Can the Gateway Hypothesis, the Common Liability Model and/or, the Route of Administration Model Predict Initiation of Cannabis Use During Adolescence? A Survival Analysis—The TRAILS Study

Andrea Prince van Leeuwen, M.Sc.\textsuperscript{a,b,*}, Frank C. Verhulst, M.D., Ph.D.\textsuperscript{b}, Sijmen A. Reijneveld, M.D., Ph.D.\textsuperscript{c}, Wilma A.M. Vollebergh, Ph.D.\textsuperscript{d}, Johan Ormel, M.D., Ph.D.\textsuperscript{e}, and Anja C. Huizink, Ph.D.\textsuperscript{a,b}

\textsuperscript{a} Research Institute of Child Development and Education, Department of Education, University of Amsterdam, The Netherlands
\textsuperscript{b} Department of Child and Adolescent Psychiatry, Erasmus University Medical Center Sophia Children’s Hospital, Rotterdam, The Netherlands
\textsuperscript{c} Department of Health Sciences, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
\textsuperscript{d} Department of Interdisciplinary Social Science, University of Utrecht, Utrecht, The Netherlands
\textsuperscript{e} Department of Psychiatry, Interdisciplinary Center for Psychiatric Epidemiology, University Medical Center Groningen, University of Groningen, The Netherlands

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ABSTRACT

Purpose: There is substantial research linking tobacco and alcohol use to subsequent cannabis use, yet the specificity of this relationship is still under debate. The aim of this study was to examine which substance use model—the gateway hypothesis, the common liability (CL) model and/or the route of administration model—best explains the relationship between early onset of tobacco and alcohol use and subsequent cannabis use initiation.

Methods: We used data from 2,113 (51% female) Dutch adolescents who participated in three consecutive assessment waves (mean age: 11.09, 13.56, and 16.27 years, respectively) of the TRacking Adolescents’ Individual Lives Survey study. (Pre)adolescent cannabis, tobacco and alcohol use was assessed using the Youth Self-Report and a TRacking Adolescents’ Individual Lives Survey developed questionnaire.

Results: We found that, during adolescence, early onset of tobacco use does not pose a significantly higher risk of initiating cannabis use than early onset alcohol use. Therefore, we can rule out the route of administration model. Moreover, we found that adolescents who reported early onset comorbid use of both tobacco and alcohol have a higher likelihood to initiate cannabis use than adolescents who have tried either tobacco or alcohol. The gateway hypothesis is not broad enough to explain this finding. Therefore, the CL model best predicts our findings.

Conclusion: Future research on adolescent cannabis initiation should focus on testing the robustness of the CL model. Furthermore, identifying adolescents who use both tobacco and alcohol, before the age of 13, may help to curtail the onset of cannabis use.

Adolescence is a critical phase for many forms of development, resulting in a unique “window” of vulnerability, especially with regard to substance use. The majority of cannabis use initiation occurs during in this stage. Early onset of cannabis use in adolescence has been associated with a higher risk of experimenting with other substances [1,2], developing a substance use disorder or dependence [3], substance related problems [2,4,5], juvenile delinquency [6], higher rates of cannabis use and other illicit substance use in (young)adulthood [7], and mental health problems [8–10]. To better understand as well as curb cannabis use, several researchers have examined which factors may be predictive of its use onset in adolescence. Among those factors,
particularly tobacco [11,12] and alcohol [13] initiation have been
linked to a higher propensity to initiate and maintain cannabis
use [14]. For example, in two previous studies among Dutch and
Finnish adolescents, Korhonen et al. found that smoking onset
before the age of 13 is a powerful predictor for subsequent use of
cannabis [11,12]. Given these findings, one would expect early
onset of tobacco use to increase the likelihood of cannabis use
during adolescence.

The gateway hypothesis (GW) and the common liability (CL)
model aim to identify vulnerable individuals who have a higher
likelihood of transitioning to other illicit types of substance use
such as cannabis. The GW proposes that drug consumption
progresses in a stage-like sequence. According to this hypothesis,
cannabis use would typically follow licit drug use such as tobacco
and/or alcohol use, whereas illicit hard drug use (e.g., cocaine or
heroin) would follow illicit soft drug use such as regular canna-
abis use [15,16]. The CL proposes that using both licit and illicit
drugs may be because of the influence of a CL. This liability may
include a genetic and individual vulnerability, such as proneness
to deviancy and familial liability to addiction. Unlike the GW,
which proposed the sequential progression of drug use, the CL
proposes that (a) the “choice” of which substance is used first can
be the result of the aforementioned factors, and (b) no a priori
order is expected in the sequence of drug use. However, neither
of these theories can account for the specific causal nature of the
association between tobacco and cannabis use that was recently
reported [11,12,17].

Alternatively, the recently postulated route of administration
(ROA) model [17] suggests that the shared route in which sub-
stances are administered (e.g., inhalation) may account for the
future initiation of other types of substance use, thus explaining
why tobacco and cannabis use commonly coexist. For example,
an adolescent who inhales tobacco may be more likely to pro-
tendy to different types of inhaled substances such as can-

The TRAILS is a large prospective population study of Dutch
adolescents. The present study involves data from the first (T1),
second (T2), and third (T3) assessment waves of TRAILS, which
2004 and September 2005–August 2008, respectively. At T1,
2,230 subjects were enrolled in the study (mean age, 11.09 years;
standard deviation [SD], .55; 50.8% girls). At T2, 2,149 subjects
participated (mean age, 13.56 years; SD, .53; with 51.0% girls).
Finally, at T3, 1,816 subjects participated (mean age, 16.27 years;
SD, .73; with 52.3% girls; for more details, see [19,20]). Before
each assessment wave, informed consent was obtained from all
adolescents and their guardian(s) after the nature of the study
had been fully explained. Furthermore, the Central Committee
on Research Involving Human subjects approved all of the
TRAILS study protocols.

Procedure

During the first and third assessments, well-trained data col-
lectors visited one of the parents or guardians at their homes to
administer an interview. In addition to the interview, the parent
was asked to fill out a self-report questionnaire. Adolescents
were assessed at school or other testing locations, where they
completed questionnaires, under the supervision of one or more
TRAILS assistants, during all three assessments (T1, T2 and T3). In
addition, information processing capacities, intelligence, and a
number of biological and physiological parameters were as-
sessed individually. The second assessment involved only self-
report questionnaires, to be completed by the adolescent, their
parents, and teachers [19,20]. All forms of (pre)adolescent sub-
stance use (i.e., tobacco use, alcohol use, and cannabis use) were
assessed using the Youth Self-Report (YSR) [21,22] and a TRAILS
developed questionnaire [23]. Lifetime use and frequency of use were assessed at T1, T2, and T3, and age of onset was assessed at T2 and T3, for tobacco use, alcohol use, and cannabis use. Confidentiality of the study was emphasized.

**Measures**

**Assessment of onset of cannabis use, tobacco use, and alcohol use**

In the present analyses, age at which the adolescent used cannabis for the first time was used as the outcome variable. Adolescents were asked, in separate questions, about the age in which they first tried cannabis, tobacco, and alcohol using the following question: “How old were you when you first (smoked tobacco/drank alcohol/smoked weed or hash)?” The options were: 0 = never tried, 1 = 9 years or younger, 2 = 10 years, 3 = 11 years, 4 = 12 years, 5 = 13 years, 6 = 14 years, 7 = 15 years, and 8 = 16 years. Self-reported age of first use was asked at waves T2 and T3. If there was a discrepancy between the age of onset reported at T2 and T3, then the age reported at T2 was preferred because less time had elapsed between the onset of substance use and assessment time, thereby decreasing the likelihood of errors in recall. This decision was supported by our findings that the adolescents in our study were more likely to report an older age of substance use onset at T3 than at T2 (Table 1).

Furthermore, all substance use questions at T3 allowed the adolescents to choose an onset age of up to only 16 years, yet some adolescents were 17–18 years old at the T3 assessment. Thus, onset of use could have taken place at later than 16 years of age. To correct for this problem we did the following: if the adolescents did not report using cannabis at T1 or T2, but did report cannabis use at T3, then the adolescent was considered to be a new onset cannabis user. We then referred to the questions: “Have you (smoked tobacco/drank alcohol/smoked weed or hash) within the past 12 months?” and “Have you (smoked tobacco/drank alcohol/smoked weed or hash) within the past 4 weeks?” If the adolescents answered yes to using cannabis within the past 12 months or past 4 weeks, we chose to use the assessment age at T3. If the adolescents answered no to (smoking tobacco/drinking alcohol/smoking weed or hash) within the past 12 months, we subtracted one year from the T3 assessment age.

To determine whether an individual smoked tobacco at an early age, adolescents were asked the following questions from a TRAILS developed questionnaire at T1: “Have you ever smoked a cigarette?” “If yes, how many cigarettes (or hand rolled cigarettes) have you had in the last 4 weeks?” The options were: 0 = I have never smoked tobacco, 1 = once, 2 = twice or three times, 3 = four through six times, 4 = seven or more times. We dichotomized cigarette smoking at T1 as: 0 = never use of tobacco and 1 = ever use of tobacco.

A similar procedure was followed to determine EOAU. The following question was asked at T1: “Have you ever drunk alcohol (for example a bottle of beer or a glass of wine)?” “If yes, how many times have you drunk alcohol?” The options were: 0 = I have never drunk alcohol, 1 = once, 2 = twice or three times, 3 = four through six times, 4 = seven or more times. Responses were dichotomized into: 0 = never use of alcohol and 1 = ever use of alcohol.

**Assessment of externalizing and internalizing problems (T1)**

Externalizing behavior problems were assessed using both the Child Behavior Checklist (CBCL) and the Youth Self-Report (YSR), which are two of the most frequently used questionnaires in current child and adolescent psychiatry research [21,22,24]. Both the CBCL and the YSR provide researchers with the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) based externalizing behavior scales (DSM-IV Ext(b)), which is a compilation of Attention Deficit Hyperactivity Problems (7 items, \( \alpha = .72 \)), Oppositional Problems (5 items, \( \alpha = .62 \)), and Conduct Problems (15 items, \( \alpha = .72 \)), as well as DSM-IV-based internalizing behavior scales (DSM-IV Int(b)), which is a compilation of Affective Problems (13 items, \( \alpha = .77 \)), Anxiety Problems (6 items, \( \alpha = .63 \)), and Somatic Problems (7 items, \( \alpha = .69 \)). Reliability and validity of the Dutch translated American version of the CBCL and YSR have been confirmed [24,25].

**Assessment of exact age**

Date of birth was assessed through the self-report questionnaires administered during T1, T2, and T3.

**Assessment of socioeconomic status (SES)**

SES was calculated as the average of income level, educational level, and occupational level of each parent, using the International Standard Classification for Occupations at T1 and was categorized into low, average, and high SES [26].

**Assessment of paternal and maternal vulnerability of addiction and psychopathology**

Familial loading information of psychopathology was collected during the TRAILS Family History Interview (T1) by interviewing a parent (usually the mother). Five dimensions of psychopathology, depression, anxiety, substance dependence, persistent antisocial behavior, and psychosis, were assessed. Each dimension was introduced by a vignette, which described the main DSM-IV characteristics, followed by a series of questions assessing lifetime occurrence, professional treatment, and medication use [27].

**Statistical analyses**

The analyses were conducted using the Statistical Package for the Social Sciences (SPSS Inc. Chicago, IL), version 15. Correlations of the variables used in our study were calculated using bivariate correlation analyses.

**Survival analyses**

We used Cox regression survival analyses [28] to examine which model (i.e., the GW, the CL, or the ROA) best explains the relationship between EOTU and/or EOAU and subsequent initiation of cannabis use. The Cox regression survival analysis method
allowed us to examine cannabis use onset by age in years. Furthermore, the survival analysis also includes censored data, which allowed us to retain a large amount of subjects in our study that would not be possible with other types of statistical testing methods. All analyses were adjusted for child-reported externalizing behavior problems, paternal vulnerability of addiction, maternal vulnerability of addiction, and SES. We defined survival time in years of age at onset of cannabis use. Given that age was calculated as a whole number of years, we used the exact method in SPSS for treatment of ties.

First, we examined whether adolescents who reported EOTU (1 = EOTU occurred) were more likely to initiate cannabis use than adolescents who had never tried tobacco by the age of 13 years (0 = EOTU did not occur). Furthermore, we examined whether adolescents who reported EOAU (1 = EOAU occurred) were more likely to initiate cannabis use than adolescents who had never tried alcohol by the age of 13 years (0 = EOAU did not occur). The existence of differences between users and nonusers would confirm the predictions of the GW and the CL. For example, both the GW and the CL suggest that individuals who have used either tobacco or alcohol should be equally likely to use cannabis than abstainers. Second, we examined whether adolescents who reported EOTU (1 = EOTU occurred) were more likely to initiate cannabis use than adolescents who reported EOAU (0 = EOAU occurred). If EOTU resulted in a higher likelihood to initiate cannabis use, as compared with EOAU, this finding would confirm the predictions of the ROA, but not of the GW or the CL.

Finally, to explore our last two aims, we examined the influence of early onset of comorbid tobacco and alcohol use (EOTAU) upon subsequent cannabis use. First, we examined whether adolescents who reported EOTAU (1 = EOTAU occurred) were more likely to initiate cannabis use than adolescents who reported that they had never used either tobacco or alcohol by the age of 13 years (0 = EOTAU did not occur). Second, we examined whether adolescents who reported EOTAU (1 = EOTAU occurred) were more likely to initiate cannabis use than adolescents that reported they had never used either tobacco or alcohol by the age of 13 years (0 = EOTAU did not occur). Our next Cox regression analysis model showed that adolescents who reported EOTAU (1 = EOTAU occurred) were more likely to initiate cannabis use than adolescents who reported ever use of either tobacco or alcohol (0 = ever use of either tobacco or alcohol by the age of 13 years). The existence of differences between comorbid users and users of either substance would confirm the predictions of the CL, but not of the GW, given that the GW does not differentiate between comorbid use and single substance use (i.e., The GW does not take into account the additive effects of using more than one substance.).

In contrast, the GW does suggest that adolescents who are comorbid users of substances such as tobacco and alcohol may be likely to use cannabis. The proportional hazard assumption was not violated in any of the conducted analyses. We assumed statistical significance at the p < .01 level.

Results

Descriptive results

Analyses were based on 2,113 adolescents (51% female) who participated in the TRAILS study. The mean age at the outcome assessment (T3) was 16.3 years (SD .73; range, 14.5–18.5). By the end of T3, 587 (34.4%) adolescents had used cannabis at least once during their lifetime. The difference in prevalence between boys and girls for cannabis use was not significant. The percentage of adolescents who reported ever using tobacco, cannabis, or alcohol is listed by age in Table 2. At T1, 302 (13.7%) adolescents reported ever use of tobacco and 681 (31.0%) adolescents reported ever use of alcohol at T1.

The association between EOAU and subsequent cannabis use

We carried out a Cox regression analysis for EOTU as a predictor of lifetime cannabis use by age. Adolescents who initiated tobacco use early are at an increased risk for cannabis use (hazard ratio, 1.80; p < .001; 95% confidence interval [CI], 1.73–2.59) compared with adolescents who had never tried cigarettes by the age of 13 years. We controlled for child-reported externalizing problems, EOAU, paternal vulnerability of addiction, maternal vulnerability of addiction, and SES.

The association between EOAU and subsequent cannabis use

Our next Cox regression analysis model showed that adolescents who initiated alcohol use early are at an increased risk to initiate cannabis use (hazard ratio, 1.43; p < .001; 95% CI, 1.19–1.72). In this model, we controlled for child-reported externalizing problems, EOAU, paternal vulnerability of addiction, maternal vulnerability of addiction, and SES.

EOAU versus EOAU as predictors of subsequent cannabis use

Adolescents who reported EOTU did not have a significantly higher likelihood of initiating cannabis use than adolescents who reported EOAU (hazard ratio, of 1.13; p > .05; 95% CI,.89–1.91).

EOAU versus no use of either tobacco or alcohol as predictors of cannabis use

When comparing EOTAU to abstainers (no tobacco or alcohol use before the age of 13), we found that adolescents who reported EOTAU were more likely to initiate cannabis use than abstainers (hazard ratio, 2.52; p < .001; 95% CI, 1.94–3.26) (Figure 1).

In the subsequent analysis, we compared EOTAU with ever use of either tobacco or alcohol as predictors of cannabis use. Our findings showed that adolescents who reported EOTAU run a higher risk to initiate cannabis use than ever users of either tobacco or alcohol (hazard ratio, 1.72; p < .001; 95% CI, 1.33–2.22) (Figure 1).

<table>
<thead>
<tr>
<th>Age*</th>
<th>% Cannabis use</th>
<th>% Tobacco smoking</th>
<th>% Alcohol use</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 years old or younger*</td>
<td>0.5</td>
<td>12.1</td>
<td>5.2</td>
</tr>
<tr>
<td>10 years old*</td>
<td>0.7</td>
<td>10.4</td>
<td>11.3</td>
</tr>
<tr>
<td>11 years old*</td>
<td>1.5</td>
<td>15.0</td>
<td>18.3</td>
</tr>
<tr>
<td>12 years old*</td>
<td>9.4</td>
<td>23.0</td>
<td>26.7</td>
</tr>
<tr>
<td>13 years old*</td>
<td>21.0</td>
<td>16.7</td>
<td>20.2</td>
</tr>
<tr>
<td>14 years old*</td>
<td>22.3</td>
<td>10.9</td>
<td>8.6</td>
</tr>
<tr>
<td>15 years old*</td>
<td>29.8</td>
<td>9.4</td>
<td>8.0</td>
</tr>
<tr>
<td>16 years old*</td>
<td>7.3</td>
<td>0.1</td>
<td>0.9</td>
</tr>
<tr>
<td>17 years old*</td>
<td>5.6</td>
<td>1.8</td>
<td>0.5</td>
</tr>
<tr>
<td>18 years old*</td>
<td>1.9</td>
<td>0.6</td>
<td>0.20</td>
</tr>
<tr>
<td>Total ever use by the end of T3</td>
<td>34.4</td>
<td>54.9</td>
<td>87.5</td>
</tr>
</tbody>
</table>

* Age of self-reported cannabis ever use: T2 age taken over T3 age.

Table 2 Percentage of adolescents who initiated cannabis use by age group

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Discussion

As predicted by the GW and the CL model \([12,15,16,18,29]\), the current study shows that both EOTU and EOAU increase the risk of initiating cannabis use. In addition, when comparing EOTAU to both abstainers (no T1 tobacco or alcohol use) and to early ever users of either tobacco or alcohol, we found that adolescents who reported EOTAU had a higher likelihood to initiate cannabis use.

When examining whether EOTU is more likely than EOAU to increase the likelihood of cannabis use initiation, we found that these adolescent user groups did not significantly differ from
each other. This finding does not support the ROA model presented by Agrawal and Lynskey [17], given that the adolescents who reported EOTU (e.g., the “experienced inhalers”) were equally likely to initiate cannabis use as adolescents who reported EOAU. It is important to mention that our population measured an adolescent population, whereas the Agrawal study [17] measured an adult population. Perhaps as substance use progresses, the ROA becomes more important and therefore replenishes the type of substance used [30]. For instance, in a recently published study, Huizink et al. [31] found that cannabis use might increase the risk (path coefficient of .32) of continued smoking behavior in an adolescent population. Therefore, the ROA may play a larger role in maintenance than in initiation of substance use. Perhaps, when taking tobacco and cannabis users into account, the experience of inhaling has to be more developed than what one usually finds in early onset tobacco users (e.g., as the amount of tobacco use increases, the likelihood of initiating or using cannabis use also increases, and vice versa).

Furthermore, findings from our EOTAU analyses indicate that comorbid users are more likely to use cannabis than ever users of either tobacco or alcohol. The GW is not broad enough to explain this increased likelihood. On the contrary, comorbid users and ever users should have an equally increased likelihood of initiating cannabis use according to the GW.

Given our findings, and the mentioned limitations resulting in the lack of support for the other predictive models, we conclude that the CL is the most robust model to predict the onset of cannabis use during adolescence.

Implications

Curbing early onset of tobacco and alcohol use with a specific focus on comorbid tobacco and alcohol use, before the age of 13, may help to diminish the amount of adolescents who initiate early onset cannabis use.

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References


