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A New Approach to Researching the Etiology of Cannabis Use Disorder: Integrating Transmissible and Non-Transmissible Risk within a Developmental Framework

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Abstract

Rapidly occurring changes in law enforcement and licensing of retail outlets to sell marijuana raises the prospect that the population of consumers will expand and accordingly the prevalence of cannabis use disorder (CUD) will increase. This report presents a novel approach to researching CUD etiology joining multivariate and ontogenetic perspectives. CUD is conceptualized as a developmental outcome consisting of transmissible (intergenerational) and non-transmissible components. Partitioning the liability for CUD into these two dimensions enables implementing interventions targeted at the particular source and severity of risk. In addition, results showing that infant temperament disturbances predict transmissible risk leading to CUD two decades later underscore the importance of implementing early prevention.

Keywords

cannabis; marijuana; etiology; prevention; development

INTRODUCTION

The 2013 annual survey of high school students indicates that 45.5% of seniors have used cannabis at least one time.¹ The actual prevalence is in all likelihood higher considering that dropouts, truants and youths residing in detention facilities who are not included in the survey have higher rates of substance use than peers who attend school. Smoking cannabis at least one time, although illegal, is thus essentially normative behavior among youths despite their near-universal participation in prevention programs, exposure to harmfulness warnings in mass media, and knowledge of negative consequences if caught distributing or possessing marijuana. Indeed, desisting marijuana use is newsworthy. Lloyd Johnston, Principal Investigator of the Monitoring the Future Survey states: “*But it should also be*

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noted that fully half of today's seniors have not tried an illicit drug by the end of high school".²

Cannabis use disorder (CUD) has lifetime prevalence of 4.0% in the U.S..³ Among daily or near daily users, the prevalence of cannabis dependence is only 20–50%.⁴ Thus, CUD diagnosis encompassing criteria indicating biological, psychological and social harm is not the inevitable outcome of cannabis consumption. It is also notable that CUD prevalence is substantially lower than other outcomes of excessive behavior. For example, lifetime prevalence of obesity in the U.S. population over 20 years of age is 34.9%.⁵

The observation that most cannabis users do not develop CUD illustrates the importance of individual differences in liability. Falconer⁶ defines liability as “...*the individual tendency to develop or contract the disease, i.e., his susceptibility in the usual sense, but also the whole combination of external circumstances that make him more or less likely to develop the disease*”. Liability encompasses three components: 1) characteristics of parents transmitted to children; 2) characteristics acquired via sibling influence; and, 3) characteristics of the extrafamilial environment. Applying the Tau model⁸ to partition these influences, Hopfer et al.⁹ observed that transmissible risk accounts for over 40% of variance underlying cannabis dependence. Extending these findings, it has also been shown that the manifold characteristics comprising transmissible¹⁰ and non-transmissible¹¹ risk are indicators of unidimensional traits.

Developmental Perspective

CUD typically develops before 20 years of age.¹² The anterior cortex is still undergoing maturation, indicating that the psychological disturbances associated with risk for substance use disorder^{14,15,16,17} have a neurobiological substrate and linked to child and adolescent development. Moreover, cannabis disrupts frontal cortex functioning^{18,19} which may cause impaired memory,²⁰ suboptimal intellectual development,²¹ schizophreniform psychosis²² and depression and anxiety.²³ In effect, neuromaturational processes evinced as cognitive, behavior and emotion disturbances during childhood and adolescence predisposes to cannabis use which disrupts neurological functioning to amplify the psychological disturbances.

Delineating the etiology of CUD requires, therefore, an ontogenetic framework to quantify age-specific indicators of transmissible and non-transmissible risk. In addition, to neuromaturation, individual differences in rate of sexual maturation also need to be taken into account. For example, appearing physically more advanced than same-age adolescent peers promotes opportunities to establish friendships with older youths. Considering that first substance use usually occurs in context of peer interactions, precocious youths are thus more likely to receive drug offers without having acquired the behavioral and cognitive competencies required to desist initiating consumption.^{24,25,26,27,28} Evincing secondary sex characteristics (e.g. facial hair in boys, breast development in girls) at a young age thus facilitates social interactions with older peers that create opportunities to initiate substance use which, contingent on subsequent circumstances, may or may not segue to CUD.

Figure 1 depicts a developmental model to guide etiology research.^{29,30} Biobehavioral and environmental factors related to risk constitute vectors ($V_1, V_2, V_3 \dots V_n$); namely, quantities having both force (severity) and direction (increases or decreases risk for disorder). The aggregate of all factors, the *Resultant Vector* (V_R), denotes overall risk. Connecting the V_R 's across timepoints graphs the ontogenetic trajectory which terminates either as CUD or other outcome. The first task in etiology research therefore requires identifying the factors pertinent to risk for the disorder aligned to chronological age. Next, the pathway toward or away from disorder is charted by connecting the V_R 's. As can be seen, concomitant to biobehavioral changes during development and changing environment, risk status (V_R) changes during ontogeny and accordingly the pathway to SUD (or other outcomes) is not linear. Moreover, the transactional pattern has two main sources of influence: 1) *selection*, in which the person's genetic and biobehavioral disposition biases preference to particular physical and social settings, and 2) *contagion*, in which a particular physical or social setting impacts the person. Myriad idiosyncratic factors operating through selection and contagion shape the direction and slope of the ontogenetic trajectory. For example, relocating to a neighborhood having low social capital, forming a friendship with a substance using peer and divorce of parents may increase the slope or alter the direction of the trajectory leading to initiating as well as maintaining substance use during adolescence. Because it is not possible to foresee future environmental events and personal experiences, it is not feasible to precisely forecast CUD. Prevention practice instead requires monitoring the transmissible and non-transmissible components of liability through the developmental period of risk.

Considering that many factors contribute to transmissible and non-transmissible liability, it is essential to measure the unique pattern of risk variables in each individual. Consistent with this person-centered focus, the Web-based self-administered Drug Use Screening Inventory (DUSI-R) measures severity (0–100%) of risk factors in ten health and psychosocial domains along with seven categories of psychiatric disorder.^{31,32,33} Intervention can, therefore, be tailored to the particular configuration of risk factors particular to each individual.

Research into CUD etiology and CUD prevention is hampered, however, by the absence of a necessary characteristic (or symptom) that must be present to confer diagnosis. One consequence of this deficiency in the DSM-IV and DSM-5 is that the same diagnosis can be assigned to individuals who do not share any characteristics or symptoms. In effect, CUD diagnosis is applied to different non-overlapping phenotypes. In the absence of a diagnostic system in which there is at least one attribute that is common to all affected individuals it is difficult, if even possible, to accurately delineate etiology.

ETIOLOGY OF CANNABIS USE DISORDER

Understanding CUD etiology requires taking into account the role and interplay of three factors: i) the agent, ii) individual differences in liability, and iii) environment and contributors to liability.

The Agent: Cannabis

Cannabis sativa has for millennia provided fiber to make cordage, oils from seeds to formulate medicines, and delta-9-tetrahydrocannabinol (THC) from the flower to increase appetite for food and relieve distress from assorted medical problems. The pharmaceutical formulation of THC is sold under the brand name *Marinol*. THC also has psychoactive properties; Specifically, it induces calm euphoria. Systematic breeding since the 1960's has produced many marijuana hybrids having distinctive aromas and flavors with THC concentrations ranging as high as 25%.³⁴ This constitutes an eightfold increase in concentration compared to "weed" smoked in the 1960's. THC concentration underlies intensity of subjective experience related to risk for CUD.³⁵

Similar to all abusable substances THC impacts on the mesolimbic dopaminergic reward system.^{36,37,38} Moreover, genetic and phenotypic liability for CUD are congenerous with all other SUD categories.^{39,40,41} Thus, consistent with common liability,^{42,43} CUD is one disorder on the spectrum of substance use disorders.⁴⁴ Accordingly, the main factor, maybe the only factor that distinguishes CUD from other categories of alcohol or drug disorder, is the drug used (based largely on availability) and not unique characteristics of the individual.

The particular type of SUD manifested in adulthood maps to severity of externalizing disorder during childhood. Externalizing disturbance presaging cannabis use disorder is less severe than disorders consequent to using "hard" illegal drugs and more severe than disorders resulting from use of legal drugs.^{45,46} This is not unexpected considering that cannabis consumption, albeit illegal, is not strongly discordant with prevailing mores. Over 40% of high school seniors approve occasional marijuana use.¹ Because social sanctions prohibiting consumption are weak, low deviance proneness prompts experimentation which, contingent on events occurring thereafter, may culminate in CUD.

Despite robust evidence demonstrating that the individual liability associated with cannabis use is the same as other abusable substances^{42,43,47} the gateway hypothesis advanced by Kandel and Yamaguchi⁴⁸ theorizes that distinct risk factors predispose to initiation of each type of abusable drug. Cannabis is claimed to be a "gateway" drug because consumption often leads to "hard" illegal drugs. It is noteworthy, however, that research has not confirmed the presence of an invariant sequence. Many youths begin cannabis use *after* using "hard" drugs.^{49,50,51} Moreover, cannabis use often *precedes* using legal substances.⁵² Furthermore, Kandel and Yamaguchi's interpretation of their data is arguably based on faulty logic. The error, termed *post hoc ergo propter hoc* (after this, therefore because of this), falsely asserts causality: "*one licit drug is **required** (emphasis added) to make the progression to marijuana use*" (p. 71). The false belief that cannabis use progresses to consumption of "hard" drugs has likely catalyzed the legislation of draconian laws to suppress cultivation, distribution and consumption of marijuana.

Individual Differences in Vulnerability

Numerous intercorrelated cognitive, emotion and behavior disturbances during childhood contribute to the individual's vulnerability to develop substance use disorder.⁵³ In severe cases the characteristics align with diagnosis of externalizing disorder such as attention

deficit hyperactivity disorder or conduct disorder. These disorders frequently presage substance abuse and substance use disorder.^{54,55,56} Impulsivity, the ubiquitous common feature of these disorders, has been shown in many studies to amplify risk for substance abuse and substance use disorders.^{57,58} Moreover, negative emotions such as anxiety and depression heighten risk for substance use disorder,^{59,60,61} indicating that internalizing disturbances are also facets of the liability.

Internalizing and externalizing disturbances are, however, not orthogonal. Krueger and Markon⁶² report a correlation of .50 between these two dimensions whereas Tarter et al.,⁶³ report a correlation of .67 between factors encompassing the internalizing and externalizing scales of the Child Behavior Checklist. The second order factor capturing the variance shared between internalizing and externalizing dimensions predicts CUD between childhood and adulthood. The observation that both internalizing and externalizing disturbances precede consumption, and are correlated, supports the conclusion that the overall liability for substance use disorder can be parsimoniously characterized as deficient psychological self-regulation.¹⁴ Diverse characteristics reflecting psychological self-regulation comprise a continuous trait. Termed the *transmissible liability index (TLI)*¹⁰ twin studies reveal that 75%⁶⁴ to 85%¹⁰ of score variance is heritable. Moreover, the TLI distinguishes boys according to presence/absence of substance use disorder in their fathers and predicts substance use disorder by early adulthood.⁶⁵ Also, the TLI predicts age at the time of first substance use presaging substance use disorder diagnosis as well as the interval between first substance use and subsequent diagnosis. Furthermore, age at the time of first alcohol use mediates the association between TLI in childhood and CUD, and age of first cannabis use mediates the relationship between TLI and diagnosis of alcohol use disorder. In effect, the TLI measures liability that is common to both disorders. In adults, the TLI predicts all substance use disorder categories⁶⁶ commensurate with the common liability model of addiction etiology.^{10, 29, 30, 42, 43}

Development of the TLI employed a multistage procedure.¹⁰ At the outset faculty at the Center for Education and Drug Abuse Research catalogued the psychological traits reported in the empirical literature to be related to risk for substance use disorder. Next, items were drawn from CEDAR's database (over 10,000 variables at baseline) and, according to their face validity, assigned to these traits. Exploratory factor analysis was performed on the items to derive unidimensional constructs that were subsequently validated using confirmatory factor analysis. Items having loading below 0.4 were pruned and constructs that did not satisfy criteria for unidimensionality were excluded from further consideration. The remaining pool of items in the constructs that discriminated sons of fathers with and without lifetime substance use disorder were submitted to exploratory and confirmatory factor analysis yielding the unidimensional *transmissibility liability index (TLI)* consisting of 45 items having internal consistency of .92 in 10–12 year old boys. Age-specific versions of the TLI having internal consistency exceeding .90 at ages 12–14, 16, 19 and 22 have also been derived for administration in a computer adaptive test format.⁶⁷ The five versions of the TLI can be found at www.pitt.edu/~cedar/TLIdocument.html. A scale to measure transmissible risk for substance use disorder in females is currently undergoing validation.

Results of a recent study indicate that children scoring high on the TLI before first time cannabis consumption evince a linear increase in risk severity following initial use that subsequently culminates in CUD by early adulthood.⁶⁸ Youths scoring low on the TLI before first cannabis use on the other hand show a significant decline in risk between childhood and adulthood. In effect, initial experience with cannabis among high risk youths is a signal event that biases future development toward CUD. These findings underscore the importance of implementing prevention before opportunities arise and motivation for initiating consumption are established.

Because first substance exposure typically occurs in context of peer interactions and dysregulated youths are inclined to develop friendships with peers who have similar disposition, the onset of cannabis use culminating in CUD is the product of individual vulnerability and a social context that promotes (or at least tolerates) non-normative behaviors. Not surprisingly, non-normative socialization during adolescence mediates the relationship between childhood transmissible risk and substance use disorder in adulthood.⁶⁹

Additionally, research at CEDAR has shown that a high score on the TLI in childhood predicts elevated testosterone level and attenuated cortisol level in mid-adolescence presaging substance use disorder.⁷⁰ This pattern of hormone activity is consistent with a motivational style marked by aggressive dominance striving. Another pathway into habitual substance use culminating in diagnosis of substance use disorder may involve a potentiated reinforcing effect of abusable substances in individuals at high transmissible risk. Strong positive (euphoria) or negative (alleviation of stress) reinforcement increases the probability of establishing a pattern of regular drug consumption which may cause adjustment problems and accordingly qualify the person for CUD diagnosis. Inasmuch as it is illegal and unethical to administer abusable substances to minors it is not possible to determine whether youths who are at high transmissible risk before first exposure or in the early stages of consumption experience differentially strong drug reward. Among regular adult substance consumers it was observed however in a recent study that the slope depicting the rate of increase in TLI severity between ages 10–22 correlates with frequency of consumption of preferred drugs which in turn correlates with magnitude of *aversive* affect during the drug use event.⁷¹ In other words consumption induced neither self-medication (relief from an aversive state) nor euphoria but, instead, a punishing experience. Factors possibly contributing to habitual use besides hedonic experience include memory of prior euphoria and/or behavioral undercontrol.^{72, 73, 74} Although systematic research remains to be conducted it appears from available results that cognitive and motivational factors among adult experienced users (including those who qualify for substance use disorder) may have a stronger influence on sustaining consumption than hedonic experience.

Social Environment

The *Uniform State Narcotic Act in 1934*, *Comprehensive Drug Abuse Prevention and Control Act in 1970* consolidated Federal policy designating *cannabis sativa* a dangerous plant. Vigorous law enforcement often accompanied by long prison sentences were intended to protect public safety. Eradicating the plant and ridding society of those associated with it constituted prevention. The expenditure of vast resources toward this effort notwithstanding,

almost half of U.S. high school seniors have smoked marijuana. Moreover, results of the 2013 Monitoring the Future Survey indicate that 81.4% of high school seniors state that marijuana is easy to obtain. Indeed, 30-day prevalence of marijuana smoking currently exceeds cigarette smoking (22.7% vs. 16.3%).

The high prevalence of marijuana use can be traced to profound changes in U.S. society beginning in the 1960's. Historically, smoking marijuana was confined to antisocial individuals and small marginalized segments of the population having low adherence to prevailing societal norms but who otherwise adhered to Federal law (beatniks, hipsters, jazz musicians, etc.). The generation born during or soon after the end of the second World War coming of age in the 1960's was faced with a destabilized society grappling with violent ideological clashes over desegregation of public schools and universities, pervasive fantasy fears of an internal communist menace, and cold war with the Soviet Union. The civil rights movement, women's movement and the Vietnam war imbued activism, rejection of traditional norms, and defiance of authority. Emergence of counterculture fostered acceptance of new lifestyles (e.g. communes, co-ed college dorms), including sex risk-free of pregnancy. Behaviors historically outside the societal norm became acceptable; this expansion of normative behavior continues to this day (e.g. body art, same-sex marriage). Smoking "weed" similarly shifted toward normative behavior catalyzed by recognition that "reefer madness" was not the inevitable outcome. In 1975 when reliable epidemiological data were first obtained, 18.1% of high school seniors perceived occasional marijuana smoking as harmful. By then the War on Drugs was already in full tilt. In 2013 the rate was 19.5%. Thus, during the past half century societal norms have been misaligned with Federal laws. As long as marijuana remains illegal it can be expected that norm-violating behaviors will be correlated with cannabis use. For example, a study conducted at CEDAR found that cannabis (but not alcohol) use mediates the association between transmissible risk for substance use disorder and number of lifetime violent offenses.⁷⁵ The strength of association between cannabis use and violent and other antisocial behavior will in all probability weaken as the normally socialized segment of the population increasingly uses cannabis concomitant with emerging legal availability.

INTEGRATING TRANSMISSIBLE AND NON-TRANSMISSIBLE RISK

Paralleling research showing that transmissible risk consists of a continuous unidimensional trait, it has also been shown that non-transmissible risk capturing primarily various aspects of the environment, comprises a unidimensional scale. The score on this measure, termed the *non-transmissible index (NTI)*, discriminates sons of fathers according to presence/absence of substance use disorder as well as predicts substance use disorder between childhood and adulthood.¹¹ In effect, the NTI measures primarily the extrafamilial component of risk for substance use disorder, thereby complementing the TLI.

The transmissible and non-transmissible indexes can be configured in a Cartesian schema as shown in Figure 2. In this fashion the source as well as severity of risk for substance use disorder can be specified in the individual. As can be seen there is extensive heterogeneity of TLI and NTI scores in a sample of 10–12 year old boys. These data adapted from Tarter et al.¹⁴ indicate that 34% of boys who scored high on both the TLI and NTI developed CUD

by age 22. Only 12% who scored low on both TLI and NTI developed CUD. Boys scoring high on one dimension and low on the other exhibited, as expected, rates of CUD that were midway between these two extreme groups. CUD was the outcome in 19% of boys who had below average TLI and above average NTI scores. The opposite pattern was associated with a 20% rate of CUD. These findings indicate that the TLI and NTI do not portend inevitable CUD outcome while underscoring the need for intervention to target the specific component of the liability.

MODELING THE ETIOLOGY OF CUD IN AN ONTOGENETIC FRAMEWORK

Strong genetic influence on substance use disorder etiology^{39,40, 41} complemented by findings showing that genetic factors largely account for individual differences in TLI scores^{10,64} suggest that infant temperament, which is also strongly heritable, may comprise features of liability during the early postnatal period. Temperament, defined by Rothbart⁷⁶ as “*constitutionally based individual differences in reactivity and self-regulation*” corresponds closely to the characteristics measured by the TLI in pre-pubertal children and adolescents.

CEDAR data were analyzed to test the hypothesis that parental load for substance use disorder (i.e. number of affected parents) predicts temperament during infancy and TLI in late childhood that in turn forecasts CUD. Mothers rated their sons on a Likert scale according to “easy/difficult”, “active/passive”, “regular/irregular routines”, “friendly/unfriendly”, “low/high arousability threshold”, and “low/high distractibility”. Results of path analysis, shown in Figure 3, indicate that number of parents with substance use disorder predicts the sum of temperament scores which, in turn, forecasts transmissible risk at age 10–12 and affiliation with delinquent peers at age 16. These latter two variables in turn predict age of first cannabis use and CUD at age 22. Moreover, temperament mediates the association between parental SUD load and affiliation with non-normative peers ($\beta = .02$, $z = 2.07$, $p = .04$) illustrating the conjoint role of individual vulnerability and social environment on development of CUD. Although infant temperament does not directly predict age of first cannabis use or CUD it predicts transmissible risk in late childhood presaging the prodrome (cannabis use) and clinical disorder (CUD). Overall model-data fit is satisfactory ($\chi^2 = 10.19$, $df = 4$, $p = .04$, root mean square error of approximation = .056, Tucker-Lewis index = .89, fit index = .97).

The demonstration that vulnerability for CUD may be measurable in infants underlines the importance of an ontogenetic focus in etiology research.^{77,78} Considering that almost half the variance related to cannabis dependence are transmissible; that is, has continuity between parents and children⁹ also informs the need for family-based interventions that are appropriate to the early stage of child development. One potentially effective approach arguably should involve inculcating affective synchrony between the caregiver and baby along with enhancing parental investment in childrearing and parenting competencies. Temperamentally difficult infants evoke negative reactions in caregivers who are also more likely (due to heritability) to have similar temperament disturbances which in adulthood manifest as poor psychological self-regulation, psychiatric disorders, and substance use disorder. Hence, concerted effort needs to be directed at promoting a positive caregiver-

infant relationship. Chaotic or insecure attachment pattern is well-known to heighten risk for disruptive behavior in middle childhood which commonly segues to substance abuse in adolescence and thereafter culminates in substance use disorder. Recently, it has been shown that parent-child attachment mediates the association between psychological dysregulation during adolescence and risk for substance use disorder in adulthood.⁷⁹ Hence, interventions which promote the developmental trajectory toward normative socialization, beginning with consolidation of a positive relationship between caregiver and infant, would most likely have substantial impact on preventing substance use disorder.

CONCLUSIONS

Cannabis use disorder (CUD) has multifactorial etiology originating during fetal development. Manifold factors contributing to etiology can be aggregated into continuous scales measuring transmissible (intergenerational) and non-transmissible risk. Measuring these two components of etiology within a Cartesian framework enables depicting the individual's source and severity of risk. Accordingly, the focus and intensity of prevention can be accurately determined. Furthermore, the finding that parental substance use disorder predicts infant temperament that in turn predicts transmissible risk in late childhood presaging CUD indicates that it is important to implement prevention before the child consolidates behaviors during middle and late childhood predisposing to cannabis use and CUD.

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Figure 1.
Ontogenetic model of substance use disorder.

Figure 2.
Integrating source and severity of risk for cannabis use disorder.

Figure 3.
Developmental pathway from infant temperament to cannabis use disorder