of use[e]	0.5*	(0.4–0.7)	0.7*	(0.6–0.8)	0.2*	(0.2–0.3)	0.5*	(0.3–0.7)	0.3*	(0.2–0.4)
Years since first onset of use[e]	0.9*	(0.9–0.9)	1.0*	(1.0–1.0)	0.8*	(0.8–0.8)	0.8*	(0.7–0.8)	0.8*	(0.7–0.8)
Tobacco use	2.0*	(1.5–2.5)	–	–	1.7*	(1.0–2.7)	1.5	(0.8–2.8)	2.0*	(1.1–3.7)
Alcohol use	–	–	2.4*	(2.0–3.0)	1.6	(0.8–3.1)	0.5	(0.1–2.0)	1.7	(0.7–4.2)
No. of illicit drugs used[f]										
None	1.0	–	1.0	–	–	–	–	–	–	–
1	3.0*	(2.5–3.5)	1.8*	(1.5–2.0)	1.0	–	1.0	–	1.0	–
2	5.4*	(4.3–6.9)	2.3*	(2.0–2.8)	6.1*	(4.5–8.3)	1.4	(0.5–4.1)	3.4*	(1.4–8.2)
3	6.3*	(4.7–8.4)	2.9*	(2.4–3.6)	15.4*	(11.1–21.5)	2.1	(0.8–6.0)	7.8*	(3.1–19.9)
4	7.7*	(5.3–11.2)	3.1*	(2.3–4.2)	35.7*	(24.6–51.8)	5.6*	(2.0–15.7)	18.9*	(7.2–49.7)
"Gateway violation":										
Cannabis use before tobacco and alcohol	0.6	(0.3–1.0)	1.1	(0.7–1.6)	0.8	(0.4–1.7)	1.0	(0.4–2.4)	1.0	(0.5–2.1)
Other illicit drug use[g] before tobacco and alcohol	0.7	(0.3–1.4)	1.0	(0.5–1.9)	0.8	(0.3–2.3)	0.5	(0.1–1.8)	1.0	(0.3–3.2)
Other illicit drug use[g] before cannabis	1.6*	(1.1–2.3)	0.9	(0.7–1.2)	0.7	(0.4–1.1)	1.3	(0.6–2.6)	1.2	(0.7–2.1)

Results are based on multivariable discrete-time survival analyses with countries as a control.
"Onset of dependence" refers to onset of the full dependence syndrome.
Odds ratios = 0.0 indicates no one having the outcome and predictor of interest.

[a] Drug was not assessed for Belgium, France, Germany, Italy, Netherlands, Spain, Israel, South Africa, Japan and New Zealand.

[b] Drug was not assessed for Belgium, France, Germany, Italy, Netherlands and Spain.

[c] DSM-IV internalizing disorders include: panic disorder, agoraphobia without panic disorder, social phobia, specific phobia, generalised anxiety disorder with hierarchy, post-traumatic stress disorder, and major depressive disorder with hierarchy/dysthymia with hierarchy.

[d] DSM-IV externalizing disorders include: bipolar disorder, oppositional defiant disorder with hierarchy, conduct disorder, attention deficit/hyperactivity disorder and intermittent explosive disorder with hierarchy.

[e] Age-of-onset, or years since onset, of the drug use concerned.

[f] This is a time-varying covariate and refers to the number of illicit drugs (grouped as cannabis, cocaine, prescription drugs or other drugs) the person had used by a given year.

[g] Other illicit drugs include cocaine and other drugs. Prescription drugs are not included in the definition of other illicit drugs.

* OR significant at 0.05 level, two-sided test. Chi-square statistics are available upon request.

the general population in these countries, and assessment involving comparable instruments, allowed for the first assessment of the extent to which initiation of drug use follows a consistent pattern across countries. Previous studies, concentrated in high income countries with relatively high levels of cannabis use, have documented: a common temporal ordering of drug initiation; an increased risk of initiating use of a drug later in the sequence once having initiated an earlier one; and the persistence of the association following controlling for possibly confounding factors (Kandel et al., 2006).

The present study supported the existence of other factors influencing the ordering and progression of drug use because (1) other illicit drug use was *more* prevalent than cannabis use in some countries, e.g. Japan; (2) the association between initiation of "gateway" drugs (i.e. alcohol/tobacco and cannabis), and subsequent other illicit drug use differed across countries, in some instances according to background prevalence of use of these gateway drugs; and (3) cross-country differences in drug use prevalence corresponded to differences in the prevalence of gateway violations.

Higher levels of other illicit drug use compared to cannabis use were documented in Japan, where exposure to cannabis and tobacco/alcohol was less common. In this case, a lack of exposure and/or access to substances earlier in the normative sequence did not correspond to reductions in overall levels of other illicit drug use. This finding is contrary to the assumption that initiation reflects a universally ordered sequence in which rates of drug use later in the sequence must necessarily be lower than those earlier in the sequence (Kandel, 2002). This has not previously been reported as research has been traditionally conducted in countries where use of tobacco, alcohol and cannabis is relatively common.

As expected by a model in which environmental factors such as access and/or attitudes toward use of a drug play some role in the order of substance initiation, gateway substance use was differentially associated with the subsequent onset of other illicit drug use in countries/cohorts based on background prevalence of gateway substance use (i.e. alcohol/tobacco more strongly associated with the subsequent onset of other illicit drug use in countries/cohorts with higher rates of alcohol/tobacco use and cannabis initiation more strongly associated with the subsequent onset of other illicit drug use in countries/cohorts with *lower* rates of cannabis use). Thus, while previous studies have consistently documented that the use of an earlier substance in the gateway sequence predicts progression to use of later substances (Grau et al., 2007; Kandel et al., 1986; van Ours, 2003; Yamaguchi and Kandel, 1984), the present analyses conducted across diverse countries and cohorts showed that the strength of associations between substance use progression may be driven by background prevalence rather than being wholly explained by causal mechanisms.

Further, differences in patterns of gateway violations seen across countries in the WMHS provided evidence in support of the likely influence of access and/or attitudes toward substance use in shaping order of initiation. The most common gateway violation was that of other illicit drug use before cannabis. Higher levels of other illicit drug use before cannabis were related to lower levels of cannabis use in these countries (Japan and Nigeria). Similarly, first use of other illicit drugs before alcohol and tobacco was found to be most prevalent in Japan and Nigeria, countries with relatively low rates of alcohol and tobacco use compared to other WMHS countries (Degenhardt et al., 2008). In contrast, use of cannabis before alcohol and tobacco was extremely rare in countries with some of the highest rates of cannabis use, such as the US and New Zealand. Cannabis users in the US were also much more likely to progress to other illicit drug use than those in the Netherlands. Taken together, cross-country differences in drug use prevalence corresponded remarkably well with differences in the prevalence of gateway violations.

What are the implications of these findings for our understanding of the relationship between the initiation of drug use and potential adverse drug-related outcomes later in life? First, consistent with other discussions of early onset drug use (Iacono et al., 2008) it may be more useful to discuss early onset drug use (regardless of the type of drug used) rather than focusing on any particular *type of drug* since: the order of onset is clearly not the same for all users; the order varies to some extent across countries and across cohorts born in different periods; and since changes in the order of onset do not seem to affect risk for later dependence. Rather, consistent with a number of lines of observational evidence, many involving prospective study designs (see Iacono et al., 2008), the risk for later development of dependence upon a drug may be more affected by the extent of prior use of *any* drug and the age-of-onset at which that use began. This was lent support in this study through the finding that the number of early onset mental disorders (prior to age 15 years) was an important moderator of risk for developing dependence. The finding that adolescents with externalising and internalising disorders were at elevated risk of developing drug dependence is consistent with prospective cohort studies, which have found that early onset drug use and mental health problems are risk factors for later dependent drug use (Toumbourou et al., 2007), and that comorbid mental health problems escalate risk of developing dependence once drug use begins.

It also suggests that, rather than focusing on specific patterns of initiation, or on the use of particular drugs in order to prevent transitions to other specific drug use or dependence, prevention efforts are probably better targeted at *all* types of drug use, particularly among young people who are already dealing with other challenges or risk behaviours, since it may be this group that is most at risk of developing problems later on.

4.1. Limitations

As with all cross-sectional survey research (it needs to be noted that the WMHS surveys were not explicitly designed to answer the current research question), there are several limitations that should be considered. First, this study found cohort differences in substance *use* within various countries as well as cohort differences in the *order of onset of use*. Although this may reflect actual cohort differences, they may also reflect response biases. Retrospective reporting of age of first substance use is subject to error, given that respondents are being asked about events that, for older persons, may have occurred decades ago. Longitudinal studies have found that estimates of the age of first use do tend to increase upon repeat assessment (i.e. as people age) (Engels et al., 1997; Henry et al., 1994; Labouvie et al., 1997), but not that the order of reporting of initiation changes. Further, background prevalence rates used here do not necessarily map to actual differences in consumer demand, supply and/or attitudes toward drug use.

There might be differential social stigma and legal practices in each country affecting self-reported drug use. Attempts were made to ensure truthful, honest answers were provided by participants in these surveys in four major ways. First, pilot testing in each country was carried out to determine the best way to describe study purposes and auspices in order to maximize willingness to respond honestly and accurately. Second, in countries that do not have a tradition of public opinion research, and where the notions of anonymity and confidentiality are unfamiliar, we contacted community leaders in sample sites to explain the study, obtain formal endorsement, and have the leaders announce the study to community members and encourage participation. The announcements were most typically made by religious leaders as

part of their weekly sermons, although there are other cases, such as the formal community leaders in each neighbourhood in Beijing and Shanghai, where secular community leaders who were given presents by the study organizers made formal announcements and encouraged members of their neighbourhood to participate in the survey. Third, interviewers were centrally trained in the use of non-directive probing, a method designed to encourage thoughtful honest responding. Finally, especially sensitive questions were asked in a self-report format rather than an interviewer-report format, although this could be done only for respondents who could read. These methods were doubtlessly not completely effective in removing cross-national differences in willingness to report, though, so it is important to recognise the possible existence of remaining differences of this sort in interpreting cross-national differences in results.

It needs to be noted that the comparisons used in this paper were very conservative for several reasons. The first reason reflects the use of "country" as the unit of comparison. Different countries are comprised of differing ethnic, religious and other social groupings, which are highly likely to affect the prevalence of drug use. We were not able to directly control for these groupings in a consistent way across countries. Future research might examine whether some of the differences in the levels of use and possibly in the order of initiation might be related to ethnicity and religious affiliation. The second reason reflects the measurement of drug use. We selected any use of a drug as the prior exposure variable when considering the gateway sequence of initiation. It could be argued that we did not use the same criteria as Kandel in her original conceptualization of the "gateway pattern" of drug use initiation; we did examine two versions (which made little difference)—no use of both alcohol and tobacco, and no use of one or the other of these. Future work might examine the relationship between onset of *regular* use to examine whether the same relationships still hold as observed in the analyses presented here.

Finally, our conclusions are limited by the fact that we did not measure instrumental variables explicitly, nor were we able to conduct the kinds of analysis required to better examine potential causal effects of preventing the use of drugs "early" in the "gateway" sequence. A more focused approach could also be used to study one place and interval of time to measure explicitly a single instrumental variable, such as a change in cigarette taxation rates, to estimate the effects of cigarette use on later substance use. This was examined for the relationship between tobacco use and physical health, using cigarette price as the instrumental variable (Leigh and Schembri, 2004). The next step in this line of research should consequently be to undertake focused analyses.

Despite these limitations, the present study is the first to describe cross-national associations between substances in the order of initiation of drug use, based on largely comparable sampling strategies and assessment tools. The most notable advantage of the WMHS is that these surveys represents 17 large, nationally representative and regionally diverse samples, and cover a wide range of ages and hence birth cohorts, over a period of changing drug markets and country-specific social norms related to drug use.

4.2. Conclusions

The present study provided suggestive evidence to suggest that drug use initiation is not constant across contexts and cultures. Although cannabis is most often the first illicit drug used, and its use is typically preceded by tobacco and alcohol use, the variability seen across countries, which is related to the background prevalence of such drug use, provides evidence to suggest that this sequence is not immutable. Violations of this sequence are not associated with the development of dependence; rather, it seems to be the age-of-onset and degree of exposure to any drugs that are more important predictors.

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Contributors

Lisa Dierker, Louisa Degenhardt, Maria Elena Medina-Mora, Yehuda Neumark, Nancy Sampson, and Ronald Kessler contributed to the conception, design and interpretation of analysis for this manuscript. Lisa Dierker, Wai Tat Chiu, Nancy Sampson, and Ronald Kessler contributed to the analysis of the manuscript. Drafting of the manuscript was done by Lisa Dierker, Louisa Degenhardt, Maria Elena Medina-Mora, Yehuda Neumark, Nancy Sampson, and Ronald Kessler. All the other authors contributed to the acquisition of data and obtaining funding for this manuscript as well as its critical revision. All authors have approved the final manuscript.

Conflict of interest statements

Dr. Degenhardt was provided by Reckitt Benckiser with an untied educational grant to monitor the extent of injection of buprenorphine–naloxone injection, following its introduction in Australia, and compared with methadone and buprenorphine. The design, conduct, reporting and interpretation of the results of the study were determined by the study investigators. Dr. Kessler has been a consultant for GlaxoSmithKline Inc., Kaiser Permanente, Pfizer Inc., Sanofi-Aventis, Shire Pharmaceuticals, and Wyeth-Ayerst; has served on advisory boards for Eli Lilly & Company and Wyeth-Ayerst; and has had research support for his epidemiological studies from Bristol-Myers Squibb, Eli Lilly & Company, GlaxoSmithKline, Johnson & Johnson Pharmaceuticals, Ortho-McNeil Pharmaceuticals Inc., Pfizer Inc., and Sanofi-Aventis. Dr. Stein has received research grants and/or consultancy honoraria from Astrazeneca, Eli Lilly, GlaxoSmithKline, Jazz Pharmaceuticals, Johnson & Johnson, Lundbeck, Orion, Pfizer, Pharmacia, Roche, Servier, Solvay, Sumitomo, Tikvah, and Wyeth. The remaining authors reported no conflicts.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.drugalcdep.2009.12.001.

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