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Transition to drug co-use among adolescent cannabis users: The role of decision-making and mental health

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Abstract

Background: Co-use of cannabis and drugs other than cannabis (DOTC) influences the risk of experiencing cannabis disorders. Accordingly, we explored whether speed of transition to drug co-use, the number of DOTC used, and/or being an experimental cannabis-only user, a regular cannabis-only user, or a regular cannabis user who co-uses DOTC (i.e., cannabis-plus user) were associated with decision-making (DM), mental health disorder symptoms, or cannabis use-related characteristics.

Methods: We analyzed baseline data from a sub-sample of 266 adolescent (ages 14 to 16) cannabis users (CU) participating in an ongoing longitudinal study. Assessments included semi-structured interviews, self-report questionnaires, and measures of drug use, DM (measured via the Iowa Gambling Task), mental health disorders, and cannabis use-related problems.

Results: Endorsing a larger number of mood disorders symptoms was associated with being a regular cannabis-plus user rather than a regular cannabis-only user (AOR = 1.08, C.I.95% 1.01, 1.15). Poorer DM was associated with a faster transition to co-use, such that for each one unit increase in DM performance, the years to onset of drug co-use increased by 1% ($p = 0.032$). Endorsing a larger number of cannabis use-related problems was positively associated with endorsing a larger number of DOTC used ($p = 0.001$).

Conclusions: This study provides new evidence on the process of drug co-use among CU. Specifically, mood disorder symptoms were associated with use of DOTC among regular CU. Furthermore, poorer DM was associated with a faster transition to drug co-use. Poorer DM and mood disorder symptoms may aggravate or accelerate the onset of adverse consequences among adolescent CU.

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Contributors

CLQ and RG conceptualized and designed the study. CLQ managed the literature review, conducted the data analysis, and wrote the first draft. RG designed and oversaw the parent study from which this data was derived and KG, SH, JCD, IPC revised the manuscript critically for important intellectual content. All authors contributed to and approve the manuscript.

Conflict of interest

No conflict to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.addbeh.2018.05.010.

Keywords

Cannabis; Co-use; Polydrug; Decision-making; Depression; Transition

1. Introduction

Legalization of cannabis use for medical and/or recreational use in 29 states, as well as mounting evidence on the health and social effects of cannabis use (Huang et al., 2015; Lubman, Cheetham, & Yücel, 2015; Volkow, Baler, Compton, & Weiss, 2014), indicates that more research is needed to characterize which individuals are most at risk for adverse consequences from their cannabis use. Approximately 6600 Americans over the age of 12 initiate cannabis use every day (Azofeifa, 2016). Approximately 9% of adult cannabis users (CU) (Anthony, Warner, & Kessler, 1994; Lopez-Quintero et al., 2011) will experience physical, mental or social problems of sufficient severity to warrant a diagnosis of a cannabis use disorder.

A myriad of intertwined factors ranging from genetic vulnerability to social and cultural exposures influence the pathway from first use to the manifestation of a clinical use disorder and other negative consequences, among both adolescents and adults (Agrawal & Lynskey, 2008; Kendler, Jacobson, Prescott, & Neale, 2003; Kendler & Prescott, 2007). This study focuses on co-use of drugs other than cannabis (DOTC) among CU. This factor has shown to significantly increase the risk of experiencing adverse consequences. For instance, while the risk of developing a drug use disorder for adult cannabis-only users is approximately 2%, it increases to about 17% for CU who also use other drugs (Lopez-Quintero & Anthony, 2015). Moreover, the rates of emergency department visits are higher among adolescent CU (12 to 17 years old) who also use DOTC than among adolescent cannabis-only users (159 visits per 100,000 vs. 79 visits per 100,000) (Zhu & Wu, 2016).

A better characterization of cannabis use patterns and the concomitant use of DOTC may enhance current preventive programs and reduce adverse outcomes. Yet, the factors characterizing the diverse subgroups of CU remain understudied. The available evidence among adolescents and adults suggest that the risk of progression to DOTC among CU is linked to genetic predisposition (Agrawal, Neale, Prescott, & Kendler, 2004), early onset and frequency of cannabis use (Fergusson, Boden, & Horwood, 2006; Lynskey et al., 2012; Moss, Chen, & Yi, 2014; Richmond-Rakerd et al., 2016), internalizing and externalizing symptoms and disorders (Secades-Villa, Garcia-Rodríguez, Jin, Wang, & Blanco, 2015; Tarter, Vanyukov, Kirisci, Reynolds, & Clark, 2006), and increased drug use exposure opportunities (Tarter et al., 2006; Wagner & Anthony, 2002). Research on the speed of DOTC use onset or the number of drugs used among adolescent CU is even more scarce, and the few studies on number of DOTC use available suggest that age of cannabis use onset and response inhibition relate to increased exposure to other drugs (Darke, Kaye, & Torok, 2012) and to a larger number of DOTC used (Nigg et al., 2006), respectively.

The current cross-sectional study adds to the extant body of knowledge by exploring the factors associated with membership in three specific subgroups of CU, namely (1) experimental cannabis-only users; (2) regular CU who exclusively use cannabis (regular

cannabis-only users); and (3) regular CU who also endorsed use of at least one DOTC (regular cannabis-plus users). In addition, we investigated the factors associated with speed of transition to drug co-use and the number of DOTC used among cannabis-plus users. The factors selected to characterize our subsample of CU include symptoms of anxiety, mood, and externalizing disorders, decision-making (DM; i.e., ability to make choices in situations with ambiguous contingencies that require tradeoffs between risks and rewards (Bechara, 2005)), and cannabis use-related characteristics (e.g., amount of cannabis used). All of these factors have been linked to more problematic cannabis use and adverse consequences. Specifically, anxiety, mood, and externalizing symptoms, as well as amount of cannabis used, have been independently associated with earlier cannabis use onset, problematic cannabis use, or use of DOTC among CU (Degenhardt et al., 2013; Fergusson et al., 2006; Lopez-Quintero et al., 2011; Secades-Villa et al., 2015). However, the respective contributions of these factors, together with DM, have not been well-studied. Furthermore, the few studies comparing cannabis users who use cannabis (but not other regulated drugs) with those who use cannabis together with other regulated drugs have rarely examined the role of decision-making. In addition, while previous research indicates that impairments in DM and other cognitive abilities are associated with regular drug use (Day, Metrik, Spillane, & Kahler, 2013; De Bellis et al., 2013; Gonzalez, Schuster, Mermelstein, & Diviak, 2015; Hooper, Woolley, & De Bellis, 2014), less is known about their role in the process of drug use involvement. The few available studies suggest that working memory and response inhibition predict alcohol and drug use onset, binge drinking among alcohol naive adolescents, and the number of drugs used (Moeller, Bederson, Alia-Klein, & Goldstein, 2016; Nigg et al., 2006; Norman et al., 2011; Peeters et al., 2015; Tarter et al., 2003). In this study, we focused on DM because its effect on the onset of drug co-use has not been well studied, and because increasing evidence supports its role as an important predictor and moderator of cannabis use outcomes (De Bellis et al., 2013; Gonzalez et al., 2015).

In this study, we anticipated that endorsing more symptoms of mental health disorders, and endorsing a larger number of cannabis use-related problems would be associated with membership in the regular cannabis-plus subgroup regardless of the individual's DM abilities. We also hypothesized that endorsing more symptoms of mental health disorders, endorsing a larger number of cannabis use-related problems, and particularly having poorer DM performance, would be associated with cannabis use group membership, a faster transition to drug co-use, and to endorsing a larger number of DOTC used among regular cannabis-plus users.

2. Study methods

2.1. Study design and participants

In this report, we analyzed baseline data from a subsample of adolescent CU (n = 266) participating in an ongoing longitudinal study that assesses DM and episodic memory in trajectories to cannabis addiction (R01DA031176, PI: Raul Gonzalez). Participants were recruited from South Florida middle and high schools distributed throughout the county. The target population included adolescents at risk for escalation in cannabis use. Inclusion criteria consisted of being 14 to 17 years old at baseline, having the ability to read and write

English, and exposure to either alcohol, cigarettes, or cannabis (even if only minimal); however, a subset of participants (approximately 10%) with no substance use at baseline were included in the study. Exclusion criteria included self-reported developmental disorders, neurological conditions, significant birth complications, history of a traumatic brain injury or loss of consciousness for 10+ minutes, a formal diagnosis or history of treatment for a mental health disorder at screening, alcohol or DOTC use patterns suggestive of a use disorder, lifetime use of DOTC (besides alcohol, cannabis, and nicotine) > 10 times, or use of DOTC in the two weeks prior to assessment, and lifetime use of DOTC to an extent greater than their cannabis use. In addition, the current study excluded participants who never used cannabis or those whose patterns of use were not consistent with those in the specified subgroups (e.g., not having used cannabis more than three times in the lifetime, and 15 experimental users who also endorsed DOTC use). All participants underwent oral fluid toxicology testing to assess for recent use of THC, cocaine, opiates, amphetamines, methamphetamines, barbiturates, benzodiazepines, and PCP using the Intercept oral fluid drug test (OraSure Technologies, Inc.: Bethlehem, PA). Study participants were not required to discontinue or change their drug use behaviors to be included in the study. Study measures consist of structured interviews, paper-and-pencil questionnaires, and computerized measures of DM. Assessment spanned demographics, mental health, patterns of substance use, prevalence of substance use disorders, and neurocognitive functioning. Participant assent and parental consent were obtained for all participants. All study procedures and protocols were approved by the Institutional Review Board at Florida International University.

2.2. Measures

2.2.1. Cannabis use and subgroup membership—Participants who indicated having used any drug at least three times completed the Drug-Use History Questionnaire (Gonzalez et al., 2012; Rippeth et al., 2004), a detailed semi-structured interview using retrospective self-report to gather information on the frequency and quantity of use of 16 drug classes. Drugs assessed in this semi-structured questionnaire included alcohol, nicotine, cannabis, and regulated drugs such as, synthetic cannabinoids (e.g., K2, spice), cocaine, methamphetamine, other stimulants, heroin, opiates, benzodiazepines, barbiturates, ecstasy, hallucinogens, other club drugs, phencyclidine (PCP), and inhalants. We estimated quartiles of lifetime amount of cannabis used (i.e., total amount of cannabis consumed in grams since the beginning of cannabis use onset until the assessment day) in order to classify “experimental” and “regular” CU, such that those in the first quartile were labeled as “experimental” users (mean number of times of cannabis use in the lifetime = 10.51 times, SD = 9.80; amount of cannabis used in grams over the lifetime = 2.48 g, SD = 1.53), and those in the second to fourth quartiles of use were labeled as “regular” CU (mean number of times used in the lifetime = 246.24, SD = 795.76; amount of cannabis used in grams during the lifetime = 234.59 g, SD = 500.69). Regular CU were further differentiated into “cannabis-only users” (CU who did not used other regulated drugs), and “cannabis-*plus*” users (i.e., participants endorsing lifetime use of cannabis plus use of at least one DOTC, with the exception of alcohol and tobacco products). Use of DOTC was minimal among the 13 drug classes explored (highest mean of number of times used in the lifetime was for benzodiazepines = 13.25, SD = 19.23), and never exceeded the use of cannabis. For the

purpose of this report, three mutually exclusive subgroups of CU were defined: (1) Experimental cannabis-only users (n = 57; 21.43%); (2) regular cannabis-only users (n = 91; 34.21%); and (3) regular cannabis-plus users (n = 118; 44.36%).

2.2.2. Speed of transition to onset of drug co-use—The speed of transition to onset of drug co-use among cannabis-plus users was assessed by estimating the elapsed time, in years, between cannabis use onset and DOTC use onset. Thus, the number of years between cannabis use and DOTC use onset was calculated by subtracting the age of cannabis use onset to the earliest age of DOTC use onset, where a value of zero or closer to zero denoted a "faster" transition to co-use. For example, the value assigned for a participant who started to use cannabis at age 14, a second DOTC at age 15 and a third DOTC at age 16 will be "1". Only four CU reported DOTC use onset earlier than cannabis use onset and were excluded from the analyses.

2.2.3. Number of drugs other than cannabis used—Self-reported lifetime use of any of the 13 drugs assessed in the DUHQ (all drugs listed above except tobacco, alcohol, and cannabis) was used to estimate the number of DOTC used by a participant. For example, for a participant who reported using benzodiazepines once and using hallucinogens four times, the number of DOTC used would be two.

2.2.4. Mental health disorder symptoms—Mental health disorder symptoms were assessed using the Computerized Diagnostic Interview Schedule for Children, Version IV (CDISC-IV; Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000). Any reported symptoms of a panic disorder, generalized anxiety disorder, or obsessive-compulsive disorder during the year prior to assessment were added and recoded as number of "Past-year anxiety disorder symptoms." Any symptoms of major depressive episode or manic episode during the year prior to assessment were grouped and recoded as number of "Past-year mood disorder symptoms". Any symptoms of attention deficit disorder, oppositional defiant disorder, or conduct disorder during the year prior to assessment were grouped and recoded as number of "Past-year externalizing disorder symptoms" (see Table 1).

2.2.5. Decision-making—DM was assessed via the Iowa Gambling Task (IGT). This computerized, performance-based task assesses DM under ambiguity; that is, when risk and probabilities are not explicitly revealed throughout the task. The task was developed to assess poor judgment and impulsive DM typically seen in patients with lesions of the orbitofrontal cortex (Bechara, Damasio, Damasio, & Anderson, 1994). Performance on the task has also been shown to involve dorsolateral, orbitofrontal, and ventromedial prefrontal cortices, insula, ventral striatum and anterior cingulate (Li, Lu, D'Argembeau, Ng, & Bechara, 2010). Participants are given a visual display of four decks of cards and told that some decks are better than others; that is, more choices selected from "advantageous decks" (decks C and D) will yield a positive expected return, while more choices selected from "disadvantageous decks" (decks A and B) will yield a negative expected value (Bechara, 2007). However, the specific contingencies associated which each deck are not revealed to the participant. The IGT net score [(C + D) − (A + B)] was used as a measure of DM in our analyses. The basic assumption is that subjects significantly preferring the disadvantageous

decks over the advantageous ones are myopic decision makers who are insensitive to negative long-term outcomes. The IGT has been successfully used with children and adolescents (Crone & van der Molen, 2004; Ernst et al., 2003, 2010). A more detailed overview of the IGT as applied in our study can be found elsewhere (Ross, Coxe, Schuster, Rojas, & Gonzalez, 2015; Ross, Graziano, Pacheco-Colón, Coxe, & Gonzalez, 2016).

2.2.6. Number of cannabis use problems—The number of cannabis use problems was assessed using the Marijuana Problems Scale (MPS), which queries participants about lifetime negative consequences experienced from cannabis use in a variety of domains, such as social relationships, occupational/educational achievement, finances, and legal problems (Stephens, Roffman, & Curtin, 2000). The MPS is a 19-item 3-point scale with response options: 0 = no problem, 1 = minor problem, and 2 = serious problem. The measure has been used in studies with adolescents (Foster, Li, McClure, Sonne, & Gray, 2016) and has demonstrated adequate internal consistency (Stephens et al., 2000).

2.2.7. Additional covariates—Other covariates included in the analyses were the participants' age and sex, the standardized score from the Reading subtest of the Wide Range Achievement Test 4 (WRAT-4; Wilkinson & Robertson, 2006), used as a proxy for general intelligence, and age of cannabis use onset. Given that length of cannabis use abstinence, as well as the use of tobacco and/or alcohol can influence the mental health status and cognitive functioning of adolescents (Cowell, Cicchetti, Rogosch, & Toth, 2015; Medina et al., 2007; White & Swartzwelder, 2005), our adjusted models included the number of days since last cannabis use, and the lifetime amount of alcohol (drinks) and tobacco (cigarettes or its equivalents) as covariates.

2.3. Statistical analysis

All analyses were performed using Stata 14 (StataCorpLP, College Station, TX). In order to test whether the number of mental health disorder symptoms, DM scores, and cannabis use characteristics differed among the three cannabis use subgroups, we conducted multinomial models with statistical adjustment for potential confounders. Multinomial logit coefficients were exponentiated and interpreted in terms of relative probabilities (herein relative odds). In addition, among the cannabis-plus users, we conducted two separate Poisson regression models to test whether the selected covariates were associated with 1) a faster transition to drug co-use, and 2) endorsing a greater number of DOTC used. Estimates from Poisson regressions are expressed as Incidence Rate Ratios (IRR). We performed two sets of additional analyses; the first one used an alternative definition of "regular" cannabis use, according to which only users in the last two-quartiles of lifetime amount of cannabis used would be considered regular users (Supplementary Tables 1a and 1b), and the second, excluded 13 participants with a positive toxicology test (10 for cannabis, 2 for cocaine and 1 for both cannabis and cocaine) (Supplementary Tables 2a and 2b). Control for mild violations of underlying assumptions, calculation of robust standard errors for the parameter estimates (Cameron & Trivedi, 2010), overdispersion test for count data, model fit and multicollinearity diagnostic statistics were also implemented.

3. Results

3.1. Characteristics of the study population

Briefly, compared to the other sub-groups, regular cannabis-plus users endorsed more mood disorder and externalizing disorder symptoms, a higher percentage of mental health disorders, a greater lifetime amount of alcohol drinks and grams of cannabis used, and more cannabis use-related problems on the MPS (Table 1). The median and interquartile range (IQR) for the number of days since last cannabis use by subgroup were 30 and 61 for experimental cannabis-only users, respectively; 7 and 28 for regular cannabis-only users, respectively; and 3 and 20 for regular cannabis-plus users, respectively.

Among regular cannabis-plus users, about 27.50% used another drug(s) within the same year of cannabis use onset, 41.67% started using other drug(s) one year after cannabis use onset, and 30.73% used other drug(s) two or more years after cannabis use onset. The mean number of years between cannabis use onset and DOTC onset was 1.28 years (SD = 1.29). Approximately 33.09% of regular cannabis-plus users used one additional drug (Supplementary file, Fig. 1), whereas 66.91% used two to eight additional drugs (mean number of additional drugs used 2.55, SD = 1.64). Non-prescribed benzodiazepines (33.5%) represented the most commonly used DOTC in this sample of regular cannabis-plus users, followed by hallucinogens (24.4%), ecstasy (17.1%), and stimulants (10.9%).

3.2. Correlates of cannabis use subgroup membership

A larger number of mood disorder symptoms was positively associated with being a regular cannabis-plus user rather than a regular cannabis-only user (AOR = 1.08, CI95% 1.01,1.15) (Table 2 and Supplementary Fig. 2). Additional analyses revealed a stronger association between use of DOTC and mood disorders symptoms among regular CU when applying a stricter definition of regular use (AOR = 1.13, CI95% 1.04, 1.23) (Supplementary Table 1a). DM was not associated with cannabis use subgroup membership (all p-value > 0.05). We also found that endorsing a larger number of cannabis use-related problems on the MPS was associated with membership in the regular cannabis-only subgroup (AOR = 1.26, 95%CI 1.09; 1.45) and the regular cannabis-plus subgroup (AOR = 1.30, 95%CI 1.12; 1.45) relative to experimental cannabis-only users.

3.3. Correlates of speed of transition to onset of drug co-use and number of DOTC used

After controlling for multiple confounders, including the level of alcohol and tobacco use, our adjusted models reveal a weak but significant positive relationship between DM and speed of transition to drug co-use among regular CU (Table 3 and Supplementary Fig. 3). Specifically, better IGT performance was associated with more delayed co-use onset, such that for each one unit increase in IGT performance, the years to onset of drug co-use increased by 1%. A positive association was also seen between the number of DOTC used and the number of cannabis use-related problems endorsed. Every additional cannabis use-related problem endorsed reflected an increase change of 3% in the incidence rate of the number of DOTC used (Table 3).

4. Discussion

As hypothesized, mood disorder symptoms helped to differentiate CU who have used DOTC from those who only used cannabis, such that the greater the number of mood disorder symptoms endorsed, the greater the likelihood of being a regular cannabis-plus user rather than a regular cannabis-only user. We also found that DM was associated with the speed of transition to drug co-use onset, so that poorer DM was associated with a faster transition to drug co-use among regular cannabis-plus users. The analyses also revealed that, as the number of cannabis use-related problems increased, the number of DOTC used also increased.

We found a relationship between co-use of DOTC and mood disorder symptoms among regular CU, in keeping with both causality and self-medication models that have linked mental health disorders to substance use (Teesson et al., 2005). The cross-sectional nature of this study precluded us from establishing a temporal causal relationship; however, we can speculate as to potential explanations for these results. Given that DOTC use was minimal, we would not expect that mental health problems would emerge from such low exposure. Our findings are more consistent with the possibility that DOTC use onset might have started driven by self-medication motives, particularly if drug co-use arose as a way to cope with mental health problems. Another potential argument in favor of a possible self-medicating mechanism is that non-prescribed benzodiazepines, opiates, stimulants, and ecstasy were among the most commonly used in this sample of regular cannabis-plus users, and previous research has linked misuse of these drugs to self-medication for depression (Rigg & Ford, 2014; Schepis & Krishnan-Sarin, 2008; Stewart, Baiden, & den Dunnen, 2013; Teter, Falone, Cranford, Boyd, & McCabe, 2010). However, it could also be argued that DOTC use, even when minimal, may predispose adolescent CU to experience mood disorder symptoms, either through physiological effects or by setting off consequences (e.g. family problems) that eventually could lead or exacerbate mood disorder symptoms.

Contrary to our hypotheses, poorer DM was not associated with cannabis use subgroup membership. However, DM performance was found to influence the speed of transition to drug co-use among regular CU. Specifically, poorer DM was associated with a shorter lapse between cannabis use onset and DOTC use onset. The results did not change after applying a stricter definition of “regular use”, excluding individuals with a positive toxicology test, or controlling for the level of alcohol and tobacco use. Prior studies of DM among CU have reported that suboptimal IGT performance correlates with regular and/or chronic cannabis use (Bolla, Eldreth, Matochik, & Cadet, 2005; Hermann et al., 2009; Vaidya et al., 2012; Verdejo-Garcia et al., 2007) and increased symptoms for cannabis use problems (Gonzalez et al., 2012; Verdejo-Garcia, Bechara, Recknor, & Perez-Garcia, 2006). Poor DM has also been found to moderate the association between amount of cannabis use and cannabis-use related problems (Gonzalez et al., 2015). Yet, research on the role of DM on the early stages of drug use involvement is scarce. Impaired performance on the IGT among adolescents has been assumed to reflect the temporal gap between the heightened arousal of reward-seeking brain systems, and the steady maturation of impulse control brain systems (Casey, Galvan, & Hare, 2005; Chambers, Taylor, & Potenza, 2003; Galvan et al., 2006; Smith, Xiao, & Bechara, 2012; Spear, 2002; Steinberg, 2007). This “maturational imbalance” is proposed to

manifest as a desire to seek out novel or exciting sensations and experiences at a time when inhibitory control and future-oriented thinking is not fully developed. Within our sample, this may explain the propensity of adolescent regular CU with impaired DM in our sample to be more likely to engage in drug co-use as drug use opportunities present themselves. Our findings suggest that the window to prevent concurrent cannabis and DOTC use during adolescence may be very limited, (Jordan & Andersen, 2016) and highlights the need to address DM impairments when designing or implementing prevention programs (Fishbein, Ridenour, Stahl, & Sussman, 2016; Verdejo-Garcia, 2016). The statistically significant but modest association found between DM and speed of transition to drug co-use warrants exploration in future studies with larger samples and longitudinal designs.

A positive association was also found between number of DOTC used and cannabis use-related problems. This finding is consistent with previous research documenting that concurrent use of cannabis and other drug(s) increases the risk of experiencing a drug use disorder (Chen, O'Brien, & Anthony, 2005; Lopez-Quintero & Anthony, 2015) and that more problematic cannabis use is associated with DOTC use (Lopez-Quintero et al., 2011; Tzilos, Reddy, Caviness, Anderson, & Stein, 2014). It is possible that use of multiple drugs and experiencing cannabis use-related problems might be the result of multiple related factors, including having access, or belonging to, social networks that facilitate availability to other drugs, using other drugs to enhance or mitigate the effects produced by cannabis (Gonzalez et al., 2004; Schuster, Crane, Mermelstein, & Gonzalez, 2015), or searching for novel risky experiences. Irrespective of a defined temporality for this association, it is of concern that drug co-use often occurs during a critical period of neuro-development in which adolescents are particularly vulnerable to the effects of drugs (Clark, Thatcher, & Tapert, 2008; Jordan & Andersen, 2016; Squeglia, Jacobus, & Tapert, 2009). In this regard, extensive human and animal research on the effects of drug use on brain development has shown that the nature and severity of any developmental disruption is largely determined by the frequency and intensity of the exposure, the type of drug(s) used, and, most importantly, the developmental timing in which those exposures occur (Bazinet, Squeglia, Riley, & Tapert, 2016). Furthermore, animal models have shown that a prior exposure to cannabis might produce lasting effects that enhance the response to other drugs (Panlilio, Zanettini, Barnes, Solinas, & Goldberg, 2013). Given than drug co-use tends to be fairly common among problematic CU (Lopez-Quintero et al., 2011; Secades-Villa et al., 2015), future research among adolescent CU should investigate whether the problems reported from cannabis use are generated, aggravated or accelerated by the pharmacological interactions of cannabis with other drugs, the behavioral or social implications of using multiple drugs, or a combination of these factors.

The findings of this report should be interpreted in light of the following limitations. The cross-sectional design of this study limits our ability to establish *causal relationships*. In addition, the selected sub-sample was composed mainly of Hispanic adolescents which limits generalizability of the results. Also, exclusion of CU with a formal diagnosis of a mental health disorder or those who received treatment for the disorder may have led to underestimation of the associations between mental health problems and the outcomes examined. However, the fact that about 29% of participants met diagnostic criteria for a past-year mental health disorder based on the CDISC-IV suggests that reports of mental health

problems in our sample are consistent with those reported in other studies of CU (Wu, Gersing, Burchett, Woody, & Blazer, 2011). Nonetheless, the above-stated limitations, our findings indicate that an increase in the number of mood disorder symptoms, even at subclinical levels, might affect the probability of being a CU who also uses DOTC.

Despite these caveats, we believe this study reveals factors that uniquely distinguish adolescent CU based on patterns of use and the concomitant use of DOTC. This, in turn, may shed light on the complex etiology and pathways to the development of drug use disorders. Specifically, the results provide a new piece of evidence regarding the role of DM and mental health disorder symptoms on the process of becoming a regular cannabis user that also uses other drugs. These findings could also inform the adaptation, design, and implementation of interventions aimed at diminishing the impact of cannabis use among adolescent CU. For instance, our results suggest that DM or mood disorder symptoms might be key factors to consider when prioritizing intervention delivery or evaluating heterogeneity in intervention response.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- Drug co-use among cannabis users (CU) increases the risk of drug use disorders.
- We explored factors associated with drug co-use among 266 adolescent CU.
- Mood disorder symptoms are associated with drug co-use among regular CU.
- Poor decision-making is associated with a faster transition to drug co-use.
- More cannabis use-related problems are associated with more drugs co-used.

Table 1

Characteristics of cannabis users by cannabis use subgroup membership (n = 266).

Characteristics	Cannabis use subgroup			Total
	Experimental cannabis-only users	Regular cannabis-only users	Regular cannabis-plus users	m(SD)/%
n (%)	57 (21.43)	91 (34.21)	118 (44.36)	
% Males	33.35	67.01	59.14	56.45
Age (m, SD)	15.47 (0.73)	15.36 (0.73)	15.54 (0.53)	15.29 (0.67)
Past-year anxiety disorder symptoms (m, SD)	6.19 (4.05)	4.94 (3.78)	5.84 (3.59)	5.61(3.77)
Past-year mood disorder symptoms (m, SD)	12.19 (7.77)	10.29 (7.27)	14.01 (6.68)	12.36 (7.28)
Past-year externalizing disorder symptoms (m, SD)	15.32 (8.94)	15.57 (9.10)	19.46 (9.26)	17.27 (9.32)
%Past-year diagnosis for any mental health disorder	25.00	26.37	33.90	29.43
WRAT-4 Reading Standardized score (m, SD)	107.19 (14.01)	109.08 (16.96)	105.53 (13.13)	107.09 (14.75)
IGT total net (m, SD)	−1.51 (25.28)	0.88 (21.73)	−1.02 (23.22)	−0.48 (23.12)
Amount of alcohol use in lifetime (drinks) (m, SD)	36.08 (61.41)	54.38 (107.79)	126.41 (364.56)	85.74 (257.46)
Amount of tobacco use in lifetime (cigarettes) (m, SD)	3.69(11.51)	16.94 (59.75)	213.03 (1570.31)	101.92 (1068.22)
Amount of cannabis use in lifetime (gr) (m, SD)	2.48 (1.52)	170.85 (384.89)	315.41 (590.59)	199.77 (470.17)
Age of cannabis use onset (m, SD)	14.14 (0.81)	13.42 (1.06)	13.28 (1.48)	13.50 (1.25)
Number of days since last cannabis use (Md, IQR)	30 (61)	7 (28)	3 (20)	14 (39)
Number of cannabis use problems (m, SD)	2.49 (3.21)	4.09 (3.70)	5.09 (4.43)	4.19 (4.07)
Number of years to co-use onset			1.28 (1.29)	
Number of DOTC used			2.55 (1.64)	

Note: m = mean; SD = standard deviation; IGT = Iowa gambling task; Md = median; IQR: Interquartile Range; DOTC = drug(s) other than cannabis. Past-year anxiety disorders symptoms include any symptoms for panic disorder, generalized anxiety disorder and obsessive-compulsive disorder during the year prior to assessment based on the CDISC-IV. Past-year mood disorders symptoms include any symptoms for major depressive episode and maniac episode during the year prior to assessment based on the CDISC-IV. Past-year externalizing disorders symptoms include symptoms for attention deficit disorder, oppositional defiant disorder, and conduct disorder during the year prior to assessment based on the CDISC-IV.

Table 2

Correlates of cannabis use subgroup membership (n = 266). Results of bivariate and multivariable multinomial logistic regression models.

Characteristics	Cannabis use subgroup membership					
	Experimental cannabis-only users[a] vs. Regular cannabis-only users		**Experimental cannabis-only users[a] vs. Regular cannabis-plus users**		**Regular cannabis-only users[a] vs. Regular cannabis-plus users**	
Mental health disorder symptoms	OR[b] (95%CI)	AOR[c] (95%CI)	OR[b] (95%CI)	AOR[c] (95%CI)	OR[b] (95%CI)	AOR[c] (95%CI)
Past-year anxiety disorder symptoms	0.91 (0.83; 0.99) *	0.93(0.81; 1.06)	0.97 (0.89; 1.05)	0.90 (0.79; 1.02)	1.06 (0.99;1.15)	0.97 (0.87; 1.07)
Past-year mood disorder symptoms	0.96(0.92; 1.00)	0.98 (0.90; 1.06)	1.03 (0.99; 1.08)	1.06 (0.98; 1.14)	1.08 (1.04;1.12) **	1.08 (1.01; 1.15) *
Past-year externalizing disorder symptoms	1.00 (0.97; 1.04)	0.99 (0.94; 1.05)	1.05 (1.01; 1.09) **	1.00 (0.95; 1.06)	0.99 (0.96; 1.03)	1.00 (0.96; 1.06)
Decision-making						
IGT total net	1.00 (0.99;1.02)	1.00 (0.99; 1.03)	1.00 (0.98; 1.01)	1.00 (0.99; 1.02)	0.99 (0.98; 1.01)	0.99 (0.98; 1.01)
Cannabis use-related factors						
Number of cannabis use problems	1.19 (1.06; 1.35) **	1.26 (1.09; 1.45) **	1.27 (1.12; 1.43) **	1.30 (1.12; 1.49) **	1.06 (0.98; 1.48)	1.02 (0.95; 1.10)

Past-year anxiety disorders symptoms include any symptoms for panic disorder, generalized anxiety disorder and obsessive-compulsive disorder during the year prior to assessment based on the CDISC-IV. Past-year mood disorders symptoms include any symptoms for major depressive episode and maniac episode during the year prior to assessment based on the CDISC-IV. Past-year externalizing disorders symptoms include symptoms for attention deficit disorder, oppositional defiant disorder, and conduct disorder during the year prior to assessment based on the CDISC-IV.

Bold indicates significant *p*-values.

[a] Baseline or reference comparison group.

[b] Odds Ratios (OR) represent relative risk ratios of relative odds.

[c] Adjusted Odds Ratios (AOR), adjusted models include all covariates in the table plus the variables sex, centered age^2, centered age of cannabis use onset^2, WRAT-4 standardized reading score, amount of alcohol use in the lifetime, amount of tobacco use in the lifetime, and number of days since last cannabis use.

* *p*-value < 0.05.

** *p*-value < 0.01.

Table 3

Correlates of transition to drug co-use and number of drugs other than cannabis (DOTC) co-used. Results of bivariate and multivariable Poisson regression models (n = 118).

Characteristics	Rate of progression to drug co-use		Number of DOTC co-used	
	IRR (95%CI)	AIRR[a] (95%CI)	IRR (95%CI)	AIRR[a] (95%CI)
Mental health disorder symptoms				
Anxiety disorder symptoms	0.98 (0.93; 1.03)	0.98 (0.93; 1.04)	1.00 (0.97; 1.03)	0.97 (0.93; 1.01)
Mood disorder symptoms	0.98 (0.96; 1.00)	0.98 (0.95; 1.01)	1.01 (0.99; 1.03)	1.02 (0.99; 1.06)
Externalized disorder symptoms	1.00 (0.99; 1.03)	1.01 (0.98; 1.04)	1.00 (0.99; 1.02)	0.99 (0.98; 1.02)
Decision-making task				
IGT total net	1.00 (0.99; 1.01)	1.01 (1.01; 1.03) *	1.00 (0.99; 1.01)	1.01 (0.99; 1.02)
Cannabis use-related factors				
Number of cannabis use problems	0.98 (0.94; 1.02)	0.99 (0.96; 1.02)	1.03 (1.01; 1.04) **	1.03 (1.01; 1.05) **

Notes: IRR = Incidence Rate Ratios.

Past-year anxiety disorder symptoms include any symptoms for panic disorder, generalized anxiety disorder and obsessive-compulsive disorder during the year prior to assessment based on the CDISC-IV. Past-year mood disorder symptoms include any symptoms for major depressive episode and maniac episode during the year prior to assessment based on the CDISC-IV. Past-year externalizing disorder symptoms include symptoms for attention deficit disorder, oppositional defiant disorder, and conduct disorder during the year prior to assessment based on the CDISC-IV.

Bold indicates significant p-values.

[a]Adjusted Incidence Rate Ratios (AIRR), adjusted models include all covariates in the table plus the variables sex, centered age^2, centered age of cannabis use onset^2, WRAT-4 standardized reading score, amount of alcohol use in the lifetime, amount of tobacco use in the lifetime, amount of cannabis use in the lifetime, and number of days since last cannabis use.

*p-value < 0.05.

**p-value < 0.01.