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The Gateway Hypothesis, Common Liability to Addictions or the Route of Administration Model? A Modelling Process Linking the Three Theories

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Abstract
Background: The aim of this study was to describe the transitions between tobacco (T), cannabis (C) and other illicit drugs (OIDs) initiations, to simultaneously explore several substance use theories: gateway theory (GT), common liability model (CLM) and route of administration model (RAM). ***Methods:*** Data from 2 French nationwide surveys conducted in 2005 and 2010 were used (16,421 subjects aged 18–34). Using reported ages at initiations, we reconstituted a retrospective cohort describing all initiation sequences between T, C and OID. Transition probabilities between the substances were computed using a Markov multi-state model that also tested the effect of 2 latent variables (item response theory scores reflecting propensity for early onset and further substance use) on all transitions. ***Results:*** T initiation was associated with increased likelihood of subsequent C initiation, but the reverse relationship was also observed. While the most likely initiation sequence among subjects who initiated the 3 groups of substances was the 'gateway' sequence T → C → OID, this pattern was not associated with substance use propensity more than alternative sequences. Early use propensity was associated with the 'gateway' sequence but also with some alternative ones beginning with T, C or OID. ***Conclusion:*** If the gateway sequence appears as the most likely pattern, in line with GT, the effects of early onset and substance use propensities were also observed for some alternative sequences, which is more in line with CLM. RAM could explain reciprocal interactions observed between T and C. This suggests shared influences of individual (personality traits) and environmental (substance availability, peer influence) characteristics.

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Introduction

Three theories compete with each other for explaining the transition from initiation of licit drugs to initiation of illicit drugs: the gateway theory (GT), the common liability model (CLM) and the route of administration model (RAM) [1]. According to GT, cannabis use typically follows licit drug use such as tobacco and/or alcohol use, whereas other illicit drugs (OIDs) use (cocaine or heroin) follows cannabis use [2]. GT is based on a temporal sequence in the initiation of different substances [3] and on

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the statistical association between patterns of use, whereby substance experiment at the beginning of the sequence increases the risk of subsequent use of another substance at the end of the sequence [4–6]. This points to the existence of definite use trajectories, also called gateway sequences, which could constitute an independent risk factor for increasing use: a subject who has used a given substance is more liable to subsequent use of another substance, this subsequent use being better explained by the sequence that he (she) has entered than by opportunity for use [7]. However, the gateway hypothesis is increasingly questioned, some alternative use sequences are observed [8–12], and the order of drug use initiation is not playing a substantial role in the etiology of substance use disorder (SUD) [13–15]. RAM was proposed to explain the reverse sequences leading from cannabis to tobacco, suggesting that the shared route by which substances are administered (e.g. inhalation) may account for the later initiation to other types of substance use, thus explaining why tobacco and cannabis use commonly coexists [16].

In contrast to the GT, which only addresses the order of drug-use initiation, the CLM proposes that using both licit and illicit drugs could be attributable to the influence of a common liability, particularly among subjects with SUD [17, 18]. This liability could include a genetic and individual vulnerability, such as proneness to deviancy and familial liability to addiction [19–21]. The CLM supposes that the 'choice' of which substance is used first can be the result of the aforementioned factors, and that no order is expected a priori in the sequence of drug use. Thus, much of the liability underlying SUDs seems to be the same across different substances, especially for early substance use and abuse that emerges in late adolescence and early adulthood [22]. The CLM is also in line with the findings that heavy substance users tend toward poly-substance use [23] and in line with the high rates of co-morbidity (i.e. meeting criteria for more than 1 disorder) among SUDs [24].

A recent review about co-morbid use of tobacco and cannabis suggests that all theories, GT, RAM and CLM could be involved [25]. In this perspective, we wanted to propose an original method to simultaneously explore several hypotheses. To achieve our aim of exploration of the respective influences of GT, RAM and CLM on substance use processes, we analysed the transitions occurring between tobacco, cannabis and OID use onsets in a sample of young adults. Then we tested the influence of 2 latent traits, able to reflect drug-use liability (propensities to early onset and current use for 7 groups of substances), on each transition. According to GT, it was ex-

pected that the probability of OID initiation would increase if cannabis was previously initiated, with cannabis initiation following tobacco initiation. According to the RAM, we also expected that this latter transition could also be reversed. Moreover, subjects with greater latent traits would be more likely to follow the gateway sequence *(tobacco → cannabis OID)*. According to the CLM, it was expected that greater latent traits, reflecting polysubstance use or misuse, would be associated with all transitions, whatever the sequence.

Methods

Sample
This study was based on data from 2 'Health Barometers', French nationwide surveys on health and behaviours, conducted in 2005 and 2010 among population aged 15–85 years, using a 2-stage sampling frame (household/individual) [26]. Data were anonymous and collected using Computer-Assisted Telephone Interviews. This protocol was approved by the French Commission on Individual Data Protection and Public Liberties (CNIL). The initial samples included 30,514 people in 2005 and 27,653 people in 2010. To obtain a homogeneous sample in terms of generation and to minimise recall bias, this study focused on the 16,421 subjects aged 18–34 (9,650 in 2005 and 6,771 in 2010).

Measures
Initially, in line with previous research, we hypothesised that for a given individual, a common drug use liability would be characterised by early initiation, poly-substance use and higher levels of use [23, 24, 27, 28]. Item-response theory (IRT) modelling, a methodology previously used in the area of addiction [29, 30], was then used to construct 2 latent variables exploring early onset and current use:
– The early onset latent variable was built using 7 dummy variables exploring an age at initiation under 25th percentile for tobacco (initiation under 13), first drunkenness (under 15), cannabis (under 15), inhalants (under 15), depressants (at least 1 substance among heroin, buprenorphine, methadone, GHB or ketamine), stimulants (cocaine, crack, ecstasy, amphetamines or MDMA), and hallucinogens (mushrooms or LSD; under 18 for these latter 3 classes);
– The current substance use latent variable was built with 7 other dummy variables: tobacco current daily use, current hazardous alcohol use according to the alcohol use disorders identification test [31], cannabis use reported in the past month, and inhalants, depressants, stimulants and hallucinogens use reported in the past 12 months.
IRT models define the relationship between observed data and the underlying latent construct using 2 parameters: a propensity parameter (threshold) and a discrimination parameter (slope) [29]. The propensity parameter shows whether the criteria (each of the variables used for a given latent construct) are endorsed less frequently. This parameter is the point of the latent construct where there is 50% endorsement. The discrimination parameter is represented by the steepness of the slope and shows the ability of
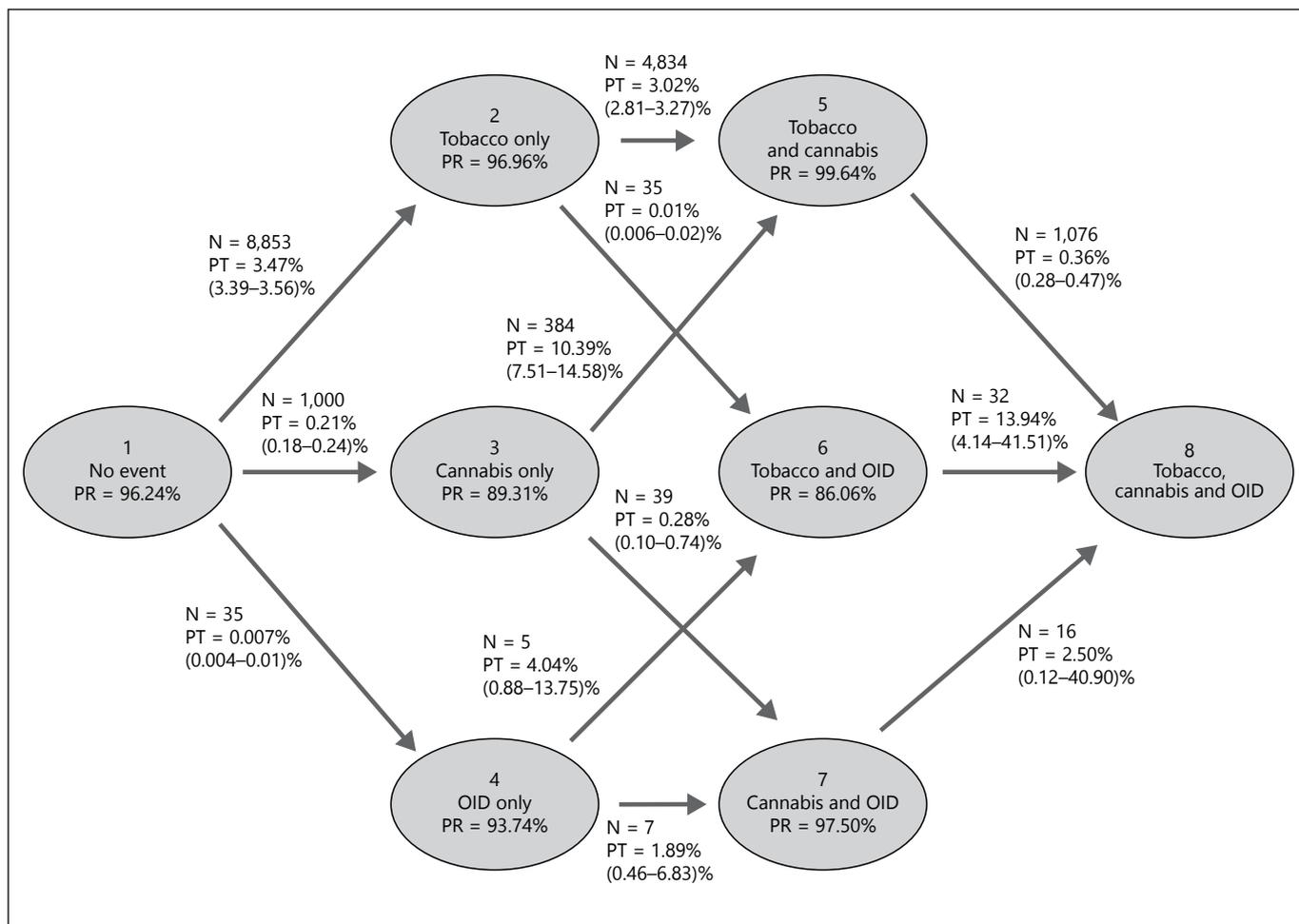
Fig. 1. Estimated probabilities of transition between different substance-use onset states – piecewise constant intensities Markov model (16,421 subjects – 17,510 transitions). Probabilities of transition presented here are computed with the covariates (time period, year of study, gender, socioeconomic level, drunkenness and inhalants initiations, and early use and substance use scores) set to their average values over the sample. For some sets of transitions, probabilities do not add to 100% due to 1,194 incompletely known trajectories (at least one missing transient state) that are not represented here (for example, probability of transition 1–5, which corresponds to subjects who may follow sequences 1–2–5 or 1–3–5, is 0.07%). N = Number of transitions observed; PT = probability of transitions at 1 year; PR = probability of remaining in the same state at 1 year.

a criterion to discriminate between participants who are low or high on the latent construct. Using the package gllamm of the Stata 11.1 software [32], we fitted a 2-parameter logistic model for each latent variable after checking the unidimensionality of each construct (a prerequisite for IRT) with exploratory multiple correspondence analyses. Mean expected a posteriori scores of IRT models were then used as approximations of continuous latent traits reflecting the propensity to early onset and current substance use for each individual [32].

Multi-State Modelling

Using the ages at initiation for three substances (tobacco, cannabis and OID), a retrospective cohort was constructed, with individuals who were followed from age 5 to 30. The data frame included 1 observation by year of follow-up (for example, a subject aged 20 at the year of study accounted for 16 observations). A Markov multi-state model (MSM) was constructed using 8 mutually exclusive substance use states (fig. 1). This model considered all the possible transitions between tobacco, cannabis and OID initiation states: no lifetime initiation of any substance (state 1), initiation of tobacco only (state 2), initiation of cannabis only (state 3), initiation of OID only (state 4), initiation of tobacco and cannabis (state 5), initiation of tobacco and OID (state 6), initiation of cannabis and OID (state 7), and initiation of the 3 substances (state 8). Probabilities of transitions (PT) within a given time t (here a 1-year period was chosen) were then computed. The algorithms used by the software allowed for the exact transition times being unknown; this enabled to take into account the subjects with an incompletely known trajectory (subjects who reported the initiation of several substances a same year, which implies at least 1 missing transient state).
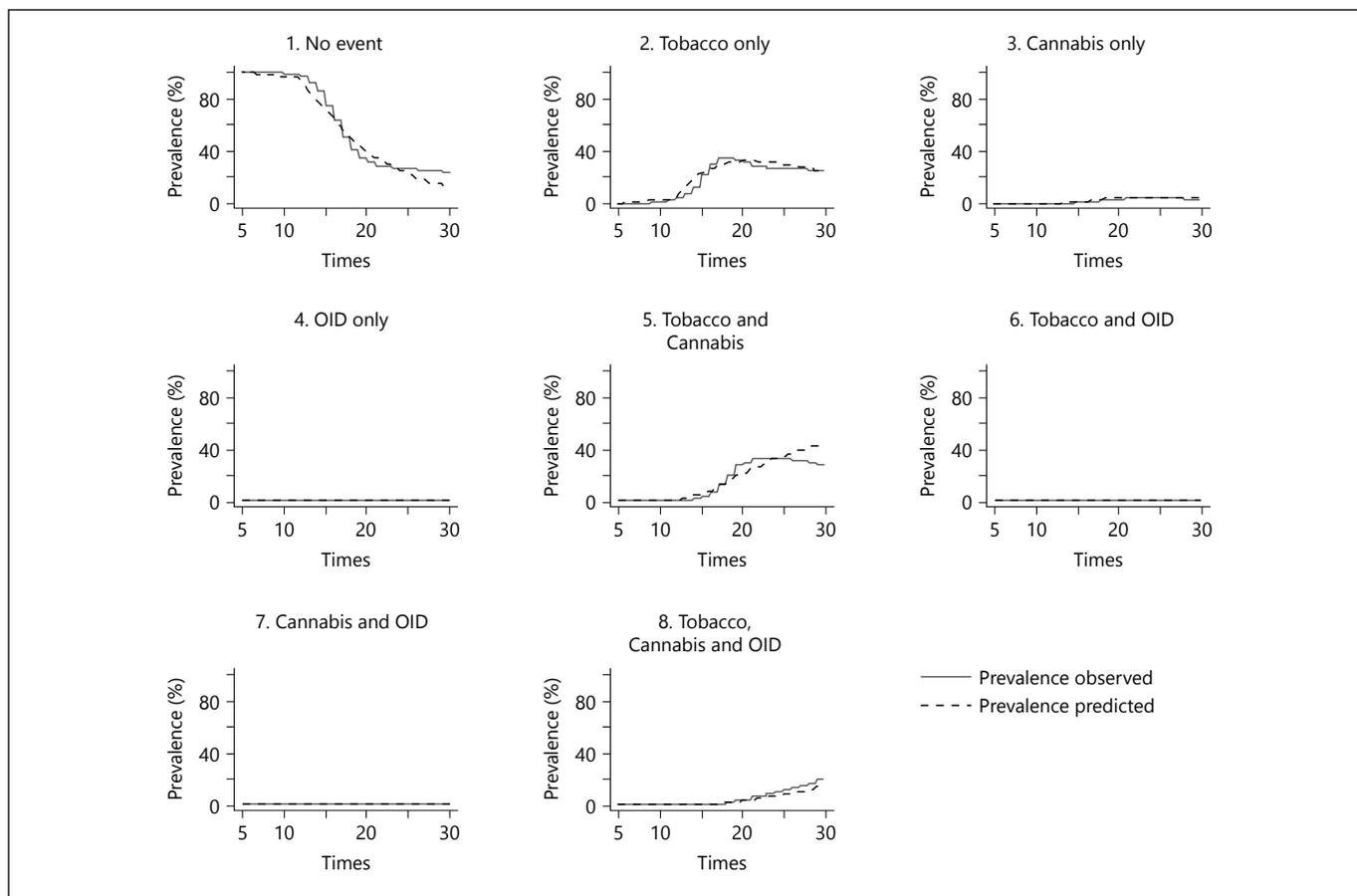
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Fig. 2. Model fit assessment over the study period: comparison, for each state, between observed and predicted prevalence – piecewise constant intensities Markov model.

Using a proportional intensities model [33], hazard ratios (HRs) were computed to estimate the effect of some covariates on transition probabilities: year of study (2010 vs. 2005), gender (women vs. men), socioeconomic level (low or unemployed vs. high or intermediate), drunkenness and inhalants initiations as time-dependent covariates (coded positive from age at initiation), and early onset and current use scores (entered as continuous variables, HRs representing here the risk of transition for subjects having a score increase of 1 compared with others).

For model fit assessment, we compared the percentages of individuals observed in each state at different times with the values expected from the model. This enabled us to identify 2 major cut-off points in use at times 12 and 16 (fig. 2), suggesting that a piecewise constant-time intensities model would be preferable to a homogenous model. These cut-off-points were modelled by controlling the model for time period, which was entered as a categorical 3-class covariate (5–12, 12–16 and 16–30 years). The MSM was fitted using R 3.2.1 software, and the MSM package version 1.5, available at http://cran.r-project.org/ [34–36]. A more detailed methodology about Markov models was published elsewhere [37]. Subjects with incompletely known trajectories were compared with others in terms of social characteristics and substance use, using a multivariate logistic model.

Results

Preliminary Analyses

Women represented 54.3% of the sample and the mean age was 26.6 years (SD = 4.8). The mean age for using the first cigarette was 15.5 years (SD = 2.8), while the mean age was 17.8 years (SD = 2.8) for the first cannabis use, 17.4 years (SD = 2.8) for first drunkenness, 18.8 years (SD = 3.6) for inhalants initiation, 20.8 years (SD = 3.7) for depressants initiation, 20.4 years (SD = 3.4) for stimulants initiation, and 19.7 years (SD = 3.1) for hallucinogens initiation. Among the subjects who reported the initiation of all tobacco, cannabis and OID, the mean duration from the first substance initiation to the last, whatever the order, was 6.1 years (SD = 3.4). Earlier ages at cannabis and OID initiation were associated with shorter sequences (respectively p = 0.001 and p < 0.0001). Earlier age at tobacco initiation was associated with a longer sequence (p < 0.0001).

Table 1. Description of substance use propensity variables and parameters of item-response theory models (n = 16,421)

	n (%)	Propensity coefficient (SD)	Discrimination coefficient (SD)
Model 1: early use[1]			
Tobacco	2,337 (14.2)	2.49 (0.05)***	1.00
Alcohol (drunkenness)	1,964 (12.0)	3.14 (0.08)***	1.29 (0.07)***
Cannabis	1,318 (8.0)	5.11 (0.20)***	2.03 (0.13)***
Depressants	41 (0.3)	10.83 (0.89)***	2.16 (0.25)***
Stimulants	201 (1.2)	7.99 (0.38)***	1.95 (0.15)***
Hallucinogens	201 (1.2)	7.51 (0.32)***	1.79 (0.13)***
Inhalants	235 (1.4)	5.95 (0.19)***	1.27 (0.08)***
Model 2: substance use			
Tobacco[2]	6,067 (37.0)	0.69 (0.23)***	1.00
Alcohol[3]	7,563 (46.1)	0.21 (0.02)***	1.02 (0.06)***
Cannabis[4]	1,500 (9.1)	4.28 (0.14)***	2.16 (0.13)***
Depressants[5]	75 (0.5)	9.75 (0.65)***	2.65 (0.26)***
Stimulants[5]	345 (2.1)	9.07 (0.58)***	3.31 (0.28)***
Hallucinogens[5]	127 (0.8)	9.07 (0.52)***	2.66 (0.23)***
Inhalants[5]	307 (1.9)	5.76 (0.18)***	1.68 (0.11)***

*** $p < 0.001$. [1] Initiation under 25th percentile of age; [2] current daily use; [3] current hazardous use; [4] use during the past month; [5] use during the past 12 months.

Item Response Theory Analysis

The 2 latent variables had 1-dimensional structures. The first multiple correspondence analyses dimension explained 85.8% of the variance for the variables exploring early onset and 88.6% for those exploring current use. The second dimension, mainly explained by depressants, stimulants and hallucinogens, contributed to only 3.0% of the variance for early onset and 2.0% for current use. In both early use and current use variables, OID (particularly depressants) were linked to greater propensity indices than cannabis, tobacco and alcohol being linked to the lowest ones (table 1). The highest discrimination indices were observed for depressants and cannabis concerning early onset, and for stimulants, hallucinogens and depressants concerning current use. The mean expected a posteriori scores obtained from the parameters of the IRT models were 0.00 (median –0.03; range –0.84 to 3.93) for the early onset latent variable and 0.00 (median –0.51; range –0.51 to 5.22) for the current substance use latent variable.

MSM

The total sample included 436,206 observations corresponding to yearly measures among 16,421 subjects, 17,510 transitions from 1 state to another being observed. For 1,194 subjects (7.3%), the exact use trajectory was in-completely known (at least one missing transient state). These subjects, most often being male and from higher socioeconomic levels, reported more current use of tobacco, alcohol and stimulants ($p < 0.001$). The piecewise constant intensities model provided good and precise predictions of prevalence for each state over the retrospective period (fig. 2), and had a better likelihood than an homogenous model ($p < 0.0001$).

Description of Transition Patterns between Tobacco, Cannabis and OID Use States

Estimations of PT at 1 year for each transition are presented in figure 1. From a temporal point of view, the most likely sequence was *no use → tobacco initiation → subsequent cannabis initiation → subsequent OID initiation* ($PT_{1-2} = 3.47\%$, $PT_{2-5} = 3.02\%$ and then $PT_{5-8} = 0.36\%$). Thus, the probability of starting the sequence with tobacco ($PT_{1-2} = 3.47\%$) appeared greater than that of starting with cannabis ($PT_{1-3} = 0.21\%$ – $p < 0.001$) itself greater than the probability of starting with OID ($PT_{1-4} = 0.007\%$ – $p < 0.001$). A gateway effect was observed for tobacco, the probability of cannabis initiation being greater after tobacco initiation than at the outset ($PT_{2-5} = 3.02\%$ vs. $PT_{1-3} = 0.21\%$ – $p < 0.001$). However, a reverse gateway effect was also observed, the probability of initiating tobacco after cannabis being greater than that of starting

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Table 2. HRs and 95% CIs associated with covariates for each transition from one state to another

Transition	1 → 2	1 → 3	1 → 4	2 → 5
Early use score (increase of 1)	**1.66 (1.64–1.68)**	**1.70 (1.62–1.79)**	**4.00 (3.29–4.86)**	**1.41 (1.38–1.44)**
Substance use score (increase of 1)	**1.66 (1.73–1.84)**	**2.24 (2.15–2.34)**	**1.55 (1.23–1.35)**	**1.76 (1.72–1.80)**
Gender (ref. males)	**1.37 (1.34–1.42)**	**0.73 (0.66–0.80)**	1.19 (0.81–1.77)	**0.89 (0.85–0.93)**
Socioeconomic level (ref. high)	**1.25 (1.22–1.28)**	**0.85 (0.78–0.93)**	0.71 (0.48–1.04)	**0.82 (0.79–0.85)**
Year of study (ref. 2005)	**1.43 (1.39–1.47)**	1.02 (0.93–1.11)	**0.38 (0.24–0.59)**	**1.29 (1.24–1.34)**
Drunkenness initiation (ref. no initiation)	**1.25 (1.20–1.29)**	**2.87 (2.60–3.16)**	**1.64 (1.03–2.62)**	**2.02 (1.94–2.11)**
Inhalants initiation (ref. no initiation)	**0.71 (0.63–0.80)**	1.12 (0.90–1.40)	**3.94 (2.19–7.09)**	**1.22 (1.13–1.31)**
	2 → 6	3 → 5	3 → 7	4 → 6
Early use score (increase of 1)	**2.46 (1.99–3.05)**	**0.88 (0.82–0.95)**	1.24 (0.98–1.58)	0.79 (0.36–1.74)
Substance use score (increase of 1)	**2.60 (2.08–3.25)**	**2.69 (2.51–2.89)**	**2.58 (2.01–3.31)**	**2.02 (1.06–3.85)**
Gender (ref. males)	**2.00 (1.29–3.01)**	**1.33 (1.13–1.56)**	0.90 (0.47–1.74)	3.12 (0.72–13.63)
Socioeconomic level (ref. high)	**2.29 (1.44–3.65)**	**1.52 (1.31–1.77)**	1.24 (0.74–2.07)	1.95 (0.46–8.26)
Year of study (ref. 2005)	1.13 (0.75–1.71)	**3.77 (3.25–4.38)**	**0.40 (0.19–0.86)**	2.71 (0.56–13.08)
Drunkenness initiation (ref. no initiation)	1.47 (0.93–2.32)	**0.68 (0.58–0.80)**	**2.09 (1.03–4.23)**	1.68 (0.39–7.15)
Inhalants initiation (ref. no initiation)	**4.26 (2.56–7.09)**	1.14 (0.79–1.64)	1.89 (0.63–5.66)	0.75 (0.03–19.66)
	4 → 7	5 → 8	6 → 8	7 → 8
Early use score (increase of 1)	**1.74 (1.15–2.63)**	**1.30 (1.26–1.34)**	0.90 (0.70–1.16)	0.98 (0.73–1.32)
Substance use score (increase of 1)	0.95 (0.58–1.56)	**2.27 (2.18–2.37)**	**1.51 (1.12–2.04)**	1.45 (0.98–2.12)
Gender (ref. males)	1.15 (0.42–3.16)	**0.91 (0.83–0.99)**	1.64 (0.79–3.42)	0.51 (0.14–1.88)
Socioeconomic level (ref. high)	**0.25 (0.08–0.78)**	0.94 (0.87–1.02)	0.87 (0.40–1.85)	0.94 (0.36–2.45)
Year of study (ref. 2005)	3.10 (0.91–10.57)	1.02 (0.94–1.11)	1.42 (0.71–2.83)	1.52 (0.45–5.07)
Drunkenness initiation (ref. no initiation)	**9.03 (2.76–29.57)**	**1.75 (1.52–2.04)**	1.42 (0.69–2.93)	3.96 (0.35–44.94)
Inhalants initiation (ref. no initiation)	**4.29 (1.35–13.62)**	**2.61 (2.40–2.84)**	**3.17 (1.49–6.75)**	1.35 (0.36–5.02)

States: 1 = No initiation; 2 = tobacco only; 3 = cannabis only; 4 = OID only; 5 = tobacco and cannabis; 6 = tobacco and OID; 7 = cannabis and OID; 8 = tobacco, cannabis and OID. The model is also adjusted on time-period (12–16 and 16–30 vs. 5–12 years), with significant relationship for the transitions as a whole. Bold values are significant at least at p < 0.05.

with tobacco (PT$_{3–5}$ = 10.39% vs. PT$_{1–2}$ = 3.47% – p < 0.001). The probability of initiating OID after cannabis did not significantly differ with the probability of starting with OID (PT$_{3–7}$ = 0.28% vs. PT$_{1–4}$ – p = 0.08). The probability of initiating OID after cannabis and tobacco was greater than that of initiating OID after tobacco but without previous cannabis use (PT$_{5–8}$ vs. PT$_{2–6}$ = 0.01% – p < 0.01).

Influence of Covariates on Transition Processes

The effect of time period was significant for all the transitions, justifying the choice of a piecewise constant intensities model (fig. 2). The estimations of adjusted HR related to other covariates are presented in table 2 and figure 3.

The substance current use score was associated with all transitions, with HR ranging from 1.51 (1.12–2.04) to 2.69 (2.51–2.89) for a score increase of 1 at the exception of the *OID → cannabis → tobacco* sequence. A significant

impact of the early-onset score was observed for all the beginnings of sequences whatever the substance used first: an increase of 1 for the score was associated with a 1.66 (1.64–1.68) times greater likelihood of starting the sequence with tobacco, a 1.70 (1.62–1.79) times greater likelihood of starting with cannabis and a 4.00 (3.29–4.86) times greater likelihood of starting by OID. Subjects with greater early-use scores were then more likely to follow the gateway sequence *(no use → tobacco → cannabis → OID)*, but also the alternative sequences *no use → tobacco → OID* and *no use → OID → cannabis*.

Concerning gender, women were more likely to initiate tobacco than men (HR = 1.37 (1.34–1.42) for *1 → 2* transition and HR = 1.33 (1.13–1.56) for *3 → 5* transition), but less likely to initiate cannabis (at first: HR = 0.73 (0.66–0.80); and after tobacco: HR = 0.89 (0.85–0.93)). Women were also more likely to initiate OID after tobacco (HR = 2.00 (1.29–3.01)), men being more likely to ini-
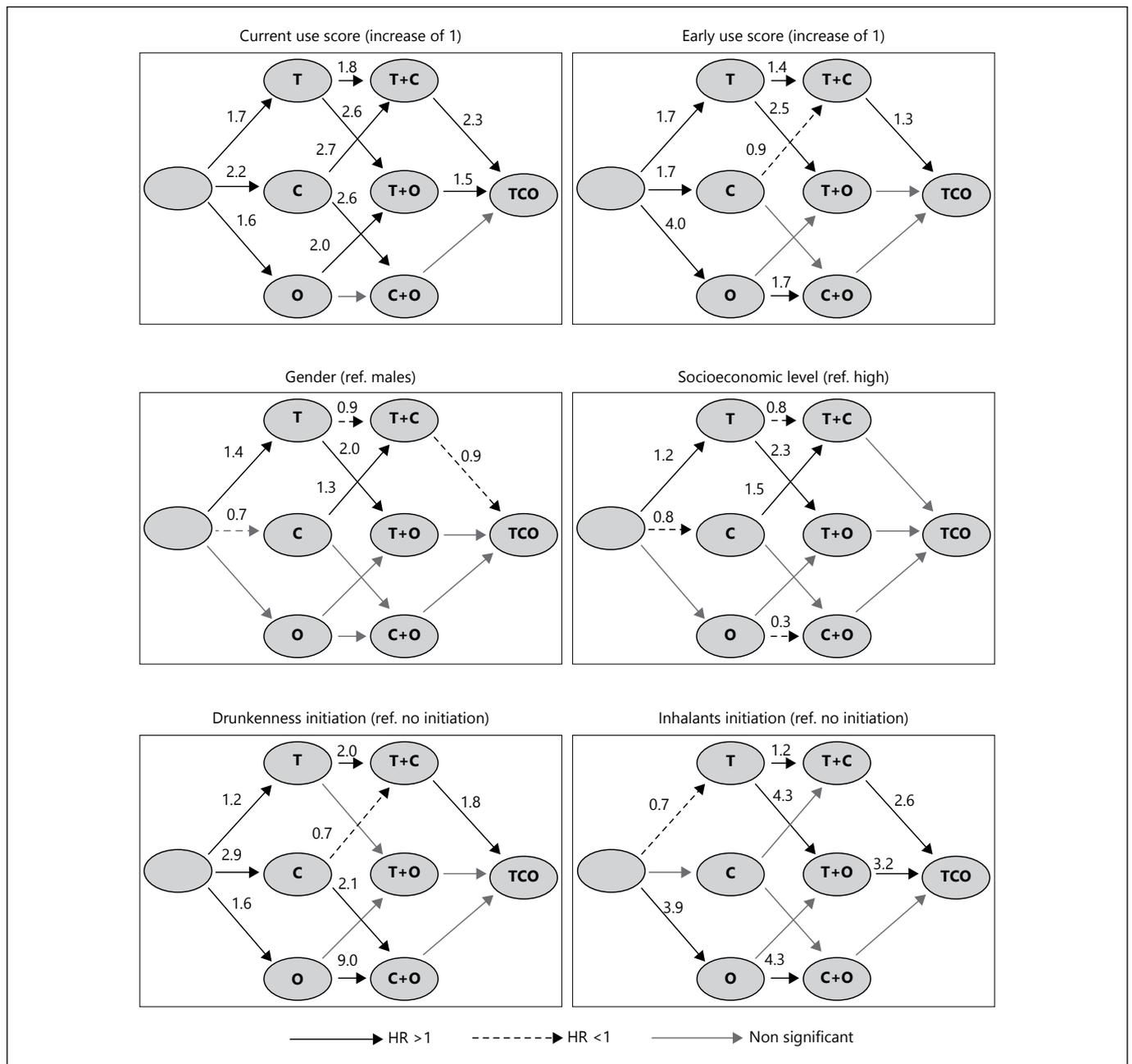
Fig. 3. HR associated with covariates for transitions between tobacco (T), cannabis (C) and OIDs. The model is also adjusted on year of study and time period (12–16 and 16–30 years vs. 5–12 years). For information about non-significant HRs and 95% CIs, please refer to table 2.

tiate OID following the gateway sequence (HR = 0.91 (0.83–0.99)). Low socioeconomic levels were associated with a greater likelihood of tobacco initiation (at first: HR = 1.66 (1.64–1.68); and after cannabis: HR = 1.52 (1.31–1.77)) but with a lower likelihood of cannabis initiation (at first: HR = 0.85 (0.78–0.93); after tobacco:

HR = 0.82 (0.79–0.85); and after OID: HR = 0.25 (0.08–0.78)). Subjects with low socioeconomic level were also more likely to follow the sequence *no use → tobacco → OID* like women.

Subjects who experienced drunkenness were more likely to follow the gateway sequence as a whole, but also

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the sequences *no use → cannabis → OID* and *no use → OID → cannabis*. Inhalants initiation was associated with the sequence *no use → OID → cannabis* and with initiation of both cannabis and OID among tobacco smokers.

Discussion

This study, using an original modelling procedure to describe initiation sequences, shows that the most likely one is *tobacco → cannabis → OID*. However, we also found that cannabis initiation was associated with a greater likelihood of subsequent tobacco initiation, while no increased cannabis initiation was observed following OID initiation. This reverse gateway effect could reflect specific relationships between tobacco and cannabis as assumed by RAM. The 'gateway sequence' was not specifically associated with early initiation or further substance use. Indeed, we found that subjects who initiated substances early are as likely to enter the sequence by tobacco, cannabis or OID. This could be in line with a common liability to substance use that is blind to the choice of the substance used first. Moreover, the current use score was associated with most of the transitions, suggesting no differential association between the sequence of initiations and further substance use or abuse.

Gateway Process

The sequence that most often observed in this study, leading from tobacco use onset to OID use onset through cannabis, is in accordance with our findings among adolescents [37] and the results of the previous research [2–6]. This 'gateway' sequence could be the consequence of a purely temporal process that we have already described as a 'string of opportunities'. Licit drugs, because of their legal status, are easily accessible in the familial environment [38]. During adolescence, nights out, during which tobacco and alcohol are used, increase cannabis opportunities under peer influence [39]. Then, as levels of cannabis use increase, consumption is no longer restricted to a festive environment and the subject consumes more frequently alone. The need for greater quantities could then lead the subject to frequent illegal environments for supply, providing some access to OID. However, we found that the order of the sequence does not seem to have any impact on further use status. This finding questions the role of the 'gateway' sequence as an independent risk factor in terms of harms and is in line with previous research suggesting that progression from one drug to another depends more on the subject's environment than on the na-

ture of the first substance used [10, 40]. Drunkenness initiation was associated with the gateway sequence, which is in line with the 'string of opportunities', but also with alternative sequences involving cannabis and OID and not followed by tobacco initiation. During adolescence, drunkenness is often initiated in a festive or recreational context in which several substances can be experimented punctually [39, 41], and the alternative sequences associated with drunkenness may reflect these particular use occasions. However, subjects who initiated inhalants and who did not start the sequence with tobacco were more at risk to initiate OID first or after tobacco or cannabis. Inhalant use is rare in France [42] but some research conducted in Brazil, where these substances are used widely, showed that first use of inhalants followed tobacco initiation but preceded the first use of some illicit substances, suggesting that inhalants should be included in the second step of the gateway model in association with cannabis [43, 44].

Common Liability to Addictions

The effect of the current use score was in the same range for most of the transitions, suggesting that subjects with greater liabilities tended to follow the gateway sequence as much as the alternative ones. This result questions GT in terms of clinical impact and is more in line with CLM. This study also shows that earlier initiation seems to contribute to the first stage of the use sequence whatever be the substance used first. Then, subjects who initiated substances earlier are at risk to complete the gateway sequence as a whole, but also to follow some alternative sequences that are incomplete (tobacco followed by OID, cannabis only and OID followed by cannabis). These results suggest that while a common liability could contribute to initiate substance use whatever the order, early users who achieve the initiation of the 3 groups of substances tend to follow the gateway sequence.

Variation in liability to drug use initiation can be explained by shared and non-shared environment [45, 46], in contrast to liability to SUD where the genetic component of variance is predominant [47, 48]. The co-existence of both GT and CLM in our model, which only explores initiation sequences, is thus not surprising. Even if our model does not formally include variables reflecting environmental exposure, we found that the probability of transition was much greater in the classic gateway path *tobacco → cannabis → OID*, than in the alternative paths, which is in accordance with the data about the availability of the three substances in the French population [42].

Thus, subjects who initiated cannabis or OID early, characterised by shorter initiation sequences, are more likely to be under the impact of individual liability than those who initiated tobacco early, characterised by longer sequences and more susceptible to be under the impact of tobacco availability. This hypothesis is strengthened by the higher levels of tobacco, alcohol and stimulants current use observed among subjects who reported the initiation of several substances a same year (incompletely known trajectories). Moreover, the impact of early onset on OID initiation (HR = 4.0) was greater than the impact on tobacco (HR = 1.7) and cannabis (HR = 1.7) at the first stage of sequence. Degenhardt et al. [10] showed that if gateway violations were largely unrelated to later dependence risk, they were associated with small increases in risk of alcohol and OID dependence for those who initiated use of OID before cannabis. Another study in Brazil showed that multiple drug seekers and gateway violators had more problematic use of illegal drugs other than cannabis [49].

A previous statistical modelling procedure has suggested that correlations between cannabis and OID use could be explained by both opportunities for consumption and a common liability to addictions [17]. However, the individual liability overlaps with environmental influences, because individuals with certain characteristics are probably more likely to reach environments facilitating access to drugs (selection of peers that use drugs, selection of type of outings associated with drug use opportunities, etc.).

RAM

If tobacco initiation seemed to increase the likelihood of subsequent cannabis initiation, a reverse cannabis gateway effect was also observed, the probability of initiating tobacco after cannabis being greater than that of starting with tobacco. This reverse gateway effect was not observed between cannabis and OID. These reciprocal relations between tobacco and cannabis were already described [50] among French adolescents [51] and are in line with RAM [25]. The role of the shared route of administration via inhalation appears realistic if we consider that users frequently mix cannabis with tobacco when smoking 'joints' in some countries. It could also reflect a physiological adaptation of the aero-respiratory system, or cultural influences surrounding smoked forms [50].

Effects of Socioeconomic Level and Gender

Subjects from lower socioeconomic levels were less prone to initiate cannabis at first or following tobacco or OID, but tended to report more tobacco initiation (at first

or following cannabis) and OID initiation following tobacco. The same trends were observed for women. These results, obtained among young subjects, are in line with the diffusion of tobacco and cannabis across generations [52]. In older generations, men and the most educated experimented more tobacco, while a shift in gender and educational level was observed in younger generations. A similar diffusion model was recently described for cannabis initiation; in France, according to this model, men from lower socioeconomic levels are presently more affected by cannabis initiation than women. The women the most exposed belong to higher levels [53].

Study Limitations

Due to the nature of the original sample, our model does not include some potential confounds like social factors (at the exception of socioeconomic level), substance availability or personality traits. Consequently, this study has to be interpreted only from a 'descriptive' point of view, to give rise to some hypotheses. Thus, some confounding factors addressed in the discussion may be added in the questionnaire of the next Health Barometer to enable the use of a more adapted model.

Our 'OID' variable included substances that are not readily comparable to each other in terms of effects or use patterns (cocaine, ecstasy, heroin, etc.). However, grouping these substances provided sufficient power to analyse rare transitions, and could be justified by the similar distributions of ages at onset for depressants, stimulants and hallucinogens. Drunkenness initiation was used in the multi-state model because age at alcohol onset was not collected here. The score exploring substance use propensity included tobacco daily use – that is able to reflect dependence – and alcohol hazardous use. Considering that current alcohol use concerns >80% of the French population [42], hazardous use may have more discrimination power here.

The use of yearly intervals of measure, the consequence of age-reported data, could also be considered restricting for the description of transitions that can occur in less than a 1-year time lapse. However, the parametric assumptions of the MSM we used makes it possible to analyse data observed at a discrete set of time points and to consider the underlying trajectories of subjects who reported the initiation of several substances the same year [54]. Finally, recall bias is likely to be limited if we restricted the analyses to subjects aged 18–34. Moreover, tobacco, cannabis or OID initiations can be viewed as important events in an adolescent's life, as they often occur in a

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novelty-seeking context or as an urge to transgress rules [5]. Limited recall bias concerning ages of initiation was already described [55].

events like progression to SUD could provide a more accurate description of use sequences in terms of clinical impact and a more complete test of CLM.

Conclusion

We implemented a global modelling method that suggests the shared role of CLM, GT and RAM in the explanation of substance-use onset sequences in adolescence and young adulthood. A common liability may contribute to the initiation of the sequence, whatever be the substance used first, while the following of the sequence, which seems to follow a 'gateway' pattern among most of users, may be more conditioned by substance availability. Our method, using variables that are relatively easy to collect (age at onset, use prevalence), can be implemented from cross-sectional samples such as those of prevalence studies existing in some countries, and could be consequently reproduced to make cross-national comparisons.

However, this study focuses only on initiation sequences. The use of MSM taking into account data about

Key Points

- This study used multi-state modeling and item response theory to investigate several substance use theories.
- Initiation sequences seem to simultaneously reflect some aspects of GT, common liability to addictions and RAM.
- This could reflect shared influences of individual and environmental characteristics.

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