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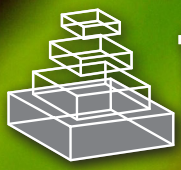
RESEARCH TOPICS

CLEARING THE SMOKESCREEN: THE CURRENT EVIDENCE ON CANNABIS USE

Topic Editors
Elizabeth C. Temple, Richard Hammersley, Margriet van Laar and Rhonda F. Brown



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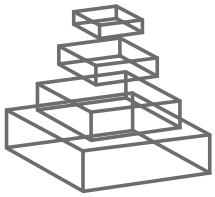

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CLEARING THE SMOKESCREEN: THE CURRENT EVIDENCE ON CANNABIS USE

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'Marijuana, Flower'. Photograph by fotobias (Zdenek Tobias) via Pixabay; CC0.

Cannabis remains the most commonly used illicit substance world-wide, with international estimates indicating that 2.8%–4.5% of the global population use cannabis each year. This prevalence rate has not changed substantially in the past decade and there is no indication that it will do so in the next decade. In line with this, many prominent organizations and individuals have acknowledged that the "war on drugs" has failed and are now calling for a rethink on drug-related policy and legal frameworks. With a growing number of jurisdictions across the world heeding this call and introducing legislation to decriminalize or legalize cannabis use, it is essential that any changes to legal frameworks and public health policies are based on the best available scientific evidence.

To facilitate the adoption of an evidence-based approach to cannabis policy, the aim of this Research Topic was to gather a comprehensive body of research to clarify the current state of evidence relating to cannabis use. Of interest were articles addressing the following questions:

- How do we study cannabis use? (e.g., recruitment; measuring dose/use; assessing dependence/problematic use; confounding; translation of findings from animal studies)
- What do we know about cannabis use? (e.g., patterns, contexts, methods of use)
- What do we know about people who use cannabis? (e.g., who uses cannabis and why)
- What are the social settings, norms and cultural values that go along with cannabis use?
- How is problematic cannabis use, as opposed to mere use, defined, judged and constructed in different societies?
- What do we know about the effects/outcomes of cannabis use? (e.g., acute, short- and long-term; harms/benefits)

- What do we know about the factors associated with the initiation, continuance and cessation of cannabis use?
- What do we know about the medicinal use of cannabis? (e.g., who uses medicinally and why; efficacy/effectiveness in different clinical populations; comparison with other medications)
- What do we know about treatment for people who engage in problematic cannabis use? (e.g., who seeks/is referred to treatment and why; efficacy and effectiveness)
- What do we know about cannabis? (e.g., pharmacodynamics/pharmacokinetics of different strains, cultivation, preparation and consumption methods)
- How do policy and legal frameworks impact on the people who use cannabis?
- What is the future for cannabis research? (e.g., potential avenues for future research; aspects needing more attention; innovative approaches; political/funding issues affecting cannabis research)

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EDITORIAL
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Clearing the smokescreen: the current evidence on cannabis use

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Decisions regarding the legal status of cannabis have long been framed (for the public at least) with reference to the perceived health risks and harms associated with use. Yet, drug policy and legislation relating to the use of cannabis are rarely based on the scientific evidence of the known risks and harms. There are many reasons for this discrepancy, with the politicization of cannabis use, where ideology and moralizing are given precedence over the science, being one. Thus, we begin this research topic with Aggarwal (1) discussion of how such politicization has contributed to the current smokescreen that is obscuring our understanding of cannabis, including the impact it has on the ability of researchers to collect and disseminate accurate information about the effects of cannabis use.

The capacity of policy makers and legislators to develop evidence-based cannabis policies and laws is also contingent on researchers explaining the existing evidence, disseminating new research findings, and collaborating with relevant people, agencies, and government departments to improve the premises on which they base their policies and legislation. Roffman (2), who took this path through his involvement in the development of the legislation to legalize cannabis use in Washington State, provides an insider's view of the processes and deliberations. While we will have to wait for the evaluation of this carefully designed model for regulating cannabis use, the following two articles provide some insight into patterns of cannabis use in contexts were consumption is relatively normalized. There are many parallels evident in the findings of Mostaghim and Hathaway (3) qualitative exploration of cannabis use among Canadian university students and Liebregts et al. (4) prospective investigation of cannabis use by young adults transitioning from university to work in The Netherlands. Of particular note are the ways in which the participants' self-identity, including priorities, roles, and responsibilities, act as constraints to their use, and the clear demarcations drawn between leisure and work.

A major consideration, discussed by Roffman (2), was the risk that legalization of cannabis might spark an increase in usage, which could, in turn, result in higher incidence and prevalence of cannabis-related harms, particularly if there was an increase in use by adolescents. The evidence underpinning concerns of adverse impacts resulting from early onset cannabis use is reviewed by Chadwick et al. (5), who report that adolescent users with genetic vulnerabilities are at increased risk of experiencing motivational, affective, and psychotic disorders, including schizophrenia. The association between cannabis and psychosis/schizophrenia is comprehensively reviewed by Radhakrishnan et al. (6), who conclude that, while, cannabis may be a component cause in the development of psychosis, this association is moderated by family history of psychoses, genetic factors, childhood trauma/abuse, and age at onset of use. The importance of differentiating between psychotic disorders and psychomimetic effects is also highlighted as being an essential step in increasing our understanding of the cannabis-psychosis association. Similarly, the two pathways from cannabis use to psychosis proposed by Burns (7) illustrate the importance of differentiating between types of cannabis-psychosis trajectories, showing how the clinical presentation profiles and treatment outcomes differ for early onset, long-term cannabis use in comparison to later onset, short-term but intense use.

Early onset/adolescent cannabis use is investigated further in the next three articles. First, Serafini et al. (8) explore the possible role of hopelessness as a mediator in the relationship between early cannabis use and suicidal behaviors, while Little et al. (9) investigate predictors of cannabis cessation within a sample of high-school students. The next article, by Fallu et al. (10), reports the findings of a latent class analysis of adolescent cannabis users, revealing four different use trajectories. The early onset, heavy cannabis and polydrug use group in this study were found to experience the highest level of use-related problems, followed by the late-heavy-polydrug group. Similarly, Connor et al. (11) report that, in a sample of adult cannabis users referred for treatment, those who engaged in polydrug use were more likely to be cannabis dependent and experiencing higher levels of comorbid psychopathology, than individuals who used cannabis, tobacco, and/or alcohol. Healey et al. (12) also focused on a treatment sample, finding that both cannabis users and their clinicians reported difficulty in establishing a therapeutic bond. A dose–response relationship was evident for the client perspective, such that heavier users reported feeling less connected, which the authors suggest may be related to effects of cannabis use such as paranoia or anxiety. The association between cannabis use and anxiety is explored by Temple et al. (13), who test the premise that the contradictory findings in the literature for this association may be due to individuals misattributing stress responses to anxiety symptomology. The finding that stated use to self-medicate for anxiety is more strongly associated with level of

stress rather than anxiety symptoms provides some support for this hypothesis.

The therapeutic potential of cannabis is one of the factors driving the push for legalization of cannabis use. Yet, as discussed by Crippa et al. (14), with the majority of past research focus being on cannabis as a whole or THC, we have limited knowledge of the mechanisms of action of the many other cannabinoids, which is impeding our understanding of their medical applications. One of the key areas of current research into the therapeutic effects of cannabis focuses on the ability of CBD to modulate the adverse psychological effects of THC; this body of evidence is reviewed here by Niesink and van Laar (15). Oliere et al. (16) similarly focus on the therapeutic potential of cannabinoids, comprehensively reviewing what is known about the role of the endocannabinoid system in addiction and demonstrating the possibility of using cannabinoids to treat stimulant dependence. The focus on individual cannabinoids is also relevant to the issue of doping in sports, as is discussed by Bergamaschi and Crippa (17), who point out that focusing on THC metabolites for drug testing ignores the performance enhancing potential of other cannabinoids, such as CBD and CBN.

The final article in this research topic, by Burns et al. (18), urges researchers to reflect on the different indicators of cannabis use, demonstrating how the data we collect and inferences drawn will differ if we focus on the prevalence of cannabis use, for example, rather than the quantity of cannabis used or the frequency of use.

This article, along with the others collected here, encourage cannabis researchers to reflect on the ways in which we frame our research questions, design our studies, and explain our findings, so as to improve the clarity of the evidence. While we may not be able to clear the politicized smokescreen currently shrouding the evidence, ultimately, it is our responsibility to ensure that there is a comprehensive body of scientific knowledge available for the development of evidence-based cannabis policies and legislation when the fresh air does eventually blow through.

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'Tis in our nature: taking the human-cannabis relationship seriously in health science and public policy

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To find clearheaded scientific perspective on cannabis use through the prevailing thick smokescreen requires recognizing just what sort of smoke obscures our better understanding. In the United States, in large part, the smokescreen is made up of culture war-charged political rhetoric and obstructionism from those in positions of authority setting up a prejudicial ideological framing for cannabis use. National leaders throughout the twentieth century have taken opportunities afforded by high office or its pursuit to publicly opine on the dangers of cannabis, such as when then-Presidential candidate Ronald Reagan famously stated in 1980 that "leading medical researchers are coming to the conclusion that marijuana, pot, grass, whatever you want to call it, is probably the most dangerous drug in the United States and we haven't begun to find out all of the ill-effects. But they are permanent ill-effects. The loss of memory, for example Grass (1999)." Not only is such rhetoric overly simplistic, it also obscures and distorts pre-existing facts. In this particular case, Reagan's statement obscures the fact that the American Medical Association testified in 1937 on record to Congress that, after nearly 100 years of professional experience in Western medical practice with over 2000 prescribable marketed cannabis preparations (Antique Cannabis Museum, 2012), practitioners found that cannabis had an irreplaceable therapeutic role as an aid in the *remembering of old and long-forgotten memories* in psychotherapy patients (U.S. Congress, 1937). When in office, Reagan's first drug czar, Carlton Turner, blamed cannabis use for young people's involvement in "anti-military, anti-nuclear power, anti-big business, anti-authority demonstrations" (Schlosser, 1997), all dissenting positions toward government initiatives. Such clear scapegoating rhetoric has roots in the government's racialized Reefer Madness campaign of the 1930s which linked cannabis use in Blacks, Latinos, jazz musicians, and juvenile delinquents to racial miscegenation and homicidal mania (Helmer, 1975).

With such a long tradition of distorting rhetoric emanating from leading political authorities and being broadcast widely by the mass media, it is apparent how politicized cannabis use has become and how scientific research and knowledge about its use have been selectively highlighted and skewed to support pre-determined political objectives. These persistent distortions and political evasions are the greatest contributors to the smokescreen that obscures collection and dissemination of accurate evidence on cannabis use. The smokescreen is perpetuated because, as the saying goes, in war, the first casualty is the truth. Maintaining existing controversial policies relegating cannabis to the status of contraband (such as, under US federal law: zero-tolerance for use, a death penalty for trafficking amounts greater than approximately 66 tons, and official denial of currently accepted medical use in treatment) tends to be of a greater priority to governmental bodies than collecting and collating basic evidence regarding its use to inform public policy and health.

What evidence is gathered is often rejected or simply ignored if politically inexpedient. Here are a few examples. On occasion, political leaders are actually caught attempting to make "backroom" deals to ensure that a scientific commission's findings on cannabis use will have a predetermined outcome intended to marginalize political enemies. Take, for example, what was explicitly caught on tape during Richard Nixon's presidency. As documented on declassified tape recordings from the White House Oval Office on September 9, 1971, Nixon privately told his appointed Commission chair, former Pennsylvania Governor Raymond Shafer, that it was "terribly important" the Commission, tasked by Congress with helping to determine what level of risk cannabis use should be understood to constitute for the purposes of legal regulation, not come out with a report that was "soft on marijuana." Strategizing for political expediency over factual review and nuance, Nixon called for obfuscation: "I think there's a need to come out with a report that is totally, uh, uh, oblivious to some obvious, uh, differences between marijuana and other drugs, other dangerous drugs…" Nixon further warned Shafer: "Keep your Commission in line (CSDP, 2012)." Despite the Commission's recommendations to the contrary, cannabis was nevertheless maintained in the most restrictive category under federal law, Schedule I, where it has remained alongside heroin for 42 years, officially deemed to be devoid of medical utility, or safety. After a 14-year-delayed evidentiary hearing on a citizen-led cannabis-rescheduling petition filed in 1972 which lasted for 2 years, a Drug Enforcement Administration (DEA) Administrative Law Judge (ALJ) ruled in 1988 that cannabis should be rescheduled to Schedule II, with painkillers and anesthetics such as morphine and cocaine with currently accepted medical uses, and that to not do so would be "unreasonable, arbitrary, and capricious (SLDP, 2012)." The presidentially-appointed head of DEA rejected his own agency judge's ruling and, in 1994, a federal court finally denied the petitioners' appeal. An additional citizen-petition to reschedule cannabis filed in 2002 was rejected by the DEA after 9 years of delay and is presently under appeal (ASA, 2012). In 2007, another DEA ALJ ruled that it would be "in the public interest" to have more than one

licensed facility to produce research-grade cannabis, and that a Plant and Soil Sciences Professor petitioner who had applied in 2001 for a production license and been denied be granted one. This DEA judge's ruling, too, was rejected by the DEA head in 2009 and is presently under appeal (MAPS, 2012). The rejection had the effect of allowing the federal government's hamstringing of scientific research to continue, with cannabis clinical studies being approved at an unacceptably slow pace, testing substandard-quality material produced under a government-backed private monopoly, and supplied only after potential investigators have waded through tremendous red tape, if supplied at all. Meanwhile, over the same timeframe, private pharmaceutical interests backed by highly-profitable international corporate pharmaceutical distributors have been granted license by the DEA to import and test in large, multicenter clinical trials in the US proprietary whole plant cannabis extracts made in company-owned cannabis production greenhouses licensed by friendlier governments (Aggarwal, 2010).

The persisting Schedule I classification of cannabis that the federal government maintains is itself a smokescreen that is directly discordant with authoritative, independent, medico-scientific evidence-based assessments. Publishing in the open-access scientific literature housed in the U.S. National Institutes of Health's National Library of Medicine, clinical investigators who oversaw seven separate, government-authorized, gold-standard design clinical trials of the safety and efficacy of smoked and vaporized inhaled cannabis for specific indications conducted at University of California medical centers over a 10 years period from 2002–2012 involving over 300 human subjects reported in an article entitled "Medical Marijuana: Clearing Away the Smoke" that all trials independently showed benefit. The authors concluded that the Schedule I classification of cannabis, based on the evidence collected and reviewed, is "not tenable," "not accurate," and one of the main "obstacles to medical progress (Grant et al., 2012)." This position is concordant with the analyses and conclusions in evidence-based positions papers and reports on cannabis medical science from leading national medical academies and specialty societies (National Research Council, 1999; American College of Physicians, 2008; American Medical Association, 2009).

To begin to clear such a thick and recalcitrant smokescreen of political rhetoric and interference surrounding cannabis use requires that a massive gust of fresh air be let into the room. This will help to spur a fundamental perspectival reorientation that will allow us to breathe freely, return to first principles, and start evidence-gathering from the beginning. An expedient smokescreen clearing approach is a historical and comparative ecological one that focuses on the human-cannabis relationship on a species to species level. We will come back to the theoretical outlines of this approach; for now, consider its results. While Cannabis sativa evolved in the Central Asian-Himalayan region ∼36 million years ago (McPartland and Guy, 2004), it has spread to all regions of human habitation due to the long-standing fondness Homo sapiens have had for this semi-domesticated botanical cultivar, evidenced by the undisputed prehistoric archaeological record (Russo et al., 2008) and ancient textual references (Hillig, 2005). Cannabis's very name belies its long-standing relationship with humanity, as it was pragmatically given the species name "Sativa" in 1542 by German physician-botanist Leonhart Fuchs, meaning "cultivated" or "useful" in Latin (Russo, 2007). It grows easily in numerous climates as a wild and hardy plant whose palmate fan leaf's geometry is iconic. Uses of Cannabis sativa include production of textiles, building material, canvas, rope, paper, and biofuel using the cellulose and fiber of its stalk; nutritive food, edible oil, and lotions using its oil- and protein-rich seeds; and, most pointedly, herbal medicines, spiritual sacraments, and psychoactive inebriants using its phytocannabinoid-rich resin-producing flowers and leaves which, when ingested after heating, have robust, non-lethal, receptor-based effects via the human endogenous cannabinoid, or endocannabinoid, signaling system. Such effects pharmacologically are properly termed "cannabinergic." The endocannabinoid system is an essential biological signaling system that appeared 600 million years ago in life (Melamede, 2005) and plays a master-regulatory role in many physiological functions that humans may naturally wish to self-adjust, such as mood, appetite, memory, inflammation, muscle tone, pain perception, and stress management, in addition to other more subtle but equally validated functions such as neuroprotection, bone growth, immunity, tumor regulation, seizure threshold, gastrointestinal motility, and intraocular pressure, to name a few (Di Marzo, 2004; Pacher et al., 2006; Vettor et al., 2008).

When gathering evidence to address behavioral questions surrounding human consumption and production of potentially psychoactive cannabis preparations, it is absolutely essential that this long, co-evolutionary arc of human history with this cannabinergic plant be appreciated in order to understand underlying human values, and desires that motivate cannabis use and prevent smokescreen prejudices from taking root. The main question is: what sorts of relationships can humans have with cannabis, aside from aberrant, pathological, and addictive ones? And, as a corollary to this question, when cannabis is consumed in contemporary settings, does it necessarily have to be as a scarce consumerist commodity, or do other relational possibilities exist? By addressing such questions, a richer understanding of cannabis use can emerge and lessen the chance that use patterns are improperly understood as pathological or deviant, when they may fact be perfectly normal and healthful. Certainly the caveat that cultural controls and norms regarding cannabis use that play an important public health role may not translate to all social groups must be acknowledged.

A broader understanding of the human-cannabis relationship beyond the dominating twentieth century American and colonial prohibitionist sociolegal frameworks is needed. When there is not a war against cannabis being fought, a less distorted picture of its effects can emerge. The element of psychological distress that cannabis prohibition regimes produce is worth seriously accounting for as it can play a significant role in the conflation of the effect of cannabis on a user with the effect of the criminal or social stigma attached to that use (Aggarwal et al., 2012). A research approach from social science known as political ecology, taken from

anthropology and geography, which is able to incorporate into its analysis the total human-plant relationship and the effects of local and global sociopolitical forces, is helpful here (Robbins, 2004). Political ecology is framework used to study human-environment relations that joins cultural ecology with political economy. Cultural ecology studies how cultural groups adapt, adjust, and relate to their natural environments, and political economy studies how political institutions, the political environment, and economic systems influence each other (Mayer, 1996; Johnston et al., 2007). A sampling of the results of applying such an approach to demystify the smokescreen was given above.

By applying political ecology to cannabis use and production, we can begin to understand and appreciate traditional ecological knowledge regarding its use and production, extant and extinct cultural practices surrounding cannabis use, and the history of their marginalization. Western delegates first heard officially from other countries who wished not to impose absolute prohibition at United Nations meetings in the early 1960s when the first comprehensive international treaty that would call for strict controls on cannabis was being negotiated. Indeed, while a number of thriving civilizations have found a way to integrate cannabis use into their legally sanctioned cultural fabrics, such alternate sociocultural and political realities were ultimately targeted for suppression.

Substantial evidence has been gathered regarding the efficacious use of cannabis as a medicine to treat specific conditions. Additionally, convincing evidence regarding the use of cannabis as a non-problematic "recreational" psychoactive substance with a low potential for addiction has been collected and become increasingly accepted in the US and abroad. Public policy regimes recognizing such use patterns—medical marijuana and adult marijuana use—have taken root in several US states and internationally. However, two human-cannabis use relationships, oft-neglected in medical and public health literature, but for which substantial evidence exists are cannabis use as a *spiritual or religious activity* and as *an herbal or dietary supplement*. These use patterns were presented by international delegates from countries such as India and Pakistan for respectful consideration at the UN but simply ignored and censured (United Nations, 1961; Times of India, 2012). I call for more research and documentation on these use patterns globally using the research framework described to fully eradicate the smokescreen and see clearly what exists.

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Legalization of marijuana: unraveling quandaries for the addiction professional

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For more than four decades, a movement to shift cannabis control policy away from prohibition has gained momentum in such countries as Australia, Netherlands, Portugal, Spain, and the United States (Caulkins et al., 2012, pp. 207–224). When the issue is debated, researchers, and clinicians in the addictive behaviors field may face a difficult choice when asked where they stand with reference to making legal the retail sale of marijuana to adults. It is clear that there are health and behavioral risks to marijuana use. But, do those risks in and of themselves close the door to considering alternative policies? Or, to frame the issue somewhat differently, does prohibition's track record in protecting public health and safety justify its continuance when considered alongside one or another non-prohibition policy?

These questions are posed with increasing frequency as public attitudes in the U.S. concerning legalizing marijuana become more accepting. In 2011 the Gallup Poll found 50% of Americans saying marijuana use should be legal (Gallup, 2011). Then, in 2013 a Pew Research Center poll found that 52% favored legalization, a 10 point increase since 2010 (Pew Research Center, 2013). These indications of greater tolerance of marijuana appear to mirror a populist push back among voters and legislators in a number of states, a willingness to carve out exceptions to complete prohibition, the stance still held by the federal government.

The U.S. is a signatory to the 1961 Single Convention on Narcotic Drugs which requires all nations to prohibit both the production and use of marijuana for all purposes whether medical or non-medical (Single Convention, 1961). The subsequent 1988 Convention further requires each country to enact criminal penalties for the production, distribution, possession, or purchase of marijuana (United Nations Convention, 1988). Nonetheless, in the past 15 years, 18 states and the District of Columbia have adopted medical marijuana laws which essentially bypass the drug's Schedule 1 classification under the Controlled Substances Act, the national implementing legislation of the Single Convention. Its placement in Schedule 1 is based on the premises that marijuana has a high potential for abuse, has no currently accepted medical use, and has a lack of accepted safety for use under medical supervision. These treaties and laws notwithstanding, in 2009 the Obama administration made an accommodation to those states that had approved medical marijuana legislation. Individuals who were in compliance with those state laws would not be subjected to federal prosecution (Caulkins et al., 2012, p. 191). Then, in the months following the November 2012 election when Washington and Colorado voters approved a legal regulated marijuana market, the Obama administration remained essentially silent as to whether it would act to prevent those two states from implementing their laws' provisions. The position taken by federal officials in the intervening months has been that marijuana will remain illegal under federal law.

Thus, the pendulum appears to be swinging further away from the full prohibition end of the policy continuum. Advocates for policy reform underscore the substantial adverse consequences of prohibition for society. First, a large black market largely nullifies efforts to prevent ready access to marijuana, with billions of dollars in profits enriching gangs and cartels and fueling egregiously high rates of violence and murder. The illicit marijuana that some 30 million Americans consume each year is therefore not subjected to regulations that might require accurate labeling of potency and cannabinoid ratios, testing to assure non-contamination, and limiting sales to adults. The burden on public coffers from the operational costs of the criminal justice system adds to the list. Then there's the question of social justice, with advocates emphasizing the dire consequences, many enduring for decades after the commission of the offense, experienced by an individual who is treated as a criminal for having possessed marijuana, e.g., loss of employment, loss of housing, loss of voting rights, loss of federal financial aid for college, seizure and forfeiture of property, termination of child visitation rights, and deportation for legal immigrants. The evidence of major racial inequities in how marijuana laws are actually enforced adds to the specter of injustice. Finally, another contributing factor is the prospect of billions in new tax revenues being generated annually (Miron and Waldock, 2010).

Yet, when the prospect of legalizing marijuana is raised as an alternative societal approach, colleagues in the addictions field often voice understandable apprehension about possible outcomes. From what I have learned as a marijuana dependence behavioral intervention researcher and addictions therapist, those concerns also trouble me. First, legalization likely will convey an erroneous message that marijuana use has no risks, and with that belief, attitudes will likely change and the prevalence of use, adverse consequences as well, may rise. Those who have been protected from harm because of their anti-drug attitudes and the stigma attached to marijuana use, due in part to its illegality, will lose that protection. Second, it can be expected to increase youth access to marijuana through diversion from legal outlets and by young people accessing their parents' or older friends' supply. Third, a legal market will attract entrepreneurs, a new industry will rapidly grow, and profit motives will fuel strong opposition to efforts to limit advertising, to selling high potency marijuana that may increase mental health risks, to labeling products to warn of adverse

effects, to limiting where sales may take place and the density of sales outlets, and so on. Fourth, societal costs due to alcohol and tobacco morbidity and mortality, as well as traffic accidents and fatalities associated with driving under the influence, suggest a hefty burden taxpayers may carry once marijuana joins them as a legal commodity. In sum, in responding to the rationale for legalization, addictions professionals express concerns about its possible adverse impact on those who are vulnerable to abuse or dependence, with a particular emphasis on youth.

But, might the public and those who are vulnerable to harm be more effectively served were marijuana to be legalized? I've come to the conclusion that a closely regulated model of legalization that incorporates a true public health approach to addressing health and safety, an approach that stands a chance of preventing the ominous outcomes feared by addictions specialists, deserves consideration.

The measure approved by voters in the state of Washington is just such a model (Wash, 2013. Laws c. 3). It includes the following provisions, all of which will be funded by excise tax and license fee revenues generated by the legal marijuana market.

(1) Empowers an agency of state government to write and enforce regulations concerning growing and selling marijuana and marijuana-infused products such as confections. The word legalization conjures up a variety of possibilities, with one end of the continuum being solely the complete repeal of all laws prohibiting growing, possessing, and selling. In contrast, Washington's law calls for a tight regulation model. It mandates an agency of state government, the Washington State Liquor Control Board, with the responsibility to write and enforce regulations concerning such matters as the criteria applicants must meet in order to qualify for licenses to legally grow, process, or sell marijuana, the location and density of marijuana sales outlets, and limits to advertising. Washington's marijuana legalization law specifies that sales may only take place in stand-alone stores, a provision designed to minimize the marketing inherent in products being visible on the shelves of grocery or convenience stores.

(2) Implements both universal and targeted science-based public education. Misinformation concerning marijuana's risks is considerable. Too many young people underestimate the adverse consequences associated with regular use of marijuana by people in their age group (Johnston et al., 2012).

The Washington law mandates several state agencies with the responsibility of educating the public through the dissemination of accurate information about marijuana and allocates earmarked funding for this purpose. Ideally, in carrying out this mandate these agencies will design their efforts to convey messages using empirically supported public education methodologies and tailor the delivery of those messages for specific population subgroups.

(3) Funds communities to mount science-based marijuana prevention programs. Much has been learned about what works in preventing young people from using drugs (National Institute on Drug Abuse, 2003), although funding limitations have considerably restricted the extent to which empirically supported prevention programming is delivered (Ringwalt et al., 2002). Earmarked funding to Washington's behavioral health and recovery agency will be devoted to implementing evidence-based primary and secondary prevention programs targeting middle school and high school-age students.

(4) Makes available empirically supported marijuana dependence counseling. A portion of the legal marijuana market tax revenues will be allocated to local health departments and/or community agencies to implement treatment interventions. Additionally, a marijuana use public health hotline will be established for the purpose of providing treatment referrals and delivering research-based harm reduction services. As is the case with empirically supported prevention, the diffusion of effective substance abuse treatment protocols remains quite limited (Garner, 2009).

(5) Evaluates the extent to which marijuana-related behaviors, adverse consequences, attitudes, and beliefs change over time, and uses these data to fine-tune the legal market's regulations. A key element in this new law is devoting funding to research activities designed to evaluate the law's impact. First, earmarked funding will support several state agencies in a collaborative biennial effort to survey students, with the goal of assessing such variables as students' use of alcohol, tobacco, and other drugs; academic achievement; age of drug use initiation; antisocial attitudes and behaviors; community norms; family management and conflict; parental attitudes concerning drug use; and perceived risks of marijuana.

Second, funding will be allocated to an independent state agency that conducts policy-focused research. Periodic reports will be required from this agency over a 20 year period. The evaluation is to focus on public health, public safety, economic impacts of the law's implementation in the public and private sectors, and impacts from the activities funded by the law's education, prevention, treatment, and research provisions.

CONCLUSION

Washington's approach to regulating marijuana undoubtedly will require fine-tuning in the years following its full implementation, a process which will unfold over time. It's anticipated that licensed retail sales outlets will first open sometime in the spring of 2014. Then, as excise taxes and license fees from the fully implemented legal marijuana system are collected by the state, the earmarked funding for the public health components of this new policy will begin to flow to the various state agencies. In essence, it will most likely be late 2014 before all of the new law's provisions have begun to be operational.

Because one component of this new policy is to fund impact evaluation from multiple sources over time, state government will have data to inform future marijuana control policies. In serving as a laboratory of democracy, Washington will have the opportunity to test a model of legalization that may point the way to more effective protection of both the general public and vulnerable populations than has been the case under prohibition (Hawken et al., 2013).

Nowhere in the United States or elsewhere has this model of legalization been adopted, thus offering little precedence on which to base projections. However, I believe that prohibition's track record in

protecting public health and public safety has been seriously deficient. Moreover, inequities in prohibition's implementation make evident it has been fundamentally flawed in terms of social justice.

When the evaluation data begin to become available over the coming years, among the outcomes I hope to see, in contrast with what we have witnessed prior to legalization, are: fewer young people initiating marijuana use prior to age 21, fewer students struggling with school performance as a consequence of marijuana use, a smaller percentage of users becoming marijuana dependent, more of those who become dependent receiving effective treatment, fewer traffic accidents in which marijuana smoking is a contributing factor, and more accurate knowledge held by the public concerning marijuana's effects on health and behavior.

As other states consider establishing a regulated marijuana market, the Washington state model deserves a careful look.

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Identity formation, marijuana and "the self": a study of cannabis normalization among university students

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Over the past half-century, as use of marijuana has become more widespread in Canadian society, there are indications of a normalizing process in societal reactions and experiences of use. Among other research avenues, these trends suggest a need for further exploration of young people's understandings of how they make the choice to use or not and how decisions relate to presentation of the self. This study draws on interviews with 30 undergraduates recruited from a larger online survey of respondents at the University of Guelph, ON, Canada. In probing their perceptions of the use of marijuana, we often found that trying/using "pot" was the default option, whereas choosing not to use required more conscious effort. With specific reference to Goffman's contribution to a situated understanding of the self, our findings are interpreted with emphasis on further theoretical development of the normalization thesis and on the role of marijuana in identity formation among persons in the process of transition to adulthood.

Keywords: cannabis, marijuana, normalization, youth, identity formation

INTRODUCTION

Young people's engagement with illicit drugs, especially cannabis, is the "single most talked about, written and broadcast about item in contemporary discourses about the state of the young" [(1), p. 12]. Research shows increasing rates of use in western countries over the last two decades among youth and adults (2–4). Observance of this trend in the United Kingdom led Parker and his colleagues to initiate a discussion about the normalization of illicit substance use. Not only has the use of drugs in certain contexts increased, but socio-cultural attitudes regarding use, they argue, have shifted "from the margins toward the center of youth culture" [(1), p. 152]. The use of marijuana in particular no longer can be described as marginal or deviant in the sense of denoting membership in a distinctive subculture (5).

Cannabis is the most widely used illicit drug in western nations. Estimates in Canada suggest that almost half of the population over age 15 has used cannabis at least once, and more than half of university undergraduate students (6, 7). Starting in the 1990s, Adlaf and his colleagues have documented increasing prevalence and incidence of use in all age cohorts, with estimated lifetime use among Canadians increasing from 23% in 1989, to 28% in 1994, to 44% in 2004. With respect to prevalence, lifetime use alone may be less indicative of normalization than increases in recent or regular use. Studies in the UK suggest that 10–15% of late adolescents are recent, regular recreational cannabis users, with this proportion rising to 20–25% among young adults (3). Similarly, young Canadians are not only more likely than the previous generation to have used the drug in their life time; they are more likely to have done so within the past 12 months. About 70% of those from 18 to 24 years old reported using cannabis at least once. And nearly half of those between 18 and 19 reported use in the past-year, a number that has doubled since 1994 (6). Marijuana use is therefore common among students, and most say they find it "easy" or "very easy" to obtain (8).

A recent European study traces attitudes of youth between 14 and 19 years of age (9). Over this period it documents a change in their opinions from being negative and skeptical to positive and accepting of the use of marijuana. This is not to say, the authors note, that use is normal in the sense that everybody uses, but normal in the sense that use is ordinarily perceived as legitimate by users and non-users alike. Despite continuation of the ban on marijuana, the stigma attached to users is increasingly connected to the context of consumption as opposed to use *per se* (10). Whereas "reefer madness" era claims are frequently rejected, concerns regarding health, and social risks still remain (11, 12).

A fuller understanding of what is meant by normalization requires attention to not only rates of substance use and availability, but also to more abstract socio-cultural dimensions of accommodation by non-users of the drug (3). Thus, further qualitative research is needed to attain "a more nuanced appreciation of how the boundaries of morality – and of deviance and problematic use – are defined, and how these definitions vary over time, context and social identities" [(13), p. 144]. To better understand the role that marijuana use plays in the identities of emerging young adults, this paper draws on interviews conducted in a study of undergraduate students at a Canadian university. The normalization process, we will argue in particular, is facilitated by a fluid view of self in which the identity of "user" and "non-user" is not fixed, but rather more contingent on the situated context or social circumstances of marijuana use. To shed more light on features of the contemporary context, and the social meaning of marijuana use, this paper draws on Goffman's understanding of identity as a situated construct which is flexible itself.

MATERIALS AND METHODS

A small pilot grant to run the study was provided by the College of Social and Applied Human Sciences at the University of Guelph. The study protocol was developed and approved through

consultation with the University Research Ethics Board. Interview participants were recruited in the Winter of 2010 from a larger online survey of students enrolled in the second author's course on introductory criminology. This course has a diverse cross-section of undergraduates from a variety of programs who take the first-year class as an elective. In addition to informed consent, the online questionnaire included an invitation to participants to take part in a face-to-face follow up interview, with instructions to provide their contact information or contact the first author by telephone or email.

SAMPLE CHARACTERISTICS

Between January 2010 and May 2010, 130 participants from a total class enrollment of about 388 students (33.5%) completed the voluntary online survey. Nearly two-in-three (63%) of the participants were female. Their ages ranged from 18 to 25 years old, though most were younger first-year students as reflected by the mean age of the sample (18.5 years). Although participants came from variety of ethnic backgrounds, the majority (80%) identified as white or Caucasian. Only five were born outside of Canada, and only four from provinces other than Ontario. Of those who responded to a family income measure, about half reported household income in the high range (more than $75,000), as compared to one-in-five who reported lower income ($15–35K) and about one-third who reported middle income ($35–50K). Forty percent reported financial support for their schooling came mainly from parents. One-in-three supported themselves through part-time work, 15% through full-time work, and 14% reported that their primary support came from student scholarships or loans. Three-quarters of respondents were pursuing a degree in social science or humanities, as compared to one-in-four reporting that their programs were in engineering or the natural sciences.

Sixty percent of the participants had used marijuana, the vast majority of whom (90%) reported having used it for the first time during high school, sometime between 15 and 17 years of age. Three-quarters of those students who had ever used it reported having done so in the past 12 months. Two-thirds of past-year users used it once a week or more. The majority (∼80%) of those who had used in the past-year reported using less than a standard "joint" (about 1/2 g of cannabis) on a typical occasion. Most respondents had not purchased marijuana for themselves during the previous month, yet found it "very easy" or "easy" to obtain. One quarter had spent less than $50 buying cannabis; only six reported spending more than $100. By contrast nearly half of past-years users indicated that it was gifted, or that friends had shared it with them. Given the high ratio of females in the sample, this finding may reflect the observation in prior studies that women in particular report they need not always purchase their own cannabis to use it regularly [see (5)]. For respondents who had not used or were no longer using cannabis, nonetheless financial costs were cited second only to work/school obligations as the most important reason for abstaining.

With regard to other drug use, nearly all who took the survey had used alcohol at least once during the past month, and about one-third had smoked tobacco. Use of other drugs was more infrequent or sporadic, with past-year use of mushrooms ($n = 16$) and ecstasy ($n = 11$) the only other substance use reported by more than one-in-ten. Survey items about attitudes toward different substances show that the majority of users and non-users of cannabis consider it less dangerous than other types of drugs – including legal substances like alcohol and tobacco. When asked about the differences, apart from use *per se*, between marijuana users and non-users, more than half of both groups said no differences at all. These survey findings indicate consistency in attitudes concerning marijuana that appear to be consistent with socio-cultural dimensions of the normalization thesis.

IN-DEPTH INTERVIEWS WITH STUDENTS

Quota sampling with respect to gender, age, and drug status was used to select 30 interview participants 18–21 years old. To attain sufficient representation of non-using as well as marijuana using students, we also sought to ensure that at least one-third of participants were either non-users or former users [see (3)]. Interview participants were each paid $20 to acknowledge their time and contribution to the study. All interviews took place in a private campus office and were digitally recorded to be transcribed verbatim.

Questions in our interview schedule were informed by sensitizing concepts from a variety of sources including work by Jenkins (14) and Hammersley et al. (13) on social identity and marijuana use. Related central themes in the analysis that follows pertain to self-perceptions, or "significations," and to different forms of "categorization" and "negotiation" of the boundaries observed. For present purposes in this paper, questions from the interviews and related probes of interest focus on young people's recollections of the process through which they made the choice to use or not use marijuana, and how they understand its role or meaning in relation to their own identity as a user or non-user.

A cross-case analysis was done during transcription, using the constant comparative method, to evaluate the qualitative data for emerging themes or concepts by seeking out disconfirming evidence (15). Rather than imposing patterns, themes, and categories, these were allowed to emerge from the data. Discovering relationships between the categories began with analysis of initial observations and continued throughout the research process, by continuous refinement of the category coding. The meaning of the category thus evolved with the research as rules of inclusions and exclusion were changed to fit the data (16). The method of constant comparison enables new topological dimensions and relationships to be discovered (17). Through this iterative process, we sought to better understand the attitudes of users and non-users in our study in terms of the extent to which they may converge or differ, and further implications of the role of marijuana for identity formation among undergraduate students.

RESULTS

CONVERGING ATTITUDES OF USERS AND NON-USERS

Converging attitudes of marijuana users and non-users about the social status of the drug were often documented by student's common recognition that the exaggerated claims of the Reefer Madness era are unwarranted, deceiving, often humorous, and foreign to the lived experience of the majority of students. One non-user, for example, said that marijuana use "won't kill anyone or make them

drop out of school but, you know, it is just not for me. I just don't like doing it."

Notwithstanding mixed opinion on the potential risks and harms, accommodating attitudes of non-users ordinarily were asserted on the basis of a person's right to choose. One non-user stated: "It's their life, it's their choice; none of my business if they are hurting themselves." Another student similarly observed:

> "Skateboarding is dangerous; it is fun but dangerous and not everyone can do it. I love doing it and it is no one else's business that I might hurt myself. It is the same thing with pot. I don't like it and I think it's bad for you, but who am I to judge anyone? If they want to risk their health, well let them do it" (21-year-old male).

Comparing it to alcohol, one non-user said: "I love to have a few drinks and get drunk, so who am I to tell people not to smoke pot? . . . as long as people are having fun, they should do what gets them in the mood to party and have a good time. After all you see pot as often as alcohol these days." Indeed it was routinely observed that marijuana use within their peer groups was so common, and taken for granted among university students, that the questions seemed surprising or perhaps naïve to some. To illustrate, when asked if she would have a problem with the presence of marijuana at a party, one non-user replied: "If there are parties without at least some pot, I have never seen one of those!"

Despite its evident ubiquity at large parties among students, use in smaller gatherings or social situations is far from unequivocally accepted by non-users. For example:

> "It's not like I don't like it you know . . . as I said, it's cool to have it around at a party, but I don't like it if I am just there to play some video games or whatever" (22-year-old male).

> "I really don't mind if people are using it, like if I am with friends and they are going to get high that's cool, but I just don't want to be around when they are doing it. When they are actually smoking, I might go out for a walk or go on my cell, you know, just till they're done" (19-year-old female).

Only one non-user in our sample indicated that he avoided socializing with his peers when they are "stoned." He said: "When my friends get stoned, they get very weird . . . it's like they're in a different world. They're just not like usual, so I don't have a good time when they do it. Maybe because I am sober you know, but well they try to not smoke or get stoned when I am around." More commonly, objections from non-users had less to do with users "getting high" than fear of sanctions from authorities and potential health risks due to smoking marijuana. Some users had these types of fears and sentiments as well. For example:

> "First of all I don't like smoke, so I just don't like to be around when people are smoking anything. But with pot, I just feel like what if cops come in? What if they get caught? Then I am in trouble too . . . they can go get high, come back, and have a good time; chances are I am having a drink at the time as well" (20-year-old non-using female).

> "I would leave if anyone smokes anything in a room. It is against residence policy and I don't want to be charged with something I am not doing. I couldn't afford the ticket and what if I get kicked out? It's just not worth it" (19-year-old female, former user).

> ". . . I hate smoke. I mean I don't care if my friends are high when I see them, but if we are inside and they are smoking, I am out of there. It makes me cough up a lung! As I said, I love pot brownies. But I don't smoke it because it's horrible for you" (20-year-old male).

Further to these caveats and boundaries observed in social interactions between users and non-users, converging attitudes between the groups were also demonstrated in their common understandings of problematic use. Many students shared the view that marijuana use in moderation – or even heavy use – is safe, assuming that the user is still "taking care of business." One user suggested, "it's not like it's alcohol, you know? You can still get stuff done . . . problematic use is when you can't get your stuff done." A non-user stated: "I didn't know you could smoke too much pot. I guess if you are not missing class or work, it's not too much. I mean my boyfriend is high all the time, and he seems fine."

To further illustrate this view of marijuana as benign, at least compared to alcohol or other substance use, respondents commonly suggested that excessive use is not determined necessarily according to use levels or amounts; it is rather more contingent on the experience of use. "It is not like drinking," for example, said one user; "someone can be stoned all the time and not have a problem, and someone can smoke once a week and even that might be too much for them." Another one observed: "There are no such things as rules of thumb when it comes to quantity of marijuana you use. It is really up to the person, as long as you can get stuff done."

To better understand the distinctions that are made between "users" and "non-users" among students in both groups, we asked about the differences that they saw between groups beyond the use of cannabis itself. Reported differences were viewed as negligible by most, though some observed that users are perhaps more "open-minded," open to new things, or "easy going" than non-users. For example: "I don't think there are much differences . . . people who use are I guess more open-minded about things. They are more likely to try new things" (19-year-old female user). And another: "I don't see much of a difference . . . My friends who use it seem to be a little bit more easy going than the rest I guess, but there is no telling" (20-year-old male non-user).

Despite the lack of clear distinction between users and non-users, social censure is still evident in both groups. However, stigmatizing labels are reserved for noted "pot heads," or those who abuse it, as opposed to the more typical representation of the marijuana user who uses it responsibly with no adverse effects. Most notably, we found that some student's designation or perception of the very existence of a "user" appears to be more fluid than the term tends to suggest. One user stated, for example: "I really don't think someone is a user . . . what I consider to be a marijuana user are really pot heads, you know people who use it way too much" (20-year-old male). And a non-user said:

> "Do I think there is such a thing as a marijuana user? Of course, but I mean they are users because they use the drug. But really I consider marijuana user as someone who abuses

it. I sometimes smoke a cigarette; that doesn't make me a 'smoker.' The same way, if someone is smoking pot at parties, they are not marijuana users . . ." (19-year-old female).

Another female student also made the point: "Simply because I play intramural soccer; that does not mean that I am a soccer player. So if I am smoking pot sometimes, I am not a 'pot smoker.' I just use it sometimes." The identity of "marijuana user" from this standpoint appears to be much like a "hat" or article of clothing that young people wear if, when and where they make the choice to use [see also (10)].

MARIJUANA AND IDENTITY

Because responsibilities and social roles may vary, it appears "the fit" is not the same for every "user." What is the role of marijuana use in identity formation? How and why do some young people choose to use cannabis? And why do others choose not to? For some of our respondents, as in the following examples, the primary reasons for abstaining were related to social obligations, prior commitments, or their responsibilities to family or to work:

"My grandmother promised that if I do not use drugs during high school she will give me a $5,000 gift to pay for my first-year tuition at the university. I mean that is a big incentive and that meant I can use my money to go traveling, so to me it just made sense to not smoke pot or use any kind of drug . . . of course I was tempted and still might try it in the future, but five grand is a lot of money" (19-year-old female).

"My boyfriend and I made a pact that we will not use pot. It was just a promise that we gave each other. I don't know if he has kept it, but I always looked at it as something that made us different than other couples" (19-year-old female).

"I guess I didn't start because there was no opportunity to start. I had to study and take care of our family shop, so I just had no time to go to parties to even get close to someone who has pot. Now in school it is the same thing, work work work. I just can't get a break to even have a beer, never mind a joint!" (21-year-old male).

By contrast, most non-users cited reasons for abstaining that appeared less practical than meaningfully symbolic, relating to perceptions of identity or status and their presentation of the self. Some of them made it clear that they intended to maintain their images as "clean-cut" and hard-working students. And some had aspirations, or positions to uphold, requiring them to set themselves apart from others by example. One student said: "I didn't smoke pot because I was the student union president at our high school. I wanted to be the clean-cut guy who people look at as responsible. Not like pot users cannot be responsible but it is the image that matters, you know?" (20-year-old male).

More generally non-users said they wanted to convey an image that is different from other mainstream youth in the sense that abstinence is the new form of rebellion, since using marijuana is increasingly the norm. For example:

"I've never smoked pot because well it seemed like a commonplace thing to do. It seemed like it was just another thing that everyone was doing. I am a rebellious person but smoking pot seemed more conformist than rebellious" (20-year-old male).

"I really didn't want to be like everyone else. You couldn't swing a cat and not hit a pot user in my high school. They were just everywhere and you couldn't get away from them all, so I made a point of not using. What's the point of being like everyone else?" (19-year-old male).

"I have always wanted to be myself; hence why I dress this way [in a style that was unique to say the least]. I have always wanted to be the girl who is different, who is not like everyone else. I think if no one smoked pot I would have been the biggest pot head" (20-year-old female).

Students' recollections of how they became a "user" converged with the perceptions of non-users that marijuana use is normal among young people that they know. Indeed, while abstinence apparently required more conscious effort, the choice to use for many seemed to be taken by default. These examples indicate that marijuana use by students can convey a wide variety of meanings, from mundane or "commonplace" to intimately connected to a sense of independence for emerging young adults:

"I don't know why I first started smoking. I guess it was just something to do. Everyone else was doing it and it seemed harmless" (21-year-old male).

"Well a lot of people I hung around with used it. I mean it's like having a drink or taking a puff off the cigarette. You give it a try to see how things go" (19-year-old female).

"It wasn't really a decision but sort of like a . . . rite of passage . . . it was like you are not a kid anymore now that you have smoked pot" (19-year-old female).

In the situated context of attending university, we encountered differing perspectives on the matter of opportunities provided for using marijuana. As noted previously, some students found that work and school commitments restricted their free time and freedom to use. Notwithstanding these experiences, it is clear that many others find life in university gives ample opportunity. One male, aged 20, said: "My pot smoking has increased now. I don't have to work. I don't have to really do anything but study, so it leaves a ton of time to go out and party and get stoned." Another male student, age 20, reported: "I never smoked pot in high school . . . now in university, it is different. I have lots of time to myself and less responsibility than before, so I have started smoking some when I go out with friends."

The majority of users in our study said attending university afforded more opportunities and freedom for using marijuana whether they had used it or never tried before. The greater freedom they reported was commonly attributed to the anonymity afforded by the university environment and community. The transition from high school to university often means moving from a small town to a bigger place. Accordingly, a 19-year-old male stated that: "I loved the fact that I could smoke pot and still keep it a secret. Do you know how hard it is to keep something a secret when you have only 20 people in your high school graduating class? If I had

even been close to a joint my parents would have found out quite quickly."

Marijuana use, for some, appears to be facilitated by being better able to blend into the environment. For others, it is more of an expression of being able to define themselves in ways they never thought they could before. This point is illustrated in these final two examples of how students understand their use of marijuana in relation to their presentation of the self:

> "I didn't smoke in high school because we lived in a small town north of Guelph. Everyone knew everyone, so if I smoked one joint then everyone would know. I really wanted to get into university and needed good letters and volunteer work and I knew that wouldn't have been possible if people knew I smoked pot, so I didn't. When I came here though, it seemed like you could get lost in the sea of students and no one would be any wiser. I could smoke all the pot that I wanted and still manage to show a face of a clean-cut girl. I just loved the anonymity" (20-year-old female).

> "I liked university; you could distinguish yourself in other ways. Like in high school we couldn't even wear our uniforms the way we wanted to. But once I came to university, my image could have been more than just that girl who doesn't smoke pot. I could define myself uniquely in a million different ways. Pot became a non-issue then" (19-year-old female).

DISCUSSION

There are several limitations of this study, so some caution is needed in interpreting results. Our two-stage process of recruitment based on an online student survey of respondents in an introductory crime class relies on self-selection and is not truly representative of university students, nor even students taking introductory criminology. We successfully recruited only one-in-three potential respondents in the class to complete the online survey. Another study underway at the same university and other universities in Canada confirms that small incentives (such as a $20 payment or 2% participation mark for volunteering) dramatically improve upon response rates in such studies. When a survey includes questions about illegal conduct, a high degree of non-response is typically expected. Yet levels of participation in Canadian drug studies are within the standards expected of most surveys (6), and self-reports on drug use have been shown to be quite valid (18). The trend toward greater acceptance of cannabis may also mitigate to some extent reluctance among users to participate in interviews and surveys (19).

Based on in-depth interviews with "users" and "non-users," we have explored how they identify the practice and how their attitudes relate to normalization of marijuana use. An important aspect of marijuana normalization is less concerned with how users perceive their use as "normal" than how it is regarded by others in society, regardless of whether they approve. Marijuana use today still carries a certain stigma, the management of which requires the user to observe boundaries and have rules about negotiating conflict (11). However, attitudes of users and non-users are converging (13, 20). The prevalence of marijuana use by young adults, and the converging attitudes of users and non-users, means we can no longer speak of users as belonging to an identifiable deviant "subculture." Rather use communicates a style that might be viewed as "conventionally unconventional" (21) by some youth and merely conventional, conformist, or commonplace by others. Indeed, the very notion of a "user," or non-user, has different connotations in this normalizing context.

Taking an opportunistic "puff" at a party more often signifies commitment to having a good time, or "fitting in," than a clear intention or desire to "use." This may be more apparent in the younger generation, but it appears that attitudes among the "over thirties" are also becoming more liberal (1, 22, 23). Marijuana use in certain settings is likely largely understood by young people as it is by many middle-aged adults. However, use by youth appears to be less ritualistic or confined to certain settings, Zinberg (24) argued; that is, young people tend to be more flexible in their use (1, 3, 25). Similarly Parker and his colleagues found that students rarely gather for the purpose of smoking marijuana. It was more often used as a complement to other activities like drinking, playing video games, or simply "hanging out."

Howard Parker situates the normalization thesis in scholarly discussions about changes in the process of transition from adolescence to adulthood. In today's "post-modern world' youths" attitudes, opinions, and their use of leisure-time all are being shaped in different ways than those of preceding generations (26, 27). The process of becoming an adult, it is argued, is fundamentally different for contemporary youth in the formative period of post-adolescence (28). The stage(s) between childhood, adolescence, and adulthood are not only longer, but more complex than in previous generations (29). Changes in the journey to adulthood, in particular, are reshaping the nature of leisure and pleasure in a way that is specific to the post-modern world (1, 30). As leisure and consumption replace work and production as the main source of identity formation (2), young people form and maintain an idea of the "self" that "expresses its integrity through parading its identity" [(31), p. 882]. Among other implications of a changing workforce and associated changes in the school to work transition, youth today have more time to participate in leisure and shape their identities through leisure-time consumption.

Through consumption young people not only shape their leisure-time; they also shape formation of their own identity. "The relationship between consumption and identity formation is one compelling explanation for why drug use has become more common" [(2), p. 443]. With increasing numbers of "ordinary" young people growing up "drug wise" and accepting of controlled or "sensible" drug use (3, 32), the recreational use of marijuana has become part of their leisure repertoire, or just another aspect of the consumer lifestyle (1). As "time out" becomes commoditized (33), the use of certain substances, much like fashion, is becoming just another form of "symbolic consumption" that conveys meanings about self, identity, and status [cf. (34–39)]. Further, notwithstanding the limitations of this study, our interpretation of the findings indicates that a more nuanced understanding of the social context of normalization among emerging young adults calls for a more flexible or fluid interpretation of identity with particular attention to the situated "self."

CONCEPTUALIZING THE POST-MODERN, FULLY SITUATED SELF

For Plato, the "reality" we think we see is really more like shadows cast upon the wall of a cave by the flickering light of the campfire. What we imagine we are seeing is but a representation

of something that exists only in our minds. Likewise, the post-modern self, in contrast to the modern which seeks a sense of order or enduring essence, is premised on rejection of an essence altogether. The post-modern self, accordingly, consists of images (not essences) which are part of relationships – not of the individual (40). Thus, the self is only real within its social context; it is wholly interactive, existing only in the interplay of images with no underlying signifiers, or essence of its own [(41); see also (42)].

Park (43) was the first sociologist to conceptualize individuals as actors who are "seeking recognition." Our need for social recognition and acceptance by our peers compels us to present ourselves to others in a way that we believe will be acceptable to them. This "mask" becomes "our truer self, the self we would like to be" (p. 739); hence Park recognizes the fluidity of the self while assuming a "true self" exists. Goffman's dramaturgical perspective calls for further "critical recognition of the conventionalizing influence of the social looking-glass" [(44), p. 277]. Goffman's self is an entirely "social self" who is either performing or preparing to perform for a particular audience. In his words, thus "while people usually are what they appear to be, such appearances [are] managed" (1959, p. 77). This view of self is not entirely dependent on the actor, but rather it develops as a result of interaction between the actor and the audience.

In his theatrical analogy, Goffman's front stage is comprised mainly of the setting and actor's personal characteristics. The setting is the physical environment; for example, marijuana smoking in parties of mixed attendance typically occurs away from other guests in a different room, or outside (13) – i.e., in the backyard, on the balcony or porch, or partakers might go for a walk around the block. Thus, successful participation in a particular setting requires the user to be familiar with "regional behaviors" that dictate the boundaries of social accommodation (45). The actor's personal front stage comprises items that are identifiable by the audience as part of the performance. Much like the sword of the sword fighter, possession of a "joint" is part of the personal front stage of the marijuana user. And much like the sword fighter can also be a basketball player when s/he is in possession of a ball, a nightly marijuana smoker might be in the position of sending citizens to jail for the same behavior garbed in a judge's robe the following morning. As marijuana use has shifted from a marginalized behavior to one considered normal within a certain context, we cannot view the "user" as a homogenous (id)entity; and we can no longer look at settings as specific to "users" (24).

Whereas manner and appearances need to be consistent or harmonious in a given setting, this consistency only needs to last as long as the front stage itself does. Our judge who must uphold the law in court may also be in favor of cannabis reform, and advocate for changes in the law in different roles on the job and as a private citizen. The front is not created by the actor *per se*; rather it is chosen from a repertoire of selves to be consistent with the setting or the situation. Providing a convincing front requires not only choosing the proper schema but also effective and consistent communication of the characteristics of the chosen role (46). There are also tactics for concealing certain secrets, such as occasional drug use, that are not in harmony with the intended performance. Hidden aspects of the front stage are present in the "back stage." Since the audience should not be aware of this deception, the actor must employ techniques to make sure that the secrets of the back stage do not leak to the front stage, which would ultimately discredit the performance.

Goffman's most important theoretical contribution is replacing the "deep value" with the "face value" by challenging the distinction between "real" and "staged" (40). His conceptualization of the self marks the transition from representations to simulations where signs are no longer real on their own but dependent on other signs within a reproduced reality (47). This wholly situated self blurs the lines between real and imaginary to the point that the distinction becomes one of style rather than substance. Goffman argues that a person is made up of multiple, loosely connected selves [(48), p. xlviii], as opposed to an essential self. The transition from a "modern" to "post-modern" view of self is most notably consistent with revisions Goffman (49) made in the second edition of The Presentation of Self in Everyday Life. Whereas the first edition conjures up a cynical vision of the world where actors manipulate their audience by hiding their real selves behind the mask of the front stage, in the later version manipulation and deception are recast as mutually accepted and expected social roles or representations played out between an actor and her audience.

Most significantly, Goffman cautions readers against taking the dramaturgical metaphor too literally. Unlike a stage performance, where actors may remove their masks after the curtain call, beneath the mask is not a face but a repertoire of other masks chosen to suit the social role, setting, or situation (50). Whilst he distinguishes between the "public" and the "private," this is not to suggest a "true private" and "false public" (51, 52). Nor is it captured by the term "impression management" which highlights the distinction between appearance and reality, wherein appearance is "manipulative" and reality is "honest" (53–56). For Goffman, representation is an end unto itself. His situated self is neither manipulative nor honest; it is not real or imaginary – rather it is fluid. In Platonic terms, it is a shadow with no person. Similarly, Goffman echoes Horace when he says "we are dust and shadows" (pulvis et umbra sumus). A more nuanced understanding of the normalization process, with respect to cannabis and other substance use, would benefit from further theoretical engagement with Goffman's situated understanding of the self.

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The role of study and work in cannabis use and dependence trajectories among young adult frequent cannabis users

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Life course theory considers events in study and work as potential turning points in deviance, including illicit drug use. This qualitative study explores the role of occupational life in cannabis use and dependence in young adults. Two and three years after the initial structured interview, 47 at baseline frequent cannabis users were interviewed in-depth about the dynamics underlying changes in their cannabis use and dependence. Overall, cannabis use and dependence declined, including interviewees who quit using cannabis completely, in particular with students, both during their study and after they got employed. Life course theory appeared to be a useful framework to explore how and why occupational life is related to cannabis use and dependence over time. Our study showed that life events in this realm are rather common in young adults and can have a strong impact on cannabis use. While sometimes changes in use are temporary, turning points can evolve from changes in educational and employment situations; an effect that seems to be related to the consequences of these changes in terms of amount of leisure time and agency (i.e., feelings of being in control).

Keywords: frequent cannabis use, cannabis dependence, young adults, qualitative research, life course approach, longitudinal study, education, employment

INTRODUCTION

Cannabis is among the most widely used illicit drugs worldwide, with between 125 and 203 million last-year users worldwide (1). In the US approximately five million persons use cannabis on a (almost) daily basis (2), and in the European Union an estimated three million individuals are (almost) daily cannabis users, most of whom are aged 15–34 years (3). Frequent (daily or nearly daily) cannabis use and particularly cannabis dependence are associated with various mental health problems and impaired functioning (4–8).

Associations between cannabis use, education, and employment have been extensively studied. Longitudinal research has shown that adolescent cannabis use is related to poor educational performance and early school dropout (9); degree attainment and university attendance (10); and reduced occupational expectations, attainment, and stability (11). A review on young adult substance use concluded that many risk and protective factors for adolescents remain for young adults, but, given the changing social contexts, factors such as college attendance and job attainment are specific for young adults (12). Regarding later life outcomes, adolescent cannabis use is related to lower income and higher unemployment in young adulthood (5). Adult past year cannabis users are more likely to quit their job to take another job, to be unemployed between jobs and to have lower levels of employment than non-past year users, including never users (13). French et al. (14) found that weekly or more frequent cannabis use was negatively related to employment, but less frequent use was not. In a longitudinal Norwegian study, cannabis users (use at least once in the past 12 months) reported lower levels of work commitment than less frequent users, regardless of individual characteristics (15). More generally, Arria et al. (11) showed that persistent drug users (at least once in every year studied) were more likely to be unemployed than non-users, and that part-time workers were more likely than full-timers to be drug dependent. Finally, Reed et al. (16) found that high job strains and low job control increased the risk on drug dependence. Together these findings suggest the presence of a reciprocal relationship between (changes in) occupational activities and (changes in) drug use and dependence, with changes in occupational activities leading to changes in drug use/dependence and changes in drug use leading to changes in occupational activities. However, little is known about the mechanisms responsible for these changes. One classical possible mechanism that could underlie this relationship is the "amotivational syndrome," as it has been proposed that heavy cannabis use would cause (temporary) cognitive impairment including diminished motivation and memory, lack of interest, and concentration problems. However, these symptoms may as well be an outcome of other factors, such as depression, and no clear evidence until now supports this association (9, 17, 18).

Life course theory considers transitions such as changes in education and work as potential turning points in explaining desistance from deviance (19). Turning points are preceded by life events, which can be abrupt or gradual. Abrupt life events make sudden, sharp distinctions between past and future. Most events, however, are more gradual, and are part of a process. Life events could (objectively) be categorized as positive or negative, but their (subjective) meaning as positive or negative depends on how they are evaluated by the person experiencing them (19). Consequently, similar events can have different meanings for different individuals. When life events lead to a lasting change over time or a redirection of an individual's course of life, including changes in deviance, they are considered turning points (20). Thus, turning points can only be identified in retrospect (21, 22). In life course theory, changes in deviance over the life course are explained within the context of age and maturation: most deviant behaviors peak in adolescence and young adulthood and then decline (19, 23). Employment has the potential to decrease deviance, because strong ties with work and informal social control could get an individual's life (back) on track; not the job *per se*, but the commitment and stability associated with work can reduce deviance (19). Also, employment limits one's time, thereby practically reducing opportunities for deviant activities (23).

Other researchers have emphasized the role of personal factors, such as "agency" in life events and desistance [cf. (24)]. In short, human agency refers to free will and (feelings of) control over one's life, and contributes to how life events are experienced and might change into a turning point (20, 24). When using the concept of agency in this study, we follow Teruya and Hser (20), who defined it as "the amount of personal choice and control over decision making individuals feel they have," and that "shapes their perceptions and the outcomes of life events and transitions and may contribute to the differential effects that the same life event may have on different people." [(20) p. 4].

Although life course theory often concerns criminal careers and desistance from crime, we assume that it also applies to cannabis use careers, since largely similar processes are involved [cf. (25)]. Life events thus can become turning points when redirecting an individual's path in substance use or dependence. In life course theory, employment, especially stable employment, is considered as one of the factors most commonly associated with desistance. The potential of employment to become a turning point is influenced by job characteristics and human agency (16, 20, 24).

Several of the earlier studies on drug use, education, and employment refer to any use in the last 12 months, which could range from only once to daily use. Consequently, it remains unclear to what extent frequent drug use, including cannabis use, is related to study and work. Probably more important is the need to better understand how and why frequent young adult cannabis users change their use, how these changes are related to transitions in and out of cannabis dependence, and how these changes and transitions are related to changes in study and occupational activities. Employment trajectories can have turning points with an impact on cannabis use and dependence, but cannabis use can also influence employment (26). To better understand the natural course of frequent cannabis use of young adults and the relation with education and work, our objectives in the current study are (1) to explore in-depth the meaning and role of education and work in using cannabis in general; (2) to analyze the relationship between events in these domains and changes in cannabis use; and (3) to analyze the role of occupational events in changes in cannabis dependence trajectories. We decided to use a qualitative approach, because the dynamics and the processes underlying the relationship of educational and work with cannabis use and dependence trajectories cannot be adequately addressed with quantitative methods and because personal narratives and in-depth interviews are deemed to improve our understanding of the processes and the context involved with these changes. This study is among the first to qualitatively capture the natural course and transitions in frequent cannabis use and dependence in young adults.

MATERIALS AND METHODS

STUDY DESIGN

The current (qualitative) study is part of a broader longitudinal study (CanDep) on cannabis use and transitions in cannabis dependence in young adult frequent cannabis users [see for details (27)]. **Figure 1** displays an overview of the different (quantitative and qualitative) interviews in the study. In brief, at baseline (T0, September 2008–April 2009) 600 frequent Dutch cannabis users (>3 days cannabis use per week in the past 12 months) aged 18–30 years were recruited in coffee shops and through respondent-driven sampling and interviewed [see for details (28)]. Participants were monitored for 3 years, with two follow-up interviews and six intermediate updates by e-mail or phone. At T0, DSM-IV diagnoses of 12-month cannabis dependence were assessed with the Composite International Diagnostic Interview (CIDI 3.0). After 18 months (T1, March–November 2010) and 36 months (T2, September 2011–March 2012) participants were interviewed again, including an assessment of their cannabis dependence status since the previous interview. At T1, four trajectories in cannabis dependence were distinguished: persistent non-dependent, persistent dependent, transition from dependent to non-dependent, and transition from non-dependent to dependent. At T2 the number of trajectories extended to eight.

In an additional qualitative sub-study, the dynamics underlying the changes in cannabis use and the transitions in cannabis dependence were investigated with special emphasis on study and occupational changes. We conducted life story interviews, in which users can express themselves through their narratives and thereby can improve our understanding of the processes and the context involved in these changes [cf. (24, 29, 30)].

From each of the four trajectories at T1, 12 participants were randomly selected, stratified for gender (8 male, 4 female), totaling 48 interviewees. At T2, these interviewees represented seven trajectories (**Table 1**). The first qualitative interview (I1) took place between December 2010 and April 2011, the second (I2) in March and April 2012. One participant could not be traced back at I2 and was excluded from the analysis, thus resulting in a final sample of 47 participants. While 47 participants is a small sample size for quantitative research methods, for qualitative methods this is not the case and a "small" sample size is considered more powerful in order to achieve depth [cf. (31, 32)].

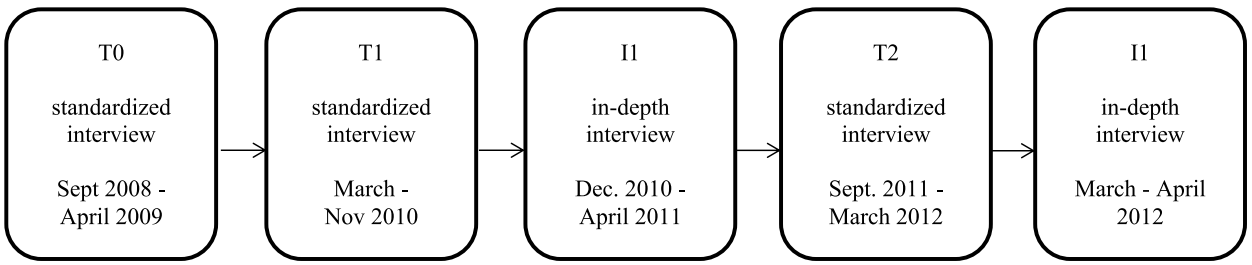

FIGURE 1 | Timeline of CanDep data collection.

Table 1 | Transitions in cannabis dependence status T0–T1–T2 and trajectory characteristics.

Cannabis dependence trajectory	*n*	T0	T1	T2	Age T0 (mean)	Age first use (mean)	Cannabis career T0 (mean years)	(Near) daily use T0	(Near) daily use T2	Female
NNN	12	Non-dependent	Non-dependent	Non-dependent	21.8	14.4	7.4	6	3	4
NDN	7	Non-dependent	Dependent	Non-dependent	20.4	14.3	6.1	4	5	2
NDD	4	Non-dependent	Dependent	Dependent	20.5	14.2	6.2	3	2	2
DNN	10	Dependent	Non-dependent	Non-dependent	21.2	13.4	7.8	7	3	3
DND	2	Dependent	Non-dependent	Dependent	22.5	14.0	8.5	1	1	1
DDN	5	Dependent	Dependent	Non-dependent	19.8	13.4	6.4	3	2	1
DDD	7	Dependent	Dependent	Dependent	22.4	15.0	7.4	5	4	3
Total	47				21.3	14.1	7.1	29	20	16

IN-DEPTH INTERVIEWS

We conducted in-depth interviews, using a topic list that included questions about participants' cannabis use career, i.e., changes in patterns of cannabis use, motives for change in cannabis use, and the occurrence of life events in various life domains. Interviewees were asked to recall changes in different life domains and in their cannabis use patterns between T0 and T1 and between T1 and T2, respectively, using detailed personal timelines [cf. (33, 34)]. One timeline referred to their cannabis use (including frequency and number of joints per occasion), the other timeline to life domains (including occupational life, i.e., education and employment). Both timelines were prepared before the interview and included data derived from the quantitative interviews and intermediate updates, which included questions about their cannabis use and occupational status (i.e., study and work). During the interviews these timelines were used as guidelines and elaborated in detail. Every interview started with an open question ["Thinking about your life between .... (T0 or T1) and ... (T1 or T2), what has happened and what experiences have been important to you?"], and ended with a similar, but slightly different question ["Looking back at the period between ... (T0 or T1) and ... (T1 or T2), what experiences or processes do you consider to have had a (positive or negative) impact on your life and cannabis use?"]. While in the first in-depth interview (I1) participants' entire cannabis career and life history until baseline (T0) were discussed, the focus in both in-depth interviews (I1 and I2) was on the period between the standardized interviews (T0–T1 and T1–T2 respectively). The study was approved by a Medical Ethics Committee. All participants provided written informed consent at the start of the study, acknowledging that their participation was voluntary. They all were assured that the interviews were confident and data was kept safe, separated from any personal information and that anonymity was guaranteed. Interviews took place at a quiet location; mostly at participants' home and sometimes at the research institute. The interviews lasted between 1.5 and 3.5 h. After completion, participants received a financial compensation of €25.

ANALYSIS

All interviews were digitally recorded (with participant's consent), transcribed verbatim, and imported into QSR Nvivo. Transcripts were analyzed combining deductive and inductive strategies. Codes and categories were partly developed beforehand, based on the literature [*a priori* coding: (35)]. In addition, new codes and categories evolved from the data, and new patterns emerged. Interview transcripts were read and reread to identify and link evolving codes, categories, and themes [pattern coding: (35)]. To guarantee anonymity, interviewees were identified with fictitious names and sometimes quotations were slightly adapted.

RESULTS

PARTICIPANTS

Age of participants at baseline ranged from 18 to 30 years (**Table 1**). One third was female (by selection). Age at first use varied from 11 to 18 years (mean = 14 years).

At baseline, the length of cannabis use careers ranged from 1 to 15 years (mean = 7 years), for some with intervals of no use.

At baseline (T0), 29 participants were (near) daily users (5–7 days per week) and the remaining 18 participants used on 3–4 days per week. During the study there was an overall decline in cannabis use frequency. At T2, 20 participants were (near)daily users, 19 participants used at least three times a week but not (near)daily, 3 participants had not used cannabis for 1 year or more and said they had quit permanently, and in the 5 remaining participants cannabis use varied from 1 day per week to less than monthly, including 3 participants who basically considered themselves as quitters, and had been using cannabis only a few times in the past year. Also quantity of cannabis used decreased, from on average 2.9 joints per using day at T0 to 2.4 at T2 (excluding three non-past year users). At T0, 24 participants were last-year cannabis dependent and 23 participants were non-dependent. At T2 this had changed to 13 dependent and 34 non-dependent participants. At baseline dependent and non-dependent interviewees were rather similar concerning mean age at initiation, mean age at baseline, gender and (near)daily use. At T2 cannabis dependent interviewees were more frequently (near)daily users than non-dependent participants, but also in NDN many participants were using (near)daily. Besides, relatively more females than males were dependent at T2.

EDUCATION, EMPLOYMENT, AND COMMITMENT

Regarding occupational status, three categories were distinguished: students, employed and neither student nor employed. At baseline, almost two-thirds of the participants (31/47) were fulltime students. At the time of the last in-depth interview some had stopped studying without a qualification, some had graduated, but most (24) were still studying. Type of study varied from a vocational training to academic studies. Most students had a job on the side; some regularly 3 days a week, others every now and then when they felt in need of money. The most popular job among these students was working in cafes or restaurants. At baseline, about a quarter of the interviewees (11/47) were in paid fulltime employment (32 or more hours weekly). At T2 more than one third was employed (18/47), all but one fulltime. By then, some interviewees still worked at the same company, and sometimes had been promoted, while others had switched work several times during these 3 years. The growing number of employed participants is partly explained by participants graduating and then starting their job career, and partly by participants quitting their study unfinished and getting employed. The employment sectors were diverse, for example some worked in bars, others in academic professions. In the course of the study, one participant became unemployed at T2. At T0, the remaining five interviewees were neither student nor employed: three defined themselves as a fulltime parent, one was on social benefits, and one was in a reintegration program (with probation). Of these participants, the one on probation had become a student at T2 and the occupational status of the other four remained unchanged. To summarize, in the course of the study the number of students dropped from 31 to 24, the number of employed (almost exclusively fulltime) increased from 11 to 18, and the number of participants without study or work remained stable at 5.

Although the importance that student and employed interviewees attached to their study or work varied, only a few of them felt that it was not very important and that life was more about social activities and "having fun."

> *My study is somewhere on the background in my life. Of course it's important for me to keep thinking about the future, and it plays a large role in that I have to go there a couple of times every week, and have to study for it, but if I fail a test, I fail a test, that doesn't really bother me. (. . .) I'm not much of a scholar, for me the fun things in life are more important.* (Julius, I1, DNN)

however, most students attached goals to their study, for instance attaining their undergraduate diploma in due time, or getting high grades. some had intermediate study delays, but sooner or later commitment often grew and study became a priority.

> *Now, my school is very important, I don't want to do retakes, because I can't choose another study again. My student grant ends at some time and anyhow I have to pay the next three years myself. I want to do it well and timely, not being 30 when I graduate. Imagine I'm 30 and by then I have to start my career, find a husband and possibly have kids. And that has to happen before a certain age. That's also why I want to pass my exams in one time.* (Kim, I1, DDD)

In their narratives, interviewees often expressed commitment to study and work, and to strive for a steady job career. Evidently, the more important participants considered their study or job, the more effort they put into it and the more committed they felt.

> *When I'm at work, I'm ambitious. In my last job I got promoted to supervisor within one year, and that is something I want to achieve. I have higher aspirations, and I cannot simply work somewhere for 8 hours and watch the clock. I envy people who are able to do that: have a job, do their work and that's it. I am not like that; my work always follows me home. Yeah, I'm pretty ambitious.* (Kevin, I2, NNN)

CANNABIS USE IN RELATION TO STUDY AND WORK

Most interviewees believed that heavy cannabis use would negatively impact their daily occupational functioning and most of them had experienced adverse effects themselves, such as difficulties getting out of bed the next day, functioning more slowly and sloppy, trouble memorizing, and postponing tasks. However, almost one in five participants (8/47) reported better functioning in some tasks when being high or stoned, mainly because they believed it improved their concentration. With cannabis, they felt like being "in a bubble" and less distracted by other people, actions or thoughts. Interestingly, all these interviewees stated to have ADHD and/or ADD (all except one clinically diagnosed), and some said that cannabis was like "natural Ritalin" or a kind of "self-medication."

> "*Recently I finished that training, and started my own company. It goes really well. I'm much more concentrated in my work after using cannabis. And when I'm programming when I'm stoned, I'm like in the codes straight away, type everything effortlessly. Sober I start thinking about how it's working, the syntaxes, commando's, but stoned all of that happens fully automatic. I get into a kind of vibe to program completely uninterrupted. It makes a big difference.*" (Ben, I1, DNN)

Almost all student and employed interviewees took it for granted not to use cannabis before or at school or work or when studying mainly to avoid adverse effects and/or out of responsibility.

Interviewer: Why don't you smoke cannabis at work? Interviewee: Well, it's kind of... On the one hand I think that they wouldn't be cool with that. I think they want to hire the sober Jacob. On the other hand: sometimes, when you have smoked a couple of joints you lose a little attention to details. And that is something that's really important in my job, the details. So, not using cannabis at work out of feelings of responsibility, but perhaps also to distinguish work from leisure. Like: you're not here to chill but to work. (Jacob, I2, NNN)

Other reasons for not using cannabis at work or at school were fear that colleagues would notice it and fear of possible consequences, such as being taken less seriously or being fired. Most interviewees said colleagues or fellow students did not know about their cannabis use. They believed that cannabis use was a private matter, and preferred to keep it to themselves. The dominant patterns in the narratives was to be rather firm in stating that it was inappropriate to be intoxicated while at work, at school or when studying. Using cannabis belonged to the leisure domain, and they reported that they only used cannabis after finishing study or work. As a result, most employed participants barely used cannabis at daytime, and more on weekends than on weekdays. With students, there was more variation, as their daily life was less structured around fixed hours throughout the week. They sometimes used cannabis at daytime, and more often during holidays. Among the participants without study and work, the three that were full time parents sometimes used cannabis at daytime when the children were at school, but more often at night when the children were asleep; they used less or not at all during school holidays.

Despite interviewees generally holding strong views on not using cannabis before and during study or work, some did admit it had happened occasionally. While employed participants seemed to be most strict in not using when at work, students sometimes believed that study differs from work, as there is less social control at college (e.g., when not showing up or not paying attention in classes).

I am very strict: when I have to work or go to school I don't smoke. Well, school ... occasionally, when my class begins late, at 2 PM, a friend drops by and then we'll have a cup of coffee and smoke a joint, but not heavy. The first class is also very boring, I go stare out the window or distract others. (Tess, I1, NDN)

It's perhaps more practical not to be too stoned during lectures, but hey, occasionally it doesn't do any harm. Sometimes, when the lecture begins at 5 PM, well, I sometimes smoke a joint at 3 PM and I think: I shouldn't have to. I'm trying to take the study really serious, but sometimes it doesn't work out and I think: oh well, I'll do it tomorrow. No one is bothered by it; it doesn't affect anyone. (Eduard, I2, DDD)

RELATION BETWEEN STUDY AND WORK EVENTS AND CHANGES IN CANNABIS USE

Not surprisingly given their stage of life, most interviewees reported life events related to study or work that had taken place in the course of our study. In total, participants reported 97 events, averaging 2.1 events per interviewee (**Table 2**). Four participants reported no events.

Most changes and events concerned starting a new study or job, graduating, finishing a study, quitting work or a study prematurely, and stress related to study or work. Slightly more events were evaluated as positive than as negative. Getting high grades, graduation, and starting a new job always had positive meanings to the interviewees, and starting a new study very often as well. Being fired from a job, getting low grades, and stress were always experienced as negative. Only a few events, although reported as important to interviewees, were perceived as neutral (neither positive nor

Table 2 | Events related to study or work.

Trajectory (*n*) > life event experienced (*n*)	Cannabis use	NNN (12)	NDN (7)	NDD (4)	DNN (10)	DND (2)	DDN (5)	DDD (7)	Total (47)
T0–T2 (TOTAL)									
Negatively (van der Pol et al., forthcoming)	More	2	–	3	3	2	3	3	16
	Stable	6	5	–	5	–	–	2	18
	Less	2	1	–	2	–	3	–	8
	Total	10	6	3	10	2	6	5	42
Neutral (5)	More	–	–	–	1	–	–	–	1
	Stable	–	1	1	2	–	–	–	4
	Total	–	1	1	3	–	–	–	5
Positively (50)	More	–	1	1	1	1	1	–	5
	Stable	14	6	1	7	3	3	2	36
	Less	1	1	1	1	–	3	2	9
	Total	15	8	3	9	4	7	4	50
AVERAGE NUMBER EVENTS PER PARTICIPANT									
Negatively		0.8	0.9	0.8	1.0	1.0	1.2	0.7	0.9
Neutral		–	0.1	0.3	0.2	–	–	–	0.1
Positively		1.3	1.1	0.8	0.9	2.0	1.4	0.6	1.1
Total		2.1	2.1	1.8	2.1	3.0	2.6	1.3	2.1

negative, or both positive and negative), all being study-related (e.g., study delay or starting graduate courses). Quitting a study was experienced the most ambiguously, mainly depending on whether or not this happened voluntary. In line with Rönkä et al. (36), we found that interviewees associated positively experienced events more often with personal choice than negatively experienced events. Nevertheless, interviewees reported almost as many negatively experienced events with little or no personal choice as negatively experienced events where personal choice was present. Over one third of the interviewees reported more than one event, mostly both a negatively and a positively experienced event, such as being fired from work (negative) and getting a new job (positive).

Interviewees talked about changes in their cannabis use in terms of more use (i.e., more frequently, more joints per occasion, or larger amounts of cannabis), or less use (i.e., less frequently, less joints per occasion, or smaller amounts), or said their cannabis use had not changed (stable use). Negatively experienced events were most frequently associated with stable use (43%), somewhat less frequently with more use (38%), and least frequently with less use (19%). In contrast, positively experienced events were most frequently associated with stable use (72%) and much less frequently with less use (18%) or more use (10%). In more than half of the events, interviewees said that they had not impacted their cannabis use. This mainly concerned events that interviewees perceived as positive, but also as planned and not really changing their daily life, or as neutral. As Wheaton and Gotlib (22) stated, "contrast" is important for events to become turning points. In our study, many participants who became graduate students after having attained their bachelor's degree, although they were surely happy with their certificate, did not change their life drastically. Likewise, employed participants who had switched from a job to a similar one, often considered their new job, although they were pleased with it, as little influential on their daily life. Therefore, these changes in study or work did not really influence their cannabis use.

Generally, increases or decreases in cannabis use were transient, and according to the interviewees these changes in cannabis use largely depended on changes in the amount of leisure time that went along with events or temporary changes. For instance, becoming unemployed or having a quiet study period led to more leisure time and thereby more cannabis use, whereas a new job or a busy study period led to less leisure time, and consequently to less cannabis use.

> *[about the timeline] The more demanding my study, the lesser I smoke. When I'm free, there is a peak in my use. Let's see. In June and July I've used less, because I worked at a bank for 2 months, nine-to-five job, little leisure time. Then in August, an increase in use, like "long live freedom! Now I can smoke again". After that, a normal level for a while. December slowly a decrease, because then the exams come closer. January a drop, heavy times and tough exams, 4-5 exams in one week, so then it's 0-1 joint per day. And then February suddenly again 'freedom!', so daily use, 2 joints anyhow.* (Zoë, I1, NNN)

> *When I have a lot of leisure time, I smoke more and sooner. When I'm busier and more serious, then I smoke less. And that is certainly a correlation, when there is an ascending line with responsibilities and working hard, there is simultaneously a descending line with cannabis use.* (Robert, I2, DDN)

In addition, agency came to the forefront as an important factor, most clearly in the narratives of students. Several students reported considerable delay in their study, which they all experienced as negative and some were facing a demanding last year of studies. Some expressed a low level of agency regarding their study, did not feel in control, gave up, and subsequently started to use more cannabis.

> *I felt really bad that period. I did go out with friends, but I didn't do much for my study and I only worked now and then. I didn't give it my all. I smoked a lot and I started to use that, as an excuse. I had no priorities, things just happened. Life happened to me, and I sort of endorsed it . . .* (Julian, I2, DDD)

In contrast, other students chose and managed to restructure their daily life and to study hard, and, although they did not necessarily blame their study delay on cannabis, they actively reduced their cannabis use. They all stated that they were highly motivated to change their cannabis use and were convinced that they could succeed. In the course of our study, three participants reported to have quit using cannabis, giving their occupational life as the main reason, as they thought cannabis was not conducive to their functioning. They said that quitting did not occur overnight, but was a gradual process: they went from daily use to only in weekends, and step-by-step cut back. At the last interview they had not used cannabis for over a year and neither had the intention to start again.

> *My medical study was suffering from my cannabis use. Whenever I have an exam I have to study very hard, a full week every day, spending the whole day in the library, otherwise I won't make it. When I was using cannabis, being there at 8:30 AM was a problem anyhow, because I couldn't wake up early. Also, after 3 PM I didn't feel like studying anymore, no concentration, I wasn't able to memorize things. Factual knowledge doesn't go together with cannabis use. I always stopped using a week before the exams, but you need three days to get active and to get adjusted, and in fact you're too late. Also, smoking cannabis at night does not go well with lectures early in the morning. I often overslept and didn't go. All in all my study delay was one year. Last year, I decided: I don't want to use cannabis, I want to catch up on my study. And I did! Now I do great, I pass the exams, so I shouldn't smoke anymore. The difference between when I was smoking cannabis and now is huge.(. . .) I feel in control of my life now more than ever.* (Sofie, I1, DDN)

Of the six participants who lost their job during our study, no one reported this was related to their cannabis use. While one could argue that cannabis may have affected their functioning and thus indirectly caused job loss, this did not seem the case as mostly their dismissal was due to cut-backs related to the crisis.

RELATION BETWEEN STRESS AND CHANGES IN CANNABIS USE

A recurring topic in many narratives was stress related to study or work, though not *per se* in conjunction with events. For students such stress mainly involved study delays and exam periods, especially their final project or master thesis. For employed interviewees it was largely connected with deadlines, having to work too many hours and reorganizations or job loss. Participants without

study or work perceived stress mainly related to financial problems and sometimes parenting. Stress came with ups and downs, and could have a strong impact on participants' mood and everyday life functioning, including cannabis use. Some interviewees explained how cannabis use could be functional in dealing with stress, because it helped them to distract their mind, making it easier to relax and taking a moment for oneself. For some, smoking a joint at the end of the day was also a reward for their hard work. Consequently, it was not uncommon for interviewees to explain increases in their cannabis use by stressful and busy times.

When I'm stressed, or more stressed, then I'm gonna smoke more. Just to forget a bit. It won't solve anything, but for the moment it does, you can simply let things go. (Samantha, I2, NNN)

When I'm stressed, the urge to smoke increases. I don't know if that's positive or negative, probably not positive, but hey, it gives me some peace. By then I think: ok, now I have a break, it's ok now. If I don't have that break I'm a bit stuck with that frustration. Additionally, it relaxes me. Except that the next day at work I'm a little less alert and probably it's not beneficial, but at least it relieves the evening itself. (Jonas, I2, DDD)

Conversely, other participants explained a decrease in their cannabis use by stressful times. Some thought that with stress cannabis use was not helpful, since it might intensify emotions and lead to more stress or worries. For some others, like Kevin, using less cannabis in times of stress was not so much because of possible unpleasant effects, but primarily a matter of time and personal choice.

Interviewee: At that time I used less. See, when you've had a really busy day and you come home at 8 PM and you want to go to the gym and cook a meal and also have to smoke a joint and get up at 7h the next morning, no, that won't work. Interviewer: To what extent is it about priorities? Interviewee: Yeah, it depends on your priorities, but for me it's not cannabis, I prioritize my job. No, when I'm stressed I'm not going to smoke more, but less instead. (Kevin, I2, NNN)

In five participants, chronic stress ended in a situation of "burnout." They all experienced this as very negative and it took them at least a couple of months to recover. Two of these interviewees thought their cannabis use was worsening their mental health and stopped using (one permanently and one temporarily with the intention to quit permanently). One of these interviewees remained stable in her cannabis use and two others used more cannabis during their burnout and said that this was because they had more leisure time.

RELATION BETWEEN STUDY AND WORK EVENTS AND CANNABIS DEPENDENCE TRAJECTORIES

Regarding cannabis dependence, seven different trajectories evolved, with persistent non-dependent (NNN; $n = 12$) and transitions from dependent at baseline to non-dependent at T1 and T2 (DNN; $n = 10$) being the most common trajectories (**Table 1**). On average 2.1 events were reported, but this was only 1.3 in the group of persistent dependent participants (DDD; $n = 7$; **Table 2**).

Although numbers of participants in most trajectories are small ($n = 2$–12), some patterns seem to become manifest. In response to occupational events, interviewees who were non-dependent at T2 (NNN, NDN, DNN, DDN) mostly had not changed their use (49/75 events) or rather equally often used less (14/75) or more cannabis (12/75). Interviewees who were dependent at T2 (DDD, DND, and NDD), though they also quite often said that their cannabis use had not changed because of events (9/22 events), were somewhat more likely to use more (10/22) than less (3/22).

Concerning occupational status (study, work, or neither) and trajectories some interesting patterns emerged. Firstly, many participants remained student during our study (23/47) and, although they can be found in six different trajectories, the overall tendency over time is away from cannabis dependence (**Table 3**). Four of these students were persistent non-dependent (NNN). While 14/23 participants who remained student were dependent at T0, only five were at T2. In general, the students who became non-dependent (7 DNN, 4 DDN, 3 NDN) stated that their study became more demanding as it progressed, which they found difficult to combine with frequent cannabis use. From their narratives it became clear that they decided for more control over their cannabis use, through being more selective in when to use and when not and/or through less frequent use.

I concluded for myself that if I really want to succeed in life, I have to fully go for this study now. And that has changed my cannabis use as well. I still use, every week I do, but not daily anymore. Because when I do, the next day I don't feel alert, I notice I can't really concentrate. That interferes with what I want to do, my study. So now I only smoke in the weekends, or when I don't have any obligations the next days. I plan my use, take it into account. More seriously. My study is the first priority now, definitely. From February till June 2011 it wasn't, and I

Table 3 | Occupational status and cannabis dependence trajectories T0–T1–T2 ($n = 47$).

T0	T1	T2	NNN (12)	NDN (7)	NDD (4)	DNN (10)	DND (2)	DDN (5)	DDD (7)	Total (47)
Study	Study	Study	4	3	2	7	–	4	3	23
Study	Study	Work	1	1	–	–	–	–	–	2
Study	Work	Work	3	–	–	2	–	–	–	5
Work	Study	Work	–	–	–	1	–	–	–	1
Work	Work	Work	2	2	2	–	1	1	2	10
Neither	Study	Study	1	–	–	–	–	–	–	1
Neither	Neither	Neither	1	1	–	–	–	–	2	4
Study	Work	Neither	–	–	–	–	1	–	–	1

used cannabis very often. That was less serious, I wasn't devoted to my study and I attended the university mainly to socialize. (Max, I2, DDN)

In contrast, four of the five participants who remained student and who were dependent at T2 (3 DDD, 2 NDD) expressed in their narratives a lower level of agency regarding their study, e.g., reported that they did not take their study very seriously, or did not spend enough time on it.

I can't convince myself of the need to quit using cannabis. I don't encounter adverse effects. There are things, such as my study delay, that cannabis contributed to. But the real decisive factor is if I really had the willpower and would go for it, then I would succeed in my study. Even when using that much cannabis. It's just my own laxity I think. I have had that my whole life. (Eduard, I2, DDD)

Secondly, all seven students who became employed, either after quitting their study (by choice or involuntary due to poor performance) or after graduation, were non-dependent at T2. Four (with stable or reduced cannabis use) showed a persistent non-dependent trajectory (NNN) and three shifted from dependent to non-dependent (1 NDN, 2 DNN) in the same period as their occupational status changed from student to employed. Although this shift co-occurred with change in occupational status, it was not necessarily induced by events related to study or work. Mike (DNN), for example, said that between T0 and T1 he felt that the use of cannabis sometimes made him a bit paranoid. Therefore he decided to decrease his cannabis use, and finally he quit. In the meantime he discontinued his study and started working fulltime. Similarly, Isabel (DNN) expressed that the way she used cannabis evolved as part of a general change in lifestyle rather than specifically because of a shift in occupational status from study to work.

Like with other things, you need to find a certain balance in cannabis use. For cannabis I have found that balance, I guess. I have that for a year now. Also because I live on my own now, I really got to know myself. You're alone, there is nobody else around. It has changed me, made me more independent. (Isabel, I1, DNN)

Regarding the group that remained employed (10/47), no clear patterns in trajectories could be observed. These participants were represented in six different trajectories (2 NNN, 2 NDN, 2 NDD, 1 DND, 1 DDN, 2 DDD). At T0 this group included four dependent participants versus five at T2. The extent to which employed participants said that they were committed to their job varied, and also their type of job, but this did not appear to be related to their cannabis dependence status. However, sometimes change in cannabis use did not result in a dynamic trajectory, as was the case with Jonas, who stated that over time he had taken more control over his cannabis use, but was diagnosed as persistent dependent (DDD).

The regularity got out of my cannabis use. I used to smoke every day, a joint before bedtime, perhaps one in the early evening and when I had a day off I could sometimes start in the afternoon. Well, that's not really something to be proud of, and I always thought: if I want, I can stop using. It was time to prove that. It was a rude awaking [laughs]. Before, I didn't try to control my use, I never saw the need to. But I began to feel the effects: the relatively easy college life was over, employed life was more demanding, and I had to better take care of myself. Perhaps I still don't fully regulate my use, I sometimes have relapses. It's difficult, because after I haven't been smoking for a while, I think: why not smoke? I don't have any problems with my use, I'm functioning fine, also when I smoke. I can do my job well, or quite well and my social life as well. (Jonas, I2, DDD)

Also in the case of the other participants (7/47) no consistent patterns could be observed in the relationship between cannabis dependence trajectories and (events in) the occupational domain. Alternatively, agency, more specifically their ability to regulate their cannabis use appears to be related to (transitions in) their dependence status. This became most clear for three participants with young children in the neither group (NNN, NDN, DDD). During our study these three mothers experienced the event of one or two children going to school for the first time, which created a considerable change in their daily time schedule. Although they all underlined not to use cannabis in presence of their children, the way they organized their cannabis use was quite different. Samantha (NNN) believed to be in control over her cannabis use. She used cannabis mainly at night, before going to sleep, and only after she had taken care of her daily responsibilities. Contrariwise, Charlotte (DDD) said that her kids often arrived too late at school, because she had difficulties getting up in the morning, and that she smoked a joint right after she had brought her children to school, even though she knew that by doing so she often postponed her daily tasks. She felt addicted, not in control over her use and in both in-depth interviews she said she would want to quit. Nathalie (NDN), on the other hand, often used cannabis after having finished her daily tasks, but between T0 and T1, when her son started to attend school, she experienced a period that she used more frequently and also in the morning. In retrospect, she believed during that time she was addicted to cannabis, and she had decided to change her use and to (successfully) retake control over it.

DISCUSSION

In this qualitative study we explored the role of study and work in cannabis use among a group of young adult initially frequent cannabis users. We were particularly interested in analyzing how study and work, and more specifically events related to these domains, contributed to transitions in cannabis use and dependence. We interviewed 47 young adults in-depth twice retrospectively covering a period of 3 years. All interviewees were frequent cannabis users at the start of the study (T0). During the follow-up period, there were wide variations and strong dynamics in their patterns of cannabis use, the presence of cannabis dependence, and their occupational situation. Overall, there was a declining tendency in frequency and quantity of cannabis use, including a few interviewees who had quit using cannabis altogether at the second in-depth interview. Various trajectories concerning cannabis dependence appeared. One quarter of the sample remained persistent non-dependent during the study. Some participants were persistent dependent, and others switched from a dependent to non-dependent status and vice versa, yet, at the end of the study more participants were non-dependent than at baseline (34 versus 23 of all 47 interviewees).

Almost two-thirds of the interviewees were students (often with a job on the side) at baseline and remained student during the total study period. Most other participants were in paid employment, and in the course of our study some students became employed as well, indicating that long-term frequent cannabis use does not necessarily restrain individuals in their professional life [cf. (37, 38)]. Most interviewees considered cannabis use as inappropriate before or during hours of study or work [cf. (39)].

As expected in this age group (mean age 21 years), life events related to study or work were quite common, nearly all participants experienced at least one such an event. Overall, participants evaluated slightly more events as positive than negative. Similar events could be valued differently, and it was evident that agency did matter. In line with Rönkä et al. (36), events were likely to be experienced positively when personal choice was felt to be present, e.g., when students decided themselves to discontinue a study rather than being forced to stop, or when individuals choose to start a new job rather than being fired. Our study shows that events in the context of study or work have the potential to, but not necessarily do, influence cannabis use. It should be noted that events that did have an impact on cannabis use often were gradual rather than abrupt, and often cannabis use changed gradually. The feeling of being in control, i.e., agency, in the case of occupational events also appeared relevant for cannabis use. Many events did not lead to changes in cannabis use, but negatively experienced events were mainly associated with stable (43%) or more (38%) cannabis use, whereas positively experienced events were mainly associated stable (72%) or less (18%) cannabis use. Our findings further suggested that increases or decreases in cannabis use related to occupational events are at least partly explained by changes in the amount of leisure time. For example, participants tended to report more use after becoming unemployed, while those who started a new job reported less cannabis use. Changes in cannabis use were also explained by job and study-related stress and how interviewees managed stress. Some reported less use, because using while stressed would enhance negative emotions, or simply because of too little time left to use. Conversely, others reported more use in stressful periods, because cannabis helped them to relax, or was a reward at the end of a day of study or work.

We also found indications for reverse causation, i.e., changes in cannabis use can lead to changes in study or work. Several interviewees, because of events such as study delays, or (expected) stressful times, gradually managed to rigorously cut back or even quit their cannabis use, which eventually was conducive to their occupational performance. Overall, interviewees, who considered their study or work as being rather important, were more committed and motivated and were more willing to rule out any possible influence of their cannabis use on their occupational functioning.

Inspections on occupational events in relation to cannabis dependence (trajectories) revealed that in response to events, participants who were non-dependent at T2 mostly had not changed their use, or equally often used less or more cannabis. In contrast, interviewees who were dependent at T2 were more likely to use more rather than less in response to (negative) occupational events. Besides, interesting patterns emerged concerning occupational status (study, work, or neither). Among participants who remained student during our study, the overall tendency over time was away from cannabis dependence. The students who switched to non-dependence found their study, as it progressed and became more demanding, hard to combine with frequent cannabis use and decided for more control, through being more selective in timing and frequency of use. All students who became employed during our study were non-dependent at T2. Besides, none of the students who entered the workforce were dependent at T2, although the transition was not necessarily induced by study or work events.

For other participants, including those who remained employed, no clear patterns in trajectories could be observed. Alternatively, agency, more specifically their ability to regulate their cannabis use, appeared to be related to (transitions in) their dependence status.

Taken together, our study supports a reciprocal relationship between occupational life (events) and frequent cannabis use and dependence. On the one hand cannabis use and dependence impact occupational life either negatively, in terms of worsened occupational functioning, or positively, e.g., when users deliberately cut back on or stop using cannabis to improve their professional performance. On the other hand our findings support Laub and Sampson's (23) line of reasoning that employment and education impact cannabis use and (indirectly) dependence by limiting leisure time and facilitating structure resulting in attenuated cannabis use. However, it could be argued, and as indicated by our findings, that the available leisure time is influenced by several factors, such as the way participants give meaning to their life and study or job, including motivation, priorities, and agency. For example, some interviewees prioritized study over cannabis use and thereby had less leisure time, while others prioritized cannabis use over study, thus had more leisure time. This might require a certain level of agency, i.e., feelings of being in control or believing in one's own capabilities. In this perspective, the restricting impact of leisure time on cannabis use might be ascribed to the amount of leisure time one *has* as well as to the amount of leisure time one *creates* to use cannabis. As our findings show the relationship works both ways, this provides a nuance for the debate on the "amotivational syndrome." Our study also supports previous research stating that occupational stress can bring about an increase in drug use (16), yet, might depend on the person (characteristics) experiencing it. For some participants cannabis use was a way of managing everyday demands [see also (37, 38)] or coping with psychiatric symptoms. Especially for AD(H)D participants, cannabis use may reduce symptoms, attenuate sleep problems, and improve social functioning (self-medication) (40). Regarding the relationship between stress, depression, and cannabis use, this self-medication hypothesis – and its potential contra productive effect – is somewhat supported by our quantitative findings that coping motives (although not specifically for depression) were one of the few cannabis related differences between dependent and non-dependent frequent users (8), a predictor of cannabis dependence onset (41), and a predictor of dependence persistence (van der Pol et al., forthcoming).

LIMITATIONS

Our findings add to the growing insight into the relationship between occupational life and cannabis use of young adult cannabis users. Nonetheless several factors might limit the results of this study.

An enriched sample was selected, and therefore we cannot guarantee representativeness. However, this does not necessarily mean that the sample is highly biased. Our sample includes many students, but being a student is rather common for young adults in the Netherlands. Cannabis use and occupational status in our study were quite dynamic, but to some extent this was affected by the study design. We deliberately included dynamic dependence trajectories between T0 and T1 for in-depth interviews. More generally, our sample of young adults is likely to be dynamic or even volatile in different aspects, including education and employment. From the life course theory perspective, a decline in cannabis use during young adulthood was to be expected with aging.

Moreover, we investigated the process of cannabis use in the periods between interviews (T0–T1–T2), whereas cannabis dependence was dichotomously captured in diagnoses of dependence versus non-dependence, based on the presence of symptoms within a certain period. Not only could much variation underlie these diagnoses, since they refer to the time between two interviews, also the "effect" of an event related to study or work on cannabis dependence might not have been revealed, and only become apparent afterward, in a next interview. Likewise, participants who had stopped using were categorized as non-dependent, while they were actually non-users.

Furthermore, it should be noted that some results presented here may not be universally replicable because they are related to the country where the study is conducted. Dutch policy officially tolerates possession and sale of small amounts of cannabis, and this may limit extrapolation of our results to countries with formal penalties. Yet, we intended to explore in-depth the role of study and work in cannabis use and dependence rather than to portray a representation of all cannabis users. Although research suggests cannabis laws have little impact on cannabis use patterns of regular users [e.g., Ref. (42–44)], their experiences of certain life events, feelings of personal choice and control, and therefore the outcomes of life events might be indirectly affected by cannabis policy. Hence, a comparable study in another country might therefore find different results.

Finally, as mentioned before, our analyses are based on the narratives of the interviewees, and they largely create their own reconstructions of their cannabis careers and lives. Consequently, their self-perception and self-reflection formed the foundation of our analyses and interpretations. It should be noted that when interpreting the results, all data were based on self-report. We mainly looked into the subjective, not objectified, meanings of (occupational) events. Although subjective, participants' evaluation of events often corresponded with how one would categorize them objectively (from an outsider's perspective). Also the use of context-based timelines, including data participants (quantitatively) reported intermediately, positively contributed to the recall of their lives and cannabis use. More importantly, our approach gave novel insights in the perceptions, experiences, and attributed meanings of participants, which is reflected in the emerging importance of agency in the narratives. For example, although many interviewees stated that they had to learn by their own experience how cannabis use can impact job or study performance, most prioritized their obligations, out of personal motivations or an overall strong work ethic.

How can we explain that occupational events left cannabis use largely unchanged? An explanation could be that for young adults, events such as a new study or a job switch are quite normal and part of a normal career. In fact, sometimes these events were not changing participants' daily lives. Besides, cannabis use appeared to be primarily a leisure activity. These findings relate to the normalization thesis, which suggests that in the past decades, for many users cannabis use has become a normal part of their life, which includes clear choices about whether, where and when (not) to use (45, 46). Cannabis use assimilates quite well with studying and/or being employed, but rules and norms are applied: users do not use cannabis just anytime and anywhere. Cannabis is preferably not used with colleagues and is reserved for leisure time. In this study we focused on the professional life domain, thereby somewhat artificially taking this domain out of its wider context. Life events in other domains, for example social relationships with relatives, partners, and friends, might be equally or even more important.

Life course theory appeared a useful framework to explore how and why education and employment are related to cannabis use and dependence over time. Our study showed that life events in the realm of education and employment were rather common in young adults' lives and can have a strong impact on their cannabis use. Changes in cannabis use are sometimes temporary, but turning points in cannabis use careers can evolve from events in education and employment, as became most clear for the interviewees who fully quit using cannabis. To conclude, and similar to desistance from crime, cessation of cannabis use often is a gradual process, in which agency plays a major role. Besides, regarding the occupational life of young adult cannabis users, leisure time is a (important) factor underlying changes in frequent cannabis use.

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Cannabis use during adolescent development: susceptibility to psychiatric illness

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Cannabis use is increasingly pervasive among adolescents today, even more common than cigarette smoking. The evolving policy surrounding the legalization of cannabis reaffirms the need to understand the relationship between cannabis exposure early in life and psychiatric illnesses. cannabis contains psychoactive components, notably Δ^9-tetrahydrocannabinol (THC), that interfere with the brain's endogenous endocannabinoid system, which is critically involved in both pre- and post-natal neurodevelopment. Consequently, THC and related compounds could potentially usurp normal adolescent neurodevelopment, shifting the brain's developmental trajectory toward a disease-vulnerable state, predisposing early cannabis users to motivational, affective, and psychotic disorders. Numerous human studies, including prospective longitudinal studies, demonstrate that early cannabis use is associated with major depressive disorder and drug addiction. A strong association between schizophrenia and cannabis use is also apparent, especially when considering genetic factors that interact with this environmental exposure. These human studies set a foundation for carefully controlled animal studies which demonstrate similar patterns following early cannabinoid exposure. Given the vulnerable nature of adolescent neurodevelopment and the persistent changes that follow early cannabis exposure, the experimental findings outlined should be carefully considered by policymakers. In order to fully address the growing issues of psychiatric illnesses and to ensure a healthy future, measures should be taken to reduce cannabis use among teens.

Keywords: cannabis, drug addiction, negative affect, schizophrenia, adolescent

INTRODUCTION

Cannabis sativa is grown worldwide for its production of Δ^9-tetrahydrocannabinol (THC), a psychoactive compound found in the recreational drugs marijuana and hashish. The pervasiveness of this drug worldwide, along with its relatively low lethality, has led many to believe that it is of little harm. Indeed, the use of cannabis currently exceeds that of tobacco smoking among adolescents in the United States (1) (**Figure 1**). Whether cannabis is harmless, and without significant physiological or mental health impact, is actively debated. Unfortunately, these discussions are often not guided by evidence-based data. Research focused on the relationship between cannabis and mental health is thus important especially considering that psychiatric illnesses are complex disorders with multiple factors contributing to vulnerability and eventual expression of the illness. Based on the accruing data to date outlined in this review, developmental cannabis exposure is an important contributing factor to psychiatric vulnerability (**Figure 2A**).

CANNABIS AND DEVELOPMENTAL PATTERN OF USE

Psychiatric illnesses are developmental in nature – the 12-month prevalence of any psychiatric illness is ∼40% in adolescents (2), but ∼25% in adults (3) – making it significantly germane to the strong developmental pattern of cannabis use. A plethora of studies and national surveys monitored the patterns of cannabis use in multiple ethnic and geographic populations worldwide. In the United States, cannabis use is highly prevalent during adolescence (**Figure 1**), the developmental period when most people initiate use. There are over 6000 first-time cannabis users per day in the US, over 60% of which are under the age of 18 (4). Approximately 34–45% of ninth through twelfth graders reported cannabis use at least once in their lifetime and the pattern of subsequent use appears more or less intermittent with 23% of 12 graders reporting use in the past month (1, 5, 6). Data from wave I–III of the National Longitudinal Study for Adolescent Health recapitulate this pattern of wide spread yet occasional use in adolescents. While the majority of teens have infrequent use, still a significant percentage, 6.6%, report daily use. Determining the long-term impact of occasional and heavy cannabis use during active periods of brain development, such as adolescence, is of critical importance. To provide such insights, data garnered from epidemiological and experimental studies is reviewed in this article. The emerging evidence strongly suggests that cannabis exposure during adolescence increases an adult's individual vulnerability to drug addiction and schizophrenia and may also produce long-lasting effects on anxiety and mood disorders.

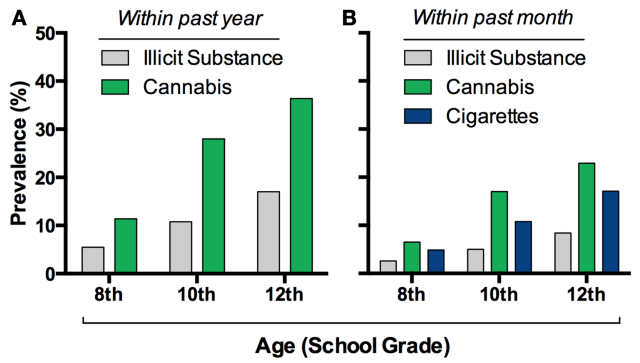

FIGURE 1 | Cannabis consumption is widespread in adolescents. Prevalence of this drug's intake exceeds other illicit drug's in eighth through twelfth graders in the USA **(A)**, and it recently surpassed cigarette use **(B)**. Graphs based on data adapted from Johnston et al. (1) **(A,B)**.

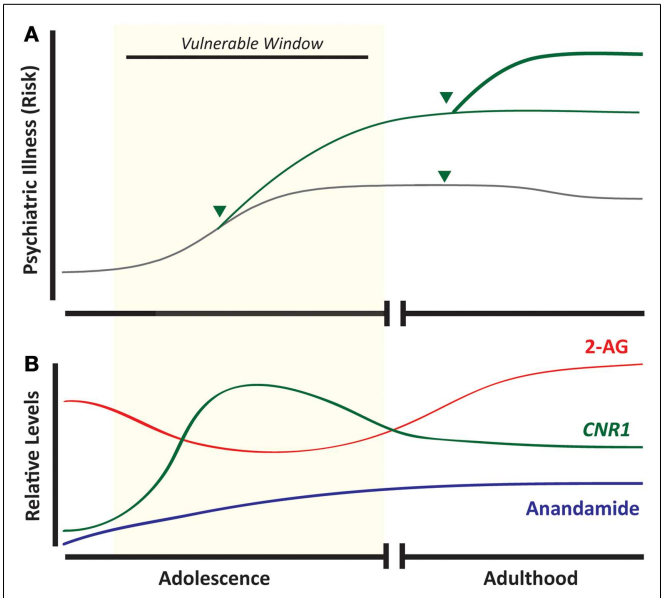

FIGURE 2 | Developmental cannabis increases vulnerability to psychiatric disease and overlaps with ontogenic changes in the endocannabinoid system. Adolescence is associated with an increased incidence of psychiatric illness, and exposure to cannabis (arrow head) during this developmental window strongly predicts subsequent development of mood disorders, addictive disorders, and schizophrenia **(A)**. Components of the endocannabinoid system appear as early as embryonic life, but maximal *CNR1* mRNA expression occurs during adolescence **(B)**. (Green line = cannabis-exposed and gray line = unexposed individuals.)

ENDOCANNABINOID SYSTEM

The psychoactive effects of cannabis, principally mediated by THC, occur via its interaction with the endocannabinoid system, which regulates numerous biological processes involved in development and neuroplasticity. The endocannabinoid system consists of lipid-derived ligands, receptors, and enzymes that orchestrate intercellular communication and intracellular metabolism. The most characterized endocannabinoid ligands – or endocannabinoids (eCBs) – include 2-AG and anandamide, which are presumably synthesized via phospholipase-mediated pathways. At least two G-protein coupled receptors, referred to as cannabinoid receptor-1 (CB_1R) and -2 (CB_2R), interact with these ligands. Additionally, recent evidence suggests that eCBs bind to ligand-gated channels, particularly TRPV1. In regard to the ligands, eCBs are synthesized from membranous precursors and immediately diffuse to nearby cannabinoid receptors, classically expressed on pre-synaptic terminals. Following these events, co-expressed enzymes, such as monoacylglycerol lipase (MGLL), α-β-hydrolase domain 6 (ABHD6), and fatty acid amide hydrolase (FAAH), degrade the ligand to terminate its signal (7, 8). Tightly regulated biosynthetic and degradative pathways ensure proper signaling throughout development, and the correct function of these processes depends on the temporal and spatial patterning of this system. Exogenously consumed cannabis produces supraphysiological effects at eCB-targeted receptors and thus usurp the normal endocannabinoid system (9).

The endocannabinoid system is critical for neurodevelopment and as such is present in early development, and maintains expression throughout life (**Figure 2B**), exhibiting a broad spatial distribution to regulate synaptic plasticity (10, 11). The CB_1R is found in numerous central nervous system structures as early as the eleventh embryonic day, and throughout the embryonic period this receptor is expressed in subcortical and cortical regions (12). In cortical projection neurons, CB_1R and local eCBs facilitate the fasciculation of descending efferents and thalamic afferents, orchestrating the tight coupling of these two tracts (13). During adolescence, the endocannabinoid system still facilitates neurodevelopment through its intricate involvement in neuroplasticity and synaptic function. Receptor levels of CB_1R in the prefrontal cortex and striatum fluctuate during adolescence depending on the specific brain region. For instance, there is a rapid, sustained increase in cannabinoid receptor binding during adolescence, particularly in the striatum, that is substantially reduced (by half) in early adulthood (14). In addition, the expression of the CB_1R gene (*Cnr1*) is highest during adolescence and gradually decreases by adulthood with the greatest decreases observed in limbic-related cortical regions such as the cingulate, prelimbic, and infralimbic cortices (15). Concomitant to developmental changes in the CB_1R, levels of anandamide and 2-AG, as well as FAAH enzymatic activity, fluctuate throughout adolescence in a region- and time-specific manner (16, 17). The distinct changes in CB_1R and other components of the eCB system during adolescence, some of which occur during a narrow time window, suggest that certain phases during this dynamic ontogenic period may incur different sensitivity to cannabis exposure. These observations highlight the fact that despite significant studies of CB_1R in the adult brain, there are still gaps of knowledge as to the role of CB_1R and the endocannabinoid system in the extensive pruning and development that is evident throughout adolescence.

ADDICTION VULNERABILITY

A gateway drug hypothesis had long been proposed implying that adolescent cannabis use predisposes individuals to use other illicit drugs as adults, thereby increasing their vulnerability to substance use disorders (18) (**Figure 2A**). Although, the term "gateway"

has sometimes been misinterpreted to imply that all individuals who use cannabis will directly abuse other drugs, this original hypothesis by Kandel (18) conducted on cohorts of high school students suggested that cannabis use is a critical illicit drug, intermediate in the transition from legal substance use (i.e., cigarettes and alcohol) to illicit drug use (i.e., heroin, amphetamines, and LSD). Over a quarter of individuals who progressed to illicit drug use had previous experience with marijuana while only 2–3% of legal drug users without marijuana experience progressed to illicit drug use. Subsequent longitudinal studies that tracked younger adolescents found that early cannabis use positively predicted cocaine and alcohol use across a 1-year period (19). Additional evidence that early-life cannabis consumption increases cocaine use later in life is supported by studies representing broad demographic populations (20), suggesting that these findings are likely generalizable.

Prospective longitudinal studies have also offered compelling evidence in support of the gateway drug hypothesis. A landmark 25 year-long study conducted on a birth cohort from New Zealand assessed associations between age of onset, and frequency of cannabis use, with the use and/or dependence of other substances (21). Even after controlling for a number of confounding variables, such as socio-economic background, other illicit substance use, family functioning, child abuse, and personality traits, early cannabis use was still significantly associated with subsequent drug abuse and dependence. Additionally this effect was age-related such that the association between cannabis use and the development of drug abuse and dependence declined with increasing age of initiation. An important strength of this study was that data collection extended beyond self-reports, and included parental interviews, medical records, psychometric assessment, and teacher reports. Twin-studies, which control for potential confounds such as genetics and shared environmental influences, have also confirmed that early adolescent onset of cannabis use increases the likelihood of developing drug dependence later in life (22).

One concern with human epidemiological studies is the inability to distinguish between casual and purely associative relationships. This is highlighted by a common-factor modeling study which suggests that correlations between cannabis and illicit drugs were principally attributed to other factors, namely an individual's opportunity for and propensity to use drugs (23). Therefore, it has been argued that the transition from cannabis use to other drugs is not causal but is simply an expected sequence engaged by individuals that would normally go on to use other illicit drugs. Moreover, many teens who routinely smoke cannabis also use other drugs (e.g., alcohol and tobacco). While sequential transitions and the co-abuse of other drugs during such times could potentially contribute to enhance psychiatric risk, it is impossible to ignore the growing body of evidence that suggest a significant contribution of early adolescence cannabis specifically to the propensity to develop substance abuse disorders later in life even when controlling for other substances (21, 22) (**Figure 3**).

Animal studies allow the possibility to directly test the causal relationship between adolescent cannabinoid exposure and subsequent risk for drug addiction, independent of subject-specific factors that confound human investigations. Although a weakness of animal studies is that they do not mimic the complex nature of psychiatric disorder, specific phenotypes relevant to such disorders can be examined. In contrast to most psychiatric disorders, modeling addiction in animals is very predictive of the human condition through the use of self-administration paradigms wherein animals control their own drug intake. Under such conditions, adolescent exposure to THC reliably increases heroin self-administration (24, 25). In a similar investigation, performed in slightly older rats (approximately late adolescence), THC pre-exposure increased heroin self-administration when the contingency for heroin was fixed, but not when the work necessary to acquire heroin was progressively increased (26). Such findings imply that adolescent THC exposure increases the hedonic, but not motivational, aspects of heroin-seeking. Limited animal investigations have examined the sensitivity of early THC exposure to other "heavy" drugs of abuse such as cocaine, but the existing studies to date do highlight the generally enhancing effects of adolescent cannabinoid exposure on future drug-seeking behaviors, and experimentally support the gateway drug hypothesis.

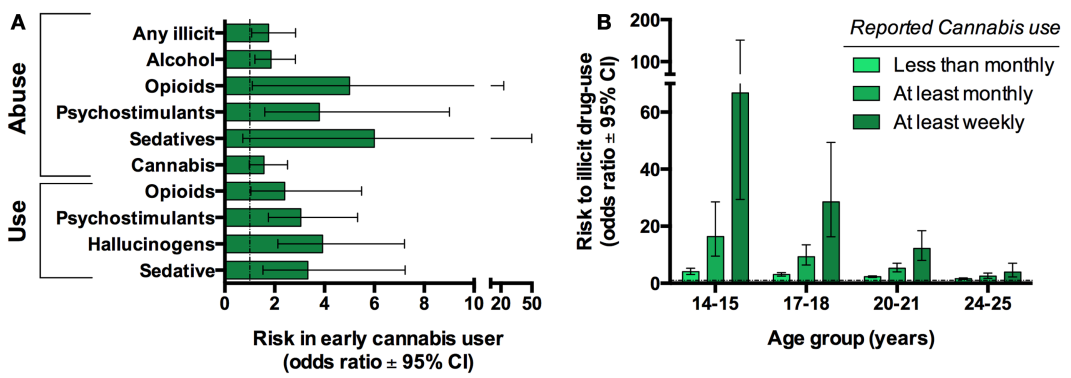

FIGURE 3 | Cannabis use is associated with progression to use other illicit substances in humans. Twin-studies illustrate that cannabis users have an increased risk of developing substance abuse disorder compared to their discordant twin. Graph based on data adapted from Lynskey et al. (22) **(A)**. Cross-sectional studies reveal that earlier and more frequent cannabis use further increases this risk. Graph based on data adapted from Fergusson et al. (21) **(B)**.

Animal studies also provide specific insights about discrete neurobiological disturbances associated with developmental cannabinoid exposure. For example, adolescent THC increases inhibitory G-protein coupled signaling in the rodent midbrain, which by modulating dopaminergic projections, enhances mesolimbic dopamine, all adaptations strongly associated with enhanced reward (24). In addition, adolescent THC exposure increased mu opioid receptor function in the nucleus accumbens, a brain region central to reward and motivated behaviors, and these receptor impairments directly correlated to heroin intake (24). Moreover, increased gene expression of proenkephalin, an opioid neuropeptide that directly modulates heroin self-administration behavior, is also induced in the nucleus accumbens of adult rats with adolescent THC exposure (25). Enhanced cocaine self-administration has also been observed in female rats as a consequence of early-life exposure to the cannabinoid agonist CP-55,940 which was associated with altered striatal dopamine transporter binding in adulthood (27), and this transporter's disturbance is highly implicated in addiction-related behaviors. Together these and other accumulating evidence in the literature emphasize that adolescent cannabinoids persistently change mesolimbic brain regions of the adult that sufficiently predict future self-administration behavior, a phenotype relevant to drug addiction vulnerability.

NEGATIVE AFFECT AND ANXIETY

Another major question regarding the impact of adolescent cannabis relates to its role in negative affective disorders, such as major depressive disorder (MDD), which are increasingly burdensome worldwide. While equivocal, several longitudinal studies demonstrate an association between MDD and early-life exposure to cannabis. A large multi-cohort longitudinal investigation that examined the effects of adolescent cannabis use on depression and anxiety showed that frequent adolescent cannabis use increased depression and anxiety in early adulthood (28). Furthermore measures of depression and anxiety during adolescence did not predict cannabis use in young adults suggesting that this relationship was not simply due to premorbid differences. Similarly, while individuals who used cannabis during early teens did not differ in depression, suicidal ideation, or suicide attempts during adolescence, by early adulthood these individuals had significantly higher incidence of suicidal ideation and suicide attempts (29). A consistent observation was reported in another large longitudinal investigation, which found that adults with early cannabis use had increased suicidal behaviors (30). Altogether these findings emphasize the important contribution of early cannabis exposure to MDD and suicidal ideation. Importantly, accumulating evidence also implies that both adolescent exposure and the continued use during adulthood are required for these associations (31, 32) suggesting that disease may be mitigated with cannabis cessation.

It is important to note that although most studies to date imply an association of early cannabis with negative affective disorders, the longitudinal cohort investigation by Harder et al. (33) did not find any difference in depression or anxiety either during early adolescence or at the last follow-up in adulthood. This inconsistency may be due to the study's lenient definition of a "cannabis user," which included any participant who ever smoked cannabis prior to age 17 (∼50% population). Although additional studies are needed to understand the long-term causative effects of adolescent cannabis on negative affect, a preponderance of the evidence accrued thus far strongly suggests a correlation between these two factors.

Future longitudinal studies are clearly still needed to examine the contribution of the developmental period of onset and cessation of cannabis to the risk of negative affect. In addition, *in vivo* neuroimaging in humans can also offer much needed neurobiological insights. Evidence already exists demonstrating volumetric impairments in the amygdala, a brain region central to affective and addictive disorders, in cannabis users during early (34), and late (35) adolescence. Similarly, structural changes in the hippocampus, which is linked to depression (36), has been reported in individuals with cannabis use during late adolescence (35, 37).

The use of animal models has also helped to fill gaps of knowledge regarding the direct link between early-life cannabis use and negative affect and anxiety. Such experimental studies have demonstrated that early exposure to cannabinoids directly leads to dysregulation of emotional processes and induces depressive-like phenotypes later in life. For instance, escalating doses of THC to adolescent rats decreases sucrose preference, a measure of anhedonia (38). Other behavioral strategies such as the forced-swim test used to measure depression-related symptoms also reveal a pro-depressive phenotype directly associated with adolescent THC (39), although these effects generally appear stronger in females (38, 40). These findings suggest that adolescent cannabinoid exposure could affect the liability to mood disorders later in life, and the potential gender differences may relate in those well-documented in human depression.

Altered anxiety-like behavior as a consequence of adolescent cannabinoid exposure is also apparent in experimental animals though the relationship is not straightforward *per se*. Anxiogenesis or anxiolysis has been reported depending on the period of cannabinoid exposure and the specific task used to model anxiety. For example, chronic exposure to cannabinoid agonists – such as THC, CP-55,940, or WIN-55,212-2 – during mid- to late-adolescence, increases social anxiety as measured with a social recognition task (41–44). Other measurements of stress that do not rely on social interaction, such as the open-field and elevated plus-maze tests, indicate varying degrees of anxiolysis, not anxiogenesis (41, 45, 46). These anxiolytic effects were observed after mid- to late-adolescent exposure, whereas earlier, pre-pubertal exposures (PND 15–40) were anxiogenic (47). Consistent with the notion of critical periods, persistent alterations in anxiety almost exclusively occur after early-life exposure and not in animals exposed as adults (39).

Few animal experimental studies have specifically focused on examining neurobiological mechanisms associated with regulation of emotion in association with adolescent cannabinoid exposure. Of the studies, Page et al. (48) demonstrated that administration of the cannabinoid agonist WIN-55,212-2 to adolescents, as compared to adult rats, more profoundly and persistently disrupted cells in the locus coeruleus, a midbrain region that contains noradrenergic neurons and is implicated with depression and anxiety. Similarly, adolescent animals treated with WIN-55,212-2 exhibit altered midbrain neuronal firing characteristics that

were not observed in adult-exposed rats (39). Specifically, the cannabinoid treatment resulted in hyperactivity of the noradrenergic neurons concomitant with hypoactivity of serotonergic cells (39). Such neuroadaptations would be predictive of enhanced anxiety and depression-like behavior as a consequence of early cannabinoid exposure.

SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDERS

Although a small fraction of teens that use cannabis develop schizoaffective disorders, a number of epidemiological studies repeatedly demonstrate elevated risk to develop these psychiatric disorders in association with early-life cannabis use. Longitudinal studies assessing the relationship between early-life cannabis exposure and schizotypal personality disorder demonstrated that early adolescent use increases adulthood symptomatology (49). Moreover, the presence and severity of schizophrenic endophenotypes, such as psychotic symptoms and prepulse inhibition, were predicted by adolescent cannabis use (50, 51).

The first longitudinal studies demonstrating an association between cannabis use before adulthood and schizophrenia were conducted in Swedish conscripts (52, 53) Although no information was known about the individuals before conscription, subjects reporting previous cannabis use at the time of conscription were significantly more likely to be diagnosed with schizophrenia later in life. These findings were replicated in multiple studies emphasizing the reproducible relationship between adolescent cannabis use and increased schizophrenia symptoms in adulthood (54, 55).

Although it is challenging to model schizophrenia in animals, phenotypes related to this disorder may be studied. Animals exposed to cannabinoids during adolescence demonstrate increased schizoaffective-like phenotypes, such as impaired sensorimotor gating, which, similar to humans, results in decreased prepulse inhibition (45). Consistent with the notion that developmental cannabinoids induce a schizophrenia-like phenotype, acute administration of the anti-psychotic haloperidol normalized prepulse inhibition in the cannabinoid-exposed rats (47).

Since not all cannabis users develop schizophrenia, early cannabis use likely interacts with other factors to facilitate the emergence of this disease (56). Accumulating data in recent years highlight that the association between early cannabis exposure and vulnerability to schizophrenia is related to individual genetics. Pioneering studies by Caspi et al. (57) demonstrated that the relationship between adolescent cannabis use and schizophreniform disorder, as well as the presence of various psychotic symptoms, was attributable to the presence of a functional polymorphism in the catechol-O-methyltransferase (*COMT*) gene. This enzyme degrades catecholamines, such as dopamine, and this functional variant (COMTvaline^{158}) catabolizes this neurotransmitter more rapidly than the methionine allele (58). In cannabis users, schizophreniform disorder is predominantly observed in persons with at least one copy of the polymorphic *COMT* gene (59–61). Moreover, clinical laboratory experiments show that THC's acute psychotomimetic effects are moderated by this *COMT* SNP with THC-induced psychotic-like experiences and cognitive impairments being more pronounced in individuals with the valine^{158} allele (62). Animal models also confirm a link between the genetic disturbance of *COMT* and developmental cannabis such that adolescent THC exposure in transgenic mice lacking endogenous *COMT* synergistically impacts behaviors relevant to schizophrenia (63). Overall, these human and animals studies highlight the significant association between early cannabis exposure and schizophrenia, supporting the so-called two-hit hypothesis which posits that both genetics and early environmental factors enhance individual risk to psychiatric illnesses.

PHYTOCANNABINOIDS AND PSYCHIATRIC VULNERABILITY

It is important to emphasize that while most studies focused on THC to understand the long-term impact of cannabis, the plant produces at least 70 cannabinoids (64). To date the most studied phytocannabinoid aside from THC is cannabidiol (CBD), the second major constituent of the cannabis plant. Interestingly, in contrast to THC, CBD appears to have more protective effects relevant to addiction, cognition, and negative affect. For example, CBD inhibits drug-seeking behavior associated with heroin-relapse in rats (65), reduces cigarette intake (66), and inhibits morphine reward (67). It also has anti-psychotic properties (68, 69) and reduces anxiety behavior in rodents (70) and humans (66). Most of these investigations, however, were carried out in adults. No published study to date has examined CBD in relation to adolescent development and subsequent behavioral consequences in later life. As such, it remains to be explored whether the potential positive effects of CBD on brain function seen in adults would also be evident with adolescent exposure. One intriguing consideration about CBD relevant to the developing brain is that cannabis plants today ingested by teens are grown for high THC, but low CBD content (71). This significant change in the THC:CBD ratio could reduce a normally apparent protective constituent of cannabis. The fact that so little is known about CBD and the developing brain highlights the need for research about this and other phytocannabinoids to more fully understand the impact of cannabis to psychiatric vulnerability.

CONCLUSION

The high prevalence of cannabis use among teens and the increasing number of states in the USA that legalize cannabis for both medicinal and recreational purposes are concerning given the surprisingly limited information known about the impact of cannabis on the developing brain and individual susceptibility. Though a causative relationship cannot be determined between marijuana's glamorization and its increasing use in teenagers, important lessons can be learned from the major inroads made in reducing cigarette use in youths such as interventions through campaigns that made smoking less socially accepted. Based on the current evidence available from human and animal models, it is evident that cannabis use during adolescent development increases risk of psychiatric diseases such as drug addiction and schizoaffective disorders with genetic interactions. No convincing data exist to support one "common cause" that exclusively predicts which individuals using cannabis as teens will progress to addiction and psychiatric disorders later in life versus those who do not. Psychiatric diseases, such as those discussed in this review, are complex and multifactorial. Indeed, the complex transition from early cannabis use to subsequent psychiatric illness involves multiple factors such as genetics, environment, time period of initiation

and duration of cannabis use, underlying psychiatric pathology that preceded drug use, and combined use of other psychoactive drugs. Whether the early onset of cannabis use relates to preexisting pathology that is then exacerbated by the drug is still debated. Additionally, it remains uncertain whether there exist specific critical windows of vulnerability during different phases of adolescent development relevant to the long-term trajectory of risk in adulthood. Longitudinal investigations, making use of neuroimaging and genetics, alongside concurrent studies in animal models are needed to fully elucidate molecular mechanisms that could provide novel treatment interventions for individuals with psychiatric disease and comorbid adolescent cannabis use.

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Gone to pot – a review of the association between cannabis and psychosis

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Cannabis is the most commonly used illicit drug worldwide, with ~5 million daily users worldwide. Emerging evidence supports a number of associations between cannabis and psychosis/psychotic disorders, including schizophrenia. These associations-based on case-studies, surveys, epidemiological studies, and experimental studies indicate that cannabinoids can produce acute, transient effects; acute, persistent effects; and delayed, persistent effects that recapitulate the psychopathology and psychophysiology seen in schizophrenia. Acute exposure to both cannabis and synthetic cannabinoids (Spice/K2) can produce a full range of transient psychotomimetic symptoms, cognitive deficits, and psychophysiological abnormalities that bear a striking resemblance to symptoms of schizophrenia. In individuals with an established psychotic disorder, cannabinoids can exacerbate symptoms, trigger relapse, and have negative consequences on the course of the illness. Several factors appear to moderate these associations, including family history, genetic factors, history of childhood abuse, and the age at onset of cannabis use. Exposure to cannabinoids in adolescence confers a higher risk for psychosis outcomes in later life and the risk is dose-related. Individuals with polymorphisms of *COMT* and *AKT1* genes may be at increased risk for psychotic disorders in association with cannabinoids, as are individuals with a family history of psychotic disorders or a history of childhood trauma. The relationship between cannabis and schizophrenia fulfills many but not all of the standard criteria for causality, including temporality, biological gradient, biological plausibility, experimental evidence, consistency, and coherence. At the present time, the evidence indicates that cannabis may be a component cause in the emergence of psychosis, and this warrants serious consideration from the point of view of public health policy.

Keywords: cannabis, psychosis, spice, synthetic cannabinoids, schizophrenia, psychophysiology, schizotypy

INTRODUCTION

Psychotic disorders are arguably the most serious of mental illnesses, the best known being schizophrenia. As yet, the etiology of schizophrenia and other psychotic disorders remains unclear. There is emerging evidence to support a number of associations between cannabis and psychosis, but the precise nature of these associations remains unclear.

Cannabis is the most commonly used illicit drug by adults, with 18.1 million current users in the U.S. in 2011 (up from 14.5 million in 2007) and ~5 million daily cannabis users (1–3). In the U.S., it was also the most commonly used illicit drug by children 12–17 years (7.9%) in 2011. The age at onset of regular cannabis use appears to be occurring earlier. About 1.3% of eighth graders endorsed daily use of cannabis in 2011 (3). Additionally, the average delta-9-tetrahydrocannabinol (THC) content of cannabis has increased from 3.4% in 1993 to 8.8% in 2008, with concentrations in high potency varieties such as sinsemilla increasing to as high as 11.1% (4). "Medical" marijuana (cannabis) is being legalized increasingly across the U.S. (5, 6). Some states have legalized recreational cannabis use and others are projected to follow suit (7). As a result, individuals, including those with a higher risk for psychosis, who would not have risked the consequences of procuring an illegal drug previously, may now consider exposing themselves to cannabis.

In parallel, there is the emerging phenomenon of the recreational use of Spice, a mixture of synthetic cannabinoids, by young people (8). Among high school seniors, 11.4% reported using Spice in the past year (9). In contrast to THC, the synthetic cannabinoids present in Spice are highly potent full cannabinoid 1 receptor (CB_1R) agonists (10, 11). There are a number of reports of acute and persistent psychosis immediately following the use of Spice, sometimes with catastrophic outcomes (12–14). In the U.S., emergency department visits related to cannabinoids (149 ED visits per 100,000 population) were second only to cocaine (157.8 ED visits per 100,000 population) (15).

Various lines of evidence point to associations between cannabinoids and psychosis [reviewed in Ref. (16–18)]. These associations may be categorized according to temporal proximity of the onset of psychosis to exposure, duration, and clinical significance of psychosis. Converging lines of evidence suggest that

early and heavy exposure to cannabis is associated with a higher risk for psychotic outcomes, including schizophrenia in later life (18–28). In addition, cannabinoids can induce immediate-onset psychotomimetic symptoms that do not persist beyond the period of intoxication (~1 h), as reviewed by us (18). Finally, less well-characterized but perhaps clinically important, cannabinoids are also associated with acute episodes of psychosis that: (1) manifest immediately following exposure, (2) last beyond the period of intoxication, and (3) require clinical intervention (29, 30).

Furthermore, although the associations between cannabinoids and psychosis have gained increasing recognition, the moderators (i.e., variables that affect the direction and/or strength of the relation between an independent, predictor variable – such as cannabis use – and a dependent, outcome variable – such as psychosis) and mediators (i.e., variables that directly account for the relationship between cannabis use and psychosis) are less well-understood. Emerging evidence suggests the crucial role of age of exposure to cannabis (with the period of adolescence being identified as a period of exquisite vulnerability), familial risk, degree of schizotypy, childhood trauma, and the role of genetic factors in moderating this association.

As a preface to this review of the literature, several important issues should be considered. Firstly, cannabis contains more than 70 different cannabinoids (31) of which THC is thought to be the main psychoactive ingredient, while another cannabinoid, cannabidiol (CBD), is thought to have antipsychotic properties (32). THC is hence not the same as cannabis, although most of the experimental studies are conducted using THC. Secondly, cannabis grown in different conditions and different parts of the world has varying potencies based on the content of THC and CBD. The type or potency of cannabis has rarely been accounted for in epidemiological studies. Thirdly, it is important to make a distinction between psychosis as a syndrome and psychosis-like experiences (psychotomimetic effects). While psychosis refers to a heterogeneous group of disorders defined as consisting of positive symptoms (delusions, hallucinations, and thought-alienation phenomena), negative symptoms (alogia, avolition, anhedonia, asociality, and affective flattening), and disorganization/cognitive symptoms (deficits in attention, working memory, problem-solving, and executive function); psychosis-like experiences are characterized by a loss of reality-testing and include derealization, depersonalization, dissociation, hallucination, paranoia, impairment in concentration, and perceptual alterations, which are transient and self-limited. The fact that schizophrenia is a syndrome that is much more than positive symptoms needs to be considered. Negative (e.g., amotivation, asociality, and anhedonia) and cognitive symptoms (e.g., deficits in attention, memory, and executive function) contribute to the disease burden of schizophrenia just as positive symptoms do.

Below herewith, we review existing literature on the association between cannabinoids and psychosis with special focus on the recent critical literature. We categorized major findings into the following categories: immediate psychotic symptoms, psychosis outlasting intoxication, delayed and persistent effects, moderators, and mediators of the association (age of exposure, family history, history of childhood abuse, and genetics), and evidence for causality.

IMMEDIATE AND SHORT-LIVED EFFECTS OF CANNABINOIDS

NON-EXPERIMENTAL EVIDENCE

Evidence from anecdotal reports and surveys of the effects of cannabis

The evidence from anecdotal reports suggests that cannabis may induce acute psychotomimetic effects and precipitate the syndrome of psychosis. One of the earliest systematic studies of the psychotomimetic effects of cannabis was that by the French psychiatrist Jacques-Joseph Moreau (de Tours) in his 1845 book, Hashish and Mental Illness (33). He reported that hashish (cannabis resin) could precipitate "*acute psychotic reactions, generally lasting but a few hours, but occasionally as long as a week; the reaction seemed dose-related and its main features included paranoid ideation, illusions, hallucinations, delusions, depersonalization, confusion, restlessness, and excitement. There can be delirium, disorientation, and marked clouding of consciousness*" (33). Numerous case reports have since then documented the acute psychotomimetic symptoms of cannabis intoxication, including depersonalization, derealization, paranoia, ideas of reference, flight of ideas, pressured thought, disorganized thinking, persecutory delusions, grandiose delusions, auditory/visual hallucinations, and impairments in attention and memory (30, 33–42) in about 20–50% of individuals (43, 44).

In a survey of ultra-high-risk and recent-onset patients with psychosis (45), 37% of subjects reported that their first psychotic symptoms appeared during cannabis intoxication. The subjects also reported feeling more anxiety, depression, and suspiciousness immediately after cannabis use than cannabis-using controls. Another recent study of first-episode psychosis (FEP) patients ($n = 109$) found that daily cannabis users were significantly more likely to have an acute onset of psychosis than non-daily users (46). Evidence from case reports and surveys is limited, however, by confounds such as observer bias, effects of other illicit drugs, and failure to exclude negative and cognitive symptoms prior to onset of positive symptoms.

Evidence from anecdotal reports and surveys of the effects of medicinal cannabinoids

With the pioneering work of Mechoulam in 1964, the individual constituents of cannabis were characterized (47). The identification of THC as the main psychoactive agent led to the synthesis of dronabinol (synthetic THC) and other non-psychotropic synthetic cannabinoids such as levonantradol and nabilone (9-trans-ketocannabinoid), which were thought to have specific antiemetic, analgesic, and antispastic effects. The use of these agents for the treatment of pain syndromes, chemotherapy-induced nausea, and spasticity in multiple sclerosis was followed by reports of transient psychotomimetic effects among patients. The psychotomimetic effects reported were similar to that with cannabis including "loss of control," thought disturbances, feelings of unreality, apprehension, fear and paranoia, anxiety and panic, dissociation, depersonalization, dysphoria, difficulty concentrating, hallucinations, perceptual alterations, amnesia, and anxiety (48–62). These effects were dose-related and proportional to the affinity of the compound for the CB_1R. The high incidence of intolerable behavioral side effects in fact, led to the discontinuation of drug development of levonantradol as an analgesic. In a systematic review of

30 studies that examined the efficacy of dranabinol, nabilone, or levonantradol for chemotherapy-induced nausea and vomiting Machado Rocha et al. (63) found that synthetic cannabinoids was responsible for 30% of dropouts; with 6% patients developing hallucinations and 5% developing paranoia. In another systematic review, Tramer et al. (64) found that patients receiving synthetic cannabinoids had a higher relative risk of developing dysphoria or depression [RR 8.06 (95% CI 3.38–19.2)], hallucinations [RR 6.10 (95% CI 2.41–15.4)], and paranoia [RR 8.58 (95% CI 6.38–11.5)] than those receiving non-cannabinoid antiemetics. Importantly, hallucinations and paranoia were seen exclusively with cannabinoids, and not with other antiemetic agents; and these effects appeared to be related to dose, potency, and frequency of administration.

Evidence from anecdotal reports and surveys of the effects of synthetic cannabinoids (Spice, K2)

The emergence of potent synthetic cannabinoids as drugs of abuse in the last decade provide another source of evidence pointing to the link between cannabinoids and psychosis (8). These compounds, collectively referred to as Spice or K2, comprise a mixture of synthetic cannabinoids such as CP-47,497, CP-47,497-C8, JWH-018, JWH-073, JWH-081, JWH-122, JWH-210, JWH-250, HU-211, and RCS-4 (65–72). It should be noted that, unlike THC, which is a weak partial agonist of brain CB_1Rs, the synthetic cannabinoids are highly potent, full agonists of CB_1R, which would predict more robust effects. Spice has gained popularity as a drug of abuse since it is more psychoactive than cannabis, is readily available over the Internet (advertised as "natural herbs" or "harmless incense" under brand names such as Spice, K2, Yucatan Fire, Skunk, Moon Rocks), and is non-detectable in standard urine toxicological tests. In some countries, including much of the United States and Canada, synthetic cannabinoids are available at gas stations and head-shops as natural herbs and incense; this contributes to its perception as safe and legal among users.

There are no controlled-studies on the psychotomimetic effects of synthetic cannabinoids (73); available information about their effects in humans consists of retrospective case reports from emergency room (ER) visits (69, 70, 74), surveys (12–14), reports from the American Association of Poison Control Centers (AAPCC) (75), and from media and law-enforcement agencies on catastrophic events related to their use (76–81). There has been a substantial increase in ER visits resulting from acute behavioral effects following use of these synthetic cannabinoids. The psychotomimetic effects reported include anxiety, agitation, disorientation, hallucinations, and paranoia (69, 70, 82–84). In an Internet survey, Spice/K2 users most commonly endorsed feeling paranoid (11%), hallucinating (3%), and feeling as if in a dream-like state (26%) "most of the time" or "every time" they used "Spice" (14). The AAPCC reported an exponential increase in call volume related to the use of Spice/K2 from 53 calls in 2009 to over 6000 in 2011 with callers reporting symptoms of agitation, drowsiness, and hallucinations (62% of calls) (75).

Case reports document the ability of these compounds to precipitate a psychotic relapse in patients with pre-existing psychotic disorders and psychotic symptoms in those with no prior history of psychosis (12, 74, 85). Müller et al. (86) reported on a 25-year-old man with a history of psychotic episodes precipitated by cannabis use and a family history of schizophrenia who had been stable for 2 years and had a psychotic relapse comprising anxiety, paranoid delusions, and hallucinations after smoking Spice on three occasions in 1 month. Every-Palmer described sudden agitation, disorganization, and delusions in five forensic patient who had consumed Spice containing JWH-018 and/or CP-47,497 (85). Of the five patients, only one retained insight into the possible psychotogenic nature of "Spice" (85). In a follow up survey of 15 inpatients with serious mental illness in a forensic psychiatric facility, Every-Palmer reported that patients commonly experienced anxiety and psychotomimetic effects, few developed tolerance, and none reported withdrawal symptoms (12).

Psychotic symptoms are also reported in patients with no previous history of psychosis. The adverse clinical events documented in case reports include altered consciousness, confusion, anxiety, irritability, agitation, paranoia, hallucinations, and psychosis (70, 82, 85–87). However, the majority of case reports to date discuss people 25 years or younger (84, 88). Therefore, it is possible that "Spice" exacerbates a pre-existing prodromal syndrome. Case reports and cross-sectional surveys are only able to show an association and cannot elucidate causation.

The sparse literature on Spice/K2 effects reviewed above has a number of limitations, including selection bias, reliance on the accuracy of written record or subject recall, uncontrolled nature of the evidence, the inadequate characterization of cases, lack of standardized assessments, confounding effects of concomitant drug use, different doses and routes of administration, and variable individual expectancy, set, and setting. Cases reported by the media and law-enforcement may represent extremes that might not be generalizable. The temporal profile, range, and intensity of Spice/K2 effects, and whether the effects are dose-related or biphasic, are not known. Furthermore, the relationship between dose, effects, and blood/urine levels of the parent compound and metabolites is not known.

IMMEDIATE EFFECTS OF CANNABINOIDS: EXPERIMENTAL EVIDENCE

Experimental studies provide an opportunity to control variables such as dose, route of administration, and setting, while employing a randomized-control paradigm. Studies have variously examined the effects of smoked cannabis, cannabis extract, oral, and intravenous THC and CBD on positive psychotomimetic symptoms, negative symptoms, cognitive, and psychophysiological measures. Although, early semi-experimental studies of cannabis in the early 1900s using oral cannabis or cannabis extract [reviewed in Ref. (18)] demonstrated cognitive and perceptual effects of cannabis, D'Souza et al. (89) were the first to characterize the profile of positive psychotomimetic symptoms, negative symptoms, and cognitive effects of intravenous THC in healthy individuals. Despite varying routes of administration, experimental studies have yielded some consistent results regarding the effects of cannabis, THC, and CBD. There have, however, not been any controlled experimental studies of the synthetic cannabinoids in humans to date.

In the following sections, we provide a brief summary of the consistent effects noted with cannabis, THC, and CBD.

Interestingly, cannabis and THC produce the full range of positive psychotomimetic symptoms, negative symptoms, and cognitive deficits seen in schizophrenia, while CBD has been shown to have anxiolytic properties and even inhibit the psychotomimetic effects of THC (90–92).

POSITIVE SYMPTOMS

Cannabis extract containing predetermined quantities of THC (93, 94) and THC alone (32, 73, 89, 92, 94–99) have been shown to produce a range of transient, positive symptoms, that are qualitatively similar to the positive symptoms of schizophrenia. These symptoms include suspiciousness, paranoid and grandiose delusions, conceptual disorganization, fragmented thinking, and perceptual alterations. Additionally, cannabis and THC also result in depersonalization, derealization, alterations in sensory perception, and feelings of unreality. These effects have consistently been demonstrated with smoked cannabis, oral cannabis extract/THC (dose range 5–20 mg), intravenous THC (dose range 0.015–0.03 mg/kg), and intrapulmonary administration via a vaporizer (32, 73, 89, 92, 94–99). In the first study of its kind in a carefully controlled laboratory setting, D'Souza et al. (89), administered intravenous THC in two doses (2.5 and 5 mg), in a double-blind, randomized, placebo-controlled study in healthy adults ($n = 22$). Subjects were screened to rule out significant psychiatric disorder or family history of Axis I disorders (89). The study found that THC produced transient positive psychotic symptoms (**Figure 1**) including perceptual alterations, negative symptoms, mood symptoms such as euphoria and anxiety, and also cognitive deficits, especially in attention, working memory, and verbal recall (**Figure 2**). In a similar study in healthy individuals, using almost identical methods except for a lower dose of THC, Morrison et al. (95) showed that intravenous THC (2.5 mg) produced similar effects on positive psychotic symptoms, mood, and cognition.

The effects of dopamine D_2-receptor antagonists on the psychotomimetic effects of THC are not clear. For example, in some studies, olanzapine (101) and haloperidol (102) were shown to attenuate the psychotomimetic effects of THC. However, D'Souza et al. showed that acute treatment with haloperidol did not attenuate the psychotomimetic effects of THC in healthy subjects (103) and chronic antipsychotic treatment failed to protect schizophrenia patients from the symptom exacerbating effects of THC (104). The potential antipsychotic and anxiolytic effects of CBD have drawn increasing attention. In a functional magnetic resonance (fMRI) study of brain responses to emotional expression of faces, Fusar-Poli et al. (90) found that while THC resulted in increased psychotic symptoms and increased skin conductance responses during processing of fearful faces; CBD, on the other hand led to a reduction in anxiety and a decrease in skin conductance response. A separate fMRI study showed that THC and CBD had opposite effects on blood oxygen-level dependent (BOLD) responses in tasks of verbal recall, response-inhibition, processing fearful facial expressions, auditory processing, and visual processing (91). Some limitations notwithstanding, this study provided some important leads into the differential effects of CBD and THC.

Time perception abnormalities are known to occur in schizophrenia, but have received little attention (105–108). Cannabinoids have been shown to alter time perception in both preclinical (109–112) and clinical studies (113–117). In the largest double-blind, randomized, cross-over, placebo-controlled study to date, Sewell et al., showed that THC at different doses induced time overestimation and underproduction compared with placebo (118). Cannabinoids have also been found to disrupt performance on visual information processing in the binocular depth inversion task, a potential surrogate marker for psychosis seen in patients with acute paranoid schizophrenic or schizophreniform psychosis (119). This effect has been observed with cannabis resin (120), nabilone (a synthetic analog of THC) (121), dronabinol (a synthetic isomer of THC) (119), and in chronic cannabis users (122).

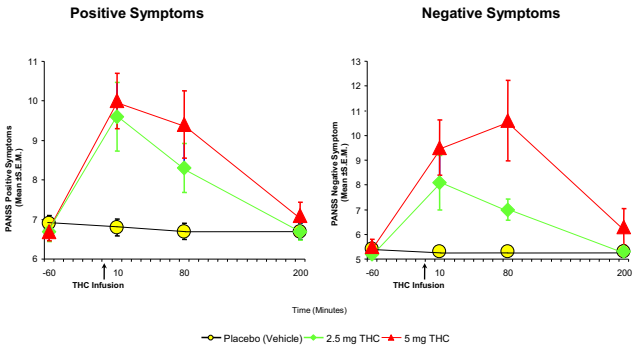

FIGURE 1 | Effects of THC on the seven-item positive symptom and negative symptoms subscales of the Positive and Negative Syndrome Scale (PANSS). THC at both a low dose (2.5 mg) (green) and moderate dose (5 mg) (100) induce an increase in positive and negative symptoms, compared to placebo (yellow). Adapted from Ref. (89).

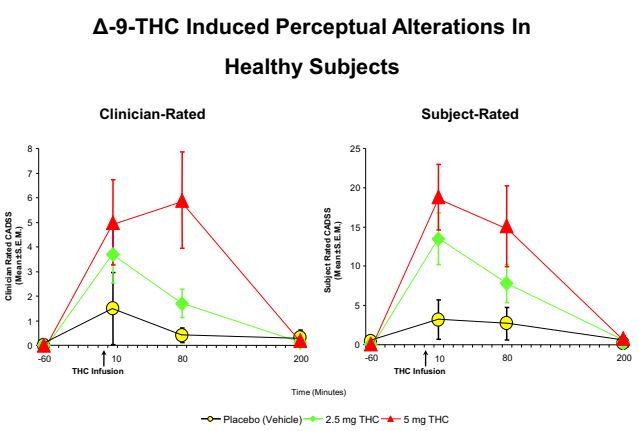

FIGURE 2 | Effects of THC on the clinician- and subject-rated subscales of the Clinician Administered Dissociative Symptoms Scale (CADSS), a measure of perceptual alterations. THC at both a low dose (2.5 mg) (green) and moderate dose (5 mg) (100) induce an increase in perceptual alterations as rated by the clinician and the subject, compared to placebo (yellow). Adapted from Ref. (89).

NEGATIVE SYMPTOMS

Delta-9-tetrahydrocannabinol also produces a range of effects similar to the negative symptoms of schizophrenia, including blunted affect, emotional withdrawal, psychomotor retardation, lack of spontaneity, and reduced rapport (89, 97). It is difficult to determine whether these "negative symptoms" were primary or were a consequence of the sedating and cataleptic effects of cannabinoids observed in animal studies. Morrison et al. (97) however, showed that the effect of THC on negative symptoms was independent of effects on sedation. It is also unclear if the negative symptoms were a manifestation of internal preoccupation with positive psychotic experiences. Furthermore, acute pharmacological studies may be limited in their capacity to model negative symptoms.

COGNITIVE DEFICITS

Cannabis, THC and other synthetic cannabinoids also produce transient, dose-related cognitive impairments, especially in the domains of verbal learning, short-term memory, working memory, executive function, abstract ability, decision-making, and attention (123–129). These effects are not limited to humans but are also seen in rodents and non-human primates [reviewed in Ref. (130, 131)]. Interestingly, the profile of impairment observed in different cognitive domains is similar to that observed in schizophrenia (132).

The cognitive impairment produced by THC is most pronounced in the domain of verbal learning and memory (129), which is also one of the domains of significant impairment in schizophrenia (132). **Figure 3** illustrates the effects of THC on the Hopkins Verbal Learning Test (HVLT) in healthy subjects (104). THC has been shown to produce robust dose-dependent impairments on both immediate and delayed (30 mins) verbal recall. THC also increased the number of "false positives" and "intrusions" on the HVLT. Similar findings have been recently reported by Henquet et al. (133) and Morrison et al. (95).

The acute effects of cannabinoids are likely modulated by genetic and personality factors. This would explain why only a small minority of people experience the psychotomimetic effects of cannabinoids. Henquet and colleagues examined the effects of the interaction of Catechol-*O*-methyl transferase (COMT) polymorphism and a trait index of psychosis liability on smoked THC (0.3 mg/kg) on cognitive performance and psychosis in 30 healthy individuals (133). They found that individuals with the Val/Val polymorphism and high scores on psychosis liability had higher THC-induced psychotic symptoms.

PSYCHOPHYSIOLOGICAL EFFECTS

Psychophysiological effects refer to measures that attempt to examine the physiological basis of psychological processes. In the study of cannabinoids, these effects have primarily been demonstrated using electroencephalography (EEG). EEG measures of information processing, such as event-related potentials (ERPs) and neural oscillations, offer a more proximal index of neural events in humans with exquisite temporal precision (134). ERPs are averaged EEG responses time-locked to particular stimuli or events. ERPs relevant to psychosis include: (1) P50 – a measure of auditory sensory gating, (2) P300b – a measure of directed attention, contextual updating of working memory, and the attribution of salience to deviant or novel stimuli (135), (3) P300a – a measure of novelty detection, and (4) mismatch negativity (MMN) – a measure of processing and memory of deviant stimuli. These ERP measures have been reported to be abnormal in schizophrenia and have been considered biomarkers of the disorder. Abnormalities in neural oscillations have also been noted in schizophrenia and in chronic cannabis users.

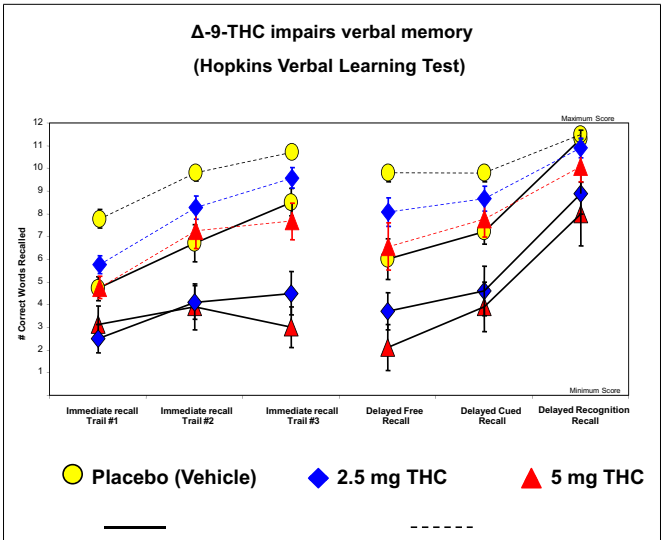

FIGURE 3 | Effects of THC on the immediate free recall, delayed free recall, delayed cued, and recognition recall measured by a 12-word learning task (Hopkins Verbal Learning Test), a measure of verbal memory. THC at both a low dose (2.5 mg) (blue) and moderate dose (5 mg) (100) induce an immediate free recall, delayed free recall, delayed cued, and recognition in patients with schizophrenia (solid line) and healthy individuals (dotted line), compared to placebo (yellow). Adapted from Ref. (89).

Deficits in auditory sensory gating, as demonstrated by a disruption in P50 response, have been shown in patients with schizophrenia (136–140). The cannabinoid agonists CP-55940 and WIN 55,212-2 have been shown to disrupt sensory gating in rats (141, 142). However, there are no studies that have examined the acute effects of cannabinoids on sensory gating (P50) in humans. In contrast, there are cross-sectional studies comparing heavy, chronic cannabis users to healthy controls that have shown that chronic cannabis users show disruptions in P50 suppression (143, 144), which was evident despite subjects abstaining for 24 h. These findings suggest that chronic cannabis use is associated with disruption in sensory gating. Furthermore, the degree of disruption in sensory gating was found to correlate positively with the magnitude of cannabis exposure (138, 145), suggesting a dose-response relationship.

The P300 is a late positive, post-attentional ERP component thought to be related to directed attention, contextual updating of working memory, and the attribution of salience to deviant or novel stimuli (135). Deficits in P300 amplitude and latency have been demonstrated in patients with schizophrenia (136, 139, 146–152). THC has been shown to cause a reduction in the amplitude of the P300 response in several paradigms such as a visuospatial N-back working memory task (153), and auditory choice reaction

task (154, 155). D'Souza et al. examined the effect of several doses of intravenous THC on the P300 response in healthy individuals and showed that THC decreased the amplitude of both the novelty P300a and target P300b (155), while also producing concomitant psychotomimetic effects. There was no impairment in the latency of the P300 response or in the N100 response, indicating that THC disrupted cortical processes responsible for context updating (P300b) and the automatic orientation of attention (P300a), without affecting early sensory registration (N100) or processing speed. Studies of chronic cannabis users have however been equivocal, with studies variably showing decreased P300 amplitudes (156), increased P300 latency (157), increased P300 amplitude (157, 158), or shorter P300 latency (159). Although the reasons behind these discrepant results are unclear, it is possible that chronic cannabis users are impaired during more cognitively challenging selective attention tasks (156, 157, 160), but retain normal ERP responses during simple dual-stimulus discrimination tasks (158, 159).

Mismatch negativity is an automatic, pre-attentive, and negative-voltage ERP component that occurs ~100–200 ms after a deviant auditory stimulus that differs in frequency or duration from a sequence of standard auditory stimuli. It is thought to represent basic auditory information processing, and sensory memory generated primarily in the superior temporal and prefrontal cortex (PFC), while being relatively independent of attention (161, 162). Deficits in MMN have been shown in patients with schizophrenia, early psychosis, and high-risk subjects (163, 164). While oral THC did not produce any acute changes in MMN amplitude (93), studies in chronic cannabis users have demonstrated decreased MMN amplitudes in the frequency deviance condition (154, 165–167). There also appears to be a dose–response effect in the MMN response with long-term and heavier users of cannabis demonstrating significantly lower MMN amplitudes compared to short-term or light users and duration of cannabis exposure showing a negative correlation with MMN amplitudes (154, 165).

Cannabinoids have been shown to disrupt theta band (4–8 Hz) neural oscillations in rats (168). Similar disruption in theta band power was demonstrated following smoked cannabis (169). The degree of disruption in theta band power correlated with deficits in working memory performance in this study. Studies of neural oscillations in chronic cannabis users have demonstrated attenuation of high frequency activity in the beta range (13–29 Hz) (145, 170) and in the gamma range (30–50 Hz) (145, 171). These findings are very interesting in light of accumulating evidence that schizophrenia may be primarily a disorder of abnormal neural oscillations and synchrony [reviewed in Ref. (172)] and that neural oscillations may also be important in the organization of the networks in the brain (173).

ACUTE PSYCHOSIS OUTLASTING INTOXICATION

The use of cannabinoids are also associated with acute *episodes* of psychosis that: (1) manifest immediately following exposure, (2) last beyond the period of intoxication, and (3) sometimes require clinical intervention. This is distinct from the effects previously described, which do not outlast the period of intoxication. Most of the literature about this phenomenon comes from small case series and case reports. The phenomenology, duration, and course of such cases – which we refer to as cannabis-induced acute and persistent psychosis (CIAPP) – have not been systematically characterized.

In the 1890s, the Indian Hemp Drugs Commission undertook a study to examine the effects of cannabis use. The commission reported that "excessive" cannabis use was responsible for psychotic reactions in 9.5% (222/2344) of cases in asylums in India. Chopra et al. reported a series of patients admitted to a psychiatric hospital in India for cannabis related psychosis (29, 30). The psychosis was typically preceded by ingestion of large doses of cannabis and was characterized by hallucinations, delusions, paranoia, depersonalization, amnesia, emotional lability, confusion, and disorientation. Similar case series have been reported from other geographical areas including Sweden, Denmark, the Caribbean, Scotland, UK, USA, and South Africa (37, 174–181). These case reports suggest that when cannabis use is stopped, the acute psychotic episodes resolve (quicker in comparison with "endogenous" psychoses) (37, 39, 177, 178, 180, 182–186), and do not recur unless cannabis use resumes [reviewed in Ref. (187)]. However, since follow up was only for a few months, the long-term course and outcome, the clinical implications, and prognostic significance of these cases remains unclear. Several recent large (n = ~20,000) studies suggest that, over long-term (~8 year) follow up, ~50% of patients without any pre-existing psychiatric disorder who were hospitalized for cannabis-induced psychosis, were later re-diagnosed with a schizophrenia-spectrum disorder (181, 188); that number increased to ~75% when the diagnosis included *any* psychotic outcome (181). These observations suggest that hospitalization for CIAPP may be a harbinger of a recurrent psychotic disorder that we currently classify as schizophrenia. More recent case reports and retrospective studies continue to demonstrate the close temporal relationship between use of cannabis and the onset of a psychotic disorder, sometimes quite indistinguishable from schizophrenia (189, 190). In fact, the International Classification of Diseases-10 (ICD-10) allows for the psychotic effects of cannabis to be coded as both an acute polymorphic psychotic disorder and a protracted substance-induced psychotic disorder. It is conceivable that, as suggested by Rounsaville (191), these cases may actually represent a distinct persistent psychotic disorder.

DELAYED AND PERSISTENT EFFECTS OF CANNABINOIDS

The evidence for persistent effects of cannabinoids in humans comes from large-scale epidemiological studies and from studies in chronic cannabis users. In the following section, we examine the evidence linking cannabis use and persistent psychotic disorder, including negative and cognitive symptoms.

PERSISTENT PSYCHOTIC DISORDER

The evidence for the association between cannabis use and persistent psychosis comes from both cross-sectional studies (192–196) and longitudinal epidemiological studies, including the Swedish military conscript cohort (197–199), the Netherlands Mental Health Survey and Incidence Study (NEMESIS) (20), the German prospective Early Developmental Stages of Psychopathology Study (EDSP) (24), the Dunedin cohort (19, 200), and the Christchurch Health and Development Study (CHDS) birth cohort (23).

The first study to draw attention to the association between cannabis use and psychosis was the Swedish conscript study (197),

in which Andreasson et al. followed a cohort of 45,570 Swedish military conscripts (97% of all Swedish males aged 18–20 years) from 1969 to 1970. The investigators observed a dose–response relationship between cannabis use (via self report) at initiation of military service and hospitalization for a psychotic disorder over the ensuing 15 years, with maximal risk among those who had smoked cannabis more than 50 times. Conscripts who reported having used cannabis at least once in their lifetime had a 2.4-fold (95% confidence interval 1.8–3.3) increased risk of developing schizophrenia over the course of 15 years. This relative risk rose to sixfold (95% CI 4–8.9) in those who had used cannabis more than 50 times in their lifetime. The risk remained significantly high despite adjusting for other factors such as psychiatric illness at the time of conscription, solvent abuse, and parental separation. In a 27-year follow up study of the same cohort and a re-analysis of the data, Zammit et al. replicated the findings of Andreasson et al., showing that cannabis use was associated with a linear increase in the risk of developing schizophrenia; the relative risk increasing from 2.2 (95% CI 1.7–2.8) in those who had used cannabis at least once, to 6.7 (95% CI 4.5–10) in those who had used cannabis more than 50 times in their lifetime (198). When potential confounders such as IQ sore, disturbed behavior in childhood, psychiatric diagnosis at conscription, cigarette smoking, degree of social integration, and place of upbringing were included in the regression analysis, the adjusted relative risk was 1.5 (95% CI 1.1–2.0) in those who had used cannabis at least once and 3.1 (95% CI 1.7–5.5) in those who had used cannabis more than 50 times in their lifetime. The relative risk for schizophrenia was significantly higher in those who developed schizophrenia within 5 years of conscription, which raises questions about the direction of causality. In other words, this preliminary analysis could not distinguish whether cannabis use led to schizophrenia or whether subjects used cannabis in an attempt to self-medicate incipient symptoms of schizophrenia. In a secondary analysis that excluded those who developed a diagnosis of schizophrenia within 5 years of conscription, the adjusted relative risk remained significant only for those who had used cannabis more than 50 times (adjusted relative risk = 2.5, 95% CI 1.2–5.1). The study needs to be interpreted with caution: while 24.3% of the sample had used any drug, a very small percent (3.4%) had used only cannabis. While the analysis controlled for cigarette smoking, it failed to control for the use of stimulants and other drugs. Also, the fact that presumably weak confounders (such as "place of upbringing" and "cigarette smoking") contributed substantially, along with other variables in reducing the adjusted relative risk by ∼50% in the regression analysis highlights the difficulties inherent in interpreting epidemiological data and raises the issue of other unknown confounders. Similar criticisms of the studies from the Swedish conscript cohort have been raised by other authors (201–203), including the facts that: (a) the use of other drugs was more common in the cannabis-using group, (b) the association between cannabis use and schizophrenia may be mediated by a third, as yet unknown factor, and (c) the follow up study, a quarter century later, failed to address the issue of confounding due to use of other drugs, many of which are also known to precipitate psychosis.

Using the NEMESIS cohort, van Os et al. reported that cannabis use at baseline was associated with an increased risk of psychosis (20). The study assessed 7076 subjects at baseline (1996), 5618 subjects at a first time-point (1997), and 4848 subjects at a second time-point (1999) via telephonic interviews, and found 10 subjects who developed psychosis, while 38 subjects endorsed individual items on the Brief Psychiatric Rating Scale (BPRS). The findings of the study are limited by the small numbers in the outcome of interest (25) despite the large sample size.

The EDSP study, which used in-person interviews in the assessment of 923 individuals from the general population (aged 14–24 years), showed that cannabis use was associated with an increased risk of psychotic symptoms and persistent use increased this risk further (28). Importantly, this study yields evidence for a unidirectional relationship between cannabis use and psychosis. This is in contrast with another recent study (22), which showed the relationship to be bi-directional, alluding to the possibility of a phenomenon of "self-medication," a topic that is further discussed below.

The Dunedin cohort study (19) examined data from 759 subjects of the population birth cohort comprising 1037 individuals born in Dunedin, New Zealand, in 1972–1973. The study collected information on psychotic symptoms at age 11, drug use at ages 15 and 18 years, and assessed psychiatric symptoms at age 26. Cannabis use by age 15 and 18 years was found to be associated with more schizophrenia symptoms at age 26 years; and the association remained significant despite controlling for the presence of psychotic symptoms at age 11 years. The association was also found to be stronger with earlier use. Those who used cannabis by age 15 years were also four times more likely to have a diagnosis of schizophreniform disorder; the risk was reduced by 31% and no longer significant after controlling for psychotic symptoms at age 11 years, pointing to the possibility of reverse-causality.

Fergusson et al. attempted to validate a possible causal link between cannabis use and psychosis in a dataset of a 25-year longitudinal study in New Zealand (the CHDS birth cohort comprising 1265 children) (23). The study showed that daily use of cannabis was associated with 2.3- to 3.3-fold higher risk of psychosis than among non-users. One of the limitations of the study is that the data was derived from 10 items of the Symptom Checklist-90, the items on which overlap with personality traits such as schizotypy and paranoia and that the study did not attempt to delineate psychotic symptoms due to the acute effects of cannabis use from persistent effects (204).

This finding of increased psychosis risk has been reported in several other prospective studies (19–21, 24). The cumulative evidence for the association between cannabis and psychosis have been examined in five systematic reviews (25, 205–208), four of which (25, 205, 207, 208) found a consistent association between cannabis use and psychosis. The review by Macleod et al. (206) did not find a consistent association, but has been critiqued for failure to perform a meta-analysis. The inconsistent results of the systematic reviews are also likely due to different inclusion/exclusion criteria, different methodology, and different outcome measures (209). In the latest systematic review by Moore et al., any cannabis use (pooled adjusted OR = 1.41, 95% CI 1.20–1.65) was associated with a 40% increased risk of psychotic disorder, and the risk increased in a dose-dependent fashion with greater cannabis exposure (OR = 2.09, 95% CI 1.54–2.84) (25).

While the evidence supporting an association between cannabis exposure in adolescence and later psychosis is largely consistent, the evidence has been challenged on many counts (210), including sampling bias; under-powered sample sizes; presence of unknown confounders; difficulty distinguishing psychotic symptoms from psychotic disorder in longitudinal studies; direction of causality; lifetime exposure to multiple drugs; and period-, time-, and cohort-effects.

NEGATIVE SYMPTOMS

Chronic and heavy cannabis use has been associated with a syndrome characterized by a predominance of negative symptoms, referred to as an "amotivational syndrome" (175, 187, 211–213). The features of this syndrome include apathy, amotivation, social withdrawal, narrowing of one's personal repertoire of interests, lethargy, impairment in memory and concentration, impaired judgment and decision-making, and poor socio-occupational functioning. All these symptoms share similarities with the negative symptoms of schizophrenia. The nosological status of the syndrome is, however, debated. Further, the confounding effects of concomitant poly-substance abuse, poverty, low socio-economic status, or pre-existing psychiatric disorders may explain the association (214, 215).

This literature is in contrast with the finding that healthy, cannabis users have lower scores on negative schizotypy compared to healthy, drug-free individuals (158, 216), and that patients with schizophrenia who use cannabis have less negative symptoms compared to those who do not use cannabis (217, 218). The cross-sectional nature of these studies and lack of information regarding scores at baseline makes it difficult to conclude if cannabis does not indeed cause a worsening of negative symptoms compared to baseline.

COGNITIVE DEFICITS

Several studies suggest that chronic, heavy cannabis use leads to impairments in memory, attention, working memory, executive function and IQ (219–227). Solowij and Mitchie suggested that cognitive dysfunction associated with long-term or heavy cannabis use is a cognitive endophenotype of schizophrenia (139). In a comprehensive review, Solowij and Battisti concluded that chronic heavy cannabis use was associated with impairments in memory (224) that persisted beyond the period of acute intoxication and was related to the frequency, duration, dose, and age of onset of cannabis use. Fontes et al. evaluated the neuropsychological performance of 104 chronic, heavy cannabis users and found that, compared to controls, chronic cannabis users had significant impairment on the cognitive domains of sustained attention, impulse control, and executive functioning (226). Additionally, similar to the literature on the risk of psychosis, individuals who used cannabis in adolescence (before the age of 15 years) had greater deficits. The authors however, did not assess whether subjects were in withdrawal or had residual effects from their last use of cannabis at the time of assessment.

While chronic, heavy cannabis users have deficits in cognitive processes, especially memory and attention in the context of ongoing cannabis use, the question of whether these impairments are persistent or a result of withdrawal and residual effects is unclear. While one study demonstrated an absence of persistent neuropsychological deficits in frequent long-term cannabis users after 28 days of abstinence (228), other studies have shown variable durations to full recovery, ranging from a week (229), to 28 days (221), to 3 months of abstinence (230), with some studies showing recovery only after an average of 2 years of abstinence (187, 231). A recent review provides a summary of the literature to date (225). Among studies in which neuropsychological assessments were performed 3 weeks or later after last use of cannabis, five out of seven studies showed no impairment in attention (221, 228, 232–236), while two showed persisting impairment (222, 231). One study revealed a trend toward impairment in decision-making/risk-taking (237). There was no impairment on response-inhibition measured by the Stroop test (221, 222, 233–235), and on working memory (236) while all (221, 222, 233, 234) but one (235) found an impairment on the Wisconsin Card Sorting Test, a test of set shifting. There was no impairment in verbal memory in two (228, 233) of the three studies that used the Buschke's Selective Reminding Test (BSRT), a test of memory of word lists. When the data from the third study (234) was stratified based on age at onset of cannabis use, significantly greater impairment was noticed in those who had first use cannabis before the age of 17 years, suggesting that, as for positive symptoms, earlier age of onset of cannabis use may be associated with greater persistent cognitive deficits. It is important to note that none of these studies were designed to determine whether the cognitive impairments predated cannabis use.

Previous cross-sectional experiments have reported inconsistent results with some suggesting that chronic cannabis use impairs performance on tests of intelligence (238, 239), while others finding no impairment (240, 241). A recent longitudinal study examined 1037 subjects followed from birth to age 38 years (242). Cannabis use was evaluated at ages 18, 21, 26, 32, and 38 years while neuropsychological testing was conducted at ages 13 and 38 years. The experiment determined that those who persistently use cannabis are more likely than non-users to experience a significant decline in IQ. The findings persisted even after controlling for level of education and impaired IQ was found to be particularly true for the subjects who began to use cannabis during adolescence as opposed to during adulthood. Those who began to use cannabis during adolescence exhibited an eight-point decrease in IQ between childhood and adulthood. Another important finding of the study was that the decline in IQ did not appear to reverse after cannabis use ceased (242).

Some studies that have examined cognitive performance among patients with schizophrenia have made a case that patients with schizophrenia and comorbid cannabis abuse have better cognitive performance than patients without comorbid cannabis abuse (243–246). Emerging evidence, however, suggests that patients with cannabis use have higher premorbid IQ (247). The findings are not inconsistent with the experimental data; it is likely that persons who smoke cannabis have higher premorbid IQ, as evidenced by their ability to procure an illegal substance while evading the law. Therefore, although continued cannabis use results in a decline in their individual cognitive performance (242, 248, 249), when compared to non-users they appear to have relatively better cognitive performance. Furthermore, abstinence from cannabis

may be associated with better cognitive performance among male patients with schizophrenia (248).

MODERATORS/MEDIATORS OF THE LINK BETWEEN CANNABIS AND PSYCHOSIS

AGE OF EXPOSURE

Epidemiological evidence suggest that the earlier the age of exposure to cannabis, the greater the risk of a psychosis outcome (19). Dragt et al. showed that younger age of onset of cannabis use is associated with earlier symptoms of anxiety, social withdrawal, derealization, memory impairment, and difficulties in concentration, with effects being more pronounced in patients with heavier cannabis use (250). Another recent study found that early onset cannabis use was only associated with earlier onset of psychosis when cannabis use began by age 14 (251). A large meta-analysis of 83 studies found that the age of onset of psychosis in cannabis users was 2.7 years younger than in non-users (252). Animal studies have shown that exposure to cannabinoids in adolescence has more deleterious effects than exposure in adulthood (253–257).

It is being increasingly recognized that adolescence may be a particularly critical period of increased vulnerability to the effects of cannabis. Additionally, factors such as schizotypy, other trait measures of liability to psychosis, and childhood abuse may moderate the risk of schizophrenia with prolonged and persistent cannabis use. As discussed above, the 26-year longitudinal study of the Dunedin cohort showed that earlier cannabis use is associated with a greater risk of psychotic disorder. However, when adjusted for psychotic symptoms at age 11, the association between cannabis use and subsequent psychotic disorder was no longer significant but remained elevated (OR = 3.1) (19). The small sample size may limit the interpretation of these results.

These studies suggest a "window of vulnerability" hypothesis: a critical period during early adolescence where the brain is particularly susceptible to the psychosis-inducing effects of cannabis (19, 250, 251, 253–258). One possible explanation for the "window of vulnerability" theory is that cannabis may affect the brain during a critical period of development and maturation. Brain development and maturation processes – including neuronal migration and differentiation, synaptogenesis, axon formation, and dendritic proliferation, myelination, pruning, apoptosis, and activity-dependent changes – begin *in utero* but continue into the early 20s or even later (259–264). Cannabis may disrupt one or more of these processes.

A retrospective study of 997 subjects by Stefanis and colleagues showed that, after adjusting for family history, there was a consistent relationship between the age of cannabis initiation and FEP, with an average time of 7–8 years (265). This finding does not support the "window of vulnerability" hypothesis, but rather indicates that the brain (at least in years 12–19) is continually sensitive to cannabis.

The association between age of onset of cannabis use and worse outcomes could simply reflect that earlier use is more likely to become longstanding, thus increasing the overall exposure to cannabis. An alternate explanation for the association between age of exposure to cannabis and psychosis is that those prone to early psychosis may "self-medicate" with cannabis to relieve symptoms (22, 266). However, this has not been supported by recent literature (28, 250, 251, 267). These studies are limited in that they have relied on measuring only positive psychotic symptoms as an indication of psychosis onset, although it is known that negative symptoms and cognitive deficits predate the onset of positive symptoms (268) and even predict conversion to psychosis in high-risk individuals (269). The interpretation of the data is also limited by the fact that cannabis use at an early age may be part of a broader pattern of externalizing behavior in response to difficult family circumstances (270, 271). Children and adolescents who begin cannabis use at an earlier age may represent a distinct sub-population that differs in ways that have not been accounted for (such as history of abuse or family socio-economic level) in the aforementioned studies.

FAMILY HISTORY

Early studies have indicated that a positive family history of schizophrenia may increase risk for cannabis-induced psychotic disorders. One such study found that among patients admitted for acute psychosis, those who tested positive for cannabinoids in urine toxicology screens were 10 times more likely (7.1 vs. 0.7%) to have a positive family history for schizophrenia than patients without a positive urine toxicology screen (272). This finding implicated a familial predisposition to persistent psychotic disorders precipitated by cannabis use. Thus, in a genetically predisposed sub-population, cannabis confers a marked risk for psychosis. Most studies since have confirmed an association between a family history of psychotic disorder and an increased risk of cannabis-induced psychosis, though the association is more modest than the original study. Bersani et al. found that among schizophrenia patients, 24% of cannabis users had a positive family history of psychotic disorder vs. 10% (217). The largest study to investigate this association ($n = 2{,}276{,}309$) found a 2.5-fold increased risk of developing cannabis-induced psychosis in children of mothers with schizophrenia but no increased risk of conversion to schizophrenia (273). Further studies that have followed patients over time have shown that among patients who are admitted with an initial diagnosis of cannabis-induced psychosis, almost 50% convert to schizophrenia or some other psychotic disorder (181, 188). Boydell et al., found, in a retrospective study of 757 first-episode schizophrenia patients (24% who used cannabis in the year prior to presentation), that among patients with schizophrenia, cannabis users did not differ significantly from those not using cannabis in terms of a positive family history of schizophrenia (15 vs. 12%) (274). More recently, investigators from the Genetic Risk and Outcome of Psychosis (GROUP) collaboration studied a large sample of patients with a psychotic disorder ($n = 1120$), their siblings ($n = 1057$), and community controls ($n = 590$). In this prospective, ongoing study, the investigators found that the effect size of the relationship between current cannabis use and both positive and negative schizotypy symptoms was significantly greater in siblings of patients with a psychotic disorder when compared to healthy, un-related control. Further, there was a significant association between cannabis-using siblings and their psychotic patient relatives (in terms of positive symptoms), whereas this association did not emerge among non-exposed siblings and their psychotic relatives. The authors proposed that the familial liability

to psychosis is expressed partially in terms of psychotomimetic experiences with cannabis (GROUP).

HISTORY OF CHILDHOOD ABUSE

More recently, the interactive effects of childhood maltreatment and cannabis abuse have been examined. In a cross-sectional study, Houston and colleagues found an odds ratio of 11.96 (95% CI 2.10–68.22) for having experienced psychosis among children with a history of abuse who used cannabis prior to age 16 (275). Another cross-sectional study by Harley et al. found a significant interactive effect of childhood trauma and cannabis use in moderating the risk of psychotic symptoms; the odds ratio of experiencing psychosis in adolescents with a history of exposure to trauma and cannabis was 20.9 (95% CI 2.3–173.5) (276). A longitudinal study has similarly shown a significant interaction between cannabis use and childhood maltreatment in the development of psychotic symptoms (277). Notably, there was no evidence in this study that baseline history of childhood abuse affected subsequent cannabis use. These findings, however, were not replicated in the EDSP dataset (278). It is important to interpret the above findings with caution. Some investigators (279) have shown a link between childhood abuse and subsequent cannabis use; others demonstrate a link between abuse and subsequent psychosis (280). Future studies, which examine the interaction between genetic liability, trait measures of psychosis liability, cannabis use, and other environmental factors may provide greater insights into the complex mechanisms that cause psychosis.

GENETIC FACTORS

Genetic factors may confer vulnerability to psychosis outcomes following exposure to cannabis, i.e., a gene-environment interaction. In specific, Catechol-*O*-methyltransferase (COMT) and *AKT1*, have been implicated in conferring such vulnerability (see **Table 1**). Preliminary evidence suggests that other genes might also moderate the cannabis–psychosis interaction.

Catechol-O-methyltransferase

In one of the first studies that drew attention to gene × environment interactions, Caspi et al. reported that the *COMT* gene moderated the risk of psychotic disorder with adolescent cannabis exposure. The enzyme COMT plays a critical role in the breakdown of dopamine in the PFC (286), in contrast to the striatum where DA is cleared by a transporter. The *COMT* gene has a common polymorphism in humans, which results in 40% higher enzymatic activity and thus more rapid degradation of dopamine when Valine (107) is substituted for Methionine (Met) at the 158/108 locus. Val/Val homozygotes have the lowest levels of dopamine; Met/Met homozygotes have the highest levels; and heterozygotes have intermediate levels. Lower cortical dopamine levels in individuals homozygous for the Val(158) polymorphism are associated with, among other things, poorer cognitive performance, and inefficient precortical functioning (287).

In a longitudinal prospective study (Dunedin cohort) of 803 individuals followed over 25 years, Caspi et al. showed that the risk of developing of psychotic disorder in association with cannabis exposure increased by 10-fold in those patients with the Val/Val allele (200). There were subsequent attempts to validate these findings with experimental evidence: a double-blind, placebo-controlled cross-over study showed that individuals with the Val polymorphism of the *COMT* gene have a higher chance of developing acute psychosis in response to THC exposure (133). These findings have been confirmed in a similar experiment (288).

Recent studies have failed to confirm the findings of the original 2005 study from Caspi and colleagues. A case-only analysis of 1438 individuals found no interaction between *COMT* polymorphism and cannabis use with regard to schizophrenia (281). Further, a 2-year longitudinal study of 2630 genotyped patients showed no interaction between *COMT* and cumulative cannabis use on the development of psychosis (282). A more recent case–control study also showed no *COMT*-mediated increased cannabis risk in the development of psychosis (284). Kantrowitz et al. were unable to find an interaction between COMT polymorphisms and cannabis-induced psychotic disorder in a population of 92 individuals with psychotic disorder, though this study was under-powered. Subanalyses based on race (African American and Caucasian) did not yield significant findings (289). In contrast to the original Caspi et al. study (200), a case-only study from Spain (155 out of 748 total schizophrenia subjects who used cannabis) actually found an association between the low-activity Met allele of *COMT* and cannabis use in psychotic disorder (283). Estrada et al. (290) showed a dose-effect of *COMT* polymorphism on the age of onset of psychosis among cannabis users: individuals who were homozygous for the Val allele of COMT had the earliest age of onset of psychotic disorders at 15.4 years; homozygotes for the Met allele had the latest age of onset at 18.8 years; heterozygotes with intermediate enzymatic activity, had an age of onset of 17.1 years. Notwithstanding, there was no overall greater risk for psychotic disorder found among any of the polymorphism groups. A similar trend regarding the interaction of *COMT* polymorphism and cannabis use in association with the age of onset of psychosis has been shown, though not all results achieved statistical significance (291).

Other studies have examined the interactive effects of *COMT* polymorphisms and other environmental factors. A cross-sectional analysis of 918 individuals in Europe found a significant three-way interaction between the *COMT* Val allele, cannabis use, and childhood abuse in moderating psychosis. Individuals homozygous for the Val polymorphism were more likely to experience psychosis in association with cannabis use in the context of a history of childhood abuse than individuals homozygous or heterozygous for the Met allele. A replicative sample as part of the same study showed the same trend but did not achieve statistical significance (292). Confirming these findings, Alemany et al. found that the three-way interaction of *COMT* polymorphism (Val allele), cannabis use, and a positive history of child abuse significantly increased the risk of both positive and negative psychotic symptoms (293).

AKT1

AKT1 is another gene thought to play a role in moderating the association between cannabis and psychotic disorders. The enzyme AKT1 functions to inactivate glycogen synthase kinase (GSK-3) by phosphorylation (294). The interaction between AKT1 and GSK-3 has been implicated to play a role in a number of

Table 1 | Gene × cannabis interactions in moderating risk of psychosis.

Gene/locus	Study	Study design	Sample size	Follow up	Outcome – odds ratio (OR)/relative risk (RR)
COMT/rs4680	Caspi et al. (200)	Longitudinal, prospective (Dunedin cohort)	803	26 years	OR 10.9 (95% CI 2.2–54.1) of developing psychotic disorder in Val/Val genotype OR 2.5 (95% CI 0.78–8.2) of developing psychotic disorder in Val/Met allele OR 1.1 (95% CI 0.21–5.4) of developing psychotic disorder in Met/Met allele
COMT/rs4680	Zammit et al. (281)	Case-only, cross-sectional analysis	493	NA	OR 0.98 (95% CI 0.76–1.27) for history of cannabis use in schizophrenia subjects with Val/Val allele
COMT/rs4680	Zammit et al. (282)	Longitudinal (Avon cohort)	2630	2 years	OR 1.0 (95% CI 0.73–1.36) of cannabis × COMT interaction OR 1.56 (95% CI 1.05–2.31) of psychosis in cannabis users with Met/Met genotype OR 1.47(95% CI 0.85–2.26) of psychosis in cannabis users with Val/Val genotype OR 1.68 (95% CI 1.23–2.28) of psychosis in cannabis users with Met/Val genotype
COMT/rs4680	Costas et al. (283)	Case-only, cross-sectional analysis	748	NA	OR 2.07 (95% CI 1.27–3.26) of history of cannabis use in schizophrenia pts w/Met/Met genotype vs. Val/Val genotype
AKT1/rs2494732	van Winkel (284)	Cross-sectional analysis	801 Subjects with psychosis 740 Unaffected siblings 419 Controls	NA	RR 1.90 ($p < 0.01$) of C/C genotype in daily cannabis users – case-only analysis OR 1.96 (95% CI 1.09–3.53) of being diagnosed with psychotic disorder in C/C allele subjects – case–sibling analysis OR 2.08 (95% CI 0.92–4.67) of being diagnosed with psychotic disorder in C/C allele subjects – case–control analysis
AKT1/rs2494732	Di Forti et al. (285)	Case–control, cross-sectional analysis	489 Subjects 278 Controls	NA	OR 7.23 (95% CI 1.37–38.12) of psychotic disorder in C/C genotype subjects with daily cannabis use vs. T/T genotype OR 2.18 (95% CI 1.12–4.31) of psychotic disorder in C/C genotype subjects with history of cannabis use

OR, odds ratio; RR, relative risk; CI, confidence interval.

important cellular processes, such as cell proliferation, apoptosis, and transcription (295). *In vitro* studies have shown that cannabinoids are capable of stimulating the AKT1 pathway via CB_1 and CB_2 receptors (296) and *in vivo* studies in mice have also confirmed this (297). Further, the gene product has been implicated in schizophrenia: postmortem studies have shown decreased AKT1 levels in lymphoblasts in the PFC of patients with schizophrenia (298, 299).

In a sample comprised of 801 patients with psychosis, 740 of their unaffected siblings, and 419 controls, van Winkel showed that cannabis users with the C/C genotype of a specific polymorphism (rs2494732) of the *AKT1* gene had a twofold increase in risk of being diagnosed with psychotic disorder (284). Additionally, among psychotic patients, those homozygous for the C allele were twice as likely to have a history of daily cannabis use compared with T/T genotypes. The significance of the AKT1 × cannabis interaction held among case-only ($p = 0.007$) and case–sibling ($p = 0.04$) sub-analyses; in the case–control sub-analysis, the AKT1 × cannabis interaction approached statistical significance ($p = 0.057$). A more recent study has replicated these findings and found an even stronger interaction. Di Forti and colleagues studied 489 patients with FEP and 278 control subjects in a case–control design; among daily cannabis users, those who carried the C/C allele had, on average, a sevenfold increase in the risk of psychosis compared to T/T carriers (285). Notably, carriers of this genotype (C/C at SNP rs2494732) also have been shown to have increased cognitive side effects from cannabis use as evidenced by lower scores on tests of sustained attention (300). Preliminary experimental evidence has also implicated a different polymorphism of the *AKT1* gene (the GG genotype of the SNP rs1130233) as a moderator of sensitivity to the acute psychosis-inducing effect of THC (301).

Other genes

Another gene implicated in moderating the effects of cannabis on the development of psychosis is *DAT1*, which codes for the dopamine transporter, which is critical in removing DA from the synapse in striatal regions. A polymorphism involving a variable number of tandem repeats (VNTR) has been described in the 3′ untranslated region of the *DAT1* gene (SLC6A3). One of the common alleles of this polymorphism (the nine-repeat allele) is associated with lower enzymatic activity and thus higher dopamine levels in the striatum. *DAT1* has previously been associated with schizophrenia (independent of cannabis use) in gene association studies (302). Bhattacharyya et al., reported that individuals with the nine-repeat allele showed increased sensitivity to THC-induced psychotomimetic effects in a small laboratory based study ($n = 35$) (301). There was also a trend toward greater THC-induced psychotomimetic effects in individuals with the G/G genotype of the rs1130233 polymorphism of the *AKT1* gene in the same sample. Furthermore, there was a synergistic interaction between these *DAT* and *AKT1* genotypes on the psychotomimetic effects of THC. In addition to studying behavioral effects of THC, this study showed interactive effects of *DAT1* genotype, *AKT1* genotype, and THC on striatal and midbrain activation during encoding and recall of verbal information, respectively. Individuals with the GG allele at *AKT1* and carriers of the nine-repeat allele of *DAT1* also showed increased activation in the striatum in response to THC in comparison to the rest.

Neuregulin 1 (*NRG1*), a leading schizophrenia susceptibility gene, is relevant to several schizophrenia-related neurodevelopmental processes (303, 304). Heterozygous deletion of *NRG1* results in increased sensitivity of mice to schizophrenia-like symptoms induced by THC especially under stressful conditions (305). These mice also showed greater increases in prepulse inhibition (PPI), a marker for sensorimotor gating known to be impaired in schizophrenia, following THC administration (305). However, to our knowledge, this work has not yet been extended to humans. Decoster et al. reported significant interactions between brain-derived neurotrophic factor (*BDNF*) genotype, cannabis exposure, and gender in a cohort of schizophrenia patients: in female patients only, cannabis use was associated with earlier age of onset of psychosis in *BDNF* Met-carriers relative to Val/Val-genotypes (306). Additionally, cannabis use may interact with specific genotypes of the cannabinoid receptor 1 (*CNR1*) gene to moderate cognitive impairment in schizophrenia patients (307), but thus far no significant interaction between *CNR1* polymorphisms and cannabis exposure on the risk for the development of psychotic disorders has been reported (281).

CANNABIS, SCHIZOPHRENIA, AND CAUSALITY

The association between cannabis and psychosis fulfills many but not all of the standard criteria for causality (308), namely temporal relationship, biological gradient, biological plausibility, coherence, consistency, and experimental evidence.

TEMPORAL RELATIONSHIP

As discussed above, evidence from experimental studies shows a clear temporal relationship between exposure to cannabinoids and symptoms of psychosis. Despite a number of limitations (discussed previously), several epidemiological studies have concluded that cannabis use generally precedes the development of psychotic disorder. In one of the earliest such studies, Allebeck and colleagues found that cannabis use preceded the onset of schizophrenia by at least 1 year in 69% of cases; in only 11% of cases did cannabis succeed psychosis (309). In a prospective cohort study, Linszen et al. found that in all but 1 patient from a sample of 24 cannabis-abusing patients, cannabis abuse preceded FEP by at least 1 year (310).

Studies from recent years suggest that in the majority of cases, cannabis use precedes the onset of psychosis, rather than vice versa. In a study of 28 FEP patients, cannabis use preceded psychosis in all patients (267). Another study of 45 psychotic disorder patients with a history of cannabis use showed that the onset of cannabis use preceded hallucinations in 74% of cases and preceded persecutory ideas in 90% of cases by at least on year (250). Schimmelmann and associates (251) reported that in 88% of cases ($n = 201$ FEP patients with cannabis use), drug exposure preceded psychotic symptoms by a mean of 5 years.

As discussed above, numerous additional studies have shown that cannabis users have a younger age of onset of psychotic disorders compared to non-users (197, 250, 258, 309–312). A recent meta-analysis of over 22,000 subjects found the onset of psychosis was 2.7 years younger in cannabis users than in non-users (252). These studies lend further evidence to the finding that cannabis usually precedes the onset of psychotic symptoms and argue against the "self-medication" hypothesis.

The findings from epidemiological studies regarding the temporal relationship between cannabis and psychosis must be qualified. Epidemiological studies have traditionally examined the relationship of cannabis use and psychosis as defined by positive psychotic symptoms. It is unclear whether the same temporal relationship holds for cognitive deficits or negative symptoms of psychosis, which usually predate the onset of positive psychotic symptoms. Furthermore, the data fails to explain why patients with schizophrenia continue to abuse cannabis. Cannabis continues to be among the most common illicit drug used by patients with schizophrenia. In the Australian Study of High Impact Psychoses (313), 49% of patients with schizophrenia reported exposure to cannabis in the past year (314). In a study among patients with schizophrenia using experience-sampling, Henquet et al. (315) found that compared to healthy control, patient with schizophrenia reported a reduction in negative affect after cannabis use, while the increase in positive affect that they experienced was comparable to controls. Schizophrenia is a disease of gradual onset and diagnosis usually occurs only when a patient's symptoms are severe enough to cause disruptions in psychosocial functioning. If, as has been hypothesized, schizophrenia is a neurodevelopmental disorder in which neurobiological changes occur years before the onset of symptoms, then these studies have been unable to examine the true temporal relationship between psychosis and cannabis. On the other hand, if cannabis induces schizophrenia in individuals who are genetically vulnerable (see discussion below) and thus exhibit "prodromal" symptoms at baseline, then the exact temporal nature of this relationship is extremely relevant.

BIOLOGICAL GRADIENT

There are a number of limitations to assessing the dose of exposure of cannabis and its effect on psychotic outcome. Whereas cigarettes and alcoholic beverages have standardized and well-known quantities of nicotine and alcohol, the THC content of cannabis varies considerably. Further, when people smoke cannabis, they may smoke the same joint over several sessions or share a joint with others. Therefore, the number of times a person has smoked is a crude proxy of the "dose" of cannabis exposure. Finally, as discussed above, CBD is thought to have antipsychotic effects in opposition to the pro-psychotic effects of THC. The variable content of CBD in marijuana further complicates the interpretation of studies investigating a dose–response effect.

Despite these limitations, a consistent dose–response effect has been shown in numerous studies. One of the earliest studies showing a biological gradient in the association between cannabis use and psychotic symptoms was done by Andreasson and colleagues. Using the Swedish military conscript ($n > 45{,}000$) followed over a 15-year period (described in detail previously), the investigators found that individuals with heavier cannabis use (>50 occasions of consumption) had a greater chance of developing schizophrenia (relative risk 6.0); intermediate users (11–50 occasions of consumption) had a relative risk of 3.0 for developing schizophrenia. After adjusting for various potential confounders (school adjustment, socio-economic status, solvent abuse, psychiatric diagnosis or medications at baseline, and others, but not including childhood abuse/trauma), the relative risk remained elevated and statistically significant (197). A follow up of this same cohort at 27 years found that this dose–response relationship between cannabis consumption and risk of developing schizophrenia persisted over time (198). Other studies previously described, including the NEMESIS (20) and the ESDP cohorts (24) have also suggested a biological gradient between exposure load and psychotic outcome. More recent evidence also supports this dose–response effect in a sample of individuals with sub-clinical psychotic symptoms; this sample showed that among heaviest users (>5 per day) the relative risk, after adjusting for confounders ("sex, age, social exclusion, alcohol, cannabis use before age 17, and heavy non-cannabis drug use"), of experiencing auditory hallucinations was 5.4 and relative risk for first-rank symptoms was 11.6 (316).

SPECIFICITY

The specificity of the association between cannabis and psychotic disorders is low. In a prospective study of 3-year follow up, of all patients who developed psychosis (assessed by BPRS), only 21% had any use of cannabis at baseline. Furthermore, of those who used cannabis at baseline, only 8 in 312 subjects (2.6%) developed psychosis (20). Similar data was reported from the Swedish military conscript cohort (197). While the association between cannabis and schizophrenia is not specific, it is stronger and more consistent than the association between cannabis and anxiety or depressive disorders. Odds ratios for the development of anxiety or depressive disorders with exposure to cannabis typically range from 0.7 to 1.5 with many studies yielding statistically insignificant results; in contrast, a meta-analysis of multiple longitudinal prospective studies found a statistically significant, adjusted odds ratio of 2.09 (95% CI 1.54–2.84) for psychosis outcome among heaviest cannabis users with all but one of the six high-quality, longitudinal studies showing a statistically significant outcome. These longitudinal studies controlled for about 60 different potential confounders, including personality traits, socio-economic markers, other substance use, and other mental health problems (25). In a longitudinal study of over 18,000 patients hospitalized for substance-induced psychosis, the 8-year cumulative risk of conversion to schizophrenia was 46% when the offending substance was cannabis. In contrast, the conversion rate to schizophrenia over the same period of time for alcohol-induced psychosis was 5%. Notably, the risk for the development of schizophrenia when the diagnosis was amphetamine-induced psychosis was 30% (188).

CONSISTENCY

While not all epidemiological studies have detected an association between cannabis use and psychosis, most longitudinal studies (described in detail previously) show a statistically significant increased risk of psychosis outcome in those who use cannabis heavily. Among each study's heaviest users, the following longitudinal studies have demonstrated a significantly increased risk of any psychosis outcome: the Swedish military conscript cohort (heaviest users being those who had used marijuana >50 times) (197–199), the NEMESIS cohort (weekly users) (20), EDSP cohort (daily users) (24), Epidemiological Catchment Area study (daily users) (317), Dunedin cohort (19, 200), and the CDHS cohort (daily users) (23). The National Psychiatric Morbidity Survey found an increased odds ratio (adjusted for alcohol consumption, gender, IQ score, marital status, and others) that was not statistically significant (even in their heaviest using subjects, those with cannabis dependence) (318). Among these same studies, an analysis of those who had ever used marijuana (even if just once), the Epidemiological Catchment Area study, EDSP study, and the NEMESIS cohort showed increased risk of any psychosis outcome but this risk was not statistically significant.

BIOLOGICAL PLAUSIBILITY

The precise pathophysiology of psychosis or psychotic disorders remains unclear; therefore, a biologically plausible mechanism whereby exposure to cannabis can increase the risk for psychosis or a psychotic disorder is yet to be established. THC, the principal active component of cannabis, is a partial agonist at CB_1Rs where it has modest affinity ($K_i = 35$–80 nmol) and low intrinsic activity (319). CB_1Rs are G-protein-mediated receptors that are distributed with high density in the cerebral cortex (particularly frontal regions), basal ganglia, hippocampus, anterior cingulate cortex, and cerebellum; these brain regions have been implicated in the putative neural circuitry of psychosis. The primary effect of cannabinoids is the modulation of neurotransmitter release via activation of presynaptic CB_1Rs. Thus cannabinoids, by activating CB_1Rs, can modulate the release of a number of neurotransmitters already implicated in psychosis, including dopamine, glutamate or GABA.

The dopamine hypothesis, which postulates that positive symptoms of psychosis may be attributed to disturbed and hyperactive dopaminergic activity, remains one of the more enduring and dominant hypotheses of schizophrenia (320). CB_1R-mediated increases in mesolimbic dopaminergic activity may explain the

positive psychotic symptoms induced by THC. Converging preclinical evidence suggests interactions between cannabinoid (CB_1) and dopamine (DA) systems [reviewed in Ref. (321, 322)]. CB_1 and D_2 receptors are co-expressed in several brain regions (323) and there is signal transduction convergence in these regions (324). Cannabinoids have been shown to induce firing of dopaminergic mesolimbic neurons and induce DA release in the striatum in animals (100, 321, 325–329). Cannabinoids regulate DA firing via a CB_1-GABAergic-mediated disinhibition of DA neuronal activation. However, the results of *in vivo* imaging studies of THC-induced striatal dopamine release in humans have been mixed (96, 330–332). The effect of cannabinoids on striatal dopamine release may be differentially affected by biological vulnerability for psychosis. While chronic cannabis use was found to be associated with decreased striatal dopamine synthesis in healthy individuals (332), THC was found to increase striatal dopamine release in first-degree relatives of individuals with psychotic disorder (333).

The effects of cannabinoids on dopaminergic systems in the PFC might account for some of their acute cognitive deficits. It is well-know that either too much or too little dopaminergic activity in the PFC is associated with impairments in PFC-related cognitive functions leading to an inverted "U" (bell shaped) relationship between dopamine levels and working memory efficiency (334, 335). Systemic administration of cannabinoids has been reported to increase prefrontal cortical DA release or turnover in several studies (100, 336–339). This may explain how cannabinoids produce acute impairments in PFC-related cognitive functions including working memory and attention.

Cannabinoids might induce psychosis and cognitive impairments via actions on GABAergic systems. Higher order cognitive processes, including working memory, are associated with θ (4–7 Hz) and γ (30–80 Hz) oscillations in the PFC. Deficits in working memory are a hallmark of schizophrenia and are associated with reduced cortical θ and γ band power. Cortical θ and γ oscillations are dependent on inhibition of pyramidal neurons. This inhibition is driven by specific cholecystokinin (CCKb cells) and parvalbumin (PVb cells) containing GABAergic interneurons. In several brain regions, CB_1Rs are present on the terminals of axons in cholecystokinin (CCK)-containing GABA interneurons that target the perisomatic regions of pyramidal cells (340). Activation of CB_1R reduces GABA release, which in turn releases the inhibition effects on pyramidal cells. While admittedly speculative, the disinhibition of pyramidal cells may lead to cortical oscillation deficits and working memory impairments.

While the acute effects of cannabinoids on DA, GABA, and glutamate neurotransmission may explain some of the acute positive, negative, and cognitive symptoms of cannabinoids, the mechanism by which exposure to cannabinoids might cause schizophrenia has not yet been established. If schizophrenia is a neurodevelopmental illness (341, 342), then the observation that early cannabis exposure is associated with a greater risk for the development of schizophrenia may offer some clues to the underlying biological mechanisms. Consistent with the human epidemiological data, animal studies suggest that early (adolescent) but not later (adult) exposure to cannabinoids is associated with persistent impaired social behaviors, including psychotic-like behaviors, cognitive, and sensorimotor gating deficits in adults (253–257).

Adolescence and young adulthood are critical phases for cerebral development. Brain development continues into young adulthood (up to 25 years) (343) and therefore, any factors that interfere with brain development during this time may have far reaching consequences. During this period of neuronal plasticity, there is sprouting and pruning of synapses, myelinization, changes in neurotransmitter concentrations and their receptor levels in brain areas necessary for behavioral and cognitive functions (344). The endocannabinoid system plays an important role in several processes important in neurodevelopment including neurogenesis, neural specification, neural maturation, neuronal migration, axonal elongation, glia formation, and positioning of inhibitory GABAergic interneurons and excitatory glutamatergic neurons (259–262, 345–349). Perturbation of the endocannabinoid system in the rapidly changing brain, as is the case in adolescence, by excessive or non-physiological stimulation, as may be the case with exposure to exogenous cannabinoids, may have far reaching consequences. This would be especially so in the presence of already altered neurodevelopmental processes. Therefore, by disrupting the endocannabinoid system and interfering with neurodevelopmental processes, exogenous cannabinoids may provide a biologically plausible mechanism by which exposure to cannabinoids during adolescence may increase the risk for the development of schizophrenia.

STRENGTH OF ASSOCIATION

In the general population, the strength of association between any cannabis exposure and the development of psychosis is modest. A systematic review of 35 longitudinal studies found the relative risk of developing schizophrenia after any cannabis exposure to be 1.4 after adjusting for about 60 potentially confounding variables, including personality traits, socio-economic markers, other substance use, and other mental health problems (25). However, as discussed above, in heavy users (as well as those who begin use at earlier ages), the risk can be much greater. A follow up of the original Swedish military conscript after 35 years yielded an adjusted relative risk of 3.7 for the development of a psychotic disorder (199).

Indirect but compelling evidence is seen in conversion of cannabis-induced psychosis to schizophrenia. Longitudinal studies have found that the risk of developing schizophrenia is nearly 50% in patients admitted for cannabis-induced psychosis (181, 188). Such findings suggest that genetic (or other predisposing) susceptibility to cannabis-induced psychosis may explain why the cannabis–schizophrenia association does not fulfill all causality criteria. That is, in a sub-population of individuals with a history of childhood abuse and genetic vulnerability, the association between cannabis and schizophrenia may be significantly stronger and more specific than in the general population. Individuals with neurobiological vulnerabilities who develop acute psychosis, which persists for a limited period after cannabis intoxication may be those who, with prolonged exposure, are more likely to develop permanent psychotic disorders.

EXPERIMENTAL EVIDENCE

As noted above, direct experimental evidence for acute and transient psychosis caused by cannabis intoxication is compelling (89,

95). In some individuals, this effect persists after the acute intoxication period has ended. In randomized, placebo-controlled, experimental settings, acute psychosis in response to THC intoxication is quite common and reproducible (89, 95, 350). Positive (paranoia, grandiose delusions, fragmented thinking, and perceptual alterations), negative (blunted affect, emotional withdrawal, and psychomotor slowing), and cognitive symptoms (impairments of abstraction, attention, executive function, and memory) have been well-documented. Thus, the main symptom clusters of schizophrenia are seen acutely with THC intoxication. Occasionally, immediate psychosis precipitated by cannabis persists beyond the period of intoxication and may require intervention, though most of these data come from case reports and small series rather than experimental evidence.

Unlike studying acute effects, an experimental approach to characterize the effects of chronic, heavy, and early cannabis exposure is neither ethical nor feasible. An alternative approach is to compare a group with chronic, heavy early cannabis use to controls. Such samples do exist and have been discussed in detail previously.

COHERENCE

There is substantial coherence between the laboratory study findings and epidemiological findings regarding the acute effects of cannabinoids. Cannabinoids induce a range of psychosis-like effects in laboratory studies and epidemiological studies are replete with reports of psychosis following the consumption of cannabinoids. Similarly, cannabinoids have been shown to exacerbate symptoms in individuals with a psychotic disorder and epidemiological studies have shown that cannabis use by schizophrenia patients is associated with a negative impact on the expression and course of the illness. However, as an experimental approach to characterize the effects of chronic, heavy, and early cannabis exposure is neither ethical nor feasible, it is impossible to determine coherence between laboratory and epidemiological studies with regard to the consequences of chronic, early, and heavy cannabis use and psychosis.

PARALLELS

Several parallels can be drawn between the cannabis–psychosis association and other associations in medicine that have been accepted to be causal in nature. For instance, excess salt consumption has been shown to be a well-established cause of hypertension (351), yet not all people who consume more than 2 g of salt daily have hypertension. Similarly, most people who smoke cigarettes do not develop lung cancer; further, there are types of lung cancer (i.e., adenocarcinoma), which develop in the absence of smoking. Yet smoking is understood to be the single most important modifiable causal component in the development of lung cancer.

It is unlikely that schizophrenia is a homogenous disorder with a single pathophysiology; instead, it is more likely a syndrome with distinct neurobiological etiologies. Similarly, the term "lung cancer" comprises several different histological types, including adenocarcinoma, squamous cell carcinoma, and small-cell carcinoma. The risk that smoking confers in the development of cancer varies considerably as the sub-type of cancer becomes more specific. For instance, the risk of developing various types of cancer (including liver, kidney, cervical, myeloid leukemia, gastric, nasopharyngeal, nasal, or esophageal adenocarcinoma) among current smokers may be relatively low, with estimates of the relative risk being ~1.5–2.0 (352). In a large meta-analysis, the relative risk of developing any *lung* cancer among current smokers is much higher at 8.43 (95% CI 7.63–9.31); the relative risk of developing squamous cell carcinoma of the lung is even higher, recently cited at 16.43 (95% CI 12.66–21.32) (353). Viewed from another perspective of the analogy, it is estimated that tobacco smoke is responsible for ~21% of all types of cancer-related deaths worldwide (354) and 87% of all deaths related to lung cancer (2013). By comparison, it is estimated that 8–14% cases of schizophrenia may be due to cannabis use (25, 207). Therefore, the magnitude of the risk for schizophrenia conferred by cannabis exposure is significantly lower than the risk of lung cancer conferred by smoking. It is unlikely that there is any single cause of an illness as heterogeneous as schizophrenia. As research progresses and our understanding of the biological causes of mental illness advances, cannabis-induced psychotic disorder may emerge as a distinct sub-type among the different disorders that constitute what we now classify broadly as schizophrenia.

In summary, the relationship between cannabinoids and psychosis fulfills many but not all of the traditional criteria for causality. Given the evidence presented above, it is likely that cannabis is an important component cause in the development of psychotic disorders (16, 205). This causal role is likely magnified when cannabis exposure occurs at an earlier age, in greater quantities, and over a longer time-course. Further, as discussed elsewhere in this review, specific populations (i.e., those with a genetic vulnerability or a history of childhood abuse) may be particularly susceptible to the causal effects of cannabis. Notably, although meta-analytical studies suggest that cannabis might account for between 8 and 14% of schizophrenia cases (25, 207), the fourfold increase in the rates of cannabis use over the last four decades (198, 355) has not resulted in a commensurate 40–70% increase in prevalence of schizophrenia. Some studies suggest that the rates of schizophrenia may be decreasing (356), while others suggest the contrary (357, 358). The discrepancy between the recent changes in the rates of cannabis consumption and relative stability of schizophrenia rates are difficult to explain in the context of the findings reviewed above; one possible explanation is that schizophrenia rates are lagging behind increased rates of cannabis consumption. Again, it is important to note that schizophrenia is likely a very heterogeneous illness, comprised of multiple sub-types. It is unlikely that there is a single causative factor. As proposed by Rounsaville, it is possible that a cannabis-induced psychotic disorder comprises one of the distinct sub-types of the schizophrenia-spectrum (191).

SUMMARY AND CONCLUSION

In summary, acute exposure to both natural and synthetic cannabinoids can produce a full range of transient symptoms, cognitive deficits, and psychophysiological abnormalities that bear a striking resemblance to some of the features of schizophrenia. Also clear is that, in individuals with an established psychotic disorder, cannabinoids can exacerbate symptoms, trigger relapse, and have negative consequences on the course of the illness. Finally, exposure to cannabinoids in adolescence confers a higher risk for

psychosis outcomes in later life and the risk is dose-related. However, it should be remembered that the majority of individuals who consume cannabis do not experience any kind of psychosis.

The findings from research reviewed above have profound implications for public health. Aside from alcohol, cannabis is currently the most prevalent drug used worldwide. In the United States, the legal status of cannabis for medical and recreational purposes is changing rapidly. Pertinent findings that are likely to impact public health include high conversion rates from cannabis-induced psychosis to schizophrenia; global and specific domains of cognitive impairment resulting from cannabis use, which may be irreversible; the effects of acute intoxication; the precipitation of psychotic disorders in genetically vulnerable populations, including individuals with a history of childhood abuse or family history of psychotic disorders; and the increased risk of negative effects of cannabis use in prolonged and early exposure. Additional high-quality epidemiological studies are needed to further characterize the extent to which cannabis causes these negative effects or unmasks them in a vulnerable subset of the population.

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Pathways from cannabis to psychosis: a review of the evidence

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The nature of the relationship between cannabis use (CU) and psychosis is complex and remains unclear. Researchers and clinicians remain divided regarding key issues such as whether or not cannabis is an independent cause of psychosis and schizophrenia. This paper reviews the field in detail, examining questions of causality, the neurobiological basis for such causality and for differential inter-individual risk, the clinical and cognitive features of psychosis in cannabis users, and patterns of course and outcome of psychosis in the context of CU. The author proposes two major pathways from cannabis to psychosis based on a differentiation between early-initiated lifelong CU and a scenario where vulnerable individuals without a lifelong pattern of use consume cannabis over a relatively brief period of time just prior to psychosis onset. Additional key factors determining the clinical and neurobiological manifestation of psychosis as well as course and outcome in cannabis users include: underlying genetic and developmental vulnerability to schizophrenia-spectrum disorders; and whether or not CU ceases or continues after the onset of psychosis. Finally, methodological guidelines are presented for future research aimed at both elucidating the pathways that lead from cannabis to psychosis and clarifying the long-term outcome of the disorder in those who have a history of using cannabis.

Keywords: *Cannabis*, psychosis, schizophrenia, causality, neurobiology, cognition, outcome

INTRODUCTION AND HISTORICAL PERSPECTIVE

Cannabis sativa is the most widely used drug in the world and archeological evidence from China indicates that humans used cannabis as early as 4000 BCE (1). An association between CU and mental illness, in particular psychotic illness, was recognized as early as 1895 in a report by the Indian Hemp Drugs Commission (2).

It is worth noting several extracts from this report, as they suggest that clinicians working more than a century ago, were similarly uncertain regarding the nature of the observed association between cannabis and psychosis. Curiously, it appears from these extracts that our clinical forbearers were indeed conscious of several fundamental issues which modern science is only now confirming in relation to the effects of cannabis on the human brain. In the twelfth chapter, the report (2) states:

In relation to a causal relationship. . .

> In answering the question, therefore, on what the evidence rests that hemp drugs may induce mental aberration, the Commission would offer the following remarks: The evidence may be considered under two heads – (a) popular; (b) scientific. The popular idea that the use of hemp drugs may induce insanity can be traced back for many centuries, and the present day views on the subject are no doubt the outcome of old popular ideas which have been handed down and become concrete.
>
> But. . . we have a number of instances where the hemp drug habit has been so established in relation to the insanity that, admitting (as we must admit) that hemp drugs as intoxicants cause more or less of cerebral stimulation, it may be accepted as reasonably proved, in the absence of evidence of other cause, that hemp drugs do cause insanity.

In relation to underlying biological processes. . .

> The acute symptoms correspond to the temporary saturation of the body with the poison, while the chronic symptoms are the expression of definite anatomical lesions in the brain gradually developed under toxic influence. . . Further, in regard to what has been said about hemp drug mania, it may be noted that it is not improbable, though it has not been established by evidence, that prolonged abuse of the drugs may give rise in some cases to definite brain lesions resulting in a progressive weakening of all the faculties leading to dementia.

In relation to differential vulnerability to psychosis. . .

> In respect to the alleged mental effects of the drugs. It may indeed be accepted that in the case of specially marked neurotic diathesis, even the moderate use may produce mental injury. . . The individual factor with its idiosyncrasies plays here, as everywhere, a very important part. . . Nervous and predisposed persons appear to be more easily affected than normal subjects.

In relation to specificity of symptoms of psychosis in cannabis users. . .

> The evidence obtained by the Commission appears to indicate that in the cases of alleged hemp drug insanity which find their way into asylums, there are no typical features in the premonitory symptoms and no pathognomonic symptoms in the insane condition on which to base a determination of causation. . . The majority of medical witnesses who have studied the subject are clearly of opinion that there is nothing typical in the symptomatology of hemp drug mania to distinguish it from mania due to other causes. But at the same time several express an opinion that the symptoms are of shorter duration in hemp drug mania than in mania due to other causes. . . The careful inquiry which has been made by the Commission into all the alleged hemp drugs cases admitted in one year into asylums in British India demonstrates conclusively that the usual mode of differentiating between hemp drug insanity and ordinary mania was in the highest degree uncertain, and therefore fallacious.

Interestingly, it seems that clinicians in British India encountered the same difficulties in establishing cannabis as the causal agent in cases of cannabis-using individuals presenting with psychotic illness. In fact, as occurs too often in contemporary clinical practice, this difficulty also led clinicians in that era to resort to over-diagnosis of cannabis-induced psychosis, as is evident in the following extract:

> Surgeon-Major Willcocks, of Agra, says: "Ordinarily it has been the practice to enter hemp drugs as the cause of insanity where it has been shown that the patient used these drugs. I cannot say precisely why this is the practice. It has come down as the traditional practice."

Reference to this historical enquiry into the relationship between cannabis and psychosis, highlights a number of key issues that lie at the center of modern research in this field. In reviewing the relationship between cannabis and psychosis, there are six questions that need to be addressed:

1. Is cannabis an independent cause of psychosis?
2. If so, what are the neurobiological processes underlying this causal relationship?
3. Is the risk for psychosis the same in all individuals using cannabis; and if not, is there a neurobiological explanation for differential risk?
4. Are there specific clinical features of psychosis in cannabis users that differentiates them from psychosis in non-cannabis users?
5. What are the cognitive effects of cannabis use in individuals with psychosis?
6. Does cannabis use impact on course and outcome in individuals with psychosis?

In this review, each of these questions will be addressed and the relevant accumulated evidence presented. In conclusion, I will consider the issue of whether there might be different pathways from cannabis use (CU) to psychotic illness; and present an evidence-based hypothesis that will hopefully offer some direction for future research in this field.

CANNABIS AND RISK FOR PSYCHOSIS – A CAUSAL RELATIONSHIP?

In examining the evidence for a causal relationship between cannabis and psychosis, it is important to acknowledge a number of limitations that are inherent in this research field. The first is the matter of definitions. Published studies vary in terms of the population upon which they focus – some studies limit their inclusion criteria to a narrow definition of schizophrenia, while others include a broad definition of psychotic disorders. Similarly, there is marked variability between studies in terms of defining "CU" (3). CU may be defined as current use or recent use or lifetime use; and within these categories there are further differences in definition. For example, recent use may be regarded as: use within the last month; daily use for at least the last month; weekly use for at least the last month; or as varying frequencies of use over the last 3 months or even 6 months. Other limitations include: most studies measure CU based on self-report, which tends to be associated with under-reporting; self-report of CU is subject to recall bias; in most cases, there is limited information on other substance use, so that analyses are often unable to control for the confounding effects of other substances such as stimulants; it is often difficult to control for factors such as potency of cannabis, frequency of use, and amount of cannabis consumed, due to statistical power issues; and finally and perhaps most importantly, most studies are unable to demonstrate temporal priority of cannabis in relation to early prodromal features of psychosis [the Dunedin study is one of the few that have achieved this methodologically (4, 5)].

These limitations are highly relevant in attempting to establish a causal relationship between "CU" and "psychosis." This is because any attempt to establish "causation" must fulfill the following criteria as defined by Susser (6): association; temporal priority; and direction (where the last implies that changes in the putative cause will actually lead to changes in the outcome, and that the association between putative cause and outcome does not derive from a third factor common to both) (5). Other criteria for causation listed by Hill (7) include: strength (i.e., a dose-response relationship); consistency; specificity; biological gradient; temporality; coherence; and plausibility (i.e., a plausible biological mechanism linking exposure and outcome). Thus the evidence-base on cannabis and psychosis should at least satisfy the majority of these criteria, and must meet the criterion of temporality which, according to Rothman and Greenland (8), is the *sine qua non-for* causality (5).

Multiple studies confirm that CU is approximately two times more frequent among people with schizophrenia than in the general population (9, 10). Furthermore, CU is considered a significant risk factor for both suicide attempts and behavior in psychotic samples (11). This raises the question of whether cannabis plays an etiological role in the onset of schizophrenia, or whether people with schizophrenia are prone to increased use of cannabis. Studies of retrospective reports on CU typically show that approximately one third of individuals commence CU prior to onset of psychotic illness (12, 13). Retrospective studies are subject to recall bias; thus prospective data is required to confirm temporal priority (and thus causality) of CU. A number of systematic reviews have focused on prospective studies only with longitudinal designs and

these report pooled odds ratios varying between 1.41 and 2.34 (5, 14, 15). Henquet et al. (14), whose analysis arrived at a pooled odds ratio of 2.1, noted that this result held regardless of whether studies with narrow clinical outcome were included (OR: 2.4) or whether those with broader outcomes were included (OR: 1.9). Interestingly, Arseneault et al. (5) who arrived at a pooled odds ratio of 2.34, included a very narrow definition of clinical outcomes; while Moore et al. (15), who arrived at a pooled odds ratio of 1.41 in their systematic review, included a very broad definition of psychotic outcomes. The impression therefore from these systematic reviews is that narrow definitions of psychosis (i.e., limited to non-affective psychosis/schizophrenia-spectrum) are associated with slightly higher odds ratios of approximately 2.3–2.4; while broader definitions are associated with slightly lower odds ratios of approximately 1.4–1.9. Notably, all studies included in these three major systematic reviews adjusted for a range of confounding factors. In summary, these reviews suggest that CU is associated with roughly a twofold increased risk of developing psychosis (specifically non-affective, schizophrenia-spectrum disorders), thereby confirming an association between exposure and outcome.

Temporal priority of CU was confirmed in at least two studies which showed that CU during early adolescence increases the risk for later non-affective psychosis outcome (4, 16). In the Dunedin Study in New Zealand, a general population birth cohort of 1037 individuals were assessed at age 11 for psychotic symptoms, at ages 15 and 18 for self-reported CU, and at age 26 for schizophrenia and schizophreniform disorder outcomes (4, 5). Thus, controlling for psychotic symptoms at baseline, the authors were able to show an association between CU at ages 15 and 18 and increased risk for psychotic symptoms at age 26 years. Early CU (by age 15) was associated with a threefold increased risk of schizophreniform disorder at age 26 years (thus confirming temporal priority); but was not associated with later depressive outcomes (thereby indicating specificity of outcome). The use of other drugs in adolescence did not predict psychotic outcomes over and above the effect of CU (indicating specificity of the exposure) (5). The Dutch NEMESIS study (10) as well as the Swedish conscript follow-up study (17) both demonstrated a dose-response relationship between increased CU and increased risk of later psychosis – in the NEMESIS study, the highest risk (OR: 6.8) was associated with the highest level of CU.

In conclusion, there is good scientific evidence, emanating from a number of key studies involving careful longitudinal designs, to conclude that a causal relationship does exist between CU and psychotic illness. Specifically, these studies suggest that this relationship exists in relation to non-affective schizophrenia-spectrum disorders. These studies have demonstrated most of the key criteria for establishing causality, namely: association; temporal priority; specificity; and strength (dose-response relationship). What remains to be considered is the question of plausibility – is there a plausible biological mechanism that could explain the etiological role of cannabis in psychosis and schizophrenia?

THE NEUROBIOLOGICAL BASIS OF CANNABIS AS A CAUSE OF PSYCHOSIS

In the early 1990s, the cannabinoid (CB) receptors were genetically determined – the distribution of CB_1 was mapped in high densities to the striatum, hippocampus, and cerebellum; and in moderate to low densities to the amygdala, midbrain, and cerebral cortex (18). CB_1 are situated on presynaptic terminals that release GABA, glutamate, serotonin, dopamine, and Ach; and interaction between this receptor and its endogenous endocannabinoid ligands (e.g., anandamide) results in limiting of neurotransmitter release (19). Thus this system plays an important role in maintaining and determining synaptic plasticity. Importantly, endocannabinoid signaling is present during gestation and early infancy and plays a critical role in neuronal proliferation, migration, axonal guidance, positioning of cortical interneurons, and synaptogenesis (20). Experimental aberrations in endocannabinoid signaling during critical periods result in significant disruptions in neurodevelopment. While the role of endocannabinoid signaling during adolescence has not been fully elucidated, one may reasonably assume that the neurodevelopmental role of this system continues during adolescence when regions such as the hippocampus and prefrontal cortex are still undergoing marked development (18). Notably too, CB_1 expression patterns increase dramatically throughout the adolescent period in areas including the frontal cortex, striatum, and hippocampus (21). Likewise, there appear to be peaks in endocannabinoid levels during the adolescent period (22, 23). Thus, as Malone et al. (18) conclude, "endocannabinoid signaling is an important determinant of maturation of the adult brain. . . it seems quite likely that disruption of normative endocannabinoid signaling during adolescence may have long-standing consequences on adult brain function." Animal models show that early exposure to CB agonists result in a variety of mostly cognitive deficits in adult animals, including working memory dysfunction, disruption in pre-pulse inhibition of startle (a measure of sensory gating), a significant decrease in social behavior and increased locomotor activity (24–26). In summary, these observations have led to the so-called "endocannabinoid hypothesis of schizophrenia" (27).

Disruption of the CB system during development impacts on several other neurotransmitter systems, notably the GABA and dopamine systems. GABAergic neurons in the prefrontal cortex are rich in CB_1 receptors which, when activated, result in a decrease in extracellular GABA release (28). It has been hypothesized that repeated exposure to cannabis during adolescence may alter the balance of GABAergic inhibitory inputs to pyramidal neurons in the prefrontal cortex that could lead to impaired cognitive function (29). Furthermore, CU leads to increased extracellular dopamine; probably through the activation of CB_1 receptors on GABAergic interneurons, which in turn disinhibit dopaminergic neurons (30). Kapur (31) has argued that psychosis results from aberrant reward prediction and abnormal attribution of salience caused by disordered dopamine transmission; while Laruelle (32) postulated that the dopaminergic abnormalities associated with schizophrenia are due to "dopamine sensitization" beginning in adolescence. Dopamine sensitization has been suggested in relation to the links between early stress and trauma (e.g., childhood sexual abuse) and the observed increased risk for schizophrenia (33). Evidence supporting the role of dopamine sensitization in CU, comes from a study by Houston et al. (34) where a significant interaction was found between early exposure to cannabis and childhood sexual trauma on psychosis outcome. Importantly,

in this study, no main effect was observed for either sexual trauma or CU on psychosis outcome; suggesting that previous exposure to stress sensitizes individuals, so that subsequent life stresses evoke progressively greater responses over time (i.e., in this case there is cross-sensitization between early stress and cannabis) (35). In terms of dopamine sensitization, the individual eventually reaches a lasting state of dopamine dysregulation (36, 37). Henquet et al. (35) note that the dose-response relationship between CU and risk for psychosis suggests a dopamine sensitization process.

THE BIOLOGICAL BASIS OF DIFFERENTIAL RISK FOR PSYCHOSIS IN CANNABIS USERS

Cannabis is the most widely used drug in the world – millions of people use it – however, only a small proportion of users develop psychotic illness. This suggests that individual genetic factors must play a role in altering individual susceptibility to the psychotic-inducing potential of cannabis; thus gene-environment interactions are implied.

There are two ways to measure genetic liability to psychosis – directly and indirectly (14). Indirect measurement involves the use of individuals who are shown to exhibit liability to psychosis (measured using psychosis proneness scales) or are liable to psychosis by virtue of being first degree relatives of psychotic probands. Individuals measured as liable to psychosis are at greater risk of developing cannabis-induced psychotic experiences during the flow of everyday life (38); and their 3–5 year risk of developing psychotic symptoms while using cannabis is 51% compared with 21% in those using cannabis who do not show psychosis liability (39). A family study by McGuire et al. (40) found that patients who developed acute psychosis after using cannabis were more likely to have a positive family history of schizophrenia than those patients who screened negative for CU.

Unlike indirect measures of genetic risk which rely on psychosis liability, presumably of genetic origin, direct measures rely on actual analysis of genes, their polymorphisms and their expression patterns. During the last 8 years, there has been considerable interest in the catechol-*O*-methyltransferase (COMT) gene in relation to liability to psychosis and various environmental factors including cannabis. The *COMT* gene is notable as a candidate gene for psychosis since: it is located on chromosome 22q11, a region already implicated in schizophrenia; a microdeletion of chromosome 22q11 is associated with velo-cardio-facial syndrome (which has a high rate of psychosis); and finally, the *COMT* gene codes for the enzyme catechol-*O*-methyltransferase which is involved in the metabolism of dopamine at synapses (41). From the Dunedin Study (described above), Caspi et al. (41) showed that a functional polymorphism of the *COMT* gene moderates the effect of adolescent CU on risk for adult psychosis. Homozygous carriers of the *COMT valine*^{158} allele (i.e., *Val/Val*) were most likely to exhibit psychotic symptoms and later develop schizophreniform disorder if they had used cannabis during adolescence (RR: 10.9). Heterozygous individuals with the *valine/methionine (Val/Met)* genotype who had used cannabis during adolescence showed an intermediate risk; while those homozygous for the *methionine* allele *(Met/Met)* showed the lowest risk (RR: 1.1). It is important to note that the authors emphasize the fact that this effect was observed in those with adolescent-onset CU and not in those with adult-onset CU. This is important for understanding the relative impact of cannabis on the developing versus the developed brain in relation to its causal role in psychosis. Several studies have subsequently partially replicated this result (42, 43), while others have failed to replicate it (44). In a double-blind placebo controlled trial in the Netherlands, Henquet et al. (42) showed that *Val/Val* carriers were more sensitive to memory and attention impairments of delta-9-tetrahydrocannabinol (THC); although a gene-environment interaction was not demonstrated as the genotype on its own was neither associated with cognitive impairments nor associated with frequency of CU or being a patient.

Notably, *COMT* is predominantly expressed in the prefrontal cortex (45), a region associated with executive functioning, working memory, and attentional deficits in schizophrenia. The *Val/Val* genotype is associated with increased *COMT* activity and Henquet et al. (35) hypothesize that this may result in a combination of (a) reduced dopamine neurotransmission in the prefrontal cortex, and subsequently (b) increased levels of mesolimbic signaling which is thought to result in increased risk of experiencing delusions and hallucinations. Conversely, the *Met/Met* genotype is associated with better prefrontally mediated executive function performance than the *Met/Val* and *Val/Val* genotypes (46). Reasoning that since *COMT* is especially important in the prefrontal cortex, and since the prefrontal cortex is developing during puberty, Barnett et al. (47) investigated the role of *COMT* genotypes on cognitive functioning during puberty. They found that among boys who had already entered puberty, those with the *Met/Met* genotype had an average IQ 10 points higher than those with the *Val/Val* genotype. This relevant to our focus on psychosis and cannabis for two reasons: first, it supports the neurodevelopmental model of schizophrenia (48) where genetic and environmental liabilities interact with normal brain development to increase risk for the disorder (49); and secondly it provides a sound neurodevelopmental framework within which the adolescent use of cannabis can be understood as conferring increased risk for later psychosis.

CLINICAL PRESENTATION OF PSYCHOSIS IN CANNABIS USERS – ARE THERE SPECIFIC FEATURES?

If cannabis does indeed play a causal role in psychotic illness and there is differential risk for psychosis in cannabis users, then it is pertinent to address the question of whether cannabis can be distinguished clinically as an etiology for psychosis? The view of the Indian Hemp Drug Commission over 100 years ago was that there are no distinguishing clinical features of psychosis due to CU (other than perhaps a shorter duration of the episode). Were these early impressions correct? In answering this question it is important to bear in mind the issue raised at the beginning of this review, namely: one must differentiate between lifetime use and recent/current use of cannabis as these may have quite different effects upon clinical presentation, course and outcome of psychosis.

Duration of untreated psychosis (DUP) is the period between the onset of the first psychotic symptoms and the initiation of antipsychotic treatment. DUP has significance in that longer DUP is associated with poorer response to treatment, more frequent relapses and poorer long-term outcome of psychosis (50, 51). Conversely, early detection and intervention improves outcome to a

considerable degree. The popular hypothesis linking long DUP to the negative long-term consequences of psychosis relates to proposed neurotoxicity; however, an analysis of the clinical and neurobiological evidence for this hypothesis suggests that it is in fact synaptic plasticity, and not neurotoxicity, that is one of the most important mediating processes underlying this association (52). The evidence-base supporting a link between DUP and outcome is significant enough to have modified clinical practice. There is therefore a good rationale for considering whether CU impacts on DUP. A recent systematic review identified nine studies with data on DUP and CU, and meta-analysis found no significant difference in DUP between cannabis users and non-users (3). However, the author noted that six of the nine studies reported shorter DUP in cannabis users; and that "this association appears to be true specifically for samples where CU is defined in terms of current or recent use rather than lifetime use. . . Conversely. . . lifetime use appeared to be associated with longer (or in one study equivalent) DUP" (3). The author argues that this, along with other evidence to be reviewed below, suggests there may be more than one pathway to psychosis in relation to CU. In their first-episode psychosis (FEP) study, Pelayo-Terán et al. (53) compared cannabis users and non-users by *COMT* genotype and reported that those with the *Met/Met* genotype showed a relatively short DUP, irrespective of CU status (53). Those with the *Val/Val* genotype who were cannabis users also showed a short DUP, while non-cannabis users with this genotype showed statistically longer DUP. Notably, in this study, CU was defined in terms of recent use and – consistent with Burns' conclusions cited above – cannabis users all showed shorter DUP, irrespective of their *COMT* genotype.

Early age of onset of psychosis is also associated with poorer outcome in schizophrenia. Meta-analysis shows that age of onset in cannabis users is 2.70 years earlier than in non-cannabis users; and multiple meta-regression showed that a higher proportion of cannabis users in the substance-using groups significantly contributed to the heterogeneity in the effect size (54). The authors argue that this finding lends support to the hypothesis that CU plays a causal role in the development of psychosis in some individuals. In addition, it appears that a temporal direct relationship may exist between the age at initiation of CU and age of onset of psychotic illness; with a period of 7–8 years intervening (55). In a sample of 997 individuals with psychosis, Stefanis et al. (55) found a linear association between age of initiation of CU and age of onset of psychosis; with those who had comorbid diagnoses of schizophrenia-spectrum disorder and lifetime cannabis dependence showing a slightly shorter period of premorbid cannabis exposure (7 years). A similar association has also been shown between earlier initiation of CU and early onset of high-risk symptoms for psychosis (56), suggesting that CU from a young age is associated with increased risk for a spectrum of psychotic phenomena. Thus the evidence on cannabis and age of onset of psychosis appears to support the hypothesis that early and prolonged use of cannabis is predictive of earlier onset, prognostically poorer psychotic disorder in some individuals.

Interestingly, the *COMT* genotype shows an interaction with CU in relation to age of onset (53). Pelayo-Terán and colleagues found that among non-cannabis users, age of onset was significantly later in those with the *Met/Met* genotype, compared with those homozygous for the *Val* allele. However, in cannabis users, there were no differences in age of onset between *COMT* genotypes with all cannabis users having earlier age of onset. The authors conclude that CU has the effect of reducing the delay effect of the *Met* allele on onset of psychosis; thereby depriving carriers of the relative protection conferred by this allele.

In terms of symptoms, most studies support the finding that cannabis users with FEP tend to present with more prominent positive symptoms (hallucinations, delusions, and thought disorder) and less prominent negative symptoms (apathy, social withdrawal, amotivation, etc.) (57–61). Prominent positive symptoms at onset are generally associated with a better course and outcome; while prominent negative symptoms are associated with poor outcome. Notably, Van Mastrigt et al. (57) defined CU in terms of recent use and showed increased positive symptoms in cannabis users at psychosis onset; while Compton et al. (60) reported a significant relationship between daily CU just before onset of psychotic symptoms, and an acute florid onset of psychosis. With respect to negative symptoms, Burns et al. (58) defined CU in terms of recent use and reported significantly lower negative symptom scores at psychosis onset. Taken together, these findings suggest that increased positive symptoms and reduced negative symptoms at psychosis onset are likely to be associated with the acute effects of recent/current CU specifically. This hypothesis is supported by the findings of Baeza et al. (62) who measured positive and negative symptoms at psychosis onset and again at 6 months in 32 cannabis-using and 78 non-cannabis-using children and adolescents aged 9–17 years. CU was defined in terms of recent use over the last month. At baseline (i.e., psychosis onset), cannabis users had significantly greater positive symptoms and lower negative symptoms. However, at 6 months follow-up, cannabis users had significantly lower positive and negative symptoms than non-cannabis users; particularly those cannabis users who gave up cannabis during the 6-month period. Some authors have argued that lower negative symptoms in cannabis users is a function of selection, whereby individuals with negative symptoms cannot easily access cannabis due to the apathy, amotivation, and social withdrawal that comprises the negative syndrome (59). However this is unconvincing given the ease of access to cannabis in many countries such as the Netherlands and South Africa (58).

COGNITION IN CANNABIS USERS WITH PSYCHOSIS

The cognitive effects of CU in individuals with psychosis is an important and, as it turns out, fascinating topic. Long-term CU in normal individuals without psychotic disorders is associated with cognitive impairments, including residual memory and attentional deficits following abstinence (63, 64). In addition, Yücel et al. (64) have demonstrated structural brain abnormalities in otherwise healthy long-term cannabis users. However, in individuals with schizophrenia, long-term CU seems to have a different effect on neurocognitive performance. Two meta-analyses show that patients with schizophrenia who have a history of CU have superior neurocognitive functioning than patients with schizophrenia without a history of CU (65, 66). This somewhat unexpected finding appears to relate particularly to performance on executive functioning, working memory, and visual functioning; although meta-analysis of a global cognitive score also showed

better performance in cannabis-using patients with schizophrenia with an overall effect size of 0.35 (66). Further analysis demonstrated that cannabis users performed significantly better (in terms of the global cognitive score) only in the studies defining CU by lifetime exposure ($d = 0.55$), but not in the studies using recent use criteria. Furthermore, Jockers-Scherübl et al. (67) found that earlier age of initiation of CU (before age 17 years) was associated with even better neurocognitive performance in patients with schizophrenia; while CU deteriorated cognitive performance in healthy controls, especially in those who initiated use before age 17 years. In a first-episode schizophrenia study, Yücel et al. (66) confirmed the finding of better neurocognitive performance in cannabis users; and replicated the finding that superior performance is specifically associated with early initiation of CU. Interestingly, more frequent CU has also been associated with better cognitive performance, specifically in the domains of working memory and attention (68).

Several explanations have been offered for this somewhat counter-intuitive finding of superior cognitive functioning in cannabis-using patients with schizophrenia. Some authors have suggested that cannabis-using patients show superior social skills, enabling them to access an illegal drug (69, 70). This however is unconvincing and is not supported by data (71). As in the case of negative symptoms (see discussion above), cannabis is readily accessible in many countries such as the Netherlands and South Africa; thus superior social skills are not necessary to obtain it.

It has also been suggested that cannabis may have a protective influence on brain functioning, especially when consumed prior to psychosis onset (67, 72). Jockers-Scherübl et al. (73, 74) found significantly higher concentrations of neurotrophins [nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF)] in schizophrenia patients with previous CU, compared to non-using schizophrenia patients. These authors suggest that "since neurotrophins like NGF and BDNF are involved in the development, plasticity, and maintenance of function of nerve cells, their up-regulation in cannabis users who later develop schizophrenia might correspond to an endogenous repair mechanism for impaired nerve cells. Cannabis might induce this mechanism, which in turn could help preserve cognitive function" (67). Supporting this hypothesis is evidence from studies of both non-clinical and other clinical (non-psychotic) populations that cannabis may have neuroprotective and even neuroregenerative properties (75–78); as well as the fact that CSF levels of the endogenous CB, anandamide, are negatively correlated with psychotic symptoms in acute untreated schizophrenia (79), suggesting an endogenous compensatory adaptation within the CB system in schizophrenia. The question of whether cannabis exerts positive neuroprotective effects on individuals who later develop schizophrenia, is likely to be controversial and highly complex and clearly further research is indicated to resolve this issue.

Perhaps, the most convincing argument for better cognitive functioning in cannabis-using schizophrenia patients is the following: those individuals who present with psychosis and a history of long-term CU, early initiation of CU increased their risk for developing psychosis, which otherwise may not have occurred in the absence of CU (66, 68, 80). In other words, early CU may induce psychosis onset in less cognitively vulnerable individuals. On the other hand, non-cannabis users who develop psychosis are likely to have greater genetic or developmental vulnerability to psychosis; thus they manifest poorer cognitive performance at psychosis onset. As Yücel et al. (66) point out, the evidence that cannabis initiation before the age of 15 years is associated with greater risk for subsequent psychosis (4, 5), supports this hypothesis. It is possible that, in the absence of cannabis, these individuals may have remained asymptomatic. Evidence that cannabis users at first-episode have fewer neurological soft signs (minor physical anomalies attributed neurodevelopmental factors) than non-users supports the hypothesis that cannabis users have less neurodevelopmental impairment (81). The fact that more frequent use of cannabis has also been associated with better cognitive performance (68), further supports this hypothesis; as here one might speculate that a greater magnitude of toxic insult is required to induce psychosis in individuals who are particularly invulnerable to psychosis.

Somewhat at odds with the hypothesis that cannabis-using schizophrenia patients have better cognitive performance and less neurodevelopmental impairment than non-users, is data suggesting structural brain abnormalities in users, especially in areas rich in CB1 receptors such as the cingulate and prefrontal cortices and cerebellum (82). In addition, two studies show reduced cortical thickness in users compared with non-users (83, 84). However, many of these studies have important limitations including: study populations are often individuals with established schizophrenia [e.g., Habets et al. (84)] and findings in these patients cannot differentiate between premorbid vulnerability markers and progressive changes during the course of the disease; and there is often comorbid alcohol or other substance use which is likely to confound results. In order to clarify this issue, first-episode samples must be studied, without other comorbid alcohol or substances. In a systematic review of the effects of CU on brain structure in schizophrenia, only four papers report on populations meeting these criteria and three of these report data from the same longitudinal cohort (82). Firstly, in Utrecht, Netherlands, Cahn et al. (85) reported from a cross-sectional FEP study no differences in global brain and caudate nucleus volumes on MRI between cannabis users and non-users. In the same group, Rais et al. (83, 86) reported no differences in ventricular size or cortical thickness at baseline in cannabis-using, first-episode schizophrenia patients; but at 5 year follow-up, those who used cannabis during the scan interval showed increased lateral and third ventricle volumes and loss of cortical thickness in the anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (DLPFC). In a different cross-sectional FEP study, Szeszko et al. (87) reported gray matter deficits in the ACC in those with a comorbid diagnosis of cannabis dependence or abuse. However, in a recent study of 54 first-episode schizophrenia patients, those with a lifetime history of CU ($n = 30$) showed higher gray matter density in the left frontal middle gyrus than those with no history of CU; and this was positively associated with better cognitive performance on the Continuous Performance Task (CPT), a measure of prefrontal cortex integrity (88). Notably, impaired performance on the CPT (in the domains of working memory, attention, and vigilance) is regarded by some as a biological trait marker for schizophrenia (89). These authors conclude that their results "provide further

support for the hypothesis of a lower vulnerability for schizophrenia in at least a subgroup of cannabis-using schizophrenia patients compared to cannabis naïve patients" (88). Finally, a very recent systematic review of MRI studies in schizophrenia comparing cannabis users and non-users, reported inconclusive results, stating: "while there is some evidence that chronic cannabis abuse could alter brain morphology in schizophrenia in patients continuing their cannabis consumption, there is no convincing evidence that this alteration takes place before the onset of schizophrenia when looking at first-episode patients" (90).

In concluding this section then, it seems the strongest evidence supports the hypothesis that early CU may induce psychosis in less vulnerable individuals who otherwise may have remained well.

DOES CANNABIS USE IMPACT ON COURSE AND OUTCOME OF PSYCHOSIS?

While assumptions are commonly made by psychiatrists that CU impacts negatively on course and outcome of psychosis, and the seminal study of Linszen et al. (91) is often cited in support of this view, Zammit et al. (92) conclude their systematic review of the issue by stating: "We were surprised how little empirical evidence is currently available to support this view." In their review of 13 studies that met criteria, these authors note that few studies of outcome adjust for baseline severity, and most make no adjustment for alcohol or other potentially important confounders. It is thus only worth reviewing here the findings of the three studies (93–95) that did adjust for baseline severity and for alcohol and other substance use – since these are major confounders which undermine the validity of the results of studies failing to include these adjustments. In Brisbane, a dose-response association was demonstrated between CU (days per week) and increased relapse, and in addition, increased psychotic symptoms predicted relapsed CU (93). This suggests a bidirectional relationship between CU and psychotic symptoms – thus one cannot assume that ongoing CU is causal of symptom relapse. Increased relapse of symptoms in association with cannabis was also reported from Melbourne (94) and Sydney (95), although it is important to note that neither of these studies were in FEP populations. There is also evidence that the greatest risk of relapse is associated with ongoing CU during follow-up (96). While some studies with less rigorous methodology have reported increases in positive and/or negative symptoms with ongoing CU, the only one of the three Australian studies cited above that reported increased positive symptoms is the Sydney study (95); while none found increased negative symptoms. The study of children and adolescents with FEP by Baeza et al. (62) cited earlier in this review, is notable in relation to symptoms at follow-up. Recent CU just prior to onset was associated with increased positive symptoms and lower negative symptoms. However, at 6 months follow-up, cannabis users had significantly lower positive and negative symptoms than non-cannabis users; particularly those cannabis users who gave up cannabis during the 6-month period. Thus, in conclusion, it seems Zammit et al. (92) are correct in their assessment and that there really is not any substantial evidence supporting assumptions made about poorer course and outcome in psychosis in relation to premorbid CU. Ongoing CU however appears to have a reciprocal impact on perpetuating psychosis into a possibly progressive, relapsing, deteriorating schizophrenia-like disorder.

PATHWAYS FROM CANNABIS TO PSYCHOSIS

Having reviewed multiple aspects of the relationship between CU and psychosis, it is now possible to propose a model which involves several pathways from cannabis to psychosis. Importantly, the factors that are key to the various pathways include;

- Early initiation/lifetime use of cannabis versus recent cannabis use.
- Underlying genetic vulnerability to psychosis/schizophrenia.
- Ongoing cannabis use after psychosis onset versus stopping cannabis use.

Two major pathways from cannabis to psychosis are proposed. Firstly, early initiation of CU during adolescence and lifetime use in genetically vulnerable individuals, gives rise to neurodevelopmental changes that sensitize individuals to later psychosis – possibly through disruption of normal endocannabinoid, GABA and dopaminergic systems (see **Figure 1**). These are individuals who are genetically vulnerable, but in the absence of cannabis they may have remained asymptomatic. The implication is that their degree of genetic vulnerability is not as significant as that in individuals who become psychotic in the absence of CU (see **Figure 2**). These individuals (cannabis users) present at psychosis onset with mixed prognostic features – early age of onset, long DUP, high positive and low negative symptoms and relatively normal cognition and brain structure on MRI. If CU ceases at first-episode, then a positive outcome with significant improvement may be anticipated. However, if CU continues after psychosis onset, a poorer course and outcome characterized by repeated relapse and neurocognitive deterioration is likely. In this scenario, it appears that ongoing CU and exacerbation of psychotic symptoms impact on each other reciprocally, in a cycle of deterioration that is mirrors the underlying progression of cognitive and structural brain impairment. In such cases, the chronic deteriorating psychotic disorder is indistinguishable from schizophrenia – and in terms of current psychiatric nosology should probably be considered as schizophrenia.

The long-term outcome of early-initiated/lifelong CU in individuals who are not genetically vulnerable to psychosis, is less clear and certainly an area for future research. It is feasible that several outcomes are possible, depending on individual genetic and developmental factors, frequency, volume, and duration of CU, as well as the presence or absence of other risk factors for psychosis (such as early trauma, abuse, and stress). It is reasonable to assume that some individuals follow a course into psychosis as described above for genetically vulnerable persons; others may experience fluctuating psychotic-like symptoms that remain clinical insignificant; while others may experience a completely asymptomatic course long-term.

The other major pathway from cannabis to psychosis occurs in individuals without a lifetime history of CU, but who begin to use cannabis shortly before psychosis onset (see **Figure 3**). Where acute psychosis is apparently "precipitated" by recent CU, it is reasonable to assume such individuals are already genetically and developmentally vulnerable to psychosis. Thus, unlike

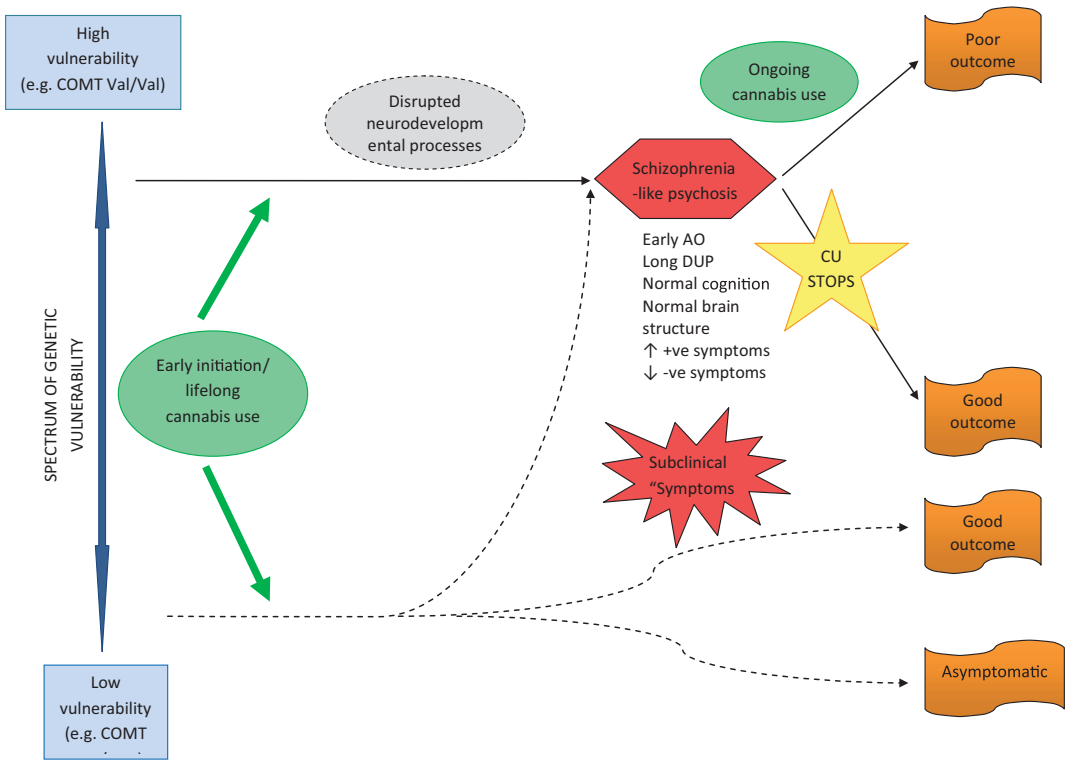

FIGURE 1 | Pathway to psychosis in early-initiated, lifelong cannabis users.

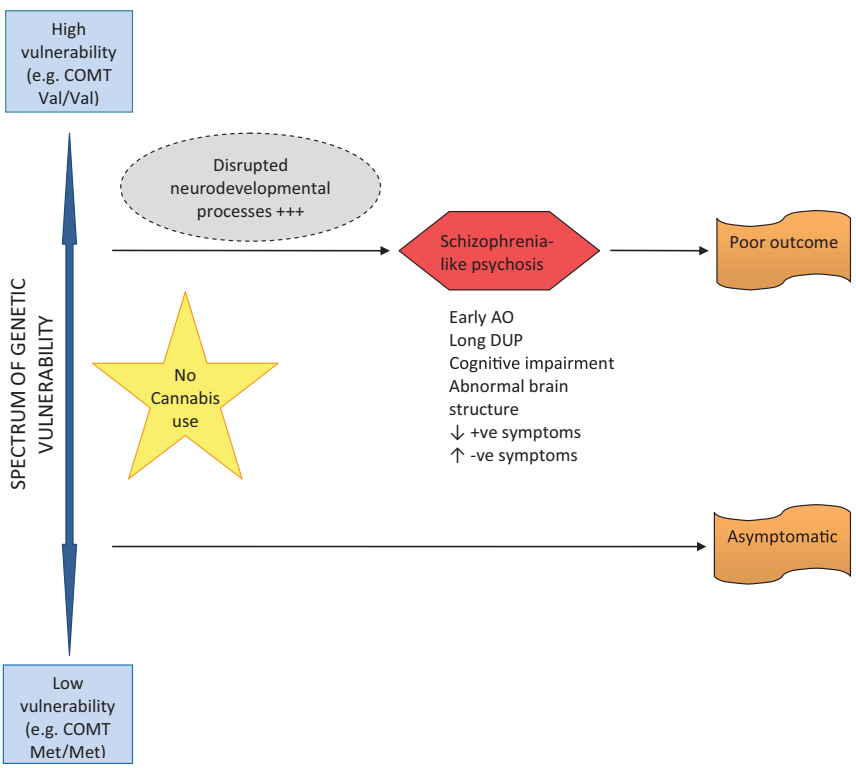

FIGURE 2 | Pathway to psychosis in non-cannabis users.

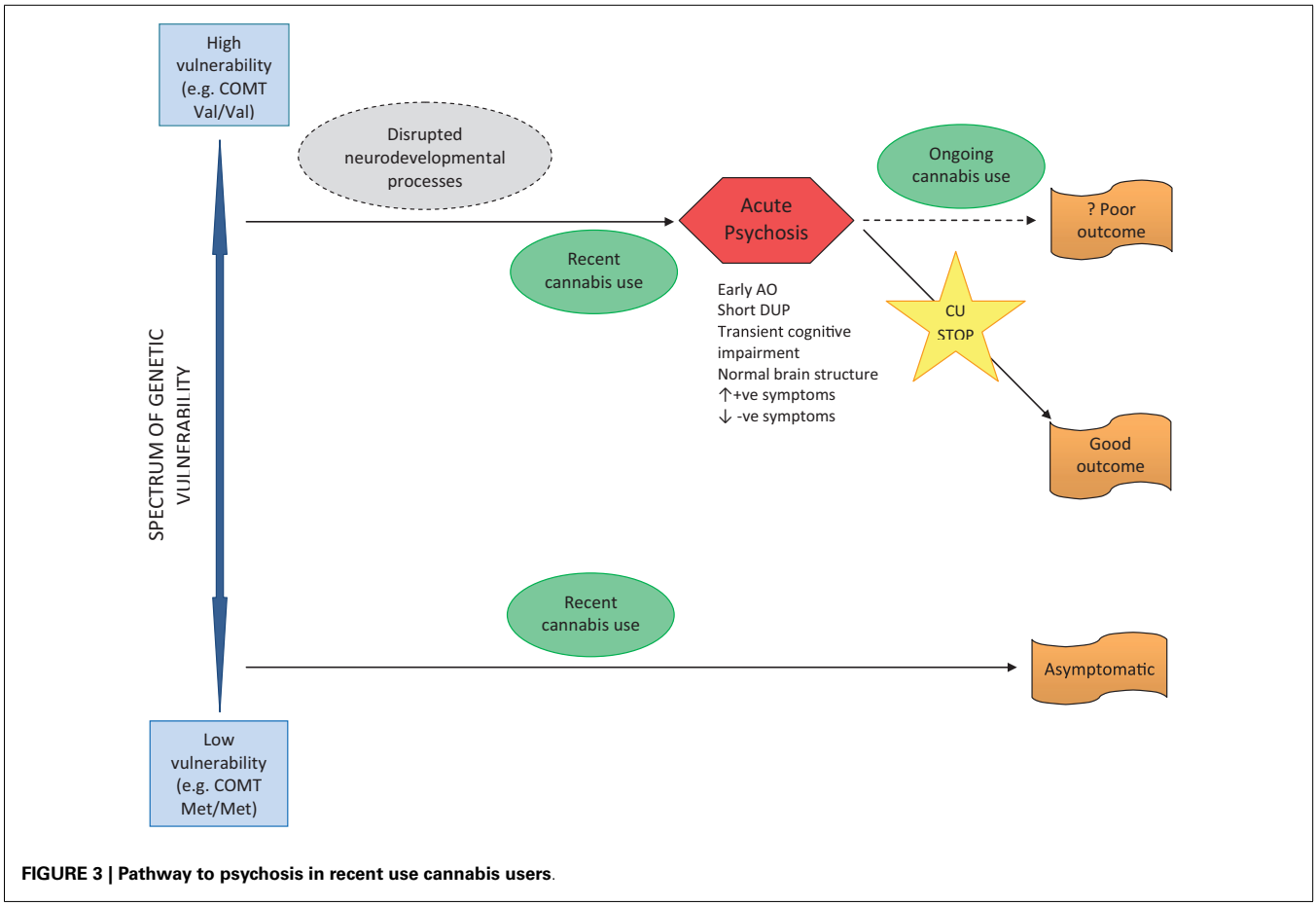

FIGURE 3 | Pathway to psychosis in recent use cannabis users.

early-initiated, lifetime cannabis users (who are vulnerable to psychosis as a result of lifelong cannabis-induced neurodevelopmental dysregulation), these individuals are susceptible to psychosis for genetic and developmental reasons alone. The acute "cannabis-induced" psychosis is characterized by prognostically better features including: later age of onset; shorter DUP; and prominent positive and absent negative symptoms. In the acute phase, cognitive deficits may be evident, but are transitory and reversible if CU ceases, with a good outcome expected. Where CU continues after psychosis onset, a poorer outcome might be expected – but this is less clear and also an area meriting further research.

A large number of people use cannabis frequently without experiencing any psychotic symptoms or disorder. Presumably, these are individuals with low genetic and developmental vulnerability to psychosis.

CONCLUSION AND FUTURE RESEARCH

In conclusion, the relationship between CU and psychosis is complex and it is not possible to describe a single scenario that pertains to all individuals whose CU contributes to subsequent psychosis. In addition, variations in cannabis composition between individuals and over time are likely to contribute to heterogenous courses and outcomes. Evidence showing that the cannabis product cannabidiol (CBD) may protect against the psychosis-inducing effects of THC (97) implies that consumption of cannabis with a high THC:CBD ratio is more likely to be associated with psychotic outcomes. It is clear that at least two pathways from cannabis to psychosis exist. Early-initiated, lifelong CU in vulnerable individuals may lead to a psychotic illness virtually indistinguishable from schizophrenia at onset. It appears that outcome however is dissimilar to schizophrenia in those who cease to use cannabis after onset. In those whose CU persists, a chronic deteriorating disorder seems to follow – in these cases one may conclude that cannabis has been played a causal role in schizophrenia. Recent use of cannabis in vulnerable individuals, just prior to psychosis onset, is clinically distinguishable from schizophrenia at first-episode. Ceasing CU after the first-episode appears to have an excellent prognosis, with full recovery achievable in most cases. The long-term consequences of continued CU however are not clear.

There is clearly a need for future research to clarify and confirm these differing pathways and complex associations between CU and psychosis. Such research should be carefully designed to take into account key factors that to date have often been blurred, thereby confusing the research field. The ideal study would include the following methods:

1. A first-episode psychosis population with narrow diagnostic definitions of non-affective or schizophrenia-like psychosis.
2. A detailed history and description of CU, including: age at initiation; frequency and extent of cannabis consumed; and a clear description of patterns of recent use.

3. History of other risk factors for psychosis (e.g., childhood trauma).
4. Measures of vulnerability or proneness to schizophrenia and psychosis – these may be indirect (e.g., familial history) or direct (genetics; neuropsychological endophenotypes).
5. A longitudinal study design with clear baseline and follow-up measures of psychopathology, cognitive functioning, and ongoing CU.

Such studies will move this field forward considerably and bring us closer to answering the long-standing questions of how CU impacts on the brain and how this leads some individuals into psychotic illness and even schizophrenia. They will also clarify the issue of outcome and prognosis for individuals with a cannabis history who develop psychosis. Finally, elucidating the pathways from cannabis to psychosis will contribute substantially to ongoing efforts to understand the causes, development and natural history of schizophrenia and its related disorders.

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The association between cannabis use, mental illness, and suicidal behavior: what is the role of hopelessness?

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INTRODUCTION: THE COMPLEXITY OF CANNABIS MISUSE

Cannabis is one of the most common illegal psychoactive substance used in European countries, in particular among adolescents and young adults (1). It has been estimated that almost 55% of adolescents aged 15–19 years have used cannabis at least once in their lifetime (2), while past year use is reported by approximately 30% of 15–17 year olds and over 47% of those aged 18–19 years (3).

Cannabis use has been associated with several adverse life outcomes including unemployment, legal problems, dependence, early school leaving, increased risk of developing both psychotic and affective disorders (3, 4) together with brain structural and functional abnormalities (5, 6). An association between cannabis use, psychiatric disorders and suicidal behavior has also frequently been reported, although the exact nature of this link is still poorly understood (4).

Globally, suicide is one of the most common causes of death among young people aged 10–24 years (6% of deaths), exceeded only by motor vehicle accidents (10%) (7). Over the last decade suicidal behavior has increased among adolescents and young adults, there has also been a trend toward the earlier initiation of cannabis use (8). This has led researchers to investigate the associations between the two factors to determine if cannabis use may be considered a factor that can trigger suicidal behavior.

Evidence indicates that cannabis use is significantly associated with both attempted and completed suicides among healthy youths (9) and both twin studies (10) and case-control comparisons (11) have shown the increased risk of suicide ideation/attempts in those who use cannabis. Moreover, a longitudinal study found that frequent cannabis use (at least several times a week) predicted later suicidal ideation in susceptible males but not females (12). The earlier that this intense use first occurred and the higher the frequency of cannabis use, faster the susceptible individuals experienced suicidal thoughts.

Frequent and early cannabis use has also been associated with impaired mental wellbeing among young individuals (13, 14), and the risk of developing psychiatric conditions such as psychosis (15) and major affective disorders (16). Specifically, evidence suggests that cannabis use may exacerbate pre-existing conditions such as bipolar disorder, and predict negative outcomes and psychosocial impairment (17, 18). According to longitudinal studies, the high and frequent use of cannabis is also associated with longer recovery times for affective conditions, more hospitalizations, poorer compliance with treatment, increased aggression, and poorer response to treatment in patients with bipolar disorder type I and II (12, 17).

Nevertheless, it is important to note that many of the studies investigating associations between cannabis use and psychiatric conditions are cross-sectional in nature and cannot establish a causal relationship between the two phenomena (19). Further, several studies (20, 21) suggest a bidirectional relationship, as cannabis use variables do not solely explain the psychiatric outcomes observed nor do pre-existing psychiatric conditions fully explain the increased use of cannabis. Some researchers (22) have suggested that individuals with high levels of anxiety sensitivity or hopelessness may be more sensitive to the negative reinforcement processes of substance use (i.e., the ability of substances to modulate negative affective states) than non-affected individuals; however, some individuals experiencing the onset of mania or depression are not more likely to report increased cannabis use than those not experiencing these disorders (23, 24). In addition, other authors (25) have questioned the hypothesis that individuals may use cannabis to self-medicate psychotic or depressive symptoms.

In summary, cannabis use may be considered only as a risk factor, and possibly one of a great many that may predict the onset or exacerbation of affective disorders and suicidal behavior (26). Thus, whether cannabis use can trigger psychiatric disorders or only precipitate or exacerbate psychiatric conditions in vulnerable individuals, is still poorly understood.

AFFECTIVE SYMPTOMS AND HOPELESSNESS: A POSSIBLE MEDIATING FACTOR?

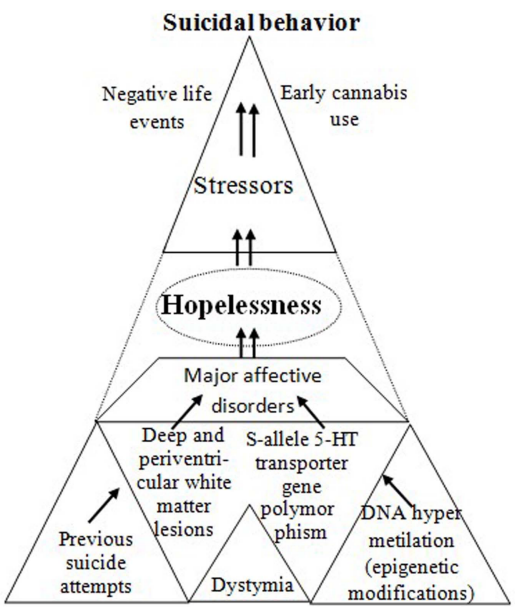
Depression, and in particular hopelessness, are widely recognized as strong predictors of suicidal behavior (15, 27–29). Specifically, hopelessness has been shown to predict completed suicides among psychiatric patients after 10–20 years of follow-up (30, 31), and it is significantly associated with both adolescent self-harm and completed suicides (32).

Studies have also reported that hopelessness may be a risk factor of substance use suggesting that the presence of hopelessness could be considered a predictor of substance misuse (33, 34). With regard to cannabis use, Malmberg et al. (22) found that adolescents

with high levels of hopelessness were more likely to have ever smoked cannabis when compared to adolescents with lower levels. The authors also suggested that increased levels of hopelessness were usually associated with earlier initiation of cannabis use. As such, it is possible that young adolescents experiencing hopelessness are more likely to use cannabis as a strategy to cope with their negative thoughts and feelings (35).

Informed by such research evidence, we suggest that the presence of hopelessness should be considered as a specific risk factor of negative outcome and suicidal behavior among depressed individuals with a history of early cannabis use. Thus in this review, we propose a theoretical model that addresses this issue (see **Figure 1** for more details). This view is consistent with the hypothesis that early cannabis use may represent a relevant risk factor that can trigger or exacerbate suicidal behavior in vulnerable adolescents and young adults, with high hopelessness levels. In addition, vulnerable individuals may show hopelessness (36) and risk factors such as dysthymic temperamental traits (37, 38), dysthymia associated with periventricular white matter abnormalities (39), possibly the S-allele of the serotonin transporter gene polymorphism (5-HTTLPR) (40), sleep disturbances (e.g., insomnia) (41), abnormal pro-inflammatory cytokines levels (42), and/or comorbid symptom development (43). We highly recommend that the complex interaction between these variables is more closely investigated in adolescents at risk, in order to understand the possible emergence of depression and suicide.

However, studies including those informing the development of this model, should be considered in the light of significant shortcomings. Many of the studies were conducted using cross-sectional designs or included retrospective evaluations of lifetime behavior while attempting to predict long-term outcome variables or making reliable causal inferences. In addition, these studies adopted different measurements and outcome variables or they assessed patients at different time points (for more details see a complete list of limitations within **Table 1** in Serafini et al. (15)). Further, not all studies included specific follow-up periods and only some of them were able to distinguish between suicide attempts and completions. Furthermore, the use of heterogeneous samples did not permit some researchers to determine a clear association between the onset of psychiatric conditions, suicidal behavior and the age of first cannabis use. Regarding retrospective studies, the absence of any strategies to ensure both inter-rater reliability and validity of the data also indicates that careful consideration must be given to the study results. Finally, the patients did not receive psychiatric assessments using structured psychometric instruments in all studies.



Modified by Serafini et al. (15)

FIGURE 1 | The complex interaction between risk factors involved in the emergence of suicidal behavior: the mediating effect of hopelessness.

IMPLICATIONS FOR PREVENTION

Psychological distress and social decline need to be carefully investigated in young adolescents in order to provide appropriate ongoing management (44). Youth suicide prevention programs aimed at identifying risk behavior and the subgroups of individuals at high suicidal risk are absolutely necessary in clinical practice. Based on the current literature, such vulnerable subgroups of individuals include those who used cannabis early during adolescence (22), those who currently experience hopelessness (15), and those at high clinical risk of psychiatric conditions (45–47). Furthermore, vulnerable individuals usually present with additional risk factors that may severely influence their childhood development [e.g., a poor performance on tasks assessing sustained attention, impulse control and executive functioning (48)], presumably affecting both their suicide risk as well as early use of cannabis (12, 22, 44, 49–51) (for more details see **Table 1**).

Early warning signs of emerging psychiatric conditions such as behavioral, emotional, and cognitive changes, should be quickly recognized by clinicians by performing a multi-dimensional assessment of the patients (52). In addition, we recommend the careful assessment of hopelessness since it has been demonstrated to significantly increase the accuracy of suicide risk assessment by allowing the collection of reliable information about suicide risk even several years after the initial assessment (53). We also suggest that clinicians assess the current and past use of cannabis in their patients, including a determination of the age of initial use.

According to the affective model of prevention, young adolescents begin to use cannabis because they have poor self-esteem, poor self-control, and poor decision-making skills (35). In this context, youths may also experience negative expectations about their self and their future related to depression or pervasive feelings of loneliness (54). Prevention programs

Table 1 | Risk factors for suicide risk and early cannabis use in adolescents.

Socio-demographic and social factors	Death/loss of a parent or close friend
	Social events including humiliation, loss, defeat, or threat
	Interpersonal problems such as romantic difficulties
	Poor social support
	Financial or employment problems
	Availability of weapons
	Occasional failure at school or in society
Parental and family factors	Family history of suicide or suicide attempts
	Family history of violence and aggression
	Parental substance abuse and/or antisocial behavior
	Parental separation or divorce
	An argument with a parent
	Disorganized family environment
	History of physical/sexual abuse as a child or childhood maltreatment
Individual factors	Psychiatric disorders such as affective disorders and psychosis
	Sleep disturbances such as insomnia
	Antisocial and conduct problems
	Loneliness
	Impulsivity and poor self-control
	Hopelessness
	Neuroticism
	Victimization
	History of suicide attempts
	Impairments in decisional competence and decision-making skills
	Aggressive threats/fantasies
	Dysthymic temperamental traits

Sources: van Ours et al. (12), Malmberg et al. (22), Beautrais et al. (49), Bridge et al. (50), Berger et al. (44), and Reinherz et al. (51).

aimed at helping young adolescents to clarify their subjective states, improve their decision-making abilities and enhance their self-esteem are available, thus potentially preventing the onset of hopelessness and subsequent suicidal ideation (55, 56). Young adolescents are expected to perceive the information provided in these programs as credible, otherwise they will not be likely to modify their behaviors (57). These prevention programs should be conducted during early adolescence and specifically focused on addressing hopelessness, although it is currently unclear whether the benefits may vary for different subgroups of adolescents (e.g., younger or older individuals) (57).

Evidence also suggests that school-based programs are very effective in preventing and/or reducing the use of cannabis among young adolescents, especially if they are able to provide active motivational strategies that inform adolescents about the prejudices against using psychoactive medications (55–57). For example, typical strategies may include actively explaining how to implement non-use behavior, such as coping skills for prodrug pressures and negative affective states, helping youths to understand that most people do not use cannabis, as well as increasing their awareness of the consequences of cannabis use and benefits related to non-use (57). In particular, research has demonstrated the efficacy of social-influence programs that use interactive (not didactic) sessions, and those that encourage active participation in small groups (55, 56).

In summary, clinicians need to be aware of the importance of preventive programs that are directed at preventing/treating modifiable factors such as adolescent hopelessness and/or delaying early cannabis use in specific subgroups of adolescents who experience major affective disorders.

CONCLUSION

Suicide, cannabis use, and psychiatric conditions (e.g., depression) are likely to be underpinned by similar complex factors. Of particular interest for clinicians is the identification of individuals at risk of suicide who show early (i.e., prodromal) affective symptoms such as hopelessness. Suicide prevention programs may provide additional benefits if they focus on delaying or reducing adolescent cannabis use as well as responding to early signs of depression and hopelessness, which are widely recognized as important risk factors for suicide (58).

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Predicting self-initiated marijuana use cessation among youth at continuation high schools

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The current article reports a large scale study of the prediction of marijuana use cessation among individuals attending alternative high schools who were regular users at baseline. Based on the Triadic Influence Theory, predictors of marijuana use cessation at 1-year follow-up were organized by type of influence (e.g., interpersonal, cultural and attitudinal, and intrapersonal) and level of influence (e.g., distal and ultimate). Among the 522 students who were past 30-day marijuana users at baseline, quitting was defined as having not used marijuana in the last 30 days at 1-year follow-up (43% of baseline users). To account for the level of influence we employed a theory-based analytic strategy, hierarchical regression. In the final multivariate model, lower level of baseline marijuana use and less of a likelihood to endorse pro-drug-use myths remained predictors of marijuana use cessation 1-year later. Implications of these findings include the need to develop cessation programs that reduce psychological dependence on marijuana use, and correct cognitive misperceptions about drug use in order to help adolescents make decisions that lead to health-promoting behaviors.

Keywords: marijuana, cessation, adolescents, youth, cannabis, self-initiated, predictors

INTRODUCTION

Marijuana is the most commonly used illicit substance among youth in the United States (1). Since 2009, the 30-day prevalence of marijuana use among youth has steadily risen to 31%, while perceived risk and disapproval of marijuana have declined (1). Recent data show that nearly one in 15 high schools seniors is a daily or near-daily marijuana user (1). Given the recent legislation that legalizes the recreational use and sale of marijuana in Colorado and Washington, one could speculate that these trends in marijuana use among American youth will continue to rise. Unfortunately, most adolescents that desire to quit are unsuccessful (2).

In order to develop effect marijuana use cessation programs, it is essential that we improve our understanding of factors related to self-initiated marijuana use cessation. However, few studies have been conducted examining predictors of marijuana use cessation among teens (3–7) and young adults (8–12).The purpose of the current study was to apply a theoretical framework to the prediction of marijuana use cessation at 1-year follow-up among a sample of adolescents attending alternative high schools who were regular users at baseline.

The Theory of Triadic Influence (13) organizes predictors of adolescent substance use into three distinct types of influence: (1) intrapersonal, (2) cultural/attitudinal, and (3) social/interpersonal. Within each type of influence, predictors are further ordered into level of influence (e.g., the adolescent's ability to control the influence and its effect on the behavior). Levels of influence include, (1) proximal, most control, and most direct influence on behavior, (2) distal, and (3) ultimate, least control, and most indirect influence on behavior. In previous studies, this theory has provided a framework for explaining variance in substance use among samples of adolescents (14–17).

Intrapersonal correlates of drug use are those that describe personality traits, affective states, and beliefs about one's ability to either use or avoid substances (13). Depressed adolescents and adolescents scoring lower on a measure of delinquency have been found to be more likely to quit use of marijuana (11). Cultural and attitudinal correlates of drug use include beliefs and evaluations regarding substance use, as well as general values and behaviors that contribute to substance use (13). Endorsing negative social and psychological consequences of marijuana use (3, 6), having alternative interests (3, 6), holding unfavorable attitudes about the acceptability of drug use (5, 6), and rating one's health as excellent (9) have all been associated with marijuana use cessation among youth and young adults. Social and interpersonal variables are those that operate within the subject's social environment, generally as reported by the subject, and influence one's perceptions of one's social world. Participation in adult social roles (e.g., marriage, being a parent) (7, 9–12), less peer use and approval (5–9), less victimization (5), and using marijuana for social reasons (4, 9, 11) have also been associated with marijuana use cessation among youth and young adults.

The best predictor of future marijuana use is past behavior. A number of studies have found that light marijuana smoking at baseline was associated with cessation at follow-up (4, 7, 9, 11). Since heavier marijuana users suffer from greater withdrawal symptoms (e.g., cravings, irritability, sleep difficulty, decreased appetite) (18), this discomfort could deter them from making quit attempts and experiencing cessation success (2). Other factors

associated with marijuana use cessation among adolescents and young adults include older age at initiation and cessation (3–5), the lack of use of other illicit drugs (8), female gender (7, 9), higher income (9), and steady employment (10).

The purpose of the current study was twofold. First, we sought to examine the relationships between baseline demographic, intrapersonal, cultural/attitudinal, social/interpersonal, and drug-use variables, and marijuana use cessation 1-year later. We did not have any predictors that fell within the proximal level of influence; however, we did explore factors within the distal and ultimate levels of influence. Secondly, because we hypothesized that heavier smokers would experience greater discomfort during the cessation attempt, we wanted to predict cessation controlling for baseline level of use which is likely to be the best predictor of cessation. Therefore, we explored how adjusting for baseline level of marijuana use affected the relationships between intrapersonal, cultural/attitudinal, and social/interpersonal variables and marijuana use cessation. We hypothesized that intrapersonal, cultural/attitudinal, and social/interpersonal variables would be found to be associated with marijuana use cessation, however the strength of the associations would diminish once the statistical models accounted for baseline level of marijuana use.

MATERIALS AND METHODS

SUBJECTS

The sample consisted of 522 past 30-day marijuana users participating in a field trial conducted to test the efficacy of a substance abuse prevention program [see (19, 20)]. A total of 24 continuation high schools in four counties in southern California were recruited as a convenience sample. Continuation high schools, otherwise known as alternative high schools, are schools designated for youth who have transferred out of the regular school system due to functional problems (e.g., behavior problems, drug use, lack of credits). Schools were randomly assigned to one of the following conditions: (1) control condition; (2) TND program condition (TND Only); or (3) TND + motivational interviewing (TND + MI) condition. Prior to enrollment, parental informed consent and subject assent were required for youth under age 18, and informed consent was obtained from participants over the age of 18. Within each school, at least two classrooms were selected to participate in the study. Of the 2,397 students enrolled in the selected classes, 1,694 (70.7%) were consented to participate in the study and 1,676 students completed the baseline survey. Reasons for subject-level decline were parent decline of consent (0.8%), student decline of consent or assent (5.1%), and parental non-response (23.4%). Of the 1676 students who completed the baseline surveys, 1186 (70.8%) completed 1-year follow-up surveys. Of the 778 past 30-day marijuana users at baseline, 522 (67%) completed 1-year follow-up surveys. Students who completed both pre- and 1-year follow-up surveys and reported they had used marijuana in the past 30 days at baseline constitute the present sample for analysis.

Students completed close-ended, self-report questionnaires during regular classroom sessions at baseline and approximately 1-year after the immediate posttest in class. Absent students were left an absentee packet with instructions for completing the survey. Surveys included measures of demographic characteristics, behavioral items, and psychosocial correlates of substance use, and took approximately 20–30 min to complete. All study procedures, including informed consent, were approved by the University of Southern California's institutional review board.

At baseline, subjects ranged in age from 14 to 20 years (mean age of 16.7, SD = 0.91). Sixty percent were male. The ethnic/racial distribution of the sample was as follows: 11.6% White, 62.6% Latino, 5.3% African American, 16.0% Mixed Ethnicity, and 4.5% Other Ethnicity (including Asian, Native American, and "other"). At baseline, 63.6% reported use of cigarettes, 81.7% reported use of alcohol, and 47.9% reported use of hard drugs in the past 30 days. At baseline, subjects reported smoking marijuana on average 14.1 days (SD = 12.2) in the past 30 days. At 1-year follow-up, 43.5% of the sample reported no marijuana use in the past 30 days.

MEASURES

Demographics

Demographic items included age (in years), gender, and ethnicity (a four-level categorical variable with response categories being White/Caucasian, Latino/Hispanic, African American/Black, or Mixed Ethnicity). This categorical variable was coded with three dummy indicators: White, Latino, and African American.

Marijuana use behavior

The main outcome in the study was past 30-day marijuana use cessation between pretest and 1-year follow-up. At both time points, subjects were asked "How many times in the last month have you used marijuana?" Responses were reported on 12-point scales, starting at "0 times," increasing in intervals of 10 (e.g., "1–10 times," "11–20 times") with the last (12th) category being "over 100 times." The "quit" status was defined as reporting "0" times of use in the last 30 days.

Other drug-use measures

Substance use items included 30-day use of cigarettes, alcohol, and "hard drugs." A hard drug use score was created, consisting of the sum of 30-day use across cocaine, hallucinogens, stimulants, inhalants, ecstasy, tranquilizers, and "other" drugs (an item that included "PCP, steroids, GHB, K, etc."; alpha = 0.89). The drug-use questionnaire items are the type used in the Monitoring the Future studies (1, 21) and previous work showing evidence of adequate test-retest reliability and/or internal consistency (22–24). The wording and response options of the other drug-use items were the same as that of the marijuana use item.

Triadic influence theory-related measures

Interpersonal influences. *Family conflict* was assessed through five items, on 4-point scales from "Describes my family 'very well' to 'not at all"' such as "We fight a lot in our family" [$\alpha = 0.64$; e.g., (25, 26)]. Four single item measures of five closest *friends' use of cigarettes, alcohol, marijuana, and hard drugs* each had six response options ranging from 0 to 5 friends [e.g., (15)]. *Family member drug abuser* was measured through one dichotomous item, "Do any members of your family abuse drugs or alcohol?" (0 = "no" or 1 = "yes"). Additionally, two items included *whom the student lives with* (both parents, only mother, only father, sometimes mother and sometimes father, other, or alone; coded as

living with both parents or not), and *having one or more children* (0 = "no" or 1 = "yes").

Cultural and attitudinal influences. *Socioeconomic status* was assessed by rooms-per-person in the home, calculated as the quotient of total number of rooms (except kitchen, bathrooms, closets, or laundry rooms) divided by the number of people living in the home. *Acculturation* was assessed through four items measuring language preference on 5-point scales from "only English" to "only another language (not English)" [$\alpha = 0.86$; (27, 28)]. *Morality of drug use* was assessed through four items on 4-point scales such as "How wrong is it to use drugs?" from "it is not wrong at all" to "it is very wrong" [$\alpha = 0.90$; e.g., (26)]. *Pro-drug-use myths* (29), were measured through four items each with a two-option forced-choice response. A sample item is "What happens when a person gets used to a drug?" [(a) one has learned how to enjoy using the drug, to control its effect, OR (b) body warning signals are giving up and addiction is beginning] (alpha = 0.55). The importance of *health as a value* was assessed through three items on 4-point scales from "not at all" to "very much" such as "How important is it for people to be physically healthy?" [$\alpha = 0.79$; e.g., (30)].

Finally, two constructs of *emerging adulthood* from the Inventory of the Dimensions of Emerging Adulthood (IDEA) scale were assessed: experimentation/possibilities and feeling in-between (31). Respondents were asked to "Please think about this time in your life. When we say 'this time,' we mean what is going on right now, plus what has gone on in the last few years, plus what you think your life will be like in the next few years. Think about a 5-year period of time, with right now in the middle. For each question below, mark the box that best describes this time in your life. Be sure to put only one check mark per line." Responses were 4-point scales from "definitely not" to "definitely yes." A set of five items measured *experimentation/possibilities*, such as "Time of exploration?" ($\alpha = 0.79$). Three items assessed *feeling in-between*, such as "Time of feeling adult in some ways but not in others?" ($\alpha = 0.68$).

Intrapersonal influences. *Social self-control* was measured using eight items (32), which were on 4-point scales from "never" to "always" such as "I enjoy arguing with people," "If I think something one says is stupid I tell them so," and "My mouth gets me in trouble a lot" (alpha = 0.73). *Depressive symptoms* were measured using five items from the short CES-D scale, measured on 4-point scales from "less than 1 day" to "5–7 days" in last week, such as "How often did you feel depressed in the last 7 days?" [$\alpha = 0.73$; see (33)]. Four items measured *assertiveness* (26, 34) on 4-point scales from "never" to "always," such as "It is hard for me to express an opinion that differs from what the person I am talking to is saying" (alpha = 0.60). *Coping* was measured through four constructs, each with three item, 5-point scales from "never" to "always" [e.g., (35)]. *Anger coping* included items such as "I yell and scream at someone" ($\alpha = 0.77$). *Social support coping* included items such as "I get emotional support from my mother/father ($\alpha = 0.87$). *Cognitive coping* included items such as "I think about the choices before I do anything" ($\alpha = 0.85$). *Avoidance coping* included items such as "I daydream about better times" ($\alpha = 0.79$). *Decision-making* was measured with two constructs each with three items on 4-point scales from "always" to "never" (36). *Decision-making confidence* included items such as "I like to make decisions myself" ($\alpha = 0.70$). *Decision-making avoidance* included items such as "I prefer to leave decisions to others" ($\alpha = 0.75$).

DATA ANALYSIS

Assessment of attrition bias

To determine the potential attrition bias, a comparison was made between the current analytic sample ($N = 522$) to the baseline past 30-day marijuana users lost to follow-up ($N = 256$) on baseline measures of demographics and use of substances other than marijuana. The comparisons utilized chi-square or t-test models to indicate statistically significant differences (p value at the 0.05 level, two-tailed). Relative to the study dropouts, the retained sample was more likely to be slightly younger (16.6 versus 16.8) and smoke cigarettes on fewer days in the past 30 days (7.2 versus 9.4). There were no significant differences on any of the other characteristics.

Prediction of marijuana use cessation

We employed hierarchical logistic regression analyses (37) to examine the associations between the predictors as assessed at baseline and marijuana use cessation at 1-year follow-up. The dichotomous quit status outcome was defined as "yes" if the subject reported not using marijuana in the past 30 days. The dichotomous outcome analysis was completed using generalized mixed-logistic modeling (38). School was treated as a random effect, which statistically accounts for the intra-class correlation within clustered units (school) on computed significance levels.

In the first step of our analyses, we established eight sets of predictors based on type and level of influence, including (1) five demographic variables, (2) four baseline drug-use variables, (3) two ultimate interpersonal variables, (4) three distal interpersonal variables, (5) two ultimate cultural/attitudinal variables, (6) five distal cultural/attitudinal variables, (7) one ultimate intrapersonal variable, and (8) eight distal intrapersonal variables. In the second step, we ran two generalized mixed-logistic regression models that included the first two predictor sets demographic characteristics and baseline drug use, to predict marijuana use cessation at 1-year follow-up. Because we assumed that distal factors were more strongly related to marijuana cessation than ultimate factors, in the third step, we employed hierarchical mixed-logistic regression analyses for the interpersonal, cultural/attitudinal, and intrapersonal predictor set models. Utilizing hierarchical regression allowed us to avoid improperly adjusting for distal factors in the relationship between ultimate factors and marijuana cessation, and consequently diminishing the effects of ultimate factors. Therefore, for each type of influence, first we ran models for predictors at the ultimate level of influence. Then, we ran models for predictors at the distal level of influence, controlling for ultimate predictors.

Lastly, we ran two final generalized mixed-logistic regression model in which we entered all of the predictors across the predictor sets that were significant at the level of $p < 0.05$. However, because past marijuana use is the best predictor of future use, we wanted to predict cessation controlling for baseline level of use. Therefore, in

the first final model, level of baseline marijuana use was excluded, and in the second final model, level of baseline marijuana use was included. All regression models controlled for experimental condition (nuisance variable in the present study). Variables were standardized (mean = 0 and standard deviation = 1). Odds ratios and 95% confidence intervals were reported using two-tailed significance tests. To compare the goodness-of-fit of the final logistic regression models we calculated the Hosmer–Lemeshow Goodness-of-Fit test, the relative operating characteristic (ROC) curve analysis, and compared the log likelihoods for the full versus the null models. Analyses were conducted using the SAS (v.9.1.3) statistical package (39).

Table 1 | Baseline demographics and drug use predicting marijuana cessation at the 1-year follow-up.

Predictors	OR (95% CI)
DEMOGRAPHICS MODEL	
Age	0.98 (0.81, 1.19)
Male	0.74 (0.62, 0.89)*
White ethnicity	1.05 (0.83, 1.32)
Latino ethnicity	1.40 (1.10, 1.78)*
African American ethnicity	1.10 (0.88, 1.37)
BASELINE DRUG USE MODEL	
30-day cigarette use	0.83 (0.65, 1.06)
30-day alcohol use	1.09 (0.86, 1.37)
30-day marijuana use	0.50 (0.40, 0.63)*
30-day hard drug use	1.09 (0.86, 1.38)

All values are standardized odds ratios and 95% confidence intervals.
**p < 0.05.*

RESULTS

Results of the regression models with baseline demographics and drug-use predicting marijuana use cessation are shown in **Table 1**. Males were less likely than females to quit marijuana use at 1-year follow-up ($p < 0.05$). Also, being of Latino ethnicity and having a lower level of baseline marijuana use predicted marijuana use cessation at 1-year follow-up ($p < 0.05$).

Table 2 shows the results from the hierarchical regression models that examined sets of predictors of marijuana use cessation that were established based on the Triadic Influence Theory (TTI). Among the ultimate interpersonal variables, having at least one child was predictive of marijuana use cessation ($p < 0.05$). Among the distal interpersonal variables, friends' substance use was inversely related to marijuana use cessation ($p < 0.05$). Among the ultimate cultural/attitudinal variables, being less acculturated was predictive of marijuana use cessation ($p < 0.05$). Among the distal cultural/attitudinal variables, having a lower likelihood to endorse pro-drug-use myths and having weaker beliefs that this was a period of life for experimentation were predictors of marijuana use cessation 1-year later (p's < 0.05). The ultimate intrapersonal variable, social self-control, was not predictive of marijuana use cessation. Among the distal intrapersonal variables, having both avoidant and confident decision-making styles were predictive of marijuana use cessation (p's < 0.05).

The final multivariate regression model that did not include level of baseline marijuana use revealed that having fewer friends who use substances, endorsing fewer pro-drug-use myths, and having weaker beliefs that this was a period of life for experimentation were significant predictors of marijuana use cessation at 1-year follow-up (p's < 0.05) (see **Table 3**). In the final multivariate regression model that included level of baseline marijuana use, having lower levels of baseline marijuana use and a lower

Table 2 | Summary of hierarchical regression analysis for social/interpersonal variables predicting marijuana cessation at the 1-year follow-up.

Level of Influence	Types of influence					
	Interpersonal	**OR (95% CI)**	**Cultural/attitudinal**	**OR (95% CI)**	**Intrapersonal**	**OR (95% CI)**
Ultimate	Living with both parents	1.11 (0.93, 1.33)	Socioeconomic status	0.83 (0.68, 1.01)	Social self-control	1.06 (0.87, 1.29)
	Have ≥ 1 children	1.25 (1.01, 1.54)*	Acculturation	1.41 (1.16, 1.71)*		
Distal	Living with both parents	1.08 (0.88, 1.32)	Socioeconomic status	0.90 (0.74, 1.09)	Social self-control	1.03 (0.81, 1.31)
	Have ≥ 1 children	1.17 (0.94, 1.46)	Acculturation	1.40 (1.13, 1.73)*	Depressive symptoms	0.99 (0.79, 1.23)
	Friends' substance use	0.72 (0.58, 0.90)*	Morality of drug use[1]	1.21 (0.97, 1.52)	Assertiveness	0.92 (0.73, 1.15)
	Family conflict	0.83 (0.67, 1.04)	Pro-drug-use myths[2]	0.72 (0.58, 0.89)*	Anger coping	0.98 (0.76, 1.27)
	Family member drug abuser	0.94 (0.76, 1.16)	Health as a value[3]	1.05 (0.83, 1.33)	Cognitive coping	1.03 (0.82, 1.29)
			Emerging adulthood		Avoidance coping	1.14 (0.91, 1.43)
			Experimentation/ possibilities	0.69 (0.53, 0.89)*	Social support coping	1.02 (0.83, 1.25)
					Decision-making avoidance	1.27 (1.01, 1.59)*
			Feeling in-between	1.00 (0.79, 1.27)	Decision-making-confidence	1.36 (1.08, 1.70)*

*All values are standardized odds ratios and 95% confidence intervals. *p < 0.05.*
[1] *Scale is drug use is not wrong (low) to drug use is wrong (high).*
[2] *Higher value denotes pro-drug-use endorsement.*
[3] *Scale is disagree (low) to agree (high) regarding health as a value.*

Table 3 | Final multivariate models: interpersonal, cultural/attitudinal, and intrapersonal variables predicting marijuana cessation (significant at <0.10).

Predictors	Excluding baseline marijuana use	Including baseline marijuana use
30-day marijuana use	–	0.68 (0.52, 0.85)*
Male	0.83 (0.68, 1.02)	0.89 (0.73, 1.13)
Latino	1.12 (0.88, 1.42)	1.16 (0.90, 1.49)
Have one or more children	1.17 (0.94, 1.46)	1.26 (0.98, 1.61)
Friends' substance use	0.79 (0.64, 0.98)*	0.87 (0.69, 1.10)
Acculturation	1.22 (0.96, 1.55)	1.08 (0.84, 1.39)
Pro-drug-use myths[2]	0.73 (0.59, 0.90)*	0.77 (0.62, 0.95)*
Emerging adulthood		
Experimentation/possibilities	0.77 (0.61, 0.98)*	0.82 (0.64, 1.05)
Decision-making avoidance	1.19 (0.95, 1.49)	1.18 (0.93, 1.49)
Decision-making self-confidence	1.19 (0.95, 1.50)	1.15 (0.90, 1.46)

All values are standardized odds ratios and 95% confidence intervals.

**p < 0.05*

[2]Higher value denotes pro-drug-use endorsement.

likelihood to endorse pro-drug-use myths remained predictors of marijuana use cessation 1-year later (p's < 0.05).

To test the overall fit of the logistic regression models, we examined the likelihood ratio test which compares the log likelihoods for the full model versus the null model. For the model that did not include baseline marijuana use, the likelihood ratio test χ^2 was 49.5, $df = 9$, $p < 0.0001$. For the model that included baseline marijuana use, the likelihood ratio test χ^2 was 63.4, $df = 10$, $p < 0.0001$. Thus, the models showed a good fit to the data. We also calculated the Hosmer–Lemeshow Goodness-of-Fit test to assess whether the observed event rates matched the expected event rates in the model population (40). For the model that excluded baseline marijuana use, the Hosmer–Lemeshow Goodness-of-Fit test χ^2 was 2.63, $df = 8$, $p = 0.96$. For the model that included baseline marijuana use, the Hosmer–Lemeshow Goodness-of-Fit test χ^2 was 7.83, $df = 8$, $p = 0.45$. Both models showed a good fit to the data. In order to further evaluate the models we performed the ROC curve analysis. The ROC curve analysis assesses the power of a model's predicted outcomes to discriminate between positive and negative cases (e.g., cessation versus use) in terms of the area under the ROC curve (i.e., plot of sensitivity versus 1-specificity), which is commonly referred to as the concordance index (c-statistic). We found that both of our models showed better-than-chance discriminating power in that the c-statistics for the models that excluded and included baseline marijuana use were 0.69 and 0.71, respectively (41).

DISCUSSION

In the present study we sought to fill a gap in the substance abuse literature by applying a theoretical framework, TTI (13), to assess the influence of demographic, drug use, intrapersonal, cultural/attitudinal, and social/interpersonal predictors of marijuana use cessation among a sample of adolescents. Using a theory-driven analytic approach, hierarchical regression analysis (37), we built upon previous research by assessing each of these types of influence at the appropriate level of influence (e.g., ultimate and distal).

Among the past 30-day marijuana users at baseline, 43% reported quitting marijuana use at 1-year follow-up. In the final multivariate model, several psychosocial predictors were negative predictors of marijuana use cessation at 1-year follow-up, including friends' substance use, pro-drug-use myths, and beliefs that this was a period of life for experimentation. These findings are consistent with previous research (3, 5–9). Interestingly, after controlling for baseline marijuana use in the multivariate model, only baseline marijuana use and fewer pro-drug-use-myths were associated with marijuana use cessation. Given the strength of the association between baseline marijuana use and cessation, it is not surprising that after accounting for baseline use, many of the effects we saw in the first multivariate model disappeared. Based on previous research (2, 18), we hypothesized that heavier smokers would experience greater discomfort during the cessation attempt, and it is possible that these negative withdrawal symptoms (e.g., cravings, irritability, sleep difficulty) could have led many of the heavier baseline smokers to relapse. However, we did not assess relapse in the current study.

Another explanation for the elimination of effects after controlling for baseline marijuana use might be that these constructs could be statistically redundant when modeled simultaneously. Friends' substance use and believing that this was a period of life for experimentation were significantly correlated with baseline marijuana use (p's < 0.05). Therefore, one could speculate that the association between friends' substance use and marijuana use cessation is mediated by baseline marijuana use. Adolescents who have friends that use marijuana may be more likely to use marijuana frequently and consequently, less likely to quit. However, mediation analyses were beyond the scope of this article. Future studies should examine whether these assumptions are true by employing mediation analysis.

Consistent with previous research (5, 7), we found a negative association between pro-drug-use myths and marijuana cessation in both final multivariate models. Drug-use myths encompass inaccurate expectancies or beliefs about drug characteristics and confusing drug effects with drug experiences (42). Cognitive restructuring of faulty or self-defeating cognitive structures has been shown to prevent drug use among high-risk youth (43, 44). Previous studies have found that Motivational Enhancement Therapy, Educational Feedback Control, and Cognitive Behavioral Treatment were effective in reducing marijuana use among adolescents (45, 46). Our findings suggest that these interventions could be strengthened by adding cognitive restructuring components.

The current study contributed to the substance abuse literature in several ways. The results of our paper are consistent with the few that have been done with teens on self-initiated marijuana cessation among a large sample of at-risk teens ($n = 522$ baseline self-reported marijuana users), adding to the literature on this topic. As there are not many such papers, and only one other with alternative (continuation) high school youth, this paper represents a welcome addition. Additionally, our paper uses hierarchical regression to assess components of TTI. This may be the first truly appropriate way to examine TTI, though only some support

for the theory was provided. Further, the finding that likelihood to endorse pro-drug-use myths is a significant predictor of self-initiated cessation is a fairly novel finding and has implications for prevention efforts.

A limitation of the current study is we did not have any predictors that fell within the proximal level of influence. In addition, marijuana use cessation was not defined by self-reported quit status, but by inferred non-use status. This has been used as a proxy for self-reported quitting in previous studies (6, 8–11). While this methodology does not account for adolescents who may have made unsuccessful quit attempts, nor does it assume that quitting was an intentional act, because we observed significant associations between predictors of marijuana use cessation and quit status, we are confident that self-initiated quitting among adolescents was modeled. Another limitation to the current study is that we relied upon self-reported marijuana use without the use of biochemical validation (e.g., urine drug screens) of marijuana use at baseline or follow-up. Given the large sample size of the original study, it would have been impractical to obtain biological samples from all participants. However, we obtained Certificates of Confidentiality from the National Institutes of Health to protect our research information from forced disclosure, which was conveyed to study participants. Furthermore, the current study focuses on self-initiated marijuana cessation; therefore there would be little incentive for participants to lie. Our previous work in which we examined both anonymous and confidential data suggest that confidential self-reports are accurate among high school youth [e.g., (47)]. Others have found similar results (48, 49). It is true that in cigarette smoking cessation work with alternative high school youth, use of biochemical validation will lead to 2% lower reported quit rates (50); however, that is a small impact. In addition, use of biochemical validation with teens in research studies, in which biochemical validation is obtained voluntarily only, is bound to be biased because only cooperative youth will provide readings. Further, only written parental consent is permitted nowadays when biochemical validation of any drug use is being measured (other than possibly in anonymous, cross-sectional work). This would lead to inclusion of non-representative, small samples of teens in longitudinal survey work. Thus, most large survey research, including the Youth Risk Behavior Survey [e.g., (51)], do not include biochemical validation. Lastly, about a third of the baseline marijuana users were lost to follow-up. However, because those lost to follow-up were only significantly different from the retained sample on two factors (age and daily cigarette use), this limitation should not bias our results.

Efforts to develop adolescent marijuana use cessation programing should build on the results in the current study. Our findings support a motivation-skills-decision-making approach to adolescent marijuana use cessation (42). It is clear that adolescents with lower levels of baseline marijuana use have an easier time quitting. Additionally, cessation programing should include lessons that address correcting cognitive misperceptions about drug use.

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Latent classes of substance use in adolescent cannabis users: predictors and subsequent substance-related harm

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Cannabis use is highly prevalent in late adolescence, but not all users experience significant negative consequences. Little information is available to identify the substance use patterns and risk factors of users who are at greater risk of experiencing negative consequences. In this prospective study, we aimed to empirically identify latent classes of substance use in adolescent cannabis users and to examine how these classes relate to antecedent psychosocial predictors and subsequent substance-related outcomes. The sample was recruited from 68 high schools in Quebec and consisted of 1618 participants who reported using cannabis in grade 10. We used latent class analysis to empirically identify classes of users based on the age of onset, frequency, and typical quantity of cannabis and other substance use, as well as substance mixing behaviors. We then compared classes in terms of (a) sociodemographic and psychosocial predictors in grades 7–8 and (b) substance-related consequences in grade 11. Four distinct classes were identified: Late-Light Users (28%); Late-Heavy + Polydrug Users (14%); Early-Moderate Users (33%); Early-Heavy + Polydrug Users (26%). Late-Light Users reported the lowest levels of substance use, while Early-Heavy + Polydrug Users reported the highest levels. Intermediate levels of substance use were found in the other two classes. Sex, age, delinquency, peer delinquency, school bonding, parental monitoring, and parental conflict all helped to differentiate classes. Class membership predicted substance-related harm, with greater consequences in early- and late-onset heavy using classes. In light of results, in addition to age and sex, screening and intervention for risky cannabis use among adolescents should focus on school bonding in order to target the most risky late-onset adolescents and on peer delinquency in order to target the most risky early-onset ones.

Keywords: cannabis use, substance use, classes, adolescents, substance-related problems

INTRODUCTION

Cannabis is the illicit drug most widely used in adolescence. By late adolescence, cannabis use is a relatively normative behavior. The latest available figures of annual cannabis use by late adolescents in North-America vary from close to 40% in the USA (1) to close to 50% in Quebec, Canada (2). More than 80% of 12 graders find it easy or very easy to have access to cannabis (1). Fortunately, not all cannabis users experience significant negative consequences (3, 4), but some do. A key task of prevention science is to better understand the classes of use, the characteristics of users, and other factors that are related to problematic use. The idea that some use classes are more at risk than others is often put forward (5, 6), but rarely put to the test. A few studies have described typologies of cannabis users, but most have studied clinical samples or have focused mostly on specific problems or solely on cannabis use indicators (6–8). Little information is currently available in the literature to allow identifying and distinguishing between subgroups of cannabis users at higher and lower risk of impairments, which would be critical to improving screening and prevention.

Examining natural heterogeneity in classes of cannabis use may be one helpful strategy to understand why some users experience more problematic consequences than others. Many studies have documented the acute and/or chronic health risks or harms associated with cannabis use. These include cannabis dependence, fatal and non-fatal motor-vehicle accidents under the influence of cannabis, cognitive impairments, respiratory impairments, and the amplification or onset of psychosis, especially in predisposed individuals (9–16). Specifically, studies suggest that several key cannabis use characteristics are most predictive of such harm outcomes. These include frequent (e.g., weekly or more often) or chronic cannabis use, and early-onset of cannabis use (11, 17–20). Because many adolescent cannabis users are polydrug users (2, 21), classes of use also have to take multiple substances into account, including alcohol. Indeed, most cannabis users take it simultaneously with alcohol (22–24), which could be a particular risk for youngsters (25). To our knowledge, no study compared the consequences of empirically derived cannabis use classes in a normative population of adolescents.

Studying psychosocial predictors of heterogeneity in cannabis use classes is also important. This allows identifying factors, which anticipate high-risk substance use patterns vs. low-risk substance use patterns. Many categories of predictors can be useful to predict

heterogeneity in patterns. For instance, a recent study by Chabrol et al. (7) applied a cluster analysis to a sample of adolescents cannabis users on the basis of personality traits and found three groups: "ordinary," below the mean on several measures of personality, "borderline," with high levels of borderline traits, depressed moods, and social anxiety, and a least prevalent cluster called "impulsive," which was well above the mean on impulsivity and callous traits but low on other measures. As expected, the frequency of use was higher in the latter two clusters.

In addition to those considered by Chabrol et al. (7), other factors from other domains of influence might be useful and important in predicting heterogeneity. Babor et al. (26) suggested that classification schemes must be multidimensional in order to be useful in predicting outcomes. Accordingly, in order to achieve such classification, one must rely on diverse individual and relational risk factors for substance abuse, use-related problems, as well as substance use patterns. Severity of substance use (27), the level of comorbid psychopathology (28, 29), or delinquency (30) have been common dimensions of classification for adolescent substance abusers, but very few studies have relied on multiple dimensions of risk, use, and related problems. A strong predictor of adolescent substance abuse, family conflict (31), that has been useful in distinguishing "Aggressive/Versatile" delinquents, the most severe and chronic subtype (32), and deviant peer affiliation, which is also a robust predictor of adolescent substance abuse (33) was rarely considered in classification efforts. In sum, relevant factors may include familial conflict and monitoring, peer substance use, school bonding and achievement as well as sex, in addition to the one considered by Chabrol et al. (7), which all proved to be useful in predicting use indicators (31, 34, 35).

Until now, past studies have proposed several typologies based on theoretical grounds and those who used an empirical approach have only shed light on some aspects of reality. Many of these studies focused on alcohol use only (36–38), but some have proposed specific typologies of cannabis users. For instance, among adults, Thomas et al. (39) used epidemiological data to derive a cannabis use typology based on use frequency as well as related harm. Their typology included abstinent and past users. Among users, they proposed three groups: low-risk (26%), moderate-risk (72%), and high-risk/dependent (2%). In terms of empirical studies, Fischer et al. (5) derived a typology of cannabis users, but this study was realized among adults, with a cross-sectional design and focused only on cannabis use indicators (e.g., onset, actual use, daily use, quantity, with whom, medical reasons) to derive their four-group typology: occasional/light use (31.8%), moderate-monthly use (20.2%), moderate-weekly use (25.2%), and near-daily or daily use (22.9%). Reboussin et al. (8) aimed to describe patterns of marijuana involvement during the middle-school years in a sample of African-American adolescents. They also included non-users and used latent class analysis (LCA) on the same cannabis use indicators measured over 3 years. Three classes were identified: little or no involvement (85, 71, 55% in sixth, seventh, and eighth grade, respectively), marijuana exposure opportunity (12, 19, and 26%), and marijuana use and problems (2, 9, and 19%). Another study looked at the typology of cannabis-related harm instead of use indicators in a community sample of 14–24 years old throughout 10 years (6). Four substance categories were considered: alcohol, nicotine, cannabis, and illegal drugs other than cannabis. Four groups were identified: Non-problematic (59.2%); primary alcohol use disorders (14.4%); delinquent cannabis/alcohol DSM-IV-abuse (17.9%); and CUD with multiple problems (8.5%). Another cross-sectional study used cluster analysis on a clinical sample of mostly juvenile justice involved adolescents who sought drug abuse treatment (40). They identified three groups based on individual and family risk factors, associated problems, and severity of substance use: Juvenile Justice Involved Substance Abusers (41%, lowest level of risk but highest juvenile justice involvement); Comorbid Substance Abusers (33%, greatest family risk and individual psychopathology); and Heavy Substance Abusers (26%, serious substance abuse and peer substance use). Variables included were substance use, psychiatric disorders, and legal involvement; peer substance use; family substance abuse; parental psychopathology; and family conflict. This multidimensional typology support the idea that risk factors, associated problems, and substance use severity are all critical in explaining heterogeneity.

Several limitations characterize previous studies. First, the variety of designs used in these studies complicates comparisons between them. Second, few studies have examined subgroups of cannabis users (or heterogeneity in cannabis use) and many of the classification efforts were limited to clinical samples (40). Finally, cannabis use severity and important risk factors, such as peer deviancy, parental monitoring, and school bonding, have typically been omitted in previous typologies.

In this study, we aim to empirically identify subgroups of adolescent cannabis users and examine how these subgroups differ in terms of early risk factors and subsequent consequences. We extend prior work by focusing on a general population of adolescent and by using a comprehensive prospective design. We use latent class analysis (41), which allows assigning individuals to relatively homogeneous classes on a probabilistic basis. An increasing number of recent studies have applied LCA to identify subgroups of substance users (5, 6, 42–46). A main methodological benefit of the LCA approach is that it groups users according to a multiplicity of observed characteristics (e.g., substance use behaviors), as opposed to examining such characteristics separately. This approach is thus a powerful tool to identify and compare multidimensional classes of cannabis users and their associated characteristics.

MATERIALS AND METHODS

PARTICIPANTS

The sample was recruited from 68 high schools in Quebec within the context of the evaluation of the new approaches new solutions (NANS) dropout prevention program (2002–2008) (47). Participants attended secondary schools in disadvantaged communities of the province of Quebec (Canada). NANS schools were selected using stratified random sampling to be representative of all schools in disadvantaged areas of Quebec in terms of geographical location, size, and language (47). Data were obtained via self-reported questionnaires administered in class by teachers supervised by trained and supervised experimenters. Seventy-seven percent of eligible participants provided free and informed consent to participate in the study. All procedures were approved from the Arts and Science Faculty Ethical Review Board at University of Montreal.

Participants for this study were a cohort assessed annually from grade 7 to grade 11 (2003–2008). The sample for the present study included all participants who provided information on cannabis use in grade 11 ($N = 1618$). Participants were mostly Quebec-born Caucasians (93%). Other participants were from a diversity of ethnicities. The sample included slightly more females (53%) than males (47%).

Self-reported substance-use behaviors were collected in grade 10. Predictors were considered in grade 7 and 8 and outcomes in grade 11. Available data for outcomes in grade 11 were 61%). Rates of available data for predictors in grades 7–8 ranged from 80 to 99%.

MEASURES

Substance use behaviors (grade 10)

Substance use measures were mostly taken from the ESPAD questionnaire (48, 49), a European national substance-use survey of a representative sample of high school students. Its reliability and validity have been verified in the content of many methodological studies [see Ref. (49)]. These measures included past-year alcohol and cannabis use frequency. Original items had seven categories: 1: "0"; 2: "1–2"; 3: "3–5"; 4: "6–9"; 5: "10–19"; 6: "20–39"; and 7: "40 or more." Some categories of the original items were collapsed together, based on their distributions and on the literature (1, 2), in order to limit the number of categories and get clinically significant grouping while avoiding the estimation of a large amount of parameters in the analyses. This resulted in three categories of alcohol and cannabis use frequency: 0: "0–5"; 1: "6–30"; and 2: "31 or more." We also used the quantity of alcohol consumed in a typical occasion. Again, some categories were collapsed together for the same reasons. This led to a variable in three categories: 0: "0–3"; 1: "4–6"; and 2: "6 or more." We also added a home measure of the quantity of cannabis taken in a typical occasion and collapsed the categories in two: 0: "1 joint or less"; and 1: "more than a joint." Binge drinking was also measured using the ESPAD item with collapsed categories: 0: "never"; 1: "1 or 2 times"; and 2: "3 or more times." Other items were taken from a validated measure of adolescent social and personal adjustment (50): stimulant-hallucinogens use ("never"; "1 or 2 times"; "3 or more times") as well as two items of alcohol and cannabis use in order to derive alcohol and cannabis use early-onset (grade 8 or earlier). The cannabis and alcohol onset measures are exceptions in the sense that contrarily to other substance use measures, they were derived from grade 7 and 8 items of alcohol and cannabis use frequency. Frequency of tobacco use was measured with a home measure in which categories have been collapsed in the following groups: 0: "never"; 1: less than one per day or "occasional"; and 2: one per day or more or "regular." Finally, the simultaneous use of alcohol and cannabis was also assessed by a house measure and was coded 0: "never"; 1: "1 or 2 times"; and 2: "3 or more times." We included this measure as this particular behavior has been associated with negative consequences in previous work (22). All items were referring to the past 12 months except for binge drinking and tobacco use (past 30 days).

Substance-related problems (grade 11)

The outcome measure is largely based on the DEP-ADO scale, widely used to screen substance related problems in Quebec (51, 52). This instrument includes 11 items to which we added 3 to include other important substance-related consequences (fights, unprotected or unwanted sex, intoxication in school) for a total of 14 items ($\alpha = 0.88$). Each item measures the occurrence of different attributed substance-related consequences covering various types of negative consequences, such as legal, school, relational, health, and dependence consequences. Items have been coded 0 (never) and 1 (yes) in accordance with participants' attributions. A confirmatory factorial analysis (53) indicated that all items could be grouped in a single scale (not shown; results can be obtained upon request).

Sociodemographic and psychosocial predictors (grade 7–8)

Sociodemographic and psychosocial factors used to predict latent classes were selected on the basis of existing theoretical and empirical literature (31, 34, 35, 54, 55). Parental monitoring and conflict with parents, delinquent behaviors, peer deviancy, and school bonding and achievement were measured with scales taken from the same questionnaire used for substance use measures, the MASPAQ (50). Parental monitoring was measured with two items asking about parental knowledge of whom their adolescent is with when not at home and where he or she is ("never," "occasionally," "often," "all the time"). Conflict with parents is measured with three items asking about disputes and disagreements with parents with the same item scale. Delinquent behaviors are measured from the presence or absence of a variety of delinquent behaviors (e.g., property crime, fights). Peer delinquency is measured from three items asking about friends' drug use, and if friends had or could have had trouble with the police. These items respectively have the following scales: "never," "now and then," "sometimes," "often," "always"; "none," "one or two," "several," "many"; "strongly disagree," "disagree," "don't know," "agree," "strongly agree." School bonding was measured with four items (e.g., I like school; I like what we do in school). The scale is a valence scale with seven categories. Finally, school achievement was measured with two items asking for grades in maths and in French. Depressive symptoms were assessed using the Center for Epidemiologic Studies-Depression (CES-D) scale (56). The CES-D includes 20 items that explore how participants felt or behaved in the past week. The CES-D has been validated for use in French and adolescents (57, 58). Internal consistency was adequate with Cronbach's alpha ranging from 0.87 to 0.91 across time points. Sociodemographic factors included sex, age, and family adversity as measured by a cumulative index of nine family risk factors (e.g., low parental occupational prestige, low family wealth, parental separation). All previous factors except age and sex were derived from a mean of scores measured in grade 7 and 8.

STATISTICAL ANALYSES

Latent class analysis was used to identify subgroups of cannabis users. This statistical method aims to identifying the most parsimonious classification of individuals into latent classes by maximizing homogeneity within, and heterogeneity between classes. In order to determine the optimal number of classes, different number of latent classes was modeled starting from 1 (e.g., only one class of cannabis users), then 2, and so on until we reach an optimal

solution. Different criteria were used to select the most appropriate model (59). These criteria included the following information criteria: deviance, the Akaike information criterion (AIC) (60), the Bayesian information criterion (BIC), and the sample-size adjusted Bayesian information criterion (SSBIC) (61), to compare the relative fit of solutions. Better fitting solutions are reflected in lower values on the indices. We also considered likelihood ratio tests, including the Vuong–Lo–Mendell–Rubin and Lo–Mendell–Rubin adjusted likelihood ratio tests – ALRTs (62). ALRT tests are adequate for non-nested mixture models and test the significance of the difference in fit between two models with a one class difference. We also considered the recommended Bootstrapped Likelihood Ratio Test [BLRT; (63)]. The criterion for significance was $\alpha < 0.05$. We also relied on entropy, which is indicative of the degree of homogeneity within and independence between classes (60). Elevated scores of entropy indicate high independence and little spillover between classes. Furthermore, we examined the substantive interest of each model by evaluating how solutions compare with theoretical and empirical knowledge. Finally, although we selected a solution based primarily on unconditional models, we also investigated all solutions with predictors to determine whether all classes could be meaningfully differentiated (59). All models were estimated using maximum likelihood, and multiple initial values (5000 starts; 100 optimizations) were used to avoid local maxima. We imputed five datasets with an EM technique in SPSS (version 20.0) and replaced missing values by the mean of all imputed values. Mplus (version 7.0) software (64) was used for the LCA (65, 66).

After selecting a solution with an optimal number of classes, the obtained classes were compared on sociodemographic and psychosocial predictors in grade 7–8 as well as on substance-related problems the following year (grade 11). We evaluated the association between classes and each predictor with all predictors simultaneously in the model. Predictors were linked to class group membership using multinomial regression. For the outcome (attributed substance-related problems), we compared the means of the class model using equality of means test across classes based on posterior probability-based multiple imputation [AUXILIARY option in Mplus; (64)].

RESULTS

DESCRIPTIVE STATISTICS

Means and standard deviation for continuous variables as well as percentages for categorical variables are presented in **Table 1**. Missing data ranged from 1 (age) to 776 (48%) (outcome) with a mean of 205 (12.7%).

Table 1 | Descriptive statistics for substance-use variables, predictors, and outcome.

	N	Mean (or %)	SD
PRÉDICTEURS (GRADE 7–8)			
Sex (1 = female)	1578	0.53	0.49
Age	1617	0.65	0.48
Family adversity	1300	1.63	1.55
Delinquent behaviors	1377	2.60	3.45
Depressive symptoms	1345	8.68	7.48
Peer delinquency	1428	1.12	1.01
Academic achievement	1448	77.30	39.62
School Bonding	1442	3.88	1.12
Parental monitoring	1390	1.90	0.70
Conflict with parents	1398	1.27	0.62
SUBSTANCE-USE (GRADE 10)			
Alcohol early-onset (grade 8 or earlier)	1169	0.76	0.43
Cannabis early-onset (grade 8 or earlier)	1103	0.61	0.49
Tobacco use (non-smoker)	1618		
Occasional		13.8	
Regular		28.2	
Alcohol use frequency (0–5 times)	1448		
6–30 Times		47.2	
31 or more		14.8	
Binge drinking frequency (never)	1610		
1 or 2 times		42.0	
3 or more		25.0	
Number of drinks in typical occasion (0–3 drinks)	1603		
(4–6 Drinks)		32.3	
(More than 6)		43.3	
Cannabis use frequency (1–5 times)	1362		
6–30 Times		26.3	
31 or more		10.0	
Number of joints in typical occasion	1370	0.46	0.50
Alcohol and cannabis simultaneous use frequency (never)	1614		
1 or 2 times		38.3	
3 or more		33.4	
Stimulants/hallucinogens use frequency (never)	1601		
1 or 2 times		20.8	
3 or more		23.8	
Outcome (grade 11)	842	0.19	0.27

SD, standard deviation.

SELECTION OF LATENT CLASS MODEL

Comparisons of entropy and spillover indices, fit indices (deviance, AIC, BIC, SSBIC), and likelihood ratio tests for the one to six class LCA models suggested that the four-class model provided the best fit (see **Table 2**). As can be seen, model fit on all indices tended to improve as the number of classes increased, but the rate of improvement started to diminish around a four-class model. This solution had close to the lowest BIC and adjusted BIC scores with the highest entropy value of 0.83 (60). Likelihood ratio tests suggest few incremental validity beyond a four-class model. Models with 5 and 6 classes did not significantly improve model fit over models with fewer classes. The removal of covariates and outcome did not result in a change to the four-class solution, contrary to other solutions, indicating that the assumption of local independence was not violated. The four-class model also appears better than simpler models and more clinically significant. The four classes are distinct and each represents a significant number of participants. And as we will see below, classes can be discriminated by their association with predictors and outcome. We thus selected a four-class model.

Table 2 | Fit statistics, likelihood ratio tests, and entropy for different class solutions.

	Fit indices				Likelihood ratio tests		Entropy	Spill
	LL	BIC	SSBIC	AIC	VLMR	Adjusted LMR		
1 Class	−45044	90361	90243	90161	NA	NA	NA	NA
2 Classes	−13095	26522	26379	26279	2837.38 (1)***	2823.731 (1)***	83	No
3 Classes	−12716	25971	25739	25578	757.79 (2)***	754.14 (2)***	83	No
4 Classes	−12477	25700	25379	25156	478.17 (3)***	475.87 (3)***	83	No
5 Classes	−12322	25598	25188	24903	308.73 (4)	307.24 (4)	81	Yes
6 Classes	−12224	25607	25109	24761	197.02 (5)	196.07 (5)	80	Yes

LL, loglikelihood; BIC, Bayesian information criterion; SSBIC, sample-size adjusted Bayesian information criterion; AIC, Aikaike information criterion; VLMR, Vuong–Lo–Mendell–Rubin likelihood ratio test for k − 1 (H0) vs. k Classes; Adjusted LMR, Lo–Mendell–Rubin adjusted likelihood ratio test.
****p < 0.001.*

CHARACTERISTICS OF THE FOUR LATENT CLASSES

Four distinct classes based on use patterns were identified. These classes were labeled Late-Light Use (1; $N = 454$, 28%), Late-Heavy + Polydrug Use (2; $N = 222$, 14%), Early-Moderate Use (3; $N = 526$, 33%), and Early-Heavy + Polydrug Use (4; $N = 416$, 26%) (see **Figure 1**). There are significant differences at the 0.05 level between all classes on all items except alcohol use precocity for comparisons with the Early-Heavy + Polydrug Use class, which had no variance on this item. There are differences between almost all items' categories. Late Onset/Light Users had the lowest levels of use on each substance-related indicator. Early-Heavy + Polydrug Users had the highest levels of use on most indicators. The other two classes fell in between. Tobacco use was the highest in the Early-Heavy + Polydrug Users, the lowest in Late-Light Users, and was similar between the two other classes. For alcohol use indicators (frequency, binge, typical quantity), Early-Heavy + Polydrug Users and Late-Heavy + Polydrug Users are at similar levels despite early-onsetters showing slightly heavier patterns. Once again, Late-Light Users showed the lowest levels with Early-Moderate Users falling in between. In terms of cannabis use indicators (frequency, typical quantity) as well as of stimulant/hallucinogens and of cannabis use and alcohol polyuse, we observe very similar patterns.

SUBSTANCE-RELATED PROBLEMS OUTCOME

As shown in **Table 4**, on a mean scale of the 14 substance-related harm items, scores were respectively 0.09, 0.26, 0.17, and 0.36 for each class and were all mutually statistically different. As expected, the Early-Heavy + Polydrug Use class had the highest levels of problems ($M = 0.36$, SD = 0.012) and the Late-Light Use the lowest ($M = 0.09$; SD = 008). Notably, the Early-Moderate Use class had a lower level of problems ($M = 0.17$; SD = 009) than the Late-Heavy + Polydrug Use ($M = 0.26$; SD = 0.017).

SOCIODEMOGRAPHIC, BEHAVIORAL, AND PSYCHOSOCIAL PREDICTORS OF SUBSTANCE-USE CLASSES

As shown in **Tables 3** and **4**, significant differences were found between all classes. Odds ratios are calculated for a one standard deviation variation in predictors. Classes Late-Heavy + Polydrug Use and Early-Heavy + Polydrug Use were similar in terms of concurrent use in grade 10. However, compared to the Late-Heavy + Polydrug Use class, Early-Heavy + Polydrug Users had more problems in grade 11, and were older, had an earlier substance use onset (alcohol and cannabis), had a higher proportion of boys, more delinquent behaviors, deviant peers, and conflict with parents and were less monitored by them. Early-Moderate Use and Early-Heavy + Polydrug Use classes both are early-onsetters, but compared to the Early-Heavy + Polydrug Use class (and Late-Heavy + Polydrug Use), the Early-Moderate Use class had more moderate patterns of use as reflected in less problems than in Late-Heavy + Polydrug Use or Early-Heavy + Polydrug Use classes. The Early-Moderate Use class had the highest proportion of female. It has lower peer deviancy proportions than Early-Heavy + Polydrug Use class, but higher than Late-Light Use and Late-Heavy + Polydrug Use classes. It also has comparable levels of delinquent behaviors and parent monitoring with the Early-Heavy + Polydrug Use class, which are at more problematic levels than in Late-Light Use and Late-Heavy + Polydrug Use classes. The Late-Light Use class had, in addition to the lowest level of problems, the lowest level of substance use as well as the lowest level of risk. This class is younger than all other three, it had higher levels of school bonding than both Late-Heavy + Polydrug Use and Early-Heavy + Polydrug Use classes, and it had the lowest peer deviancy but had similar levels of delinquent behaviors with the Late-Heavy + Polydrug Use class, which were lower than in Early-Moderate Use and Early-Heavy + Polydrug Use classes. A similar pattern emerged regarding parental monitoring. The Late-Light Use and Late-Heavy + Polydrug Use classes had similar levels, which were higher than in Early-Moderate Use and Early-Heavy + Polydrug Use classes. The Late-Light Use class had also lower levels of conflicts than the Early-Heavy + Polydrug Use.

DISCUSSION

This study aimed to identify distinct latent classes of adolescent cannabis users based on their substance-use patterns in grade 10 and to distinguish these classes in terms of (1) sociodemographic and psychosocial predictors in grades 7–8 and (2) substance-related problems in grade 11. We identified four classes of cannabis use in adolescence: (1) Late-Light Use (2) Late-Heavy + Polydrug Use (3) Early-Moderate Use, and (4) Early-Heavy + Polydrug Use. Past typologies have generally found three or four cannabis users categories (5–8). However, some of these often relied on clinical

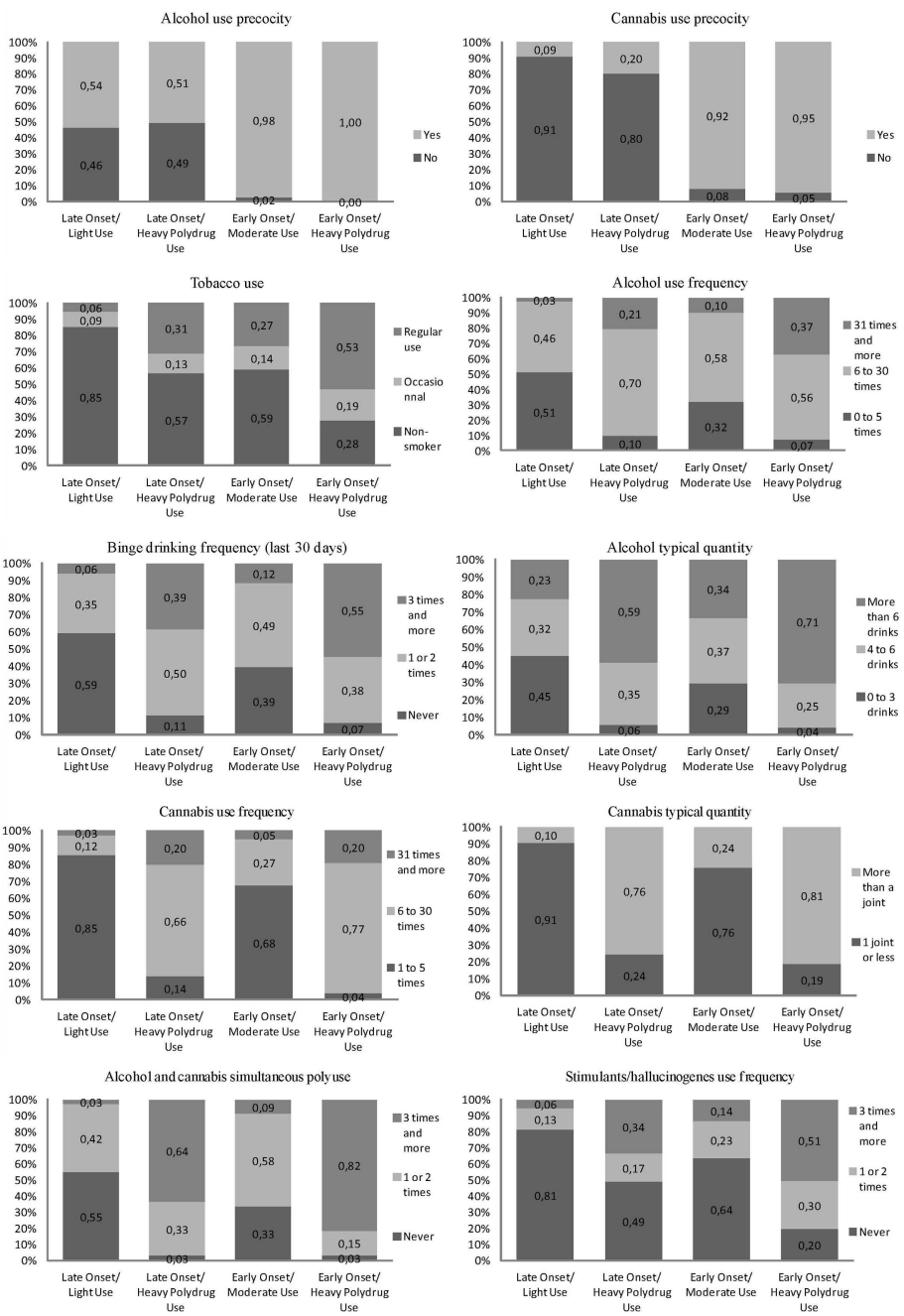

FIGURE 1 | Substance use items' category frequencies by classes.

samples (40) or adult population (5), whereas the current study examines a normative population of adolescents. As in other typologies, we found early and late onset classes. In general, Early-Heavy + Polydrug Users had the scores associated with the greatest risk in early adolescence and reported the most problems in late adolescence. The category with least problems and risk was the Late-Light Use class. These two classes at the extremes of the continuum differed on almost every substance use indicators and predictors.

One major contribution of the present study was to distinguish between two types of early-onset classes. Interestingly, the Early-Moderate use class had an early alcohol and cannabis use onset as in the Early-Heavy + Polydrug use class but has less substance-related problems. It even has fewer problems than the Late-Heavy + Polydrug use class, which has a late onset but heavier use patterns. This suggests that proximal substance use behavior has an influence on the level of problems experienced obviously. Except for age and sex, the only variable to distinguish between early-onset

Table 3 | Adjusted associations between psychosocial predictors (grade 7–8) and class membership.

	Class membership, OR (95% CI)					
	Reference = late-onset-light-users			Reference = late-onset-heavy-poly-users		Reference = early-onset-moderate-users
	Late-onset-heavy-poly-users	Early-onset-moderate-users	Early-onset-heavy-poly-users	Early-onset-moderate-users	Early-onset-heavy-poly-users	Early-onset-heavy-poly-users
SOCIODEMOGRAPHIC PREDICTORS						
Sex (1 = female)	0.58 (0.46, 0.72)***	1.93 (1.46, 2.57)***	1.36 (1.03, 1.80)*	3.36 (2.42, 4.65)***	2.36 (1.70, 3.29)***	0.70 (0.58, 0.86)***
Age	0.95 (0.79, 1.14)	1.44 (1.18, 1.76)***	1.37 (1.11, 1.68)**	1.52 (1.21, 1.91)***	1.44 (1.14, 1.83)**	0.95 (0.81, 1.12)
Family adversity	1.00 (0.78, 1.26)	1.18 (0.94, 1.48)	1.22 (0.98, 1.52)	1.19 (0.91, 1.56)	1.23 (0.94, 1.61)	1.03 (0.89, 1.20)
BEHAVIORAL AND PSYCHOSOCIAL PREDICTORS						
Delinquency	0.94 (0.56, 1.56)	4.82 (2.98, 782)***	5.21 (3.20, 8.51)***	5.15 (2.98, 8.89)***	5.56 (3.20, 9.68)***	1.08 (0.90, 1.29)
Depressive symptoms	1.01 (0.77, 1.33)	1.08 (0.82, 1.42)	1.12 (0.86, 1.45)	1.06 (0.76, 1.49)	1.10 (0.78, 1.55)	1.04 (0.87, 1.24)
Peer delinquency	1.55 (1.04, 2.30)*	6.44 (4.71, 8.79)***	8.47 (6.11, 11.75)***	4.16 (2.61, 6.64)***	5.48 (3.44, 8.72)***	1.32 (1.08, 1.60)**
Academic achievement	0.96 (0.77, 1.20)	0.93 (0.74, 1.16)	1.12 (0.97, 1.30)	0.96 (0.77, 1.20)	1.16 (1.00, 1.35)	1.16 (0.93, 1.45)
School bonding	0.81 (0.66, 1.00)*	0.84 (0.67, 1.04)	0.80 (0.63, 1.01)	1.03 (0.80, 1.32)	0.98 (0.75, 1.29)	0.96 (0.81, 1.13)
Parental monitoring	1.05 (0.84, 1.31)	0.74 (0.58, 0.95)*	0.73 (0.57, 0.93)*	0.71 (0.52, 0.95)*	0.69 (0.51, 0.94)*	0.98 (0.82, 1.18)
Conflict with parents	1.00 (0.78, 1.28)	1.28 (0.99, 1.65)	1.35 (1.05, 1.73)*	1.27 (0.94, 1.73)	1.35 (0.99, 1.82)	1.06 (0.89, 1.25)

$^{***}p < 0.001$; $^{**}p < 0.01$; $^{*}p < 0.05$.

classes is peer delinquency, and between the late-onset classes is school bonding. Indeed, the Early-Heavy + Polydrug use class shows higher scores of peer delinquency than the Early-Moderate use class and the Late-Heavy Polydrug use has lower school bonding scores than the Late-Light use class. Moreover, despite possibly contributing to delaying onset (it is higher in both late onset classes), parental monitoring is no panacea because early-onset classes are high and indistinguishable on that characteristic while showing an important difference in substance-related harm. Regarding the two intermediary classes (Late-Heavy + Polydrug use and Early-Moderate use), noteworthy are the lower delinquency and peer delinquency as well as higher parental monitoring scores in the Early-Moderate use class that has a generally lower level of use and consequences. Adolescents in the Early-Moderate use class may well be the popular ones [see Ref. (67)]. The inclusion of multidimensional predictors was useful to discriminate between classes. Indeed, age, sex, delinquent behaviors, peer deviancy, school bonding, and parental monitoring all contributed to discriminate classes. The inclusion of multiple substance use indicators seems to have also improved the discrimination between classes.

IMPLICATIONS

The results have many implications. First, they discriminate two different types of early as well as late onset cannabis users. They do so by shedding light on their distinctive relationships with risk factors from multiple dimensions as well as substance-related problems. Furthermore, our results, taken together, also shed light on the fact that not all early-onsetters are at elevated risk and experience a high level of substance-use related problems and that they are even at a lower level of risk than some late-onsetters. These results should be used to more meaningfully target and inform effective interventions toward users experiencing elevated levels of risks and harms. Moreover, a typology provides a useful heuristic for clinicians conducting assessment or screening with cannabis-involved adolescents. Our results suggest that screening and intervention for risky cannabis use among adolescents should focus on school bonding in order to discriminate late-onset classes and on peer delinquency in order to discriminate early-onset classes. Intervention should be prioritized for the Early-Heavy + Polydrug use and Late-Heavy + Polydrug use classes. School bonding and peer deviancy seem to be good targets for intervention with either Early- or Late-Heavy + Polydrug Users and parental monitoring and conflict with parents seem to be further good targets for intervention with Early-Heavy + Polydrug users. In both cases (Early- or Late-Heavy + Polydrug), binge drinking, cannabis use frequency and alcohol and cannabis simultaneous use seem to be the most important substance-use behaviors to target in interventions. In the first case, working simultaneously on these use patterns, in addition to stimulants/hallucinogens use frequency, and psychosocial risk factors, with demand and harm reduction interventions, would probably be a good strategy whereas intervention with the latter group should focus primarily on use patterns. Indeed, it is noteworthy and important to take into account that the Late-Heavy + Polydrug use class is mostly constituted of females with lower levels of risk. These cannabis users are more difficult to predict, but they have important intervention needs.

Table 4 | Adjusted outcomes at age 16 of substance-use classes.

	Estimated means			
	Late-onset-light-users	**Late-onset-heavy-poly-users**	**Early-onset-moderate-users**	**Early-onset-heavy-poly-users**
Attributed substance-related problems	0.093	0.257	0.174	0.364

The Early-Moderate Users would on their part benefit from early intervention strategies in order to prevent their use to shift from moderate to heavy as well as to prevent it to become more problematic. Overall, other than substance use behaviors, the main factors to target would generally be school bonding, delinquency, peer delinquency, and parental monitoring. In terms of policy implications, the current legal framework in Canada and elsewhere is characterized by the criminalization of all use; any cannabis use is defined as problematic (68). This approach differs from the one prevailing for alcohol, which has evolved to a public health framework (69, 70). Rather than focusing on use *per se*, priority is given to the risks and harms associated with problematic patterns of use (e.g., drunk driving). This way, targeted interventions may be applied to relevant behaviors (71). In our study, this could mean targeting binge drinking frequency and substance mixing behaviors as well as other substance use. Harm reduction strategies also seem to be potential useful tools in order to reduce cannabis-related problems.

STRENGTHS AND LIMITATIONS

This study has multiple strengths, including the simultaneous consideration of substance use severity indicators, predictors, and outcomes as well as their multidimensionality, and use of a large prospective community-based sample. However, this study is not without limitations. First, despite the fact that confidentiality was assured, response bias and common method variance could have influenced our results. Fortunately, the validity and reliability of self-reported data on substance use have been established (72–74), but this has not been proved for self-report of problems. In addition, the sample comes from deprived areas, which is a limitation to the generalization of results. However, even if schools from deprived areas were sampled, individual scores of familial adversity vary and include participants from low familial adversity. Another limitation is related to the large amount of missing data and potential attrition bias. Also, the results do not provide information on the sequence of problem as well as the subgroup development over time. Finally, the inclusion of age of onset in the typology, while substance use indicators have been selected from grade 10 is another potential limitation to the current study.

FUTURE STUDIES

Future prospective studies should examine factors that explain transitions across these subtypes in time. This would however be complex because age of onset is included in the typology. Another important area of development is in the study of specific harm categories (relational, health, school, etc.) related to different patterns of use in order to better inform prevention and treatment efforts to target specific harms. Indeed, if different outcomes are related to different classes, intervention should not only target specific factors related to specific patterns but also focus on specific problems related to each. Which are the most important problems related to each class? Which classes are disproportionally represented for each problem? Another potential improvement over the current study is the use of more specific items for each other drugs than alcohol, Tobacco, and Cannabis (e.g., ecstasy, LSD, Speed, GHB, Ketamine, etc.) as well as substance use motives. Finally, a nationally representative sample would also improve the external validity of the typology.

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Polysubstance use in cannabis users referred for treatment: drug use profiles, psychiatric comorbidity and cannabis-related beliefs

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Background: Population-based surveys demonstrate cannabis users are more likely to use both illicit and licit substances, compared with non-cannabis users. Few studies have examined the substance use profiles of cannabis users referred for treatment. Co-existing mental health symptoms and underlying cannabis-related beliefs associated with these profiles remains unexplored.

Methods: Comprehensive drug use and dependence severity (Severity of Dependence Scale-Cannabis) data were collected on a sample of 826 cannabis users referred for treatment. Patients completed the General Health Questionnaire, Cannabis Expectancy Questionnaire, Cannabis Refusal Self-Efficacy Questionnaire, and Positive Symptoms and Manic-Excitement subscales of the Brief Psychiatric Rating Scale. Latent class analysis was performed on last month use of drugs to identify patterns of multiple drug use. Mental health comorbidity and cannabis beliefs were examined by identified drug use pattern.

Results: A three-class solution provided the best fit to the data: (1) cannabis and tobacco users ($n = 176$), (2) cannabis, tobacco, and alcohol users ($n = 498$), and (3) wide-ranging substance users ($n = 132$). Wide-ranging substance users (3) reported higher levels of cannabis dependence severity, negative cannabis expectancies, lower opportunistic, and emotional relief self-efficacy, higher levels of depression and anxiety and higher manic-excitement and positive psychotic symptoms.

Conclusion: In a sample of cannabis users referred for treatment, wide-ranging substance use was associated with elevated risk on measures of cannabis dependence, co-morbid psychopathology, and dysfunctional cannabis cognitions. These findings have implications for cognitive-behavioral assessment and treatment.

Keywords: cannabis, latent class, drugs, comorbidity, expectancy, self-efficacy, treatment seeking

INTRODUCTION

Between 2.8 and 4.5% of the world's adult population have used cannabis in the past year (1), making it globally the most widely used illicit substance. General population estimates indicate that up to 1.3% are cannabis dependent (2). Individuals who use cannabis are also more likely to use other illicit substances (3). The association between cannabis use and mental health problems is well documented (4, 5). Analyses of cannabis users in population-based surveys have identified substance use 'typologies' though latent class modeling [e.g., (6)]. These typologies can inform public health and targeted prevention approaches. The 'typology' of cannabis users referred for treatment is likely to differ from that in the general population. Polysubstance use, mental health comorbidity and underlying acquired cannabis-related beliefs associated with these substance use profiles require further investigation.

Latent Class Analysis (LCA) has been widely applied in population-based alcohol and drug research to estimate probability of substance use sub-classes, or 'typologies.' Most generate class solutions that include: (a) no or limited substance use, (b) moderate substance use, and (c) wide-ranging substance use. In addition to varying range of substances captured across studies, the final number of class solutions and prevalence rates per solution varies as a function of the population sampled and period of drug use captured (typically lifetime or past 12 month use). For example, a representative sample from the British National Household Survey ($n = 8538$, mean age 42.55 years) generated a three-class solution of 12 month illicit drug use: (1) no polydrug use (95.78%), (2) moderate polydrug use (3.44%), and (3) wide-ranging polydrug use (0.77%) (3). Based on lifetime illicit substance use data from an Australian Twin Study ($n = 6265$, mean age 30 years), Lynskey et al. (7) identified a 5-class model: (1) low use (68.5%), (2) moderate

use of all substances (17.8%), (3) high use of stimulants and hallucinogens and low use sedatives and opioids (6.6%), (4) high use sedatives and opioids and low use of stimulants and hallucinogens (3.0%), and (5) uniformly high use across all substances (4.2%).

Examining lifetime use of all substances (illicit and licit) of younger age groups from the Australian National Drug Strategy Household Survey ($n = 1402$, 12–17 years), White et al. (8) found a three-class model that included: (1) alcohol only (79.6%), (2) limited range multidrug users (18.3%), and extended range multidrug users (2%). In community-based samples of cannabis users the percentage of wide-ranging substance use increases to 21% (past 3 months) (9). The prevalence rates of de Dios et al.'s (9) other two LCA cannabis classes were Unaffected/Mild Users (37%) and Moderate Problem Users (42%).

Comparisons between studies are difficult because narrower substance use time frames reduce prevalence rates. Targeting specific substance using populations increases the prevalence of polysubstance use. Broader timeframes (e.g., lifetime use) are less reliable in reporting recent polysubstance use patterns. Narrower assessment timeframes represent more clinically relevant data, but can lack power because of the low prevalence of use of some substances.

Mental health problems often co-occur with substance use disorders, including psychotic-like symptoms (10–12). Substance use LCA studies permit a more precise investigation of patterns of psychiatric comorbidity. Wider-ranging LCA substance use classes have previously been associated with elevated psychological distress (8), increased mood and anxiety problems, suicide attempts (3, 7) and treatment seeking (3). When alcohol dependent subjects are examined within population-based surveys, those classified by LCA as having a high probability of heavy alcohol consumption as well as heavy illicit drug use, are more likely to have co-existing generalized anxiety and major depressive disorders (13). Studies that have extracted cannabis users from nationally representative data sets, observe similar deficits in functioning within those classes reporting higher risk for multiple substance use (6). These findings suggest psychiatric severity increases linearly with increased polysubstance use.

No LCA studies have examined the substance use profiles and accompanying mental health comorbidity of individuals referred for cannabis use treatment. These profiles are likely to be different from population-based studies. To improve assessment and treatment of this group, it is also of benefit to extend beyond broader mental health functioning measures and examine additional etiological factors, especially cannabis-related beliefs which can serve as targets for evidence-based psychological interventions. Two such targets for cognitive-behavioral treatment are outcome expectancies and substance-refusal self-efficacy. Both carry strong Social Cognitive Theory (SCT) pedigrees (14–16).

Outcome expectancies are sometimes referred to as 'if ... then' statements that reflect the perceived behavioral and affective consequences of engaging in specific behaviors (17). Cannabis expectancy scales are typically represented by two higher-order expectancy factors, representing positive (e.g., "I have more self-confidence when smoking cannabis") and negative (e.g., "Smoking cannabis makes me confused") expectancies [see (18)]. Self-efficacy refers to a person's belief they can successfully or unsuccessfully regulate their behavior (e.g., "I am very sure I could not resist smoking cannabis when I feel upset"). Cannabis refusal self-efficacy is considered a central psychological mechanism that predicts post-treatment consumption (19) and abstinence (20, 21). Expectancy 'challenges' have been applied in alcohol use prevention and treatment (22), but progress in cannabis has been hampered by a lack of cannabis-specific assessment tools. Cannabis expectancy and refusal self-efficacy scales have recently been validated for use in clinical populations (18, 23).

Polysubstance use varies widely in definition. Here we define it as two or more substances used in the past month. In this study of cannabis users referred for treatment, we predicted a continuum of past month polysubstance use that would range from cannabis only (and no/low licit drug use) to wide-ranging polysubstance use. We make no *a priori* assumptions about the number of LCA solutions, but predicted a higher prevalence of polysubstance use within wider-ranging profiles compared to community [e.g., (9)] and general population [e.g., (3)] samples. Mental health functioning should be poorer across all class solutions, when compared to community population norms. Consistent with the findings of Lynskey et al. (7) and Smith et al. (3), symptoms of mood and anxiety disorders are likely to be more impaired in users with wider-ranging drug profiles. Psychotic-like symptoms, on the other hand, are likely to show a dose-response relationship, such that the classes with more severe cannabis dependence will display a higher symptom severity (11). Patients who use cannabis with no or limited other substance use are expected to have greater opportunities to form more salient cannabis-related beliefs (18), and should have higher cannabis expectancy and lower cannabis refusal self-efficacy.

The main aim of this study is to identify polysubstance typologies for cannabis users in treatment. Based on these typologies, it is expected that additional information on associated mental health functioning and cognitive treatment targets will assist researchers and health practitioners provide more effective assessment approaches. These assessments are likely to result in more tailored interventions for this group.

MATERIALS AND METHODS

PARTICIPANTS

The sample comprised 827 individuals who were referred for assessment as part of the Queensland Illicit Drug Diversion Initiative (QIDDI). The program involves a 2-h comprehensive assessment of substance use and psychosocial functioning that incorporates motivational interviewing (MI). Where indicated, referral for further treatment is provided. Of the 827 participants, 623 (77.2%) were men, and the mean age was 25.46 years ($SD = 8.35$). The majority were born in Australia (692; 83.7%) or New Zealand (53; 6.4%), and 49 (5.9%) identified themselves as Indigenous Australians. Almost half (46.4%) scored above the Severity of Dependence Scale-Cannabis (SDS-C) screening cut-off for cannabis dependence [≥ 3, (24)]. Average weekly cannabis consumption was 3.54 ($SD = 4.90$) g and the average SDS-C score was 3.13 ($SD = 3.20$). Past month alcohol and other drug use is presented in **Table 1**. The 4-week window was chosen to better reflect current polysubstance use. Previous studies reporting 12 month or lifetime use have less clinical utility (e.g., a patient

Table 1 | Past month alcohol and other drug use ($N = 827$).

	% used in past month	No. days used in past month	Average amount used per occasion
Alcohol	84.8	6.87 (SD = 8.46)	76.46 g (SD = 82.99)
Tobacco	64.8	27.31 (SD = 7.56)	14.13 (SD = 9.13)
Amphetamine	17.4	2.88 (SD = 4.32)	2.08 'points' (SD = 2.41)
Ecstasy/MDMA	13.2	2.15 (SD = 2.36)	1.40 'tabs' (SD = 1.15)
Heroin	4.5	8.32 (SD = 10.57)	3.87 g (SD = 11.02)
Benzodiazepines	4.2	15.09 (SD = 12.52)	16.88 mg (SD = 23.23)

A 'point' is approximately 0.1 g.

who used cannabis once and alcohol once would fit criteria of a polysubstance user in lifetime studies). Of the original sample, 20 participants (2.4%) were excluded from the main analysis due to missing values on one or more drug-related variables, leaving a final sample of 807 cases. This sample was drawn from an ongoing clinical study conducted in an alcohol and drug outpatient setting. Connor et al. (18, forthcoming) and Young et al. (23) have used these data to validate cannabis expectancy and self-efficacy measures. Feeney et al. (25) examined the differences in mental health functioning between those who were and were not dependent on cannabis, as well as providing descriptive drug use data on 12 month and lifetime use. Human ethics approval was obtained from the Metro South Hospital and Health Service.

MEASURES

Cannabis expectancy questionnaire

The Cannabis Expectancy Questionnaire (CEQ) is a 45-item questionnaire assessing positive (18 items, e.g., "I get better ideas when smoking cannabis") and negative (27 items, e.g., "I am more worried about what others are saying about me when I am smoking cannabis") cannabis use outcome expectancies (18, 26). There is a 5-point, Likert-style response format (1 = *Strongly Disagree* to 5 = *Strongly Agree*). The questionnaire was initially developed with a community sample and validated on a large sample of cannabis users recruited from a hospital outpatient clinic. The two subscales have high internal reliability ($\alpha \geq 0.90$), and the CEQ's factor structure and criterion validity have been established across two samples (18).

Cannabis refusal self-efficacy questionnaire

The Cannabis Refusal Self-Efficacy Questionnaire (CRSEQ) is a 14-item questionnaire assessing an individual's belief in their ability to resist smoking cannabis across various situations (23, 27). Items ask respondents to rate their ability to resist smoking cannabis on a 6-point Likert-type scale ranging from 1 (*I am very sure I could NOT resist smoking cannabis*) to 6 (*I am very sure I could resist smoking cannabis*). Similar to the Drinking Refusal Self-Efficacy Questionnaire [DRSEQ; (28)], it comprises three subscales: *Emotional Relief Self-Efficacy* (six items, e.g., "When I feel upset"), *Opportunistic Self-Efficacy* (five items, e.g., "When someone offers me a smoke"), and *Social Facilitation Self-Efficacy* (three items, e.g., "When I want to feel more confident"). The questionnaire was developed with a community sample and validated on a large sample of cannabis users recruited from an outpatient treatment service. The internal reliability is good/excellent ($\alpha = 0.84$–0.97), and its factor structure and criterion validity has been previously established (23).

Severity of dependence scale-cannabis

The SDS-C is a 5-item screening questionnaire measuring the severity of cannabis dependence (29). The SDS-C is sensitive to severity of cannabis dependence (30). Using Australian normative data, the SDS-C cut-off for likely cannabis dependence is ≥ 3 (24).

General health questionnaire-28

The General Health Questionnaire-28 (GHQ-28) is a 28-item self-report measure which identifies short-term changes in health perception (31). It has four sub-scales (i) Somatic Symptoms, (ii) Anxiety, (iii) Social Dysfunction, and (iv) Depression (31). Higher sub-scale scores reflect poorer functioning. The GHQ-28 is a widely used measure of psychological health with strong psychometric properties (31–33).

Psychotic-like symptoms

Psychotic-like symptoms were assessed using the Positive Symptoms (five items) and Manic-Excitement (six items) sub-scales of the 24-item Brief Psychiatric Rating Scale [BPRS; (34)]. The BRPS is a clinician-rated scale measuring 24 different psychiatric symptoms, each rated on a 7-point scale, ranging from 1 (*not present*) to 7 (*extremely severe*). It is a reliable and valid measure of psychiatric symptoms (35), and has previously been administered to assess psychotic-like symptoms in injecting drug users (36). Masters- and PhD-qualified clinical psychologists administered the BPRS. Psychologists had between 2 and 25 years experience ($M = 10.5$ years).

Quantity and frequency

Quantity and frequency of alcohol and other drug use *in the past month* was assessed by Masters- and PhD-qualified clinical psychologists using a retrospective diary approach over the past month, past 12 months, and lifetime. As recommended by the State Health Service, to ensure consistent measurement of cannabis quantity across state-wide clinics 'joints' (cannabis cigarette) were quantified as 0.25 g of cannabis, and 'cones' (use of 'bong' or 'pipe'), 0.10 g of cannabis.

ANALYSIS

Latent class analysis was performed to identify patterns of multiple drug use using last month use of seven drugs: cannabis, alcohol, amphetamine, heroin, benzodiazepine, ecstasy (MDMA), and tobacco. LCA is a technique that identifies sub-classes within a population based on similarity of response to measured variables (37). This technique is characterized by two sets of parameters: (1) The estimated proportion of each class in the population and (2) the probability of an individual in a particular class using a certain drug. Determination of the correct number of classes was based on the Bootstrap Likelihood Ratio Test (38) and Sample Size Adjusted Bayesian Information Criterion [SSABIC; (39)]. These two criteria have shown excellent performance in identifying the correct number of classes (40). In

BLRT, a significant *p*-value indicates that a given model fits the data better than a model with one less class. For SSABIC, a lower value indicates better balance between model parsimony and model fit. In addition to these two criteria, the average posterior probabilities of class membership were used to evaluate classification quality. Average posterior probabilities close to one suggest clear classification. Model fitting began with a 1-class solution, and the number of classes was successively increased up to a 4-class solution. Once the optimal number of classes was determined, the profiles of participants in different classes were compared using ANOVA, Kruskal–Wallis, and χ^2 test.

RESULTS

Model fit statistics for 1–4 class solutions are presented in **Table 2**. The 3-class solution had the lowest SSABIC and results from the BLRT indicate that it fitted the data significantly better than a 2-class solution, but not worse than the 4-class solution. In addition, the average posterior probabilities of class membership of a 3-class solution were over 0.90, which indicated clear classification. Therefore, it was selected as the optimal model.

Figure 1 shows the probability of last month use for each substance by class. Class 1 was characterized by wide-ranging substance use. Participants in this class had a high probability of cannabis, tobacco, alcohol, and amphetamine use, a moderate probability of ecstasy use, and a low probability of heroin and benzodiazepine use. This class was labeled as *wide-ranging substance use*, and the prevalence estimate of this class was 189 (23.5%).

Table 2 | Fit statistics of the unconditional latent class analysis.

	Loglikelihood	BIC	SSABIC	BLRT *p*-value
1 Class	−2216.117	4479.087	4456.858	
2 Classes	−2168.662	4437.723	4390.090	<0.001
3 Classes	−2153.480	4460.907	4387.869	<0.001
4 Classes	−2145.417	4498.326	4399.883	0.21

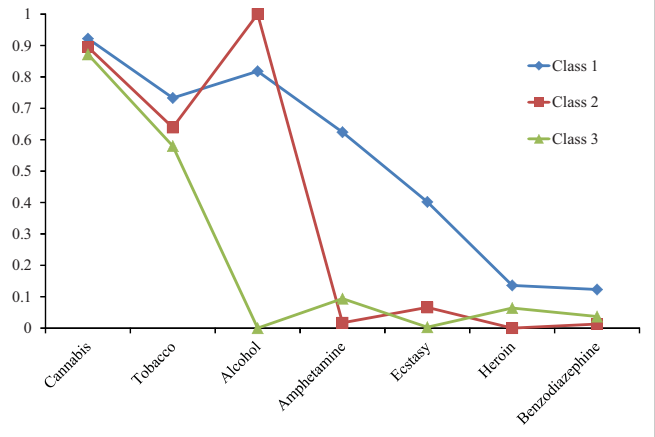

FIGURE 1 | Probability of last month substance use from the 3-class solution.

Class 2 was characterized by universal alcohol use, high probability of cannabis and tobacco use, and negligible probability of other drug use. This class was labeled as *cannabis, alcohol, and tobacco*, and the prevalence estimate of this class was 458 (56.8%). Class 3 was characterized by a high probability of cannabis and tobacco use, but negligible probability of other drug use. This class was labeled as *cannabis and tobacco*, and the prevalence estimate was 156 (19.8%).

Table 3 shows the profiles of the three classes. Participants in the *wide-ranging substance use* class had significantly higher negative cannabis expectancy, anxiety, and depression scores, lower emotional relief self-efficacy and lower social facilitation self-efficacy, and higher manic-excitement and positive psychotic symptoms ($p < 0.05$). They were also more likely to be cannabis dependent ($p < 0.05$). However, as shown in **Table 3**, the effect sizes were generally small, and in the case of psychotic-like symptoms, were very low in all groups. Cannabis users scored significantly higher than the Australian normative sample [Somatic Symptoms. 84, Anxiety. 77, Social Dysfunction. 64, Depression. 21; (41)] on all GHQ-28 subscales ($ps < 0.05$).

DISCUSSION

This is the first study to examine the substance use profiles and co-existing mental health symptoms of individuals referred for cannabis use treatment, applying LCA. Previous LCA studies in cannabis users drawn from population and community samples typically assess lifetime or past 12 month use. To more precisely examine current polysubstance use, we restricted the timeframe to the past 4 weeks. LCA generated a three-class solution that included Class (1) *Wide-Ranging Substance Use*, Class (2) *Cannabis, Alcohol, and Tobacco Use*, and Class (3) *Cannabis and Tobacco Use*. As anticipated, prevalence rates of substance use were markedly higher than population-based studies. *Class 1* patients represented approximately one quarter of the sample. They reported a high probability of cannabis, tobacco, alcohol, and amphetamine use, as well as moderate ecstasy use and low heroin and benzodiazepine use in the previous month. *Class 1* also had significantly higher levels of cannabis dependence. Representing just over half of the sample, *Class 2* had high probabilities of alcohol, cannabis, and tobacco use, with limited other drug use. The final LCA solution (*Class 3*) consisting of approximately one fifth of the sample were characterized by low probability of alcohol and other drug use, but frequent cannabis and tobacco use. Given the shorter time period under investigation compared to population-based studies, this finding is particularly significant.

Across all three classes, mental health functioning of patients was significantly more impaired than community norms (41). Also consistent with our hypotheses, patients classified as Wide-Ranging Substance Users (Class 1) had significantly higher Depression and Anxiety scores than Classes 2 and 3. Wide-Ranging Substance Users also displayed significantly higher positive psychotic-like and manic symptoms compared to Class 2 (*Cannabis, Alcohol, and Tobacco Use*). However, given the low prevalence of such symptoms across all groups, this finding should be interpreted with some caution. These findings are similar to population-based LCAs that have measured mood and anxiety

Table 3 | Profile of the three substance use classes.

	Wide-ranging substance use			Cannabis, alcohol, and tobacco			Cannabis and tobacco			*F*	η^2
	N	***M***	**SD**	***N***	***M***	**SD**	***N***	***M***	**SD**		
Age	132	24.92	6.45	498	25.16	8.61	176	26.79	8.77	2.85	0.007
CANNABIS EXPECTANCY											
Positive expectancy	120	49.85	11.44	450	49.78	10.71	153	50.07	11.78	0.04	0.001
Negative expectancy	117	69.63[a]	17.31	449	63.10[b]	16.38	147	61.83[b]	16.34	8.72***	0.024
GHQ SUBSCALES											
Somatic symptoms	131	1.23	1.68	499	0.91	1.44	175	0.84	1.41	3	0.008
Anxiety	131	1.60[a]	1.98	498	1.05[b]	1.69	175	1.10[b]	1.7	5.15**	0.013
Social dysfunction	131	0.87	1.41	496	0.7	1.41	172	0.84	1.52	1.11	0.003
Depression	131	0.85[a]	1.65	496	0.46[b]	1.28	172	0.60[ab]	1.55	3.94*	0.01
CANNABIS REFUSAL SELF-EFFICACY											
Emotional relief self-efficacy	120	21.93[a]	9.75	457	24.70[b]	9.01	149	23.39[ab]	9.13	4.73**	0.013
Opportunistic self-efficacy	121	15.63[a]	7.68	448	17.40[ab]	7.49	150	18.09[b]	7.5	3.83*	0.011
Social Facilitation self-efficacy	122	14.38	3.92	456	15.01	3.45	151	14.68	3.38	1.76	0.001
BRIEF PSYCHIATRIC RATING SCALE											
BPRS positive symptoms[†]	131	5.66[a]	1.35	499	5.48[b]	1.44	172	5.46[ab]	1.32	$p = 0.022$	
BPRS manic-excitement[†]	131	7.17[a]	1.91	498	6.69[b]	1.58	172	7.05[ab]	2.20	$p = 0.007$	
	N	**%**		***N***	**%**		***N***	**%**		χ^2	**Cramer's *V***
GENDER											
Male	103	78.03		394	79.12		125	71.02		4.9	0.078
Female	29	21.97		104	20.88		51	28.98			
CANNABIS DEPENDENT											
Dependent	76	57.58		213	42.77		85	48.3		9.52**	0.109
Not dependent	56	42.42		285	57.23		91	51.7			

[ab] Means with the same superscript were not significantly different.

[†] Overall group difference tested using Kruskal–Wallis test. Follow-up pairwise comparisons tested using Mann–Whitney U tests with a Bonferroni-like adjustment to α (0.05/3 = 0.016).

**p < 0.05; **p < 0.01; ***p < 0.001.*

(3, 7), as well as more broadly defined psychological distress (8). This study provides additional evidence that cannabis users in treatment have a higher prevalence of poor co-morbid mental health functioning. Severity of mental health dysfunction increases when substances other than alcohol and tobacco are introduced.

In this young population of cannabis users, a clinically important finding was low probability of alcohol use in Class 3 (frequent cannabis and tobacco use only). Our original research hypotheses anticipated that patients who limited use of substances to cannabis only were expected to have more salient cannabis-related beliefs, and should have higher cannabis expectancy and lower cannabis refusal self-efficacy scores. In contrast, the Wide-Ranging Substance group (Class 1) reported significantly higher negative cannabis expectancies and lower emotional relief and opportunistic cannabis refusal self-efficacy beliefs, when compared to Class 2 and 3. In alcohol studies, consistent with SCT (14, 15), this combination of high expectancies and low self-efficacy has been associated with highest levels of consumption [e.g., (42–44)] and poorest treatment outcomes [e.g., (45)]. More recently, the combination of high expectancy/low self-efficacy has been demonstrated to be predictive of higher levels of cannabis dependence and cannabis consumption (Connor et al., forthcoming), placing wide-ranging substance users at elevated risk.

Given the psychometric similarity between expectancy and self-efficacy factors across drug classes (Connor et al., forthcoming), drug specific scales may be capturing additional risk of using multiple drugs. Support for this can be observed with generic, non-drug (general) self-efficacy being highly associated with substance use (46). Front line treatments for cannabis use disorders that hold strongest evidence for efficacy include Cognitive-Behavioral Therapy (CBT), MI, and Contingency Management (CM) (47). In the country this study was undertaken (Australia), CBT and MI are most widely used. Both expectancy and self-efficacy are key targets for CBT-based addiction treatments [e.g., (19, 22, 45)]. Cannabis users engaging in wide-ranging substance use may benefit from greater focus on enhancing strategies to cope with distress (for emotional relief self-efficacy, anxiety, depression) and general refusal skills (for opportunistic self-efficacy), and less on building motivation for change (negative expectancies).

The research has some limitations. The cross-sectional design does not allow interpretation of causality. Substance use was assessed though self-report. Biological verification would provide

a more robust assessment of substance use. The design does not allow assessment of the specific role of cannabis versus other drugs in the severity of co-existing mental health problems, or cannabis-related cognitions. While the sample size for a clinical population is robust, the findings may not be generalizable to all treatment seeking populations. All patients attended under court direction as an alternative to a criminal prosecution. This may have had a proximal effect on self-reported health and functioning. Future work could assess patients over multiple time points to detect changes in substance use, mental health functioning, and cannabis-related beliefs. Prospective comparisons between patients formally engaged in cannabis treatment could assess the prognostic capacity of the three cannabis groups identified.

This LCA study in a group of cannabis users diverted to treatment identified that high levels of cannabis dependence and illicit polysubstance use were strongly associated with impaired mood and anxiety, as well as higher positive psychotic-like and manic symptoms. Treatment approaches for this more complex group may include combined CBT and pharmacotherapy to more effectively target these symptoms directly. Patients with wide-ranging substance use profiles may additionally benefit from psychologically based strategies that focus on more effectively coping with symptom distress. Based on findings that this higher risk profile has lower cannabis refusal self-efficacy beliefs, enhancing skills, and confidence to resist situational cues through behavioral training may provide additional clinical benefit in this higher risk group.

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Avoiding emotional bonds: an examination of the dimensions of therapeutic alliance among cannabis users

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There is a growing need to provide treatment for cannabis users, yet engaging and maintaining this population in treatment is particularly difficult. Although past research has focused on the importance of therapeutic alliance on drug treatment outcomes, this is the first study to examine the dimensions of therapeutic alliance for cannabis users compared with users of alcohol or other drugs in a naturalistic setting. The acceptability of Internet-delivered interventions for drug and alcohol treatments is also investigated. Participants ($n = 77$) included clients who were receiving outpatient drug and alcohol treatment at a publicly funded health service, including a Specialist Cannabis Clinic. The results indicated that one particular domain of alliance, Bond, was consistently lower, from both client and clinician perspectives, for current cannabis users relative to those not currently using cannabis. Client perceptions of Bond decreased as the severity of cannabis use increased ($r = -0.373$, $p = 0.02$). Cannabis Clinic clients did not report a significantly lower Bond with their clinicians, suggesting that specialized cannabis services may be better placed to provide appropriate treatment for this population than embedding cannabis treatment within traditional drug and alcohol treatment teams. In addition, Internet/computer-based treatments may be one potential way to engage, transition, or retain cannabis users in treatment.

Keywords: cannabis use, therapeutic alliance, treatment engagement, substance misuse, Internet

INTRODUCTION

Cannabis is the most common illicit substance in the US, Australia, and in most developed countries, and is increasing in popularity (1, 2). However, fewer than 10% of cannabis users access treatment for their cannabis use directly (3).

For people with cannabis use problems (as with users of other substances), the effects of the drug itself, multiple co-morbidities, and/or chaotic lifestyles present constant challenges to treatment engagement, often resulting in short windows of opportunity in which to provide treatment (4). However, when cannabis users do attend counseling treatments, including computerized therapy, they report significant improvements in mood and substance use (5).

There is therefore a need for research to target cannabis users in treatment, and to better understand and identify potential strategies to maximize engagement. This is particularly important given the evidence suggesting cannabis users respond better with longer term treatment (5, 6), and that therapeutic alliance may be an important factor in maintaining cannabis users in treatment over the longer term (8, 9).

THERAPEUTIC ALLIANCE

It is generally accepted that forming a strong therapeutic alliance during counseling will improve treatment outcomes (7, 8). Therapeutic alliance is multidimensional, but generally refers to the nature of the affective bond and collaborative relationship between the client and therapist, who are working in cohesion on therapeutic goals and tasks (9, 10). The therapeutic bond is considered a core component of alliance, and is assessed in most therapeutic alliance measures. Bond encompasses the emotional connection, understanding, and support in the client/therapist relationship. Other dimensions of alliance, such as tasks, goals, and partnership, are considered more intellectual and outcome-based, focusing on the client and therapist working jointly toward therapeutic goals (11, 12).

THE EFFECT OF CANNABIS USE ON ALLIANCE AND TREATMENT OUTCOMES

Only one previous study has reported on the relationship between therapeutic alliance and cannabis use. Diamond et al. (13) conducted an investigation using the Cannabis Youth Treatment Study population ($n = 600$) to explore the impact of therapeutic alliance on treatment outcomes and attendance in adolescent cannabis users. Early alliance, as perceived by the clients, predicted fewer days of cannabis use at both 3 and 6 months follow-ups.

A range of factors is suggested to have an impact on the establishment of therapeutic alliance, regardless of the clinical group under consideration. These include mental health severity (in particular symptoms of depression and anxiety), age, and gender (14) and should be considered in any examination of alliance

in treatment. However, other factors, unique to substance using populations and cannabis users in particular, may pose further threats to the establishment of therapeutic alliance in this group. For example, the intoxication and long-term physiological effects of cannabis may in part explain why this group may be challenging to engage and retain in traditional substance abuse counseling treatment. Euphoria, relaxation, time distortion, perceptual alterations, intensified sensory experience, loss of sense of personal identity, difficulties with the formation and retrieval of memories and attention difficulties are associated with the short-term effects of cannabis use (15, 16). Cannabis use also has psychological impacts on anxiety, panic, depression, and psychosis, which can be associated with chronic consumption (17). In addition, research findings by Kay-Lambkin et al. (18) suggested that people who used cannabis presented to a treatment trial with significantly lower levels of functioning [$F(1, 223) = 6.009$, $p = 0.015$], and significantly higher levels of interpersonal sensitivity [$F(1, 216) = 4.674$, $p = 0.032$], than did users of other drugs. Interpersonal sensitivity was indicative of recent distress due to feelings of self-consciousness and inferiority, having feelings easily hurt, and others being unfriendly or disapproving. Cannabis users also reported significantly higher paranoid ideation than did users of other drugs [$F(1, 218) = 9.042$, $p = 0.003$]. These factors are suggestive of the potential difficulties for cannabis users to engage in therapy and could potentially result in them feeling disconnected from the treatment process and their therapist, impacting on alliance. The may be particularly true for the emotional aspects of therapeutic alliance, namely the core component of therapeutic bond.

THE INTEGRATION OF INTERNET-DELIVERED TREATMENTS FOR DRUG AND ALCOHOL CLIENTS

Internet-based treatments may be one-way of improving engagement with cannabis users in a treatment for their cannabis use, given their heightened paranoia, anxiety, and interpersonal sensitivity relative to users of other drugs. Such treatments have been shown to be effective across a number of therapeutic contexts (19), and as the demand for Drug and Alcohol Services has remained strong, the use of Internet-based treatments has grown into the general substance abuse field (20). After comparing Internet-based interventions with traditional psychotherapy, and finding similar results between the two methods, Carroll et al. (21) provide support for the idea of a computer-assisted therapist model to augment the treatment provided by clinicians working in services as a feasible way of improving treatment outcomes. Marsch (22) also supports this idea, claiming that technology-based interventions for substance use disorders can function as "clinician-extenders" to reduce some of the barriers to treatment.

In the first RCT conducted in this area, Kay-Lambkin et al. (5) investigated the clinical efficacy of the SHADE (Self-Help for Alcohol and other drug use and Depression) computer treatment program. It consisted of 10 sessions of combination motivational interviewing and cognitive behavior therapy delivered via a computer program, and was compared to a therapist-delivered equivalent. Results indicated that both computer- and therapist-delivered treatments yielded similar outcomes in substance use and depression at 12-month follow-up. Interestingly, SHADE was most efficacious for people with cannabis use problems and comorbid depression when compared to other substances of concern and therapist-delivered treatment, with SHADE cannabis users reporting twice the reductions in cannabis use as their therapist-delivered counterparts (5).

THE CURRENT STUDY

This study aims to investigate the association between cannabis use and therapeutic relationship within a publicly funded Drug and Alcohol Service, from both client and clinician perspectives, comparing a general counseling and cannabis-specific services. It is hypothesized that current users of cannabis will report lower levels of therapeutic alliance relative to people not currently using cannabis. It will also examine the acceptability of computers/the Internet in providing information about and treatment for alcohol/other drug use, hypothesizing that cannabis users will be more open to these modalities than users of other drugs.

MATERIALS AND METHODS

PARTICIPANTS

A total of 77 client participants who were receiving outpatient drug and alcohol treatment at the Northern Sydney Central Coast Area Health Service (NSCCAHS, NSW, Australia) were recruited to this study. Participants were referred from the teams within the counseling portfolio including; Cannabis Clinic ($n = 21$), Drug and Alcohol Counseling ($n = 50$), and The Magistrates Early Referral into Treatment program (MERIT) ($n = 6$). Participants were aged between 19 and 69, with a mean age of 40. The majority of participants were Australian born ($n = 69$, 89.6%), with 2.6% ($n = 2$) of Aboriginal or Torres Strait Islander decent. One third of participants were living alone ($n = 25$), 31% were living with a spouse and/or children ($n = 24$) and 14% were living with their parents ($n = 11$). Sixty-four percent were unemployed ($n = 49$), 55% were males ($n = 42$) and 46% were single and had never married ($n = 35$). At baseline assessment, 51% ($n = 39$) participants indicated they were seeking treatment primarily for concerns regarding alcohol, 27% ($n = 21$) for cannabis, 9% ($n = 7$) for methamphetamine, 6% ($n = 5$) for tobacco, and 3% ($n = 2$) for heroin and hallucinogens (ecstasy) respectively. Abuse/dependence criteria were not measured as part of the current study, however information provided by the referring clinicians indicated that the majority of the sample ($n = 56$, 72%, those referred via the MERIT and Drug and Alcohol Counseling programs) met DSM-IV criteria for alcohol dependence at study entry. Twenty-one participants (27%, those referred via the Cannabis Clinic) met criteria for cannabis dependence. Participants could have met dependence criteria for several substances concurrently, however all participants with cannabis dependence were referred via the Cannabis Clinic. No participants referred to this service were excluded from participation in the study.

The clinician participants in this study ($n = 16$) were employes of NSCCAHS with tertiary qualifications in psychology ($n = 5$) or nursing ($n = 11$) and were registered in their fields with the relevant professional organization. Participants in the clinician group reported a mean age of 42.90 years (SD = 11.17, Range 25–58) and were, for the most part, female ($n = 11/16$). They all

provided assessment and treatment according to evidence-based psychosocial guidelines (23).

MEASURES

A range of demographic and treatment variables were assessed at the baseline interview. These included age, gender and marital status as per Kay-Lambkin et al. (24).

The Opiate Treatment Index [OTI; (25)] was used to assess the quantity and frequency of alcohol/other drug use across 11 individual substances (alcohol, cannabis, heroin, other opiates, methamphetamine, cocaine, tranquilizers, barbiturates, hallucinogens, inhalants, tobacco). For each substance, clients were asked to report on their last three use occasions in the month prior to assessment, estimating the amount of each drug consumed on each of these occasions. An average use index for the previous month was calculated (OTI *q* score) as an estimate of quantity and frequency of use, with a score of 1 indicating once daily use, 2 twice daily use, and so on. Participants received an OTI *q* score for each substance. Cannabis use (OTI *q* score – Cannabis) was used as a continuous variable in the analysis, and was also categorized according to the following to facilitate comparisons with users of other drugs combined (including alcohol):

"Current cannabis use" – this group included people who reported using any level of cannabis at baseline ($n = 37$) and was compared to people not using any cannabis currently (but were using other drugs including alcohol), as measured by the OTI *q* score ($n = 40$). A proportion of "current cannabis use" participants ($n = 21$, referred via the Cannabis Clinic) met criteria for cannabis dependence, however the remainder ($n = 16$) did not. This provided a group reporting a range of severity of cannabis use to be analyzed. No participants in the comparison group met criteria for cannabis dependence at study entry. All participants, regardless of categorization, could have been using other substances concurrently.

"Cannabis Clinic" – this group included people referred to the study by the Cannabis Clinic clinicians ($n = 21$) and was compared to people seeking treatment from the Drug and Alcohol Counseling and MERIT teams ($n = 56$). The Cannabis Clinic comprised clinicians specifically trained in engaging and treating clients with cannabis use problems, and offers services to people aged 16 years and over who want to quit or reduce their cannabis use (23). All Cannabis Clinic clients met criteria DSM-IV criteria for cannabis dependence (provided by the referring clinician). The comparison group were using a range of substances, but all met criteria for alcohol dependence at study entry.

The DASS-21 (Depression, Anxiety, and Stress Scale) was used to measure depression, anxiety, and stress scores (26). Henry and Crawford (27) assessed the reliability of the DASS-21. A Cronbach alpha of 0.93 for the total measure was found, as well as high reliability for the stress and depression scales and adequate for the anxiety scale (0.93, 0.90, and 0.82 respectively).

The Agnew Relationship Measure (ARM) Client Questionnaire (11) was used to measure therapeutic alliance from both client and clinician perspectives. The dimensions include Bond (acceptance, support, and understanding in the relationship), Partnership (working together of tasks in therapy), Confidence (respect and optimism for the therapist's competence), Openness (client's feeling toward disclosure of personal information without embarrassment or fear), and Client Initiative (client's responsibility for direction in therapy). It consists of 28 items used to measure the five dimensions of the client-therapist alliance. Agnew-Davis et al. (11) rated the internal consistency and found that all dimensions had an alpha value between 0.77 and 0.87, except for Client Initiative, which was 0.55. The ARM has been used in prior drug and alcohol research and also has strong convergent validity with the Working Alliance Inventory [WAI; (28)] another popular method of measuring alliance (12).

The Computer Anxiety Questionnaire which includes a Computer Anxiety rating scale [CARS; (29)] and a Computer Thoughts Survey [CTS; (29)] were used to measure client's opinions and anxiety around using computers. The CARS asks respondents to indicate on a Likert scale ("very much" to "not at all") how anxious each of 20 items would make them feel. The CTS asks respondents to indicate how often they currently have one of 20 specified thoughts when they use a computer or think about using a computer ("not at all" to "very much").

Further questions were also asked to explore clients' openness to using computer/Internet-delivered treatment for their primary drug of concern. The questions included; "*Have you ever used any computer or Internet-delivered treatment for your mental health or drug and alcohol use issues*?" and "*If you were offered computer/Internet-delivered treatment, would you utilize it as part of your treatment for drug and alcohol and/or mental health problems*?" Using a 4-point Likert scale from "not at all" through to "a lot" clients were also asked to rate how much they agreed with the following statements; "*Computer/Internet-delivered treatment could be useful in helping me deal with my alcohol and other drug use*" and "*Computer/Internet-delivered treatment could be useful in helping me find information about alcohol/other drug use.*" The Likert scale questions were then re-coded into two categories (not at all and not much = no, a little and a lot = yes) due to sample size and for ease of analysis.

RESEARCH DESIGN

The detailed methods and study design have been outlined elsewhere (24). The study received ethics approval from the relevant organizations (e.g., Northern Sydney Central Coast Human Research Ethics Committee Approval Number: 08/HARBR/78/79).

Participating clinicians from the Cannabis Clinic and MERIT teams were asked to introduce the research project and gain consent to release their client's contact details to the research team during the initial assessment. It was necessary to ensure that the clients' decision to participate in the research was entirely independent of their treatment with the service, and that if they did not choose to participant their treatment would not be impacted on in anyway. There was a longer waitlist for clients seeking treatment from the Counseling Team therefore consent to release contact details was done while clients were on the waitlist in order to engage them with the research earlier in their treatment episode.

Clients were contacted via phone by the research assistant and invited to participate in the study. At this stage clients were asked if

they agreed to be contacted in 1 week, during which they received and considered the information sheet and consent form for the study. Following the provision of informed consent, assessment measures were collected over the phone, Clients were offered a $20 reimbursement for their time for completing the phone assessments. Clinicians were unaware if the clients they had referred had consented to the research, unless told so by the client in therapy. Clinicians completed therapeutic alliance measure for all clients after the initial session for the duration of the study.

RESULTS

RECRUITMENT

Recruitment for this study was from August 2010 through to April 2011. During this time 166 clients were referred, of which 56 refused participate, 24 were unable to be contacted and 9 did not return their consent documents.

STATISTICS AND DATA ANALYSIS

Chi-square analysis was used to examine the interaction between the two variables "Current cannabis use" (yes/no) and "Cannabis Clinic" (yes/no; $X_1^2 = 28.14$, $p = 0.00$, $n = 77$). All participants referred from the cannabis clinic ($n = 21$, 27% of total) reported cannabis use at baseline. Of the remainder (those referred from the Counseling/MERIT teams), 18 (23% of total) reported current cannabis use, and 38 (49%) reported no current cannabis use. No participant referred from the Cannabis Clinic reported zero cannabis use at baseline. Given the significant overlap between the "Current cannabis use" and "Cannabis Clinic" variables, and the zero value of the cell Cannabis Clinic + no baseline cannabis use, separate one-way Analysis of Variance (ANOVA) are reported for examining relationships between each of the cannabis variables (Current cannabis use and Cannabis Clinic) and the outcome of interest (e.g., therapeutic alliance, depression, anxiety, stress), rather than conducting a two-way ANOVA.

At baseline, participants reported use of a range of substances in the month prior to assessment, including alcohol (Mean = 3.74, SD 5.62 standard drinks per day), heroin (Mean = 0.10, SD 0.31 use occasions per day), cannabis (Mean = 3.86, SD 8.18 use occasions per day), other opiates (Mean = 0.22, SD 0.62 use occasions per day), methamphetamine (Mean = 0.16, SD 0.45 use occasions per day), cocaine (Mean = 0.19, SD 0.61 use occasions per day), tranquilizers (Mean = 0.23, SD 0.62 use occasions per day), barbiturates (Mean = 0.16, SD 0.49 use occasions per day), hallucinogens (Mean = 0.16, SD 0.49 use occasions per day), inhalants (Mean = 0.21, SD 0.62 use occasions per day), and tobacco (Mean = 12.28, SD 12.64 cigarets per day). This was based on participant self-report using the OTI, with a score of 0.14 equating to once weekly use for the prior month, a score of 1 indicating once daily use for the prior month, and so on. Polydrug use was common, with participants reporting an average use of 2–3 drug types in the month prior to baseline (including tobacco; Mean = 2.60, SD 1.55). One-way ANOVAs indicated no significant differences in the use of any drug type (with the exception of cannabis) at baseline for Current versus Non-current cannabis users and participants referred from the Cannabis Clinic versus those who were not. As expected, significantly higher cannabis use was reported by participants referred from the Cannabis Clinic (Mean = 9.39, SD12.17 use occasions per day) versus those referred from the other treatment teams (Mean = 1.50, SD 3.97 use occasions per day; $F(1, 56 = 13.654$, $p = 0.001$). The same was true for Current versus non-current cannabis users.

The impact of demographic variables on client perceptions of therapeutic alliance

A one-way ANOVA revealed that there were no significant differences between age and gender on the therapeutic alliance subscales. The youngest age group (19–30) did score lower, on average, on all five dimensions of the therapeutic alliance than the other age groups, however this was not statistically significant. Overall, there was a trend on the openness dimension of alliance related to age [$F(3, 63) = 2.34$, $p = 0.082$], with Bonferroni *post hoc* analysis indicating that 19–30 year olds scored lower than the other age groups. For gender, males on average scored lower across all of the therapeutic alliance dimensions than females, although these differences were not significant.

The impact of cannabis use on client perceptions of therapeutic alliance

Correlational analysis using cannabis as a continuous variable (OTI q score) was conducted, and revealed a significant negative correlation between the amount of cannabis used and Bond on the client ARM ($r = -0.373$, $p = 0.02$, see **Table 1**). There were no significant correlations found between amount of cannabis use and any other dimension of the client therapeutic alliance measure.

One-way ANOVAs compared past-month cannabis users with those who did not use cannabis in the past month on the dimensions of the client ARM. There was a significant difference found between people using cannabis in the past month and people who did not on the Bond dimension of the ARM, $F(1, 65) = 4.923$, $p = 0.03$. This result, shown in **Table 2**, suggests that clients who use any level of cannabis found it significantly more difficult to develop a therapeutic bond with their clinician at the beginning of treatment than those who did not use cannabis.

The "Cannabis Clinic" group were compared to people engaged with either the counseling or MERIT teams on the client ARM (see **Table 3**). There were no significant differences between these groups on the measures.

The impact of mental health symptoms on therapeutic alliance

There were no significant correlations found between depression, anxiety, and stress (DASS-21) scores and cannabis use in the month prior to survey (OTI q scores, see **Table 1**). In addition, no significant correlations were found between DASS-21 scores and subscales of the ARM.

A one-way ANOVA also indicated no significant difference between current cannabis users and non-cannabis-users on the DASS-21 subscales. However, the mean scores for depression, anxiety, and stress were lower for the "current cannabis" and "Cannabis Clinic" groups, relative to their counterparts (see **Tables 4** and **5**, respectively).

The prediction of client perceptions of therapeutic alliance

Given the associations between cannabis use and the ARM subscale of Bond, a linear regression model was also used to determine the

Table 1 | Pearson correlation analysis for depression, anxiety, stress scores (DASS-21), subscales of the Agnew-Davies Relationship Measure (ARM) of therapeutic alliance (client-rated) and past-month cannabis use (OTI *q* Score).

	DASS-21 depression	DASS-21 anxiety	DASS-21 stress	Past-month cannabis use#
ARM-bond	−0.020	−0.006	0.040	−0.373*
ARM-partnership	0.084	0.118	0.057	−0.196
ARM-confidence	−0.062	−0.114	−0.096	−0.123
ARM-openness	0.103	0.031	0.100	−0.032
ARM-initiative	−0.078	0.069	−0.028	−0.149
DASS-21 depression	###	0.748*	0.883*	−0.063
DASS-21 anxiety	###	###	0.730*	−0.059
DASS-21 stress	###	###	###	−0.078

*$p < 0.05$ #OTI q score.

Table 2 | Current cannabis# users compared to no current cannabis users on client-rated subscales of the Agnew-Davies Relationship Measure of therapeutic alliance.

Therapeutic alliance subscales	*N**	Mean	SD	ANOVA
Bond				
Current cannabis use	33	5.91	0.821	$F(1, 65) = 4.923$,
No current cannabis use	34	6.31	0.674	$p = 0.03$
Partnership				
Current cannabis use	33	5.97	0.848	$F(1, 64) = 0.511$,
No current cannabis use	33	6.13	0.929	$p = 0.477$
Confidence				
Current cannabis use	33	5.81	0.842	$F(1, 65) = 0.853$,
No current cannabis use	34	6.19	2.17	$p = 0.359$
Openness				
Current cannabis use	33	5.21	0.996	$F(1, 65) = 0.040$,
No current cannabis use	34	5.16	1.18	$p = 0.843$
Initiative				
Current cannabis use	33	3.38	0.974	$F(1, 65) = 0.095$,
No current cannabis use	34	3.46	1.05	$p = 0.759$

#*Current cannabis use refers to people who nominated they had used cannabis (at any level) in the month prior to assessment. "No current cannabis use" includes people using a range of substance, but no cannabis, in the month prior to assessment.*

**Note some missing data due to incomplete ARM at baseline.*

independent contribution of cannabis use to this ARM subscale. Predictor variables were included in the model if their univariate significance was <0.1. Based on this criterion, age, gender, and OTI cannabis *q* scores were included in the regression model. The regression equation was statistically significant in predicting Bond [$F(3, 63) = 3.800$, $p = 0.014$, $r^2_{\text{adj}} = 0.113$], with cannabis use being the sole significant predictor ($p = 0.008$).

The impact of cannabis use on clinician perceptions of therapeutic alliance

One-way ANOVAs were also used to compare the clinician ratings of the therapeutic alliance dimensions of the ARM for cannabis users. As shown in **Table 6**, there was a significant difference found between current and non-current cannabis users on the Bond subscale of therapeutic alliance [$F(1, 64) = 4.257$, $p = 0.043$], indicating that clinicians seeing clients who were current cannabis users reported a lower therapeutic bond early in therapy than non-current cannabis users.

There was also a significant difference found for clinician-rated Bond for the "Cannabis Clinic" participants when compared to those from other teams [$F(1, 64) = 5.560$, $p = 0.02$].

Table 3 | "Cannabis Clinic" group compared to other teams (Counseling and MERIT)# on the client-rated subscales of the Agnew-Davies Relationship Measure of therapeutic alliance.

Therapeutic alliance subscales	*N*	Mean	SD	ANOVA
Bond				
Cannabis clinic	19	5.92	0.73	$F(1, 65) = 1.664$,
Counseling/MERIT	48	6.10	0.78	$p = 0.202$
Partnership				
Cannabis clinic	19	5.96	0.94	$F(1, 64)0.272 =$,
Counseling/MERIT	47	6.09	0.87	$p = 0.604$
Confidence				
Cannabis clinic	19	6.53	2.79	$F(1, 65) = 2.758$,
Counseling/MERIT	48	5.79	0.84	$p = 0.102$
Openness				
Cannabis clinic	19	5.51	1.08	$F(1, 65) = 2.474$,
Counseling/MERIT	48	5.06	1.07	$p = 0.121$
Initiative				
Cannabis clinic	19	3.28	1.17	$F(1, 65) = 0.555$,
Counseling/MERIT	48	3.48	0.91	$p = 0.459$

#*Cannabis Clinic participants all met criteria for cannabis dependence at study entry, and were referred via a treatment team specifically trained to engage and treat clients with cannabis use problems. Participants from Counseling/MERIT teams did met criteria for alcohol dependence, but not cannabis dependence, at study entry. Participants in each group could have met dependence criteria for other substances concurrently.*

Table 4 | Current cannabis* users versus non-current users as a function of current depression, anxiety, and stress, as measured by the DASS-21.

DASS-21 subscales	*N*	Mean	SD	ANOVA
Depression				
Current cannabis use	37	16.81	11.99	$F(1, 75) = 0.194$,
No current cannabis use	40	18.10	13.57	$p = 0.661$
Anxiety				
Current cannabis use	37	9.84	10.77	$F(1, 75) = 0.355$,
No current cannabis use	40	11.25	10.02	$p = 0.553$
Stress				
Current cannabis use	37	19.96	10.52	$F(1, 75) = 0.869$,
No current cannabis use	40	22.35	11.84	$p = 0.354$

**Current cannabis use refers to people who nominated they had used cannabis (at any level) in the month prior to assessment. "No current cannabis use" includes people using a range of substance, but no cannabis, in the month prior to assessment.*

Table 5 | A comparison of Cannabis Clinic versus MERIT/Counseling Team[#] participants on measures of depression, anxiety, and stress (DASS-21).

DASS-21 subscales	*N*	Mean	SD	ANOVA
Depression				
Cannabis clinic	21	15.24	9.02	$F(1, 75) = 0.890$,
Counseling/MERIT	56	18.32	13.89	$p = 0.349$
Anxiety				
Cannabis clinic	21	8.10	7.76	$F(1, 75) = 1.669$,
Counseling/MERIT	56	11.50	11.08	$p = 0.200$
Stress				
Cannabis clinic	21	18.51	9.50	$F(1, 75) = 1.685$,
Counseling/MERIT	56	22.21	11.72	$p = 0.198$

[#]Cannabis Clinic participants all met criteria for cannabis dependence at study entry, and were referred via a treatment team specifically trained to engage and treat clients with cannabis use problems. Participants from Counseling/MERIT teams did met criteria for alcohol dependence, but not cannabis dependence, at study entry. Participants in each group could have met dependence criteria for other substances concurrently.

Table 6 | Clinician-rated therapeutic alliance (as measured by the Agnew-Davies Relationship Measure) for current versus non-current cannabis users*.

Therapeutic alliance subscales	*N*[#]	Mean	SD	ANOVA
Bond				
Current cannabis use	32	5.75	1.01	$F(1, 64) = 4.257$,
No current cannabis use	34	6.19	0.70	$p = 0.043$
Partnership				
Current cannabis use	32	6.20	4.50	$F(1, 64) = 0.098$,
No current cannabis use	34	6.53	4.12	$p = 0.756$
Confidence				
Current cannabis use	32	5.26	0.99	$F(1, 64) = 0.740$,
No current cannabis use	34	5.45	0.80	$p = 0.393$
Openness				
Current cannabis use	32	5.28	4.53	$F(1, 64) = 0.260$,
No current cannabis use	34	4.87	1.06	$p = 0.612$
Initiative				
Current cannabis use	32	4.40	1.09	$F(1, 64) = 0.046$,
No current cannabis use	34	4.34	1.09	$p = 0.831$

**Current cannabis use refers to people who nominated they had used cannabis (at any level) in the month prior to assessment. "No current cannabis use" includes people using a range of substance, but no cannabis, in the month prior to assessment.*

[#]Note some missing data due to incomplete ARM at baseline.

This suggested that Cannabis Clinic clinicians reported lower therapeutic bond with their clients early in therapy, see **Table 7**.

No significant differences were found for any other subscale of the clinician-rated therapeutic alliance between Cannabis Clinic participants and their Counseling/MERIT counterparts. However, a non-significant trend emerged for clinicians who see clients at the Cannabis Clinic to report lower confidence in therapy at baseline compared to clinicians from other teams [$F(1, 64) = 2.955$, $p = 0.090$], see **Table 7**.

Table 7 | "Cannabis Clinic" group compared to other teams (Counseling and MERIT)[#] on the clinician-rated subscales of the Agnew-Davies Relationship Measure of therapeutic alliance.

Therapeutic alliance subscales	*N**	Mean	SD	ANOVA
Bond				
Cannabis clinic	18	5.57	0.98	$F(1, 64) = 5.560$,
Counseling/MERIT	48	6.13	0.80	$p = 0.021$
Partnership				
Cannabis clinic	18	5.22	1.18	$F(1, 64)$ 1.790 =,
Counseling/MERIT	47	6.80	4.91	$p = 0.186$
Confidence				
Cannabis clinic	18	5.05	1.03	$F(1, 64) = 2.955$,
Counseling/MERIT	48	5.47	0.82	$p = 0.090$
Openness				
Cannabis clinic	18	5.82	5.88	$F(1, 64) = 1.340$,
Counseling/MERIT	48	4.79	1.27	$p = 0.251$
Initiative				
Cannabis clinic	18	4.11	0.88	$F(1, 64) = 1.439$,
Counseling/MERIT	48	4.46	1.14	$p = 0.235$

[#]Cannabis Clinic participants all met criteria for cannabis dependence at study entry, and were referred via a treatment team specifically trained to engage and treat clients with cannabis use problems. Participants from Counseling/MERIT teams did met criteria for alcohol dependence, but not cannabis dependence, at study entry. Participants in each group could have met dependence criteria for other substances concurrently.

**Note some missing data due to incomplete ARM at baseline.*

Openness to receiving computer-based treatments

Results on the CARS, the CTS, and questions exploring participants' openness to using a computer-delivered treatment were compared between cannabis and non-cannabis groups using a one-way ANOVA (see **Table 8**). There were no significant differences found between the cannabis and non-cannabis groups on the CARS and CTS. There was a tendency for the cannabis users to report lower average scores on the CARS than people using other drugs, particularly for referrals from the Cannabis Clinic ($M = 28.29$) compared to other teams ($M = 31.70$). This indicates that cannabis users were somewhat less anxious about the idea of using a computer, albeit that this was not a statistically significant difference. Conversely, current cannabis users and Cannabis Clinic participants reported fewer positive thoughts about computers, although again, this was not statistically significant.

A continuity-corrected chi squared analysis was used to explore differences between participants on their openness to using an Internet-delivered treatment for their primary substance of concern. Although there were no significant differences observed, a higher proportion of current cannabis users reported previous use of Internet-delivered treatments compared to non-current cannabis users [53 versus 35%; $\chi^2(1) = 0.634$, $p = 0.426$]. Similarly, 62% of people from the "Cannabis Clinic" group reported prior use of Internet-delivered treatments compared to 32% from other teams [$\chi^2(1) = 1.97$, $p = 0.161$]. There was a tendency

Table 8 | Responses to the Computer Anxiety Rating Scale (CARS) and the Computer Thoughts Survey (CTS) as a function of current/non-current cannabis* use and Cannabis Clinic versus Counseling/MERIT participants#.

	CARS	CTS	
	Mean (SD)	**Positive thoughts *Mean (SD)***	**Negative thoughts *Mean (SD)***
Current cannabis use	29.03 (14.01)	22.43 (9.02)	17.59 (9.13)
No current cannabis use	31.70 (12.56)	24.86 (9.03)	19.62 (7.47)
ANOVA	$F(1, 75) = 0.78$, $p = 0.38$	$F(1, 72) = 1.35$, $p = 0.25$	$F(1, 72) = 1.09$, $p = 0.30$
Cannabis clinic	28.29, (11.63)	22.81, (8.86)	19.48, (10.88)
Counseling/MERIT	31.21, (13.83)	23.98, (9.18)	18.26, (7.20)
ANOVA	$F(1, 75) = 0.74$, $p = 0.40$	$F(1, 72) = 0.25$, $p = 0.62$	$F(1, 72) = 0.31$, $p = 0.58$

**Current cannabis use refers to people who nominated they had used cannabis (at any level) in the month prior to assessment. "No current cannabis use" includes people using a range of substance, but no cannabis, in the month prior to assessment.*

#Cannabis Clinic participants all met criteria for cannabis dependence at study entry, and were referred via a treatment team specifically trained to engage and treat clients with cannabis use problems. Participants from Counseling/MERIT teams did met criteria for alcohol dependence, but not cannabis dependence, at study entry. Participants in each group could have met dependence criteria for other substances concurrently.

for cannabis users to think that Internet-delivered treatments could be useful in locating information about or treatment for their primary drug of concern. For example, 87% of current cannabis users people agreed that the Internet would useful in helping them deal with their primary drug, compared to 70% of people with no current cannabis use [$\chi^2(1) = 0.675$, $p = 0.411$]. Ninety-two percent of Cannabis Clinic participants indicated they would utilize Internet-delivered treatment if offered to them, compared with 75% of people referred from other teams [$\chi^2(1) = 0.712$, $p = 0.389$].

DISCUSSION

This is the first study to explore differences in therapeutic alliance for cannabis users compared with users of alcohol or other drugs in a naturalistic setting. The results indicate that one particular domain of alliance, Bond, is consistently different, from both client and clinician perspectives, for current cannabis users relative to people not currently using cannabis. There was evidence for the client's perception of Bond to decrease as the severity of cannabis use increased. Cannabis use remained a significant independent predictor of client-related Bond when age and gender were taken into account via the regression analysis. This was also the case for clinicians' perceptions of Bond. The results are elaborated on below.

THE BOND DIMENSION OF THERAPEUTIC ALLIANCE

The Bond dimension is different from the other therapeutic alliance dimensions. Questions on the Bond dimension of the client ARM include; "*I feel friendly toward my therapist*," "*I feel accepted in therapy no matter what I say or do*," "*I find therapy warm and friendly*," and "*My therapist is supportive*." These statements incorporate emotional language and ask the client to report on their feelings toward the therapist on an individual level. The other core dimensions of alliance measured by the ARM, partnership and confidence, focus more on practical issues and ask the client to comment on the working relationship such as "*My therapist and I agree how to work together*," "*My therapist and I are willing to work hard together*," "*I have confidence in the therapy and the techniques being used*," and "*The professional skills of the therapist are impressive*" (11).

The impact of cannabis on clients' perceptions of Bond

Client perspectives of therapeutic bond were significantly lower for current cannabis users than non-current users however this difference was not seen for the "Cannabis Clinic" groups. Given that the Bond dimension incorporates the emotional attachment between the client and clinician, one possible explanation is that the effects of current cannabis use might impact on a person's ability to form this emotional connection. Perhaps a combination of the lower interpersonal sensitivity, heightened paranoia, loss of personal identity, and anxiety that have been associated with chronic cannabis use (15, 16, 18) result in the client feeling emotionally numbed or disconnected from the clinician during treatment. Anecdotally, current cannabis users often describe a pattern of smoking cannabis throughout the night and first thing when they wake of a morning. It may be that current cannabis users are likely to attend treatment whilst intoxicated by the effects of their drug then people who are seeking treatment for methamphetamine or alcohol who may have a different pattern of use. This may explain the reported differences and difficulties in establishing a therapeutic bond with their therapist.

EXPLORING THE IMPACT OF A SPECIALIZED CANNABIS SERVICE ON PERCEPTIONS OF ALLIANCE

Interestingly, people referred to the study from the Specialist Cannabis Clinic did not report a lower perception of therapeutic bond than clients seeking treatment from other teams. Perhaps this might be explained by treatment motivation. Cannabis Clinic clients typically want to engage in treatment for the purpose of reducing or ceasing their cannabis use. Perhaps, in this context, the partnership with the therapist around tasks and goals is established more easily, allowing the clinician more time to focus on their emotional connection with the client. This is perhaps one demonstration of the benefits and importance of a specialized cannabis treatment team, physically located

separately from people seeking treatment for other drugs, and staffed by specialist clinicians with additional training and support in how to engage and manage people with current cannabis use problems.

Therapist-related factors may also have impacted on this result, as different clinicians were operating across the three clinical settings targeted in the current study. Given the development of therapeutic bond is one involving personal factors, and that the therapist too, brings their own qualities to the therapeutic relationship, it is also possible that these qualities differed across the clinics and thus contributed to the differences in results between clinics. A testament to this was the significantly lower ratings of the clinicians' perspective of Bond, which was significantly lower for Cannabis Clinic clients than for clients from other teams. There was also a trend for clinicians from the Cannabis Clinic to report lower scores on the Confidence dimension then clinicians from other teams, suggesting that Cannabis Clinic clinicians have less confidence and optimism in therapy and their techniques. When considering these results it is important to note that there were a small number of people using cannabis in the other teams and individual clinician differences may have influenced these outcomes. However, these results may also indicate that clinicians working within the Specialized Cannabis Clinic are more aware of the difficulties of engaging cannabis users and in some way account or compensate for the lack of emotional connection with their clients. These findings provide useful information for individuals providing supervision or training for therapists working with cannabis clients.

THE IMPACT OF AGE, GENDER, AND MENTAL HEALTH ON THERAPEUTIC ALLIANCE

In general, there was a tendency for the youngest age group to score lower on the client therapeutic alliance subscales, particularly for Openness. Males also scored consistently lower on the therapeutic alliance measure than females. There were no significant differences found between age and gender on the therapeutic alliance dimensions, in contrast to previous research (14). Perhaps in the current study, the effects of drug use over-ride any potential age and gender differences in the establishment of therapeutic alliance; an issue that warrants further investigation.

There were no significant correlations found between depression, anxiety, and stress (DASS-21) scores, the dimensions on the client therapeutic alliance measure and amount of cannabis use. This finding is similar to Diamond et al. (13) who found no significant impact of mental health symptoms on early therapeutic alliance in their study with young cannabis users. There were also no significant differences found between current and non-current cannabis users on the DASS-21 scores. This may have been due to a ceiling effect, whereby our study participants scored much higher than population norms on the depression, anxiety, and stress subscales. If the notion of the intoxication and chronic effects of cannabis use resulting in a person becoming emotionally disconnected is correct, then perhaps cannabis might impact on a person's own level of insight into their emotional health, given the negative correlation between amount of cannabis use and perceived Bond with their clinician.

EXPLORING THE USE OF COMPUTER-BASED INTERVENTIONS FOR CANNABIS USERS

In general, our hypotheses related to differences between cannabis users and users of other drugs in terms of openness to computer/Internet-delivered treatment modalities were not supported. However, current cannabis users tended to be less anxious than non-current users about the idea of using computers, scoring lower on the CARS. Conversely, the current cannabis group reported fewer positive thoughts about computers than did their counterparts on the CTS. Both of these results were not significant. This finding potentially also supports the above notion of cannabis users being emotionally disconnected from their experiences in general, rather than specifically about the use of computers/the Internet. In this context, however, the potential advantage of this finding is that cannabis users may be willing to at least try alternative modes of delivery of treatment.

A higher proportion of people from the current cannabis use groups reported previous exposure to Internet-delivered treatments; thought that Internet-delivered treatments could be useful managing their primary drug of concern; and were more willing to use Internet-delivered treatment when compared to non-current cannabis users. Although not significant, these results generally highlight the potential of the Internet in supporting treatments for cannabis users. This particular modality of treatment is of relevance because the Internet can increase the reach of therapy outside an individual treatment session, and can overcome logistical and emotional barriers to attending regular treatment appointments with a therapist. Such barriers might include basic issues of organization and functioning, such as getting to the treatment session in a clinic, through to reducing any anxiety or reluctance that might be associated with interacting with a clinician in a treatment program. Internet-delivered treatment could also be used as a transition into therapy for current cannabis using clients by introducing psychological concepts and building insight. Future research could consider these issues specifically for cannabis users relative to those using other drugs.

Previous research has indicated there is no negative impact of computer-based treatments on the therapeutic alliance when integrated with existing psychosocial treatments (30), so given cannabis users reported particular difficulty building a therapeutic bond with their therapist, have heightened paranoia and interpersonal sensitivity, Internet-based treatments may be one potential way to engage, transition, or retain this growing population in treatment.

LIMITATIONS

A limitation of this study was the referral of client participants by clinicians. Due to client confidentiality within the service this method appeared the most ethical option however it did leave the door open for clinician bias. Clinicians may have unintentionally put their own bias on their referrals potentially referring a certain type of client and not referring others. In addition, even though clinicians did not know which of their clients had actually consented to participate in the study they were aware of who had been referred, potentially impacting on their ratings of therapeutic alliance. It may also be difficult to generalize these findings beyond an outpatient treatment setting, as cannabis users who do

not access treatment may be different from those who do. However, it is likely that similar issues with emotional numbing and interpersonal difficulties would be evident in non-treatment seeking cannabis users, and may in fact be pivotal in their decisions not to seek treatment. Future research with general community samples might be important to pursue.

CONCLUSION

Cannabis users can be reluctant to seek treatment and there are often high treatment "drop-out" rates associated with counseling interventions, which have proven effectiveness, and are often preferred (20). Given that service factors have the ability to influence engagement with clients in drug treatment (31) and from the evidence found in this study, it is clear that research needs to focus on the engagement and retention of this particularly difficult client group from a service perspective, and how to better support and train clinicians working with cannabis users. Our results suggest that a focus on developing and improving the therapeutic bond between client and therapist is an important starting point in this process. The implementation of Internet/computer-based interventions for the treatment of cannabis use and associated problems may take us one step closer to improving treatment outcomes. To date, no research has investigated the effectiveness of computerized treatments, integrated with standard psychosocial treatments, specifically with cannabis users in a real world setting.

TRIAL REGISTRATION

Australian Clinical Trial Registration Number: ACTRN12611000382976

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Cannabis use and anxiety: is stress the missing piece of the puzzle?

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Objective: Comorbidity between anxiety and cannabis use is common yet the nature of the association between these conditions is not clear. Four theories were assessed, and a fifth hypothesis tested to determine if the misattribution of stress symptomology plays a role in the association between state-anxiety and cannabis.

Methods: Three-hundred-sixteen participants ranging in age from 18 to 71 years completed a short online questionnaire asking about their history of cannabis use and symptoms of stress and anxiety.

Results: Past and current cannabis users reported higher incidence of lifetime anxiety than participants who had never used cannabis; however, these groups did not differ in state-anxiety, stress, or age of onset of anxiety. State-anxiety and stress were not associated with frequency of cannabis use, but reported use to self-medicate for anxiety was positively associated with all three. Path analyses indicated two different associations between anxiety and cannabis use, pre-existing and high state-anxiety was associated with (i) higher average levels of intoxication and, in turn, acute anxiety responses to cannabis use; (ii) frequency of cannabis use via the mediating effects of stress and self-medication.

Conclusion: None of the theories was fully supported by the findings. However, as cannabis users reporting self-medication for anxiety were found to be self-medicating stress symptomology, there was some support for the stress-misattribution hypothesis. With reported self-medication for anxiety being the strongest predictor of frequency of use, it is suggested that researchers, clinicians, and cannabis users pay greater attention to the overlap between stress and anxiety symptomology and the possible misinterpretation of these related but distinct conditions.

Keywords: cannabis, anxiety, stress, self-medication, path analysis

Globally, cannabis is the most commonly used illicit drug (1) and anxiety is the most prevalent mental disorder (2). Large cross-sectional population-based surveys, such as the Australian *National Survey of Mental Health and Wellbeing*, the United States *National Comorbidity Survey*, and *National Epidemiological Survey of Alcohol and Related Conditions*, consistently find that cannabis users report a higher incidence of anxiety disorders and symptoms than non-cannabis users [e.g., Ref. (3–5)]. Australian data, for example, indicates a 40.5% prevalence rate for anxiety disorders in current cannabis users with a 12-month cannabis use disorders (CUD) and a rate of 20.8% for current users without CUD, in comparison to 11.2% for non-users (5). As such, the existence of comorbidity between anxiety and cannabis use is well known.

Similarly, well known is that the subjective effects of acute cannabis intoxication, which typically include feelings of euphoria and relaxation, also include feelings of anxiety and/or paranoia for a significant proportion of users (6, 7). Thus, many people report using cannabis to relieve symptoms of stress and/or anxiety, while concurrently some users report experiencing acute anxiety symptoms when intoxicated (8). Inconsistent with both of these types of user experiences, Tournier et al. (9) found no evidence for the anxiolytic (i.e., anxiety-reducing) or anxiogenic (i.e., anxiety inducing or increasing) effects of cannabis use in daily life when using an experience sampling method. Tournier et al. (9) also failed to find a significant association between state-anxiety and cannabis use, but found that use was associated with agoraphobia. Cannabis use has also been found to be related to panic disorder [e.g., Ref. (10, 11)], social phobia [e.g., Ref. (10)], and posttraumatic stress disorder [e.g., Ref. (12)], yet other studies have reported that cannabis use disorder is unrelated to anxiety disorders other than social anxiety disorder [e.g., Ref. (13)], or that associations between cannabis use and anxiety are non-significant after controlling for confounders [e.g., Ref. (14)].

These apparent contradictions suggest that there is a need to more clearly distinguish between the different types of anxiety (i.e., state-anxiety, drug-induced anxiety) that occur in the context of cannabis use. There is also clearly a need to clarify *how* cannabis use is related to the development and perpetuation of anxiety

and/or how anxiety contributes to the use of cannabis. Furthermore, it is important to investigate whether the common tendency for lay people to use the words "anxiety" and "stress" interchangeably, which stems from a lack of awareness of the distinguishing features of each (15) has contributed to the mixed results evident in the literature investigating cannabis use and anxiety.

THE RELATIONSHIP BETWEEN CANNABIS AND ANXIETY

Four main theories have been proposed to explain the relationship between cannabis use and anxiety (16), each of which has supporting evidence. The *common factor theory* proposes that the associations found between cannabis and anxiety exist because both have common antecedents, which may include biological, social, and environmental factors such as childhood trauma, personality, and socioeconomic adversity (16–18). This theory is supported, for example, by the findings from two longitudinal studies, the *Netherlands Mental Health Survey and Incidence Study* (19) and the *Christchurch Health and Development Study* [e.g., Ref. (20)], where associations between cannabis use and anxiety were non-significant after potential confounding factors were taken into account.

The *self-medication hypothesis* proposes the association exists because individuals experiencing anxiety are motivated to use cannabis to alleviate their negative affective symptoms (16, 18, 21). This theory is concordant with prior study results indicating that stress relief, relaxation, and anxiety/tension reduction are the most common reasons for cannabis use (22, 23), and that cannabis can induce anxiolytic effects (24). Further supporting evidence comes from past findings that a large proportion of individuals with comorbid anxiety and CUD experience the onset of their anxiety disorder prior to the onset of cannabis use (3). Moreover, Buckner and Carroll's (25) finding that reductions in anxiety symptomology within a cannabis-dependent sample led to reduced cannabis use, but that reductions in cannabis use did not lead to decreased levels of anxiety, also support the self-medication hypothesis.

The third theory posits a direct *causal association* between cannabis use and anxiety, whereby the use of cannabis increases the risk of the subsequent development of an anxiety disorder (16, 18). This hypothesis is consistent with clinical observations that panic symptoms can occur during or immediately after cannabis use (26, 27), suggesting that the drug might also directly contribute to, or at least augment, anxiety symptoms (18, 28). It is also supported by findings from longitudinal studies, such as the *Victorian Adolescent Health Cohort Study* [e.g., Ref. (17, 18)], where frequent cannabis use during adolescence has been found to be associated with greater risk for subsequent anxiety disorders during adolescence and early adulthood, even after potential confounding factors were controlled statistically.

The final, somewhat unifying, theory suggests that the associations between cannabis use and anxiety can be explained by a *reciprocal feedback loop*, with simultaneous causation between cannabis use and anxiety arising from *common factors,* and where each condition leads to the exacerbation of the other through *direct causality* and/or *self-medication* (16). This theory is supported in part by the findings from Van Dam et al.'s (29) investigation of differences between clinically anxious and non-anxious heavy cannabis users (daily/near daily use for 12 months or longer). Anxious users consumed more cannabis (in grams) per week, reported more cannabis use-related problems, and had higher levels of depression and schizotypal symptomology than non-anxious users, yet the groups were matched demographically and did not differ in relation to age at onset of cannabis use, average high, or duration of use. The authors noted that these findings suggest anxiety that may be causally related to the development of abuse/dependence for heavy users of cannabis. This proposition is somewhat supported by findings from the longitudinal *CanDep* study, which followed frequent cannabis users (used >3 times per week for at least 12 months) over 3 years (10, 30).

Cross-sectional analysis of the baseline *CanDep* data comparing non-users to dependent and non-dependent users found that dependent users were more likely to experience anxiety disorders than non-dependent users and non-users, with these two latter groups reporting comparable levels of anxiety (10). Similar to Van Dam et al. (29), van der Pol et al. (10) found that the two cannabis user groups did not differ in relation to key cannabis use factors, including age of first use and onset of regular use, duration, and frequency of use. However, in contrast to Van Dam et al. (29), van der Pol et al. (10) found that dependent and non-dependent users also did not differ in relation to the quantity of cannabis used (number of joints per day, dose). Nevertheless, dependent users were more likely than non-dependent users to use cannabis alone, use for coping and expansion motives, to be experiencing a mood disorder, and to report other current substance use (10).

As such, these two cross-sectional studies (10, 29) suggest that there is a subgroup of frequent cannabis users that is more prone to experience cannabis dependence and anxiety (as well as other psychopathology) than other users with similar exposure to cannabis use. These studies do not tend to shed light on the direction and/or existence of any causal relationships between cannabis use and anxiety. This issue is, however, addressed by longitudinal findings from the *CanDep* study (30), where non-dependent frequent users were followed from baseline for 3 years to investigate the development of cannabis dependence. In this study, anxiety was not found to be predictive of dependence, nor was dependence predicted by cannabis exposure (e.g., age at onset, frequency, quantity, dose, etc.) or any of the many stable factors that are commonly considered to be risk factors for dependence (e.g., childhood adversity, demographics, etc.) that were assessed in the study. Rather, cannabis dependence was predicted by living alone, coping motives for use, and stress (measured as number of negative recent life events).

STRESS, ANXIETY AND CANNABIS USE

Other than van der Pol et al.'s (30) study, no prior studies appear to have investigated the distinction between stress and anxiety in cannabis users. Anxiety and stress are overlapping but quite distinct states. For example, the *stress* subscale of the Depression Anxiety Stress Scales (DASS) asks respondents about tension, persistent arousal symptoms, irritability, and difficulty relaxing, whereas the *anxiety* subscale asks about symptoms of arousal/tension and *fear-related* symptoms and cognitions (31). Hence, while autonomic arousal is a core feature of both states, suggesting that there may be a natural continuity or overlap between the two syndromes, there are salient differences between the disorders, such that fear

cognitions occur in anxiety but not in high stress conditions. In the past, researchers have experienced substantial difficulties in separating the two constructs (31), so it is likely that cannabis users may also not appreciate the salient differences between the two states.

Accordingly, we advance a fifth explanation for the associations seen between anxiety and cannabis use, the *stress-misattribution hypothesis*, which suggests that some proportion of the associations evident between anxiety and cannabis are due to users misattributing their stress symptomology, believing that they are actually symptoms of anxiety. This hypothesis fits within the self-medication hypothesis, such that users reporting self-medication to relieve anxiety symptomology are expected to in fact be self-medicating stress/tension rather than (or in addition to) anxiety symptoms. Additionally, it is posited that this hypothesis is in keeping with the reciprocal feedback loop hypothesis, with stress playing a central role, along with anxiety, in the escalation of cannabis use and, in turn, also being exacerbated by increased cannabis use.

Consistent with this hypothesis, there is evidence in the literature to suggest that cannabis users are exposed to more stressors than non-users, and dependent users to more again than non-dependent users. In a review of the literature investigating stress as a risk factor for cannabis use/misuse, Hyman and Sinha (32) identified family dysfunction, social disadvantage, and maltreatment (i.e., physical, emotional and sexual abuse, and neglect) during childhood as stressful conditions commonly found to be associated with both early onset of cannabis use and later dependence, while trauma occurring during adulthood (e.g., interpersonal violence, combat trauma) and chronic stress were similarly implicated in the development of cannabis dependence. These types of traumatic life/events and life stressors are typically reported more often by cannabis users than non-users, and by dependent users than non-dependent users [e.g., Ref. (10, 20, 33)]. The model put forward by Hyman and Sinha (32) links these stress-inducing life events/circumstances to altered stress responses and coping deficits/disruptions and then the consumption of cannabis for coping motives and an associated increased frequency of cannabis use. These changes are posited to cause neuroadaptations in the stress and reward circuits (e.g., via cannabis-related activation of the hypothalamic-pituitary-adrenal [HPA] axis and increased dopamine release), with an exacerbating cycle then eventuating, whereby chronic cannabis use is associated with maladaptive coping and poor life decisions, which lead to increased stressors/stress/distress and, thus, increased cannabis use for coping/relief. As such, this cycle of exacerbation is consistent with the reciprocal feedback loop theory.

It is possible that maladaptive coping and/or poor decision-making in everyday life may be associated with a range of other differences commonly seen between cannabis users and non-users. For example, cannabis users are more likely than non-users to be unemployed/welfare dependent and single/living alone, and more likely to report lower levels of education, income, and life and relationship satisfaction [e.g., Ref. (10, 14, 30, 34)], with these life circumstances often associated with, or indicative of, higher levels of stress/stressors in everyday life. Further to this, the diagnostic distinctions drawn between cannabis use and cannabis abuse/dependence (DSM-IV) or cannabis use disorder (DSM-5) reflect, at least in part, an escalation of stressors in an individual's life. For example, an individual experiencing use-related social/interpersonal problems (i.e., interpersonal stress) as well as physical or psychological use-related problems (e.g., health-related stressors) meets DSM-5 criteria for cannabis use disorder (35). Thus, by definition alone, dependent users may be experiencing higher levels of stress in their everyday lives than non-dependent users.

Furthermore, the rapidly growing body of research investigating the endocannabinoid system and, specifically, its inhibitory role in the modulation of neuronal and behavioral stress responses [e.g., Ref. (36–38)], also provides support for the existence of stress-related differences between cannabis users and non-users. Essentially, the psychoactive effects resulting from cannabis ingestion are caused by the binding of exogenous cannabinoids (e.g., THC, CBD) to cannabinoid receptors (CB_1, CB_2) within the endocannabinoid system. In part, this impedes the ability of endogenous cannabinoids (i.e., 2-AG, AEA) to bind with these receptors, disrupting the usual functioning of the endocannabinoid system. The endocannabinoid system is central to the regulation of emotion and acute and chronic stress responses, also acting to constrain basal activation of the HPA axis (39). Consistent with this, cannabis ingestion has been found to activate the HPA axis, particularly when used in high doses, with recent research suggesting that frequent cannabis use may result in persistent hyperactivity of the HPA axis (38). Thus, increased endocannabinoid signaling is associated with reductions in stress and anxiety symptomology and, conversely, disruption of signaling is associated with stress, anxiety, and depression (40).

To summarize, epidemiological data indicate that cannabis users report greater exposure to historical stressors (e.g., childhood maltreatment) and stressful circumstances in everyday life (e.g., unemployment/welfare dependence) than never/non-users, and dependent users report higher levels of these stressors as well as cannabis use-related stressors than non-dependent users. Frequent cannabis use may alter the functioning of the endocannabinoid system, affecting the modulation of HPA axis stress responses, and, thereby, increasing cannabis users' vulnerability to stress and anxiety. Further, it is possible that cannabis users who are experiencing stress but not anxiety, or stress and anxiety, may misattribute at least some of their stress symptoms to anxiety. As such, individuals reporting the use of cannabis for the self-medication of anxiety symptoms may actually be (at least in part) medicating symptoms of stress/tension rather than symptoms of anxiety. This would be consistent with findings that more cannabis users report using the drug to reduce stress/tension than to reduce their anxiety (22, 23).

THE CURRENT STUDY

Each of the four theories outlined above should predict a different pattern of results in relation to the association between anxiety and cannabis use. The *common factors* theory suggests that cannabis use is inconsequential to the development of anxiety, whereas the *self-medication*, *direct causation,* and *reciprocal feedback loop* theories suggest differing roles for cannabis use in the development and management of anxiety symptoms. The proposed *stress-misattribution* hypothesis suggests that misidentification of stress symptomology may account for at least part of the association commonly reported between cannabis use and anxiety. Thus,

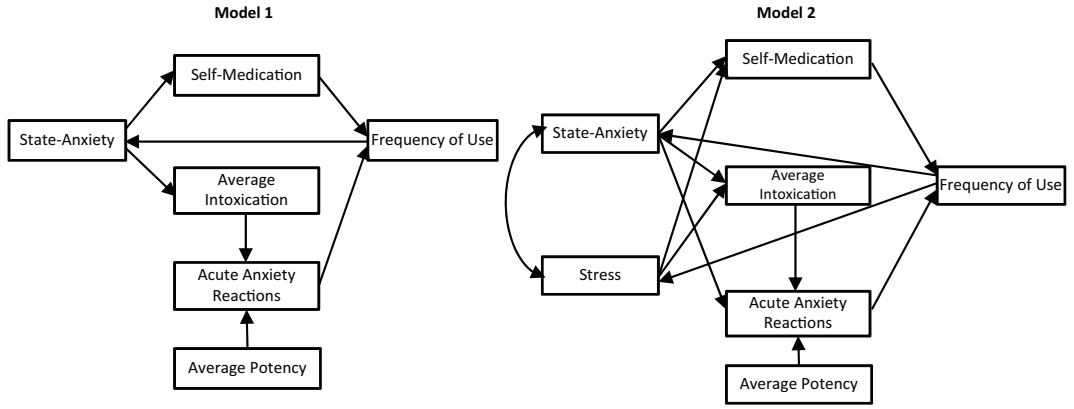

FIGURE 1 | Proposed models with reciprocal feedback loop between anxiety and cannabis use variables: (1) without stress; (2) including stress.

in this study, we examined the relationship between stress, anxiety, and cannabis use to test the ability of these different theories to explain the commonly reported association between cannabis use and anxiety.

Accordingly, it was hypothesized that:

1) if cannabis use and anxiety are associated solely because of *common underlying factors*:
   a) current and past users will be more likely to report lifetime anxiety than participants who have never used cannabis, with prevalence for current and past users being similar and
   b) current and past users will not differ in relation to state-anxiety, but will report higher levels than participants who have never used cannabis,
2) if the anxiety experienced by cannabis users is *caused by their cannabis use:*
   a) current users will have higher levels of state-anxiety than both past users and participants who have never used cannabis and
   b) an exposure/dose–response relationship will be evident, with levels of state-anxiety reported by current users predicted by acute anxiety reactions and/or cannabis use factors (i.e., frequency, potency, intoxication), after controlling for potential confounding variables,
3) if anxious people use cannabis to *self-medicate* their symptoms of anxiety:
   a) frequency of self-reported use of cannabis for self-medication purposes by current users will be predicted by state-anxiety, after controlling for potential confounding variables and
   b) the frequency of cannabis use reported by current users will be predicted by state-anxiety and frequency of reported use for self-medication, after controlling for potential confounding variables,
4) if the association between anxiety and cannabis use involves a *reciprocal feedback loop* path analysis will indicate good fit for a model with cannabis use for self-medication of anxiety central to the reciprocal associations between anxiety-related variables (i.e., state-anxiety, acute anxiety reactions) and cannabis use variables (i.e., frequency of use, potency, intoxication), as per Model 1 in **Figure 1**, and
5) if the *stress-misattribution hypothesis* posited above is relevant:
   a) current cannabis users will report higher levels of stress symptomology than both past users and participants who have never used cannabis, with the latter two groups also differing,
   b) levels stress symptomology reported by current users will be more strongly predictive of both self-medication and frequency of use than state-anxiety in relation to hypotheses 3a and 3b, and
   c) the best fit path analysis model will indicate stress symptomology, which is an integral aspect of the associations between anxiety and cannabis use variables, as per Model 2 in **Figure 1**.

METHOD

PARTICIPANTS

Participants were primarily recruited via advertisements placed on online forums and message boards relevant to cannabis use (e.g., www.cannabisculture.com) or anxiety and panic disorder (e.g., www.panicsurvivor.com). In addition, some participants were recruited through the University of New England's (Australia) Research Participation Opportunities program, which enables first-year psychology students to receive course credit for participation in a range of available studies. The single inclusion criterion was being aged 18 years or older.

The anonymous online questionnaire was completed by 321 participants (52.0% male) aged between 18 and 71 years ($M = 32.3$ years; SD = 11.92). Most respondents were employed (61.7%) or university students (25.9%), with small proportions being either unemployed (8.9%) or retired (3.5%). The vast majority of participants (86.0%, $N = 267$) reported using cannabis at least once in their life, with 53.9% ($N = 173$) using it during past 12 months. In relation to other substance use, 43% drank alcohol at least weekly, 37.8% were current tobacco smokers, and 12.1% had used another illicit drug at least once in their lifetime.

One-fifth of the current cannabis users reported using it on a daily basis (21%), while 45% used weekly, 11% monthly, and 23% used less frequently. Cannabis using participants most commonly consumed it by smoking a joint (36.6%), with fewer typically using a bong/waterpipe (16.8%), and 31.6% reporting both methods. The most common preparation type consumed was heads/buds (64.0%), with the use of leaf (10.6%) and hash/resin (3.0%) being less common; 22.4% of cannabis users reported using a range of preparation types.

MATERIALS

The questionnaire collected demographic data (i.e., age, gender, employment status) and contained a range of items designed to assess various aspects of cannabis use and mental health. Qualtrics Online Survey Software was used for the questionnaire.

Participants were asked if they had ever tried *cannabis* and, if so, their *age at first use*. Those who had used cannabis were also asked to report whether or not they had used cannabis in the past 12 months. These questions were used to categorize participants into three cannabis use groups: never used, past use, and current use.

Current cannabis users were asked a number of additional questions about their use of cannabis in the previous 12 months. *Frequency of use* was assessed on a 9-point scale (1 = "only once or twice" to 9 = "every day"). *Average potency* of cannabis consumed was assessed by asking participants how often (0 = "never" to 4 = "every time") they used cannabis with six different levels of potency (1 = "very weak" to 6 = "extremely strong"). Scores could range from 4 ("very weak" * "every time") to 24 ("extremely strong" * "every time"). Similarly, *average level of intoxication* was calculated by asking participants how often (0 = "never" to 4 = "every time") they experienced six different levels of intoxication (1 = "not intoxicated" to 6 = "very stoned"), with scores ranging from 4 ("not intoxicated" * "every time") to 24 ("very stoned" * "every time"). Frequency of *acute anxiety reactions* was assessed by asking current cannabis users to report how often they had felt anxious or panicky when using cannabis (1 = "never" to 5 = "every time"), while use to *self-medicate for anxiety* was assessed by asking current users how often they had used cannabis to reduce feelings of anxiety (1 = "never" to 5 = "every time"). All of these items specified that respondents answer in relation to their use/experience of cannabis in the previous 12 months.

History of anxiety was assessed by asking respondents if they had ever experienced anxiety (1 = "never" to 6 = "this is always an issue for me"), with this item used to classify participants in relation to *lifetime anxiety* (0 = "no," 1 = "yes"). All affected participants were asked to report the age at which they had first experienced anxiety. This item, in conjunction with reported age at first use of cannabis, was used to determine *pre-existing anxiety* (0 = "no," 1 = "yes"). Participants were also asked to report whether there was a history of anxiety and/or depression within their family (0 = "no," 1 = "yes").

State-anxiety and *stress* were assessed using the 42-item version of the DASS (31). Participants rated the extent to which each state had been experienced over the past week using a 4-point scale (0 = "did not apply to me at all" to 3 = "applied to me very much or most of the time"). Each of the three subscales, depression, anxiety, and stress, consists of 14 items and has a maximum scoring range of 0–42, with higher scores indicating higher levels of the relevant state. Convergent and discriminant validity of the DASS is reported to be adequate and internal consistency reliabilities for the DASS subscales are high, with subscale Cronbach's alphas ranging from 0.90 to 0.95 (41). In this study, Cronbach's alphas for the subscales were high, ranging from 0.93 to 0.97. For the purposes of this study, only results relating to the anxiety and stress scales are reported.

PROCEDURE

To gain access to the online questionnaire, participants clicked on the link that was provided to them in the recruitment message. They were first presented with an information page outlining the purpose of the study and providing relevant information to enable informed consent to participate to the study. If consent was indicated, participants were then directed to the first page of the questionnaire. It took approximately 20 min for questionnaire completion. This study was conducted with full human research ethics committee approval.

STATISTICAL ANALYSES

Due to the large number of hypotheses and overlapping analyses planned to test them, a summary is provided in **Table 1**.

A chi-squared analysis was used to test hypothesis 1a, with the three cannabis use groups (never, past, current) compared in relation to prevalence of lifetime anxiety (yes, no). Hypotheses 1b, 2a, and 5a were tested with two one-way analysis of variances (ANOVAs) examining cannabis use group (never, past, current) differences in state-anxiety and stress. Pearson's bivariate correlation coefficients were calculated on data from current cannabis users to identify variables (independent and potential confounds) for inclusion in the three hierarchical multiple regression analyses that were completed to test hypotheses 2b (dependent variable [DV]: state-anxiety), 3a/5b (DV: self-medication), and 3b/5b (DV: frequency of use). A fourth hierarchical multiple regression analysis, with acute anxiety reactions as the dependent variable, was completed to assist in the development of a path analysis model. All these statistical analyses were completed using IBM SPSS Statistics 22 Software.

Finally, path analyses were completed to test hypotheses 4 and 5c. Three models were tested: state-anxiety only (Model 1, depicted in **Figure 1**), state-anxiety and stress (Model 2, depicted in **Figure 1**), and a third model that was informed by the results from the correlation and hierarchical regression analyses (Model 3, depicted in **Figure 4**). Path analyses were performed in IBM SPSS Amos 22 using the maximum likelihood method of estimation. In accordance with Hu and Bentler (42), good model fit was assessed using the combination of chi-squared ($\chi^2 > 0.05$), the Tucker–Lewis index (TLI > 0.95), comparative fit index (CFI > 0.95), and root mean square error of approximation (RMSEA < 0.05).

RESULTS

DIFFERENCES BETWEEN CANNABIS USE GROUPS

As can be seen in **Table 2**, participants in the three cannabis use groups were found to differ in relation to gender and age, with current users younger on average than past users and the current use group containing disproportionately more males than the other two groups. Lifetime anxiety rates were also found to

Table 1 | Statistical analyses planned to test each theory and hypothesis.

Theory and hypotheses	Planned analyses
1. Common underlying factors	
a. Lifetime anxiety: CU = PU > NU	Chi-square: cannabis group × lifetime anxiety
b. State-anxiety: CU = PU > NU	ANOVA: IV = cannabis group, DV = state-anxiety
2. Anxiety caused by cannabis use	
a. State-anxiety CU > PU and NU	ANOVA: IV = cannabis group, DV = state-anxiety
b. State-anxiety: exposure/dose-response for CU	Regression: IV = cannabis use factors, DV = state-anxiety
3. Self-medication	
a. Self-medication predicted by state-anxiety	Regression: IV = state-anxiety, DV = self-medication
b. Frequency of use predicted by state-anxiety and self-medication	Regression: IV = state-anxiety, self-medication DV = frequency
4. Reciprocal feedback loop	
Cannabis use for self-medication of state-anxiety central to reciprocal associations	Path analysis: Model 1
5. Stress misattribution	
a. Stress: CU > PU > NU	ANOVA: IV = cannabis group, DV = stress
b. Stress stronger predictor of self-medication and frequency of use than state-anxiety	Regression: IV = state-anxiety, stress, DV = self-medication
c. Cannabis use for self-medication of stress central to reciprocal associations	Path analysis: Model 2

CU, current users; PU, past users; NU, never used; IV, independent variable; DV, dependent variable.

Table 2 | Means and standard deviations (SD) and cannabis use group differences.

	Never used (NU; $N = 45$)	Past use (PU; $N = 102$)	Current use (CU; $N = 173$)	All ($N = 320$)	Group differences
Gender (% male)[a]	33%	40%	64%	52%	CU > PU and NU***
Current age[b]	32.3 (13.95)	37.1 (10.71)	29.5 (11.19)	32.3 (11.92)	CU < PU***
Lifetime anxiety[a]	40%	72%	68%	65%	NU < CU and PU**
State-anxiety[b]	5.7 (9.75)	5.3 (7.26)	5.3 (6.77)	5.3 (7.39)	Nil
Stress[b]	8.6 (10.05)	10.8 (9.19)	8.7 (8.99)	9.4 (9.23)	Nil
Depression[b]	8.3 (12.06)	8.4 (10.25)	7.5 (9.56)	7.9 (10.15)	Nil
Age at anxiety onset[b]	20.1 (12.88)	19.6 (8.60)	17.4 (7.62)	18.5 (8.75	Nil
Age cannabis onset[b]	–	16.9 (3.95)	16.3 (5.07)	16.5 (4.69)	Nil
Family history anxiety[a]	50%	66%	53%	57%	Nil
Family history depression[a]	59%	75%	65%	68%	Nil

[a] *Chi-squared analyses;*

[b] *ANOVAs; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.*

differ between the three user groups. Specifically, 40.0% ($n = 18$) of the participants who had never used cannabis reported having experienced anxiety at some time during their lifetime, which was significantly lower than the 67.6% ($n = 117$) of current users and 71.8% ($n = 73$) of past users who reported lifetime anxiety: $\chi^2(2, N = 321) = 15.03$, $p = 0.001$. However, no cannabis use group differences were found in relation to state-anxiety [$F(2,290) = 0.06$, $p = 0.944$, $\eta^2 < 0.001$] or stress symptomology: $F(2,290) = 1.71$, $p = 0.182$, $\eta^2 = 0.012$ (see **Table 2**).

ASSOCIATIONS BETWEEN VARIABLES

The inclusion of independent (IV) and potentially confounding (CV) variables in the four hierarchical multiple regressions was guided by the Pearson's bivariate correlation analyses results for current cannabis users (see **Table 3**), with CVs entered at step 1 and IVs entered in subsequent steps in the analyses.

In the first regression analysis, a significant proportion of variance in state-anxiety was predicted by current age, pre-existing anxiety, average intoxication, and acute anxiety reactions: $R = 0.43$, Adj. $R^2 = 0.16$, $F(4,126) = 7.02$, $p < 0.001$. However, acute anxiety reactions ($\beta = 0.27$, $p = 0.003$) were the only significant predictors in the final model (see **Table 4**). In the second regression analysis, the use of cannabis for self-medication of anxiety was significantly predicted by pre-existing anxiety, state-anxiety, and stress: $R = 0.35$, Adj. $R^2 = 0.10$, $F(3,150) = 6.79$, $p < 0.001$. While state-anxiety was a significant predictor in the second model of this regression ($\beta = 0.23$, $p = 0.004$), it was no longer significant ($\beta = 0.06$, $p = 0.587$) once stress was entered. As such, stress ($\beta = 0.25$, $p = 0.021$) was the only significant predictor of self-medication in the final model (see **Table 4**).

The third regression analysis, investigating frequency of cannabis use, contained only two variables: acute anxiety reactions

Table 3 | Correlations between key variables for current cannabis users.

	1	2	3	4	5	6	7	8	9	10
State-anxiety	–									
Stress	0.690***	–								
Lifetime anxiety	0.355***	0.404***	–							
Pre-existing anxiety	0.181*	0.116	0.252**	–						
Acute anxiety reactions	0.355***	0.329***	0.257**	0.061	–					
Self-medication	0.257**	0.309***	0.398***	0.182*	−0.082	–				
Frequency of use	0.014	0.074	0.135	0.109	−0.179*	0.459***	–			
Average intoxication	0.286***	0.352***	0.131	0.076	0.355***	−0.022	−0.166*	–		
Average potency	−0.073	0.076	−0.038	−0.027	−0.031	0.106	0.262**	0.134	–	
Age at 1st use	−0.006	−0.019	<0.001	0.223**	−0.151	0.072	−0.021	−0.078	−0.136	–
Current age	−0.231**	−0.095	−0.127	−0.120	−0.245**	0.033	0.099	−0.320***	0.060	0.276***
Gender	−0.034	0.133	−0.024	0.011	0.102	−0.123	−0.144	−0.024	−0.085	−0.091

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Table 4 | Summary of hierarchical regression analyses for variables predicting state-anxiety, self-medication, frequency of use, and acute anxiety reactions.

	Model 1			Model 2			Model 3		
	B	***SE B***	β	***B***	***SE B***	β	***B***	***SE B***	β
State-anxiety	$R^2 = 0.080$; F for $\Delta R^2 = 5.36$**			$R^2 = 0.125$; F for $\Delta R^2 = 6.45$*			$R^2 = 0.187$; F for $\Delta R^2 = 9.24$**		
Current age	−0.13	0.05	−0.21*	−0.09	0.05	−0.15	−0.07	0.05	−0.11
Pre-existing anxiety	2.32	1.22	0.17	2.07	1.19	0.15	2.14	1.16	0.15
Average intoxication				0.65	0.26	0.23*	0.41	0.26	0.14
Acute anxiety reactions							1.78	0.59	0.27**
Self-medication	$R^2 = 0.038$; F for $\Delta R^2 = 5.85$*			$R^2 = 0.089$; F for $\Delta R^2 = 8.37$**			$R^2 = 0.122$; F for $\Delta R^2 = 5.43$*		
Pre-existing anxiety	0.53	0.22	0.19*	0.42	0.22	0.15	0.42	0.22	0.15
State-anxiety				0.04	0.15	0.23**	0.01	0.02	0.06
Stress							0.04	0.02	0.25*
Frequency of use	$R^2 = 0.029$; F for $\Delta R^2 = 4.05$*			$R^2 = 0.221$; F for $\Delta R^2 = 33.52$***					
Acute anxiety reactions	−0.47	0.23	−0.17*	−0.37	0.21	−0.13			
Self-medication				0.96	0.16	0.44***			
Acute anxiety reactions	$R^2 = 0.058$; F for $\Delta R^2 = 5.74$*			$R^2 = 0.124$; F for $\Delta R^2 = 3.47$*			$R^2 = 0.141$; F for $\Delta R^2 = 0.90$		
Current age	−0.02	0.01	−0.24*	−0.01	0.01	−0.17	−0.01	0.01	−0.16
Frequency of use				−0.05	0.04	−0.12	−0.06	0.04	−0.15
Average intoxication				0.09	0.05	0.22*	0.07	0.05	0.16
State-anxiety							0.01	0.02	0.06
Stress							0.01	0.02	0.09

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

and use of cannabis for self-medication of anxiety. Together these variables accounted for 21% of variance in frequency of cannabis use [$R = 0.47$, Adj. $R^2 = 0.21$, $F(2,138) = 19.27$, $p < 0.001$]; however, only self-medication ($\beta = 0.44$, $p < 0.001$) explained a significant proportion of variance in the final model. In the final regression analyses, the five predictor variables explained 9% of variance in acute anxiety reactions to cannabis use: $R = 0.38$, Adj. $R^2 = 0.09$, $F(2,148) = 2.29$, $p = 0.016$. Nevertheless, none of the variables independently explained a significant amount of variance in the final model (see **Table 4**).

MODEL TESTING

Path analyses were completed to test three alternate models of the relationships between anxiety and cannabis use variables. The first model included state-anxiety but not stress (see **Figure 2**). The second model included both state-anxiety and stress (see **Figure 3**). The third model also included both state-anxiety and stress, but differed from the second model in that it was informed by the correlation and hierarchical multiple regression findings. As such, pre-existing anxiety was included as a variable and average potency was excluded. Furthermore, the paths

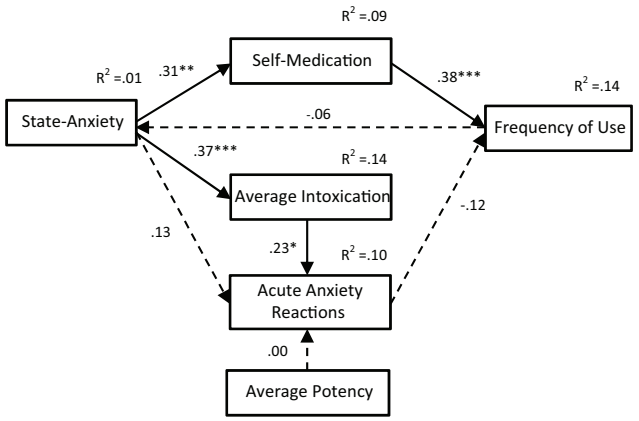

FIGURE 2 | Path analysis of Model 1. With the exception of noted R^2 values, all values are standardized regression weights (β), dashed lines indicate non-significant associations. Model fit: $\chi^2(7) = 11.12$, $p = 0.133$; TLI = 0.804; CFI = 0.909; RMSEA = 0.079 (0.000, 0.162). $^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

between variables in this third model were guided by suggested mediation effects indicated within the regression results. That is, when an IV was significant in one regression model and then became non-significant after the addition of a second IV, this suggested that the relationship between the first IV and the DV in question may be mediated by the second IV. For example, in the second regression analyses, state-anxiety was a significant predictor of self-medication until stress was entered, thus suggesting that the association between state-anxiety and self-medication is mediated by stress. This third model is illustrated in **Figure 4**.

The fit indices for all three path analysis models are displayed in **Table 5**. A non-significant chi-squared result indicates that the proposed model is consistent with the data; all three path models met this criterion for good model fit. The TLI typically ranges from 0 to 1 (values occasionally fall slightly outside this range) with values greater than 0.95 indicative of a good fit; only Model 3 met this criterion. Similarly, the CFI ranges from 0 to 1 with values above 0.95 being indicative of good fit; Models 2 and 3 met this criterion. RMSEA values also range from 0 to 1; however, values less than 0.05 are considered indicative of good fit; only Model 3 met this criterion. These results indicate that Models 1 and 2 do not fit adequately with the data. In contrast, the fit indices for Model 3 indicate an excellent fit.

The path analysis results for Model 3 indicate that: (1) pre-existing anxiety is associated with increased levels of state-anxiety ($\beta = 0.22$, $p = 0.026$), which is then associated with increased levels of stress symptomology ($\beta = 0.75$, $p < 0.001$), with this in turn associated with increased frequency of use of cannabis to self-medicate for anxiety symptoms ($\beta = 0.45$, $p < 0.001$), leading to increased frequency of cannabis use ($\beta = 0.36$, $p < 0.001$); (2) state-anxiety is associated with higher average levels of intoxication ($\beta = 0.34$, $p < 0.001$), which is associated with more frequent acute anxiety reactions ($\beta = 0.23$, $p = 0.025$). While non-significant, the positive association between acute anxiety reactions and state-anxiety ($\beta = 0.16$, $p = 0.120$) and the negative associations with self-medication ($\beta = -0.18$, $p = 0.056$) and frequency of use ($\beta = -0.13$, $p = 0.168$) contributed nonetheless to the amount of variance explained within the model.

DISCUSSION

This study aimed to clarify the nature of the associations evident between cannabis use and anxiety variables and to explore the role of stress within these relationships. To do this, key elements of each of the four theories commonly posited to explain the relationship between cannabis use and anxiety were tested. Additionally, a fifth possible explanation for the associations evident between cannabis use and anxiety was posited, with the stress-misattribution hypothesis based on the possibility that stress/tension symptomology could be misconstrued as anxiety, thus contributing, at least in part, to the high levels of comorbidity reported between anxiety and cannabis use. A large number of hypotheses were tested, with mixed results. These will be discussed in turn, and are summarized in **Table 6**.

The *common factors theory* suggests that cannabis use and anxiety are unrelated, with apparent associations simply the by-product of underlying factor/s that lead to the development of cannabis use and anxiety independently (16–18). The veracity of this theory was tested by comparing the prevalence rates of lifetime anxiety across three cannabis use groups: never used, past use, and current use. In line with the hypothesis, the prevalence of lifetime anxiety was significantly lower in the never used group than for past and current use groups, with the latter two groups having similar levels of prevalence. This finding is consistent with reported differences in comorbidity commonly reported from large epidemiological studies for non-and current users [e.g., Ref. (3–5)]. The second hypothesis testing the common factors theory was also supported, with current and past cannabis users found to be experiencing similar levels of state-anxiety. The lack of difference between these groups suggests that current exposure to cannabis does not increase levels of state-anxiety and vice versa. Together these findings support the common factor theory by indicating that the tendency to use cannabis and experience anxiety is highly comorbid but, with state-anxiety found not to be associated with current cannabis use, it is suggested that such comorbidity is associated with a common underlying factor (e.g., childhood adversity or maltreatment).

It is important to note, however, that to be consistent with the core argument of this theory, individuals who have never used cannabis should report lower levels of state-anxiety on average than both current and past cannabis users. This was not found in the present study. Further to this, if comorbidity between lifetime anxiety and cannabis use is due to common factors occurring during childhood/adolescence that are disproportionately experienced by cannabis users (past and current) in comparison to never users, then we would also expect to see the onset of any anxiety occurring at an earlier age for individuals who had used cannabis than for individuals who had not. This was also not evident for the present sample. As such, the common factors theory is partially supported by these results, yet it seems that the assumed distal events/circumstances responsible for independently increasing the incidence of lifetime anxiety and cannabis use for some individuals

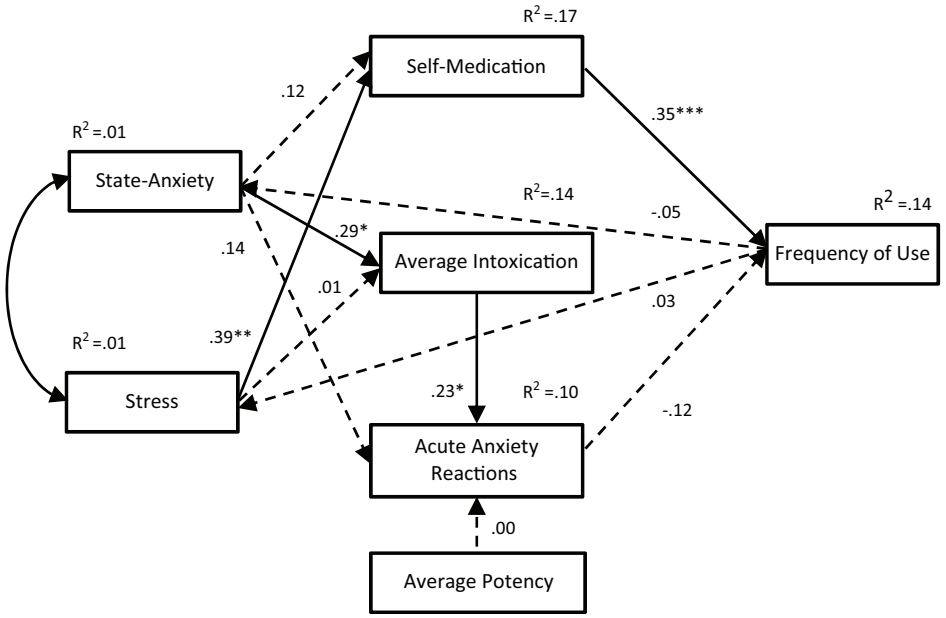

FIGURE 3 | Path analysis of Model 2. With the exception of noted R^2 values, all values are standardized regression weights (β), dashed lines indicate non-significant associations. Model fit: $\chi^2(9) = 13.23$, $p = 0.152$; TLI = 0.924; CFI = 0.967; RMSEA = 0.070 (0.000, 0.146). $^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

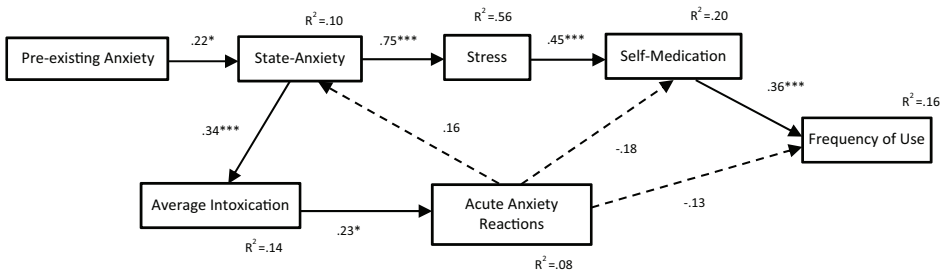

FIGURE 4 | Path analysis of Model 3. With the exception of noted R^2 values, all values are standardized regression weights (β), dashed lines indicate non-significant associations. Model fit: $\chi^2(12) = 9.96$, $p = 0.620$; TLI = 1.027; CFI = 1.000; RMSEA = 0.000 (0.000, 0.089). $^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

Table 5 | Fit indices for the path analysis models.

	Model 1 State-anxiety	Model 2 State-anxiety and stress	Model 3 State-anxiety and stress with mediation
χ^2	$\chi^2(7) = 11.12$, $p = 0.133$	$\chi^2(9) = 13.23$, $p = 0.152$	$\chi^2(12) = 9.96$, $p = 0.620$
TLI	0.804	0.924	1.027
CFI	0.909	0.967	1.000
RMSEA	0.079 (0.000, 0.162)	0.070 (0.000, 0.146)	0.000 (0.000, 0.089)

may not result in ongoing repercussions that lead to subsequent increased levels of state-anxiety.

Similarly, reported stress symptomology did not differ significantly between the three cannabis use groups. These findings may suggest that the current cannabis users in the present study were no more afflicted by proximal or distal stressors than past users or those who had never used cannabis, which would be inconsistent with past research [e.g., Ref. (10, 14, 20, 30, 33, 34)]. However, as the participants were not specifically asked about life stressors (current or past), as per van der Pol et al. (30), we cannot rule out

Table 6 | Summary of findings in relation to each theory and hypothesis.

Theory and Hypotheses	Outcome
1. Common underlying factors	
a. Lifetime anxiety: CU = PU > NU	Supported
b. State-anxiety: CU = PU > NU	Partial: CU = PU = NU
2. Direct causation	
a. State-anxiety CU > PU and NU	Rejected: CU = PU = NU
b. State-anxiety: exposure/dose-response for CU	Partial: only intoxication, but became non-significant when acute anxiety reactions added as IV
3. Self-medication	
a. Self-medication predicted by state-anxiety	Partial: became non-significant when stress added as IV
b. Frequency of use predicted by state-anxiety and self-medication	Partial: predicted by self-medication, not state-anxiety (or stress)
4. Reciprocal feedback loop	
Cannabis use for self-medication of state-anxiety central to reciprocal associations	Rejected: Model 1 met only one of the four fit criteria
5. Stress misattribution	
a. Stress: CU > PU > NU	Rejected: CU = PU = NU
b. Stress stronger predictor of self-medication and frequency of use than state-anxiety	Partial: for self-medication but not frequency of use
c. Cannabis use for self-medication of stress central to reciprocal associations	Rejected: Model 2 met two of the four fit criteria
d. Adjusted model, informed by correlation and regression findings	Supported: Model 3 met all four fit criteria

CU, current users; PU, past users; NU, never used; IV, independent variable; DV, dependent variable.

the possibility that there were unassessed group differences, such that past users and those who had never used cannabis may have been exposed to a similar or greater number stressors than the current cannabis users. Nevertheless, this finding is not consistent with the *stress-misattribution hypothesis* put forward in this paper.

The *direct causation theory* proposes that the association between cannabis use and anxiety is causal, with cannabis use causing anxiety in otherwise unaffected individuals (16, 18). For this theory to hold, we would expect to see an exposure/dose relationship between cannabis use and anxiety. Two hypotheses were proposed to test this. As noted above, the first of these, that current cannabis users would report higher levels of state-anxiety than both past and never used groups, was not upheld for the present sample. This finding suggests that current exposure to cannabis use is not associated with increased state-anxiety. Similarly, the lack of group differences discussed above in relation to stress symptomology suggests that current exposure to cannabis is not associated with increased stress/tension.

The second hypothesis involved investigating cannabis dose-related variables (i.e., frequency, potency, and intoxication) and acute anxiety reactions as predictors of state-anxiety. Interestingly, bivariate analyses indicated that neither frequency of use or average potency was significantly related to state-anxiety. Intoxication was found to account for a significant amount of variance in state-anxiety, after controlling for current age and pre-existing anxiety, in the regression analyses. However, this association was no longer significant after acute anxiety reactions was entered into the analysis, with this variable being the only significant predictor of state-anxiety in the final regression model. Given the moderately strong bivariate association indicated between level of intoxication and acute anxiety reactions, and the known links between them [e.g., Ref. (6, 43)], this result is not altogether surprising. Nevertheless, these findings suggest that there is not a direct causal relationship between cannabis use and state-anxiety but, rather, that higher levels of intoxication can induce acute anxiety reactions, which may then lead to increased levels of state-anxiety for some users – acute anxiety reactions are estimated to occur in 20–30% of users (6).

The *self-medication hypothesis* posits that the association between cannabis use and anxiety is due to anxious individuals using cannabis to relieve their anxiety symptoms (16, 18, 21). If this is the case, then state-anxiety should be positively associated with, and predictive of, the frequency with which cannabis is used specifically to relieve symptoms of anxiety. This hypothesis was partially upheld, with state-anxiety accounting for a significant proportion of variance in self-medication after controlling for pre-existing anxiety. However, once stress was entered into the regression analysis, state-anxiety was no longer significant. While this finding is evidently related to the large overlap in variance between state-anxiety and stress ($R^2 = 0.56$), it is also suggestive of a mediation effect, whereby the effects of state-anxiety on self-medication are mediated by the effects of stress – self-medication was more strongly associated with stress ($r = 0.31$) than state-anxiety ($r = 0.26$) in the bivariate analyses.

The second hypothesis proposed to test the self-medication hypothesis, that frequency of cannabis use would be predicted by state-anxiety and use for self-medication, was also partially upheld. As noted above, state-anxiety was not associated with frequency of use; however, there was a strong positive association indicated between self-medication and frequency of use. Putting these findings together, it appears that any impact of state-anxiety (or stress) on frequency of use comes by way of self-medication. That is, individuals experiencing state-anxiety and/or stress who use cannabis to relieve their symptomology tend to use cannabis more frequently than unaffected/less affected individuals, and it is the stated use of cannabis for such self-medication purposes that

seem to drive frequency of use rather than actual levels of symptomology. Hence, there is some support here for the veracity of the self-medication hypothesis, but it appears that an individual's belief that they are using cannabis to relieve anxiety symptoms is more indicative of their frequency of use than the actual severity of the symptomology for which they are self-medicating. Additionally, they are more likely to be self-medicating symptoms of stress than of state-anxiety.

Evidently, these associations between anxiety, stress, and self-medication provide support for the *stress-misattribution hypothesis* posited in the current paper, being consistent with the idea that cannabis users may be misattributing symptoms of stress/tension to anxiety. That is, affected individuals may believe that they are using cannabis to relieve symptoms of anxiety, and thus report use for the self-medication of this disorder, while, in fact, what they are experiencing are symptoms of stress (e.g., tension, persistent arousal symptoms, irritability, and difficulty relaxing) as well as, or instead of, symptoms of anxiety [e.g., arousal/tension and fear-related symptoms and cognitions; (31)]. It should be noted, however, that stress was not found to be associated with frequency of cannabis use. Thus, even though cannabis users may misidentify the condition for which they are self-medicating, experiencing more severe stress/tension symptomology was not found to be directly associated with increased frequency of cannabis use.

Path analyses were used to test the *reciprocal feedback loop* hypothesis, which posits that cannabis use and anxiety result from common factors but then act to exacerbate each other through direct causality and/or self-medication (16). Two models were tested, one with (Model 1) and one without (Model 2) stress included as a variable. In Model 1, two significant paths were indicated: (i) from state-anxiety to average intoxication to acute anxiety reactions and (ii) from state-anxiety to self-medication to frequency of use. However, paths from state-anxiety and average potency to acute anxiety reactions and from frequency of use to state-anxiety were not significant. Furthermore, this model only met one of the four fit criteria. Model 2 was a better fit with the data, meeting two of the criteria, suggesting that the addition of stress to the model was an improvement. While the path from state-anxiety to average intoxication to acute anxiety reactions remained significant in this second model, the association between state-anxiety and self-medication in the second path was no longer significant. Rather, the significant path ran from stress to self-medication to frequency of use. Nevertheless, the majority of associations between variables proposed in this variable was non-significant, and the model was not deemed to be a good fit for the data. Therefore, a third model was developed, with the correlation and hierarchical regression results used for guidance.

In Model 3, the pathway from state-anxiety to average intoxication to acute anxiety reactions remained significant, but was lengthened with the addition of a positive association from pre-existing anxiety to state-anxiety. The second pathway was also modified, now running from pre-existing anxiety to state-anxiety to stress to self-medication to frequency of use. Pathways from acute anxiety reactions to state-anxiety (positive), self-medication (negative), and frequency of use (negative) were not found to be significant. Thus, Model 3 suggests that pre-existing anxiety (i.e., onset of anxiety prior to any cannabis use) is associated with higher levels of state-anxiety, which is then associated with higher levels of stress symptomology, leading individuals to self-medicate with cannabis and use cannabis more frequently. Additionally, it is suggested that higher levels of state-anxiety are associated with higher average levels of intoxication, which increases the frequency with which acute anxiety reactions are experienced. This model was found to be an excellent fit with the data, exceeding suggested cutoffs for all four fit indices (42).

This model provides some support the self-medication hypothesis, on the proviso that self-medication is primarily for stress symptomology, but does not support the direct causation theory. If pre-existing anxiety is considered a possible indicator of adverse events/circumstances in childhood/early adolescence, the model could be deemed to be somewhat consistent with the common factors theory. However, as this model does not include any variable that is representative of early cannabis use (age at onset of cannabis use was not significantly associated with any other cannabis variables, state-anxiety, self-medication, acute anxiety responses, or stress), the analysis cannot reasonably be considered to assess the common factors theory in any meaningful way. Nevertheless, Model 3 is somewhat consistent with the reciprocal feedback loop theory, indicating that state-anxiety, and through its pre-existing anxiety, plays a role in the escalation of cannabis use via stress and self-medication, while also playing a role in the exacerbation of acute anxiety reactions via increased average levels of intoxication. It is important to note that, in the model, neither frequency of use nor average intoxication was found to be predictive of state-anxiety, stress, or self-medication and associations between acute anxiety reactions and state-anxiety and self-medication were not significant. Hence, these findings are not in keeping with the theory's central argument that cannabis use exacerbates state-anxiety.

The model does support the stress-misattribution hypothesis, suggesting that participants reporting self-medication of anxiety were likely to be treating stress symptomology instead of, or as well as, anxiety symptomology. Such an interpretation is consistent with prior study results indicating that the most common reason for cannabis use is to relieve stress/tension and anxiety [e.g., Ref. (8, 22)]. Further to this, Model 3 is consistent with the posited mood amplification effects of cannabis, which suggests that people with underlying anxieties may be especially vulnerable to experience acute adverse drug effects (43). The model is also concordant with study results indicating that anxiety may occur during or after cannabis intoxication (27, 44). Additionally, the results are consistent with Van Dam et al.'s (29) finding that clinically anxious heavy drug users exhibited greater drug use than non-anxious heavy drug users.

A number of limitations may, however, have lessened the veracity of the study results. First, an online survey methodology was used to capture self-reported anxiety symptoms from a general population, rather than clinical, sample, thus limiting the generalizability of the findings. Further to this, clinical anxiety diagnosis details were not collected or verified. Second, while current users were asked to report the potency of the cannabis they typically consumed, there was no opportunity for them to report the actually effects of use (beyond intoxication) to reflect known differences in effects associated with different cannabis species/breeds/hybrids

or growing techniques (e.g., high vs low THC and CBD content, hydroponic vs naturally grown, etc.). Further to this, it is possible that the variations in potency encountered by cannabis users could increase the likelihood of anxiety-related experiences of use, such as when there is a higher than expected level of THC, which is not accounted for by the users (i.e., through titration of dose). Third, it is possible that some participants may have mixed tobacco with their cannabis or used other substances concurrently, potentially confounding the observed findings. Fourth, while the path models appear to suggest causal pathways between the variables, the fact that the data were cross-sectional means that causal inferences cannot be drawn. Furthermore, as there is a large range of variables that have been found in past studies to be associated in some way with cannabis use and/or anxiety that were not assessed in this study, it is possible that important factors may have been overlooked.

Nevertheless, the results of this study have important implications for the prevention and treatment of anxiety/stress disorders in cannabis users. These may also be of some benefit in relation to cannabis use-related panic attacks, which could be similarly related to stress misattribution. First, while cannabis users often report using the drug to relieve anxiety, they may actually be self-medicating symptoms of stress, the symptoms of which are readily treated by a range of well-accepted stress-reduction techniques. For example, highly stressed cannabis users could be provided with alternate stress-reduction techniques (i.e., relaxation training, physical exercise, mindfulness exercises) to reduce their symptoms of stress/anxiety and prevent the escalation in cannabis use that appears to be associated with its use for self-medication purposes. Second, cannabis users with pre-existing or current anxiety may be particularly vulnerable to experience the anxiogenic effects of cannabis, especially if they get highly intoxicated when the consume cannabis. Such individuals could be advised to restrict sessional intake/dose to reduce the likelihood of experiencing acute cannabis-related anxiety reactions. Furthermore, as two different anxiety-related paths were indicated, though both including the link from pre-existing anxiety to state-anxiety, treatments could be tailored to reflect that individuals vulnerable to experiencing acute anxiety reactions to cannabis use do not appear to be the same individuals who are using cannabis for self-medication purposes.

In summary, the findings provided some support for all of the theories, with the exception of the direct causation theory. However, none of the theories was fully supported. The common factors theory was supported by the finding that participants who had never used cannabis were less likely to report lifetime anxiety than either past or current cannabis users, but was not consistent with the finding that the three groups did not differ in relation to age at onset of anxiety, or their levels of state-anxiety or stress. The self-medication theory holds only if it is broadened to account for the treatment of stress symptoms and also acknowledges that cannabis users' belief that they are self-medicating anxiety is a stronger predictor of frequency of use than the actual severity of the anxiety symptomology they report they are relieving. The reciprocal feedback loop theory was only partially supported by the link from state-anxiety to intoxication to acute anxiety responses. However, with frequency of use not being predictive of state-anxiety, there was no clear feedback loop to support the premise that cannabis use exacerbates state-anxiety. These results suggest that the relationship between cannabis use and anxiety is complex and likely to be obscured, at least in part, by the misidentification of overlapping symptoms of stress and anxiety. As such, the posited stress-misattribution hypothesis was partially supported.

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Marijuana, *feijoada* and the debate on drug legalization

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Feijoada is one of the most typical dishes of Brazilian cuisine, commonly made from a mixture of black beans and several cuts of pork and beef. It is served with rice, *farofa* (toasted, seasoned manioc flour), sautéed collard greens, and sliced oranges, among other side orders. In the most sophisticated recipes it can take more than 30 ingredients, including spices and side dishes. One does not have to be a cook, chef, or expert to distinguish beans—the main ingredient of the dish—from complete *feijoada*.

Marijuana, the popular name of *Cannabis sativa*, has more than 400 compounds, many of which are named "cannabinoids" (substances that affect receptors carrying the same name) (Pate, 2002). In an analogy with *feijoada*, Δ9-tetrahydrocannabinol (Δ9-THC), responsible for the psychoactive effects of the drug (Zuardi, 2008), could be the beans.

In the early twentieth century, when the active principles of the drug had not yet been isolated, marijuana extracts were marketed by large pharmaceutical companies for a number of indications (Fankhauser, 2002). However, the therapeutic use declined within a few years due to the difficulty in obtaining reproducible effects and to the introduction of other drugs for the same indications of marijuana at that moment. Marijuana extracts have a wide variability in their composition, stability, and potency. Thus, consonant with the principles of the evolution of pharmacotherapy, effort has been put into the development of purer cannabinoid compounds that can be accurately measured, thus reducing the risk of significant undesirable side effects.

In the first half of the 1960s the chemical structures of the major cannabinoids were determined by Professor Raphael Mechoulam from Israel, including Δ9-THC. Around 80 cannabinoids have been described to date, with different effects and many with therapeutic potential.

Cannabidiol (CBD), for example, which makes up to 40% of marijuana extracts, has several effects opposite to those of Δ9-THC, including anxiolytic and antipsychotic properties (Crippa et al., 2010). Differently from Δ9-THC, the use of CBD alone does not cause the typical effects of marijuana, and Brazilian, American, British, and Israeli groups are in the leading edge of research on the therapeutic potential of this compound (Carlini, 2010). Today, CBD is being tested in Brazil in Parkinson's disease, schizophrenia, social phobia, post-traumatic stress disorder, smoking, epilepsy, depression, and other conditions (Crippa et al., 2010; Schier et al., 2012).

It can be said, therefore, that cannabinoids are components of marijuana, but that the two are not synonyms. That is, cannabinoids are not marijuana.

Marijuana is the most commonly used illicit drug in many countries, despite evidence showing that it may cause transient psychiatric symptoms and cognitive alterations depending on the dose. Moreover, chronic marijuana use may also cause long-lasting cognitive alterations and trigger the onset of psychiatric disorders in vulnerable individuals, depending on the dose, frequency, and earliness of use (Solowij et al., 2002; Manrique-Garcia et al., 2012), although these findings are still under debate.

The marijuana withdrawal syndrome has gained increased recognition and it is known that some individuals may develop dependence (Hasin et al., 2008). Currently available therapeutic interventions—both pharmacological and non-pharmacological—have shown less than optimal efficacy. Modern neuroimaging studies show alterations in brain function with chronic, repeated use of marijuana (Bhattacharyya et al., 2012). Furthermore, clinical complications such as cancer and breathing and immunological problems have also been associated with the use of the drug. However, as cannabis is often smoked in conjunction with tobacco and/or other drugs, the relationship between chronic use and these problems is so far inconclusive (Lader, 2009).

Therefore, the effects of chronic marijuana use on health need careful evaluation. The existing evidence about these effects is also confounded and misleading, as it considers marijuana and cannabinoids to be equivalent.

All scientific debate concerning the legalization of marijuana should necessarily be informed by empirical data from clinical trials and epidemiological studies. Any debate occurring on a background of political positions, ideological biases and, even worse, personal beliefs will only increase confusion, and postpone concrete decisions.

Cannabinoids and drugs that act in the endocannabinoid system have been shown to have a fantastic therapeutic potential and there is reason to believe that they could benefit millions of people worldwide. A better understanding of the mechanisms of action of these compounds, with the ensuing legalization of cannabinoids, would be an outstanding scientific breakthrough, leading to a significant decrease in burden, and improved quality of life for people with many diseases and disorders. Conversely, the debate on the legalization of marijuana for recreational purposes should only take place after society and the scientific community is clearly informed about the potential complications of the drug or its possible low-risk profile. In order to do this, however, it is crucial to separate the wheat from the chaff, beans from *feijoada* or—in this case—cannabinoids from marijuana.

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Does cannabidiol protect against adverse psychological effects of THC?

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The recreational use of cannabis can have persistent adverse effects on mental health. Delta-9-tetrahydrocannabinol (THC) is the main psychoactive constituent of cannabis, and most, if not all, of the effects associated with the use of cannabis are caused by THC. Recent studies have suggested a possible protective effect of another cannabinoid, cannabidiol (CBD). A literature search was performed in the bibliographic databases PubMed, PsycINFO, and Web of Science using the keyword "cannabidiol." After removing duplicate entries, 1295 unique titles remained. Based on the titles and abstracts, an initial selection was made. The reference lists of the publications identified in this manner were examined for additional references. Cannabis is not a safe drug. Depending on how often someone uses, the age of onset, the potency of the cannabis that is used and someone's individual sensitivity, the recreational use of cannabis may cause permanent psychological disorders. Most recreational users will never be faced with such persistent mental illness, but in some individuals cannabis use leads to undesirable effects: cognitive impairment, anxiety, paranoia, and increased risks of developing chronic psychosis or drug addiction. Studies examining the protective effects of CBD have shown that CBD can counteract the negative effects of THC. However, the question remains of how the laboratory results translate to the types of cannabis that are encountered by real-world recreational users.

Keywords: tetrahydrocannabinol, cannabidiol, cannabis, psychosis, anxiety, drug dependence, cognition

Tetrahydrocannabinol (THC) is the main psychoactive substance in cannabis. Cannabidiol (CBD) is a cannabinoid that appears in cannabis resin but rarely in herbal cannabis. In recent years, many positive attributes have been ascribed to CBD. Is cannabis that contains CBD less harmful than cannabis without CBD? Are people who smoke cannabis resin, therefore, less susceptible to psychosis or less likely to become addicted than are people who smoke herbal marijuana? In this article, several of the health aspects of CBD will be reviewed. The article will focus on the role played by CBD in contributing to the psychological effects that are experienced during recreational cannabis use.

PHARMACOLOGY

Cannabis sativa contains more than 80 different cannabinoids, of which THC is principally responsible for the pharmacological actions, including the psychoactive effects. THC binds to specific proteins in the brain – the cannabinoid receptors (CB-Rs) (1). Two different receptors have been discovered: the CB1 and CB2 receptors (2, 3). CB1-R is mainly found in the central nervous system (CNS); CB2-R is predominantly present in the immune system (3–5). Endocannabinoids are naturally occurring substances that attach to these receptors (6–8).

Cannabinoid receptors, endocannabinoids, and the enzymes involved in the synthesis and degradation of these substances together form the endocannabinoid system (9). The activation of the CB-Rs affects the actions of various neurotransmitters, such as acetylcholine, dopamine, GABA, glutamate, serotonin, norepinephrine, and endogenous opioids (10, 11). Under normal physiological circumstances, CB-Rs are activated by endocannabinoids (12). The activation of CB-Rs by endocannabinoids inhibits excessive neurotransmitter release. Endocannabinoids are lipid-soluble compounds, which prevent them from traveling long distances within the brain. As a consequence of this feature, endocannabinoids are ideally suited for small-scale, local physiological processes (13).

Tetrahydrocannabinol mimics the effect of endocannabinoids. In contrast to these substances, THC is not rapidly broken down at the site of operation, and it not only works at specific locations but simultaneously activates all CB receptors throughout the brain (14).

The mechanisms by which CBD exerts its effect are not precisely known, but it is clear that the pharmacological actions of CBD follow from many different mechanisms [for reviews, see Ref. (15, 16)]. CBD weakly binds to CB-Rs but is capable of antagonizing the effects of THC, even when the former is present in low doses. By inhibiting the degradation of the endogenous cannabinoid anandamide, CBD intensifies, and prolongs its effect (17). The (extended) presence of anandamide prevents THC from interacting with CB-Rs. CBD also interacts with several other recently discovered CB-Rs, and it is an agonist for the 5-HT_{1A} receptor (18, 19), which may explain some of the antipsychotic and anxiolytic effects of CBD (20). Through its effect on intracellular calcium concentrations, CBD might protect neurons against the possible neurotoxic effects of THC (21). CBD itself has almost no effect

on normal physiological processes. Only when a stimulus (such as pain or a shock reaction) or another cannabinoid (such as THC) upsets the normal "tone" of the endocannabinoid system is the effect of CBD expressed (12).

The amount of CBD administered, the ratio of CBD to THC and the timing of administration all seem to be important in determining the possible effects of CBD (22, 23). Most clinical studies on the effects of CBD are not relevant for generalizing to the effects of CBD in "recreational" cannabis users. In many of these studies, the doses that have been used are not relevant to the situation typically encountered by recreational cannabis users.

Clinical research has focused on the physical effects of cannabis use, such as pain relief, appetite promotion, and inflammation. For recreational cannabis users, the substance's psychological effects are the most important. In many experimental studies, the routes of administration used for both THC and CBD are not comparable to the routes of administration found in recreational cannabis use. The high dosages of CBD that have been used in experimental studies increase the concentration of CBD in the blood to levels that can never be reached by smoking a joint. The method that is most comparable to smoking is exposure through a vaporizer, but little research has been conducted involving the administration of cannabis, THC, or CBD via a vaporizer (24, 25). Therefore, it is unknown to what extent the effects of a single administration procedure can be extrapolated to recreational cannabis users given such differences in usage patterns.

TOXICOLOGY OF CBD

Research on the pharmacological and toxicological properties of CBD has been performed on different types of animals. In general, the metabolism of CBD in different species seems similar to that observed in humans, but some differences exist (26). It is possible that differences in metabolism and kinetics among different species have been responsible for some of the observed differences in pharmacological and toxicological effects.

Little research has focused on the safety and side effects of CBD in humans. However, several studies have described the effects of CBD for therapeutic applications in clinical trials. Only a few, generally mild side effects have been observed after administration of CBD in these human studies, though a wide range of effects over a wide dose range, including acute and chronic administration, have been examined. Few undesirable effects are reported, and tolerance for CBD does not seem to occur.

Based on an extensive literature review, Bergamaschi and colleagues concluded that CBD, to the extent that it has been studied, is a substance with low toxicity (27). Notably, however, the absence of harmful effects of CBD in humans has been described in research that was not primarily aimed at investigating these same side effects or toxicities of CBD. Because no specific research on these issues has been performed, it is currently impossible to draw conclusions about differences in toxicity between hashish and marijuana.

Chronic cannabis use is associated with psychiatric toxicity and cannabis has been implicated in the etiology of long-term psychiatric conditions (28). Several *in vivo* brain scanning techniques have been conducted to investigate whether chronic, heavy cannabis use leads to structural changes in the brain [for reviews, see Ref. (29, 30)]. The results of these studies have been relatively inconsistent. In general, no differences in total brain volume between cannabis users and non-users have been found. With respect to CB1 receptor concentrations in different parts of the brain, it can be expected that structural changes after chronic intensive cannabis use would most likely eventually be situated in the orbitofrontal cortex (OCC), the anterior cingulate cortex (ACC), the striatum, the amygdala, and the hippocampus (31–33). In some structural magnetic resonance imaging (sMRI) studies, reductions in the volumes of the hippocampus, the amygdala, and the cerebellum have been found in adult heavy cannabis users when compared with healthy controls (21, 34, 35). Using a PET scan technique, Wilson and colleagues found age-dependent morphological changes in early-onset cannabis users. In subjects who started their cannabis use before the age of 17, it has been found that the ratio of cortical gray to white matter is smaller when compared with subjects who had started using cannabis after their 17th birthdays (36). Structural abnormalities due to chronic cannabis use have been most consistently identified in the hippocampus (21, 34, 35). Using a voxel-based morphometry (VBM) approach, Demirakca and colleagues studied gray matter (GM) concentrations and volumes of the hippocampus in 11 chronic recreational cannabis users and 13 healthy controls and correlated their findings with THC and CBD measurements made from hair analyses. They found that cannabis users showed lower GM volume in the right anterior hippocampus. Higher THC and lower CBD were associated with this hippocampal volume reduction, suggesting neurotoxic effects of THC and neuroprotective effects of CBD.

The conflicting results among volumetric brain studies seem to result from differences in time span (e.g., age of onset), patterns of cannabis use (e.g., frequency, duration of use, cumulative lifetime use), and type of cannabis used (e.g., potency, CBD/THC ratio) (29, 30).

PSYCHOLOGICAL EFFECTS

The effects of cannabis on psychological functioning mainly concern psychotic symptoms, anxiety, depression, cognitive functioning, and the potential for abuse and dependency. Several studies show that high doses of cannabis can provoke acute and transient psychotic reactions in both "healthy" users and in people with a certain predisposition for psychosis (37–39). These effects are dose-related (i.e., more THC produces a greater effect) and are stronger and longer-lasting in naive and occasional users than they are in frequent and transient cannabis users. Rottanburg and colleagues were the first to propose a protective effect of CBD on THC-induced psychosis. They suggested that the high incidence of cannabis-related psychosis among their patients occurred because cannabis variants in South Africa are more potent in terms of THC content and because they lack CBD (40).

As early as 1982, there were indications that the psychosis- and anxiety-inducing effects of THC can be suppressed by CBD (41, 42). Several other studies have found support for the antipsychotic effects of CBD. fMRI studies have shown that the effects of THC are correlated with a decrease in brain activity in the striatum. The striatum plays an important role in planning activities, modulating motor activity (movement), and performing cognitive tasks. CBD has been found to increase the activity in this brain area (43).

Moreover, in other brain areas, the effects of CBD on neurological activity have been shown to be opposite those of THC.

In one Dutch and three English studies, associations between the consumption of certain types of cannabis and the occurrence of psychotic symptoms were reported (41–47). The results of these "naturalistic" studies suggest that CBD exerts a dampening effect on THC-induced psychotic symptoms. It is not clear for which CBD/THC ratio and for what minimum CBD concentration the protective effects of CBD may be expressed. The main features of these "naturalistic" studies are summarized in **Table 1**.

Longitudinal studies that have investigated the relationship between chronic cannabis use and the occurrence of psychosis have shown that cannabis use increases the risk of later psychotic symptoms and disorders by a factor of 2–3. The magnitude of the risk depends on the degree of exposure, the age of onset of cannabis use and the "vulnerability" of the user (50–52). No longitudinal studies have distinguished between the type of cannabis having been used, and no studies give an indication of the THC/CBD ratio.

One case-control study has shown an association between the occurrence of a first psychotic episode and the use of high-potency cannabis (skunk or sinsemilla) (47). Patients with psychotic symptoms had more frequently used skunk or sinsemilla cannabis instead of hashish than had non-patients. Patients experiencing first-episode psychosis were also more likely to be daily users of high-potency cannabis than were controls. This finding suggests that both the daily use and consumption of cannabis with a high-THC and low-CBD content increase the risk of developing psychosis.

Cannabis use can lower the age of a first psychotic episode (53, 54). Epidemiological and clinical studies suggest an adverse effect of cannabis use on the course of the disease in terms of relapse, exacerbation of symptoms and number of hospitalizations (38, 55–57). With the exception of a study by Di Forti et al. (47), no study has investigated the use of different types of cannabis in patients with a psychotic disorder. The extent to which the presence or absence of CBD in cannabis will influence the early occurrence of a first-episode psychosis or to what extent it will affect the course of the disease is, therefore, unknown.

Anxiety and panic attacks are the most commonly reported adverse reactions following the use of cannabis. Inexperience and use in a foreign environment play a major role (58). Though anxiety and panic attacks are often reported, many users take cannabis for its fear-inhibiting effects [for a review, see Ref. (59)]. THC seems to be responsible for the anxiogenic effects of cannabis [e.g., Ref. (58, 60, 61)].

By the early 1980s, it had been shown that THC led to a significant increase of acute anxiety symptoms, while CBD had no effect (42). When CBD and THC were administered together, the anxiogenic effect of THC was halved. This was an important indication that the anxiety-inducing effects of THC could be antagonized by CBD. The results from later studies, however, were inconsistent; the anxiety-reducing effect of CBD was not found in all subsequent studies. Ilan and colleagues investigated the contribution of THC and CBD to the subjective and behavioral effects of smoked marijuana (62). In their study, 23 healthy marijuana users were randomly assigned to a low- or a high-THC group and low or high levels of CBD. In the four sessions under blinded conditions, subjects smoked marijuana cigarettes containing placebo (no active cannabinoids) or cigarettes containing THC with low or high levels of CBD. Compared with the placebo, cannabis caused a slight short-term increase in anxiety symptoms (VAS). These effects were greatest in the high-THC condition and appeared to diminish when the CBD content was high, but this latter effect was

Table 1 | Summary of "naturalistic" studies in which the effects of cannabidiol and cannabis with a high dosis of THC on psychological functions have been investigated.

Reference	Subjects	THC/CBD	Results	Remarks
Di Forti et al. (47)	"First-episode" psychiatric patients ($n = 280$)	Self reported frequency and type of cannabis used	The chance that high-potent cannabis (THC) has been used is higher among "first-episode" psychotic patients than among non-psychotics	Also more frequent use in "first-episode" psychotic patients
Morgan and Curran (45)	Cannabis users ($n = 154$)	Grouping based on presence of THC and/or CBD in hair	More psychotic symptoms among THC group in comparison with no THC group and in group with THC and CBD in hair	THC might be psychotogenic and CBD might protect against this effect
Schubart et al. (48)	Websurvey among cannabis users ($n = 1877$)	Grouping based on self reported preference for type of cannabis	Less psychotic symptoms in cannabis users who use cannabis with high level of CBD (hash)	Personal communication with author (Schubart)
Morgan et al. (46)	Cannabis users, at least once a month ($n = 134$)	Choosing cannabis by cannabis user	Acute effects on mood, psychotic symptoms, and cognition	CBD attenuates the THC-induced memory impairment; CBD does not affect psychotomimetic symptoms
Morgan et al. (49)	Recreational cannabis users ($n = 54$) versus daily users ($n = 66$)	Measuring THC and CBD in hair	THC increases possibility of negative psychotic symptoms, CBD antagonizes (part of) THC-induced effects	

Table 2 | Overview of studies investigating the effect of cannabidiol or cannabidiol in combination with THC on psychological functions in humans. Studies in which cannabis extracts have been used are not included.

Reference	Subjects	Dosing THC/CBD	Results	Comments
Karniol et al. (64)	Healthy volunteers ($n = 40$)	30 mg THC (oral); 15, 30 of 60 mg CBD (oral) or in combination with 30 mg THC (both oral)	Antagonizing (part of) the THC-induced effects	CBD decreased the anxiety component of THC effects; no effect of CBD alone
Hollister and Gillespie (65)	Healthy volunteers ($n = 30$)	20 mg THC + 40 mg CBD (both oral)	CBD delays onset of the effect of THC and prolongs the effects of THC	
Dalton et al. (66)	Healthy volunteers ($n = 15$)	25 μg/kg BW THC and 150 μg/kg BW CBD via smoking a joint	CBD reduces euphoric effect of THC	Only effective when CBD and THC are administered simultaneously
Hollister (67)	Healthy volunteers ($n = ?$)	CBD 5–30 mg i.v.	No effects	
Carlini and Cunha (68)	Healthy volunteers	Acute 600 mg CBD; 10 mg/kg/BW CBD 20 days	CBD does not have psychological or physical effects	Light drowsiness after CBD administration
Zuardi et al. (42)	Healthy volunteers ($n = 8$)	0.5 mg/kg BW THC + 1 mg/kg BW CBD (both oral)	CBD antagonizes psychological effects of THC (anxiety)	CBD itself has no effect and does not antagonize the physical effects of THC (HR, BP)
Zuardi et al. (69)	Treatment resistant schizophrenic patients ($n = 3$)	CBD during 29 days upwards from 40 to 1280 mg/day (oral)	CBD does not antagonize symptoms	No side effects of CBD reported
Crippa et al. (70)	Healthy volunteers ($n = 10$)	CBD 400 mg oral	Anxiolytic effects; light mental sedation	SPECT results: effects in left amygdala-hippocampus complex radiating to hypothalamus
Leweke et al. (71)	Psychiatric patients ($n = 43$)	CBD oral 800 mg/day; during 4 weeks	CBD more effective as antipychotic than amsulpride	Less side effects of CBD than with amsulpride
Zuardi et al. (72)	PD patients with psychoses	CBD 150 mg/day; during 4 weeks	CBD possibly effective for treatment of PD patients suffering from psychoses	No significant side effects of CBD reported
Borgwardt et al. (73), Fusar-Poli et al. (74), Fusar-Poli et al. (75), Bhattacharyya et al. (76)[a]	Healthy volunteers ($n = 15$)	CBD oral 600 mg; 10 mg THC (not simultaneously); in comparison with placebo	No effect in contrast with THC; CBD activates other brain areas than THC no effects of CBD in verbal learning task and no induction of psychotic symptoms	No sedation and no inhibition of locomotion by CBD; THC induces psychotic symptoms, anxiety, and sedation
Zuardi et al. (77)	Patients with bipolar disorder ($n = 2$)	CBD oral 600 – 1200 mg/day during 25 days	CBD has no effect on symptoms	No side effects of CBD reported
Bhattacharyya et al. (43)	Healthy volunteers ($n = 6$)	CBD 5 mg i.v. immediately followed by 1.25 mg THC i.v.	CBD antagonizes THC-induced psychotic symptoms	CBD and THC have opposite effects on regional brain function
Bergamaschi et al. (78)	Healthy controls ($n = 12$) and patients with social phobia ($n = 24$)	CBD oral 600 mg	Reduction of anxiety scores in patients, no effect in controls	No physical effects or side effects of CBD reported

(Continued)

Table 2 | Continued

Reference	Subjects	Dosing THC/CBD	Results	Comments
Crippa et al. (79)	Patients with social phobia ($n = 10$)	CBD oral 400 mg	No effect on psychological scores	No physical effects; SPECT: CBD exerts its effects via limbic and paralimbic areas
Nicholson et al. (80)	Healthy volunteers ($n = 8$)	CBD 5 mg + THC 5 mg; CBD 15 mg + THC 15 mg, via mouth spray	THC (15 mg) increases drowsiness, antagonized by CBD (15 mg)	
Hallak et al. (81)	Schizophrenic patients ($n = 28$)	CBD oral 300 and 600 mg acute	No positive effects in Stroop Color Word Test	No significant side effects of CBD reported
Hallak et al. (82)	Healthy volunteers ($n = 10$)	CBD oral 600 mg and ketamine i.v.	CBD increases activating effects of ketamine (BPRS); reduction of ketamine-induced depersonalization (CADSS)	No effect of CBD on HR and BP

[a]*This concerns experiments with one group of 15 subjects from which the results have been spread over four different publications; BP, blood pressure; BW, body weight; CADSS, Clinician Administered Dissociative States Scale; HR, heart rate; i.v., intravenously; PD, Parkinson disease.*

not statistically significant. Because this increase in anxiety was generally mild and because not all subjects responded with fear, a follow-up analysis with only the anxious subjects was performed. There was a non-significant trend for less anxiety in the high- versus the low-CBD condition in subjects who reported higher levels of anxiety after smoking the joints. A reason for the absence of significant results in this study might be that neither the THC nor the CBD concentrations were high enough to have significant effects. In the studies in which anxiety-reducing effects were reported, high oral doses of CBD typically were involved. Cannabis that is used for recreational purposes does not contain such high amounts of CBD.

People with cannabis dependence are more likely to suffer from an anxiety disorder and, in particular, from social anxiety disorder [for a review, see Ref. (58)].

So far, studies investigating the relationship between cannabis dependence and anxiety disorders have not clarified the nature of the relationship in question: does cannabis use lead to anxiety disorders or do anxiety disorders lead to the (over-) use of cannabis? There are no studies in which the relationship between cannabis use and anxiety disorders is examined and in which an inquiry about the type of cannabis used or its THC/CBD ratio is included.

In two experiments using patients suffering from social anxiety disorder along with healthy volunteers as controls, the subjects had to speak in front of a video camera, regardless of whether they were under the influence of CBD. In this experimental situation, CBD was effective in preventing symptoms of anxiety, both in healthy volunteers and in patients with social anxiety disorder (41, 63). CBD suppressed the symptoms of anxiety, similar to the action of the sedatives diazepam and ipsapirone. The main features of the studies on humans that have investigated the psychological effects of administering CBD (singularly or in combination with THC) are summarized in **Table 2**.

Several studies have shown that cannabis and THC dose-dependently cause cognitive and psychomotor function impairments along with memory, (selective) attention, locomotion, perception, and response impairments (83–85). The effects occur most strongly during the first hour after smoking a joint and between 1 and 2 h after oral intake. Little experimental research exists on the effects of CBD alone or in conjunction with THC on cognitive and psychomotor functions. The studies performed so far show few "protective" effects of CBD on cognitive functions. Morgan and colleagues identified a few such effects on memory functions, but the research on this aspect of CBD has inconsistent findings (45, 49).

Although no human studies have specifically investigated the long-term effects of the combined effect of THC and CBD on cognitive functioning, there are indications that CBD may have some neuroprotective properties. In some neurodegenerative diseases that are often associated with declines in cognitive functioning, such as Alzheimer's and Parkinson's diseases, CBD may have some role in treatment or prevention (86–89).

The ratio of THC to CBD may play a role in the risk of addiction (90). Morgan and colleagues examined whether there is a difference in attentional bias between users of cannabis having a relatively high CBD/THC ratio versus cannabis having a low-CBD/THC ratio. Much weaker attentional bias for cannabis-related stimuli was found for users of cannabis with a high CBD content than for users of cannabis with a low-CBD content. Furthermore, the extent to which both groups appreciated the self-selected drug and the strength of the desire for their drug ("wanting") were investigated. High CBD content led to diminished appreciation and weaker desire for the drug relative to low-CBD content. The researchers concluded that cannabis with a high CBD content confers less risk for developing an addiction than cannabis with a low-CBD content (90). Whether smoking hashish in practice diminishes addiction risk in comparison with smoking highly potent marijuana should be further investigated.

CONCLUSION

Cannabis is not a safe drug. Depending on how often someone uses, the age of onset, the potency of the cannabis that is

used and someone's individual sensitivity, the recreational use of cannabis may cause permanent psychological disorders. Many recreational users of cannabis will never be faced with serious or permanent health deficits. However, for some users, the use of cannabis may cause undesirable psychological side effects, such as cognitive impairment, anxiety and paranoia, and an increased risk of developing chronic psychosis and addiction. Despite all of the publicity surrounding cannabis, remarkably few studies have been performed that examined the relationship between a possibly harmful effect of THC and a possibly protective effect of CBD. The few studies that exist on the effects of CBD show that this cannabinoid can counteract some of the negative effects of THC, although their results have not always been consistent. The question remains how the findings from laboratory studies, often employing high doses of CBD and high CBD/THC ratios, can be extrapolated to the typical practices of the recreational cannabis user. Few or no adverse effects of CBD have been proffered, and where CBD has been found to have an effect, it is usually in a "positive" (i.e., salubrious) direction. The evidence favoring a beneficial effect of CBD therefore merits further investigation in studies in which the amounts and ratios of CBD and THC correspond to the daily practices of recreational cannabis use.

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Modulation of the endocannabinoid system: vulnerability factor and new treatment target for stimulant addiction

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Cannabis is one of the most widely used illicit substance among users of stimulants such as cocaine and amphetamines. Interestingly, increasing recent evidence points toward the involvement of the endocannabinoid system (ECBS) in the neurobiological processes related to stimulant addiction. This article presents an up-to-date review with deep insights into the pivotal role of the ECBS in the neurobiology of stimulant addiction and the effects of its modulation on addictive behaviors. This article aims to: (1) review the role of cannabis use and ECBS modulation in the neurobiological substrates of psychostimulant addiction and (2) evaluate the potential of cannabinoid-based pharmacological strategies to treat stimulant addiction. A growing number of studies support a critical role of the ECBS and its modulation by synthetic or natural cannabinoids in various neurobiological and behavioral aspects of stimulants addiction. Thus, cannabinoids modulate brain reward systems closely involved in stimulants addiction, and provide further evidence that the cannabinoid system could be explored as a potential drug discovery target for treating addiction across different classes of stimulants.

Keywords: addiction, stimulants, psychostimulants, cocaine, cannabis, cannabinoids or endocannabinoids

INTRODUCTION

Addiction to psychostimulants such as cocaine, amphetamine, and its derivatives [i.e., methamphetamine, *N*-methyl-3,4-methylenedioxymethamphetamine (MDMA)] is a significant global public health problem which affects many aspects of social and economic life. Worldwide, between 16 and 51 million people are users of these types of substances (1). Amphetamines have been identified as the second world's most widely used illicit drug after cannabis, with an annual prevalence ranging from 0.3 to 1.2% in the adult population. Methamphetamine consumption has increased dramatically the last years, especially in the western and mid-western parts of the United States, although there also appears to be an eastward trend in use (2). Over 15 million people worldwide are cocaine users and 5.9 million of them live in North America (3, 4). Although the prevalence of cocaine consumption has declined in the past decade, cocaine use increased in 2011; dependence to this drug remains a significant issue in North America, Western and Central Europe, particularly in metropolitan areas where crime and violence have increased (4). Given its association with high rates of mental and physical problems as well as premature mortality, cocaine abuse is still an unresolved medical and socio-economic concern which carries a heavy burden for abusers and their families alike (3, 5–7).

In recent decades, development of new treatments for psychostimulant addiction has been a major focus of multidisciplinary research efforts and have included molecular approaches, preclinical behavioral studies, and clinical trials. However, in spite of these research endeavors, no specific pharmacological therapy has been found to be truly effective in alleviating psychostimulant cessation symptoms like craving and anxiety, or to prevent relapse (8–11). Neuropharmacological agents such as antidepressants, anticonvulsants, and antipsychotics have been tested as treatments for cocaine dependence but these medications have yielded negative clinical outcomes (12–14). Subsequent attempts at targeting other neurotransmitters such as the dopaminergic and γ-aminobutyric acid (GABA) systems (10, 15, 16), and developing a cocaine vaccine (17) to promote abstinence in cocaine-dependent individuals, have shown promising results but still require further investigation. Importantly, many clinical studies have focused on cocaine addiction rather than other psychostimulants such as amphetamines and methylphenidate. Whether the outcomes related to cocaine addiction can be applied to other psychostimulants remains unclear (18).

Given the need to better understand neurobiological mechanisms that underly psychostimulants addiction and to develop innovative treatment strategies, researchers have explored the involvement of specific neurotransmitter systems and brain structures in the motivational and addictive properties of this class of drugs. Increasing evidence indicates that the endocannabinoid system (ECBS) - a group of neuromodulatory lipids and receptors – plays a central role in various cognitive and physiological processes associated with addiction such as reward, stress responsiveness, and drug-related synaptic plasticity (19–21). The potential of ECBS modulation in treating stimulant addiction has recently been highlighted in human and animal studies investigating its effects on acquisition, maintenance, and relapse of drug-taking behavior. Moreover, endogenous and exogenous cannabinoids such as plant-derived cannabinoid ligands (i.e., Δ^9-THC,

cannabidiol, CBD) modulate specific neurotransmitter systems which are also pharmacological targets for cocaine. Interestingly, cannabis is widely used by psychostimulant-dependent individuals (22); while it is recognized that components of the ECBS are implicated in psychostimulants, more specifically in cocaine-seeking behaviors, very few studies have focused on an understanding of the neural and behavioral effects of cannabis on psychostimulants use in humans.

The current review will focus on the neurobiological basis of the addictive process from psychostimulant initiation to drug abuse and addiction. The involvement of critical neurotransmitters and neural circuits underlying the pathological modifications at each of these stages will be highlighted with a specific attention given to the ECBS. In turn, this overview will serve as foundations to look at the ECBS as a specific target of pharmacotherapeutic interventions to reduce the addictive effects of psychostimulants.

NEUROBIOLOGY OF PSYCHOSTIMULANTS

Occasional use of psychostimulants like cocaine, at low doses, provokes a so-called "rush" (i.e., euphoria) in humans, giving them a sensation of vigilance and increased energy. Higher doses of cocaine induces symptoms described as "cocaine high," which include enhancement of a euphoric sensation, an increase in motor activity, amplification of sensory perception, talkativeness, and suppression of appetite and thirst (23). Unfortunately, these positive subjective effects (i.e., euphorigenic state) are often followed by repetitive and frequent cocaine abuse which develops into addiction. Drug addiction is a chronically relapsing disorder characterized by loss of control over drug-seeking and the compulsive desire (referred as craving) to use drugs in spite of negative consequences (24). Drug cravings increase with exposure to drug and drug-related-cues, and in the context of emotional stress or negative moods (25, 26). Because addiction is a highly complex disorder, numerous studies have attempted to determine the molecular and cellular factors implicated in the pleasurable effects induced by drug consumption, and their role in the development of addictive behaviors (27–31).

NEUROTRANSMITTERS INVOLVED IN PROCESSES LEADING TO PSYCHOSTIMULANTS ADDICTION

Psychostimulants affect the central nervous system by modulating the mesocorticolimbic dopamine (DA) system which is involved in several physiological processes such as cognition, memory, and reward-driven learning (32). The mesocorticolimbic system, which has been found to play a role in drug reward and addiction, includes DA projections from cell bodies in the ventral tegmental area (VTA) to limbic structures such as the nucleus accumbens (NAc) (33), amygdala in the forebrain (34, 35), hippocampus (36), and to cortical areas such as the prefontal cortex (PFC), including the orbitofrontal cortex (OFC) and anterior cingulate (AC) (37). Psychostimulants exert their effects on the CNS via a number of mechanisms; cocaine, amphetamines, methamphetamines, and methylphenidate alter normal DA receptor functions by binding the dopamine transporter (DAT) and forming a complex that blocks the transporter's function. The psychostimulant/DAT complex inhibits DA reuptake into the presynaptic nerve terminal, leading to an excess of DA in the synaptic cleft within the NAc – recognized as the center of the rewarding process (38–40). This phenomenon results in an increased and prolonged post-synaptic effect of dopaminergic signaling at DA receptors on the receiving neuron (30, 31). However, unlike cocaine, which interferes mainly with plasma membrane transporters, other psychostimulants modulate the CNS through a host of mechanisms. First, methamphetamines and amphetamines act as substrate-type releasers (41, 42) to enhance DA efflux. These substrate-type releasers have two modes of action: (i) they reverse the process of transporter-mediated exchange by interacting with specific transporter proteins which are subsequently brought into the cytoplasm of the nerve terminal; (ii) they also increase cytoplasmic levels of DA by interfering with vesicular storage (43, 44). Moreover, these drugs increase cytosolic DA levels by shutting-down the activity of the monoamine oxidase (MAO) – an important enzyme for the catabolism of monoaminergic neurotransmitters. Finally, psychostimulants also enhance the activity and expression of the tyrosine hydroxylase (TH), the DA-synthesizing enzyme [reviewed in Ref. (45)]. However, exactly how these high levels of DA in the NAc mediates drug reward remains partially understood.

Even though DA has been identified as one of the primary mechanisms involved in drug reinforcement initiation, studies reveal that mice lacking the gene expressing the DAT continue to self-administer cocaine (46, 47). Interestingly, several reports have suggested the indirect implication of other neurotransmitter systems [i.e., serotonin (5-HT), norepinephrine (NE), glutamate (GLU), GABA, opioid peptides, and endocannabinoids (48–50)] in the incentive sensitization and reinforcing effects of psychostimulants (29, 51). Indeed, psychostimulants also reduce 5-HT and norepinephrine NE reuptake, which in turn leads to an increase in extracellular monoamines concentrations and contributes to the rewarding subjective feelings mediated by these drugs (42, 52–54). Surprisingly, knock-down of NET, or SERT, or NET/SERT genes does not abolish but rather potentiates the rewarding or aversive effects of cocaine (55, 56). Recently, further lines of evidence have suggested that NE plays a role in the reinstatement of drug seeking, although it does not influence the maintenance phase of cocaine self-administration (SA) (57–59). Blockage of NE cognate receptors – α1-adrenergic receptors (α1ARs) and β-adrenergic receptors (βARs) – in a mice model of addiction diminishes cocaine-primed and foot shock-induced reinstatement respectively, whereas inhibition of both receptors reduces cue-induced reinstatement (60, 61).

Long-term use of psychostimulants leads to homeostatic dysregulation of normal (i.e., without cocaine) dopaminergic signaling. This hypo-dopaminergic state contributes to the appearance of some withdrawal symptoms (i.e., depressive mood disorders), often observed in abstinent psychostimulant addicts, and, also the maintenance of drug-use behaviors. Similarly, withdrawal symptoms from chronic cocaine use have been also associated with cocaine-induced alterations in 5-HT neurotransmission. Interestingly, rodent studies show that enhancement of serotonergic transmission in the NAc through administration of exogenous 5-HT served to offset the DA deficit caused by cocaine withdrawal (62); indeed, accumulating studies suggest that increasing brain 5-HT activity could reduce the behavioral-stimulant and reinforcing properties of psychostimulants (reviewed in Ref. (44)]. Thus,

modulation of 5-HT and DA levels might sensitize an important brain reward circuit to the reinforcing effects of psychostimulants contributing to the intractable nature of addiction and relapse.

The glutamatergic system is another important neuronal substrate of behaviors induced by drugs of abuse (63, 64). Indeed, GLU is an excitatory neurotransmitter essential to numerous processes including neuroplasticity, linked to long-term potentiation (LTP), long-term depression (LTD), extinction, and reward-related learning (65–68). Like DA, GLU levels in the NAc core decrease during the early phase of cocaine abstinence (69, 70), whereas both stress and drug-induced reinstatement of cocaine-seeking are associated with an increase of extracellular GLU levels in the NAc in rodents (63, 64, 70–73). Thus, the data suggests that both a decrease in basal GLU transmission and an enhanced GLU response may constitute a neurobiological substrate of cocaine-, cocaine-associated cue-triggered relapse.

While discovery of numerous neurotransmitter systems have yielded significant advances in defining psychostimulants' effects on the brain neurochemistry, the precise mechanisms underlying their role in addictive behaviors are not as straightforward. While DA and GLU appear to be critical in the development and persistence of stimulant addictive behaviors, a growing body of evidence points toward the impact of other neurotransmission systems, including the ECBS, in various physiological and behavioral processes associated with psychostimulant addiction, through both DA/GLU related and unrelated mechanisms. An overview of this evidence will be presented in Section "The Endocannabinoid System," with a particular focus on the potential exogenous and endogenous cannabinoids influence on psychostimulant reinforcement, drug-related synaptic plasticity, and drug-seeking behavior.

NEURAL REGIONS INVOLVED IN ADDICTION PROCESS TO PSYCHOSTIMULANTS

A central challenge in addiction research is understanding the neurobiological substrates involved in drug-taking behavior. Over the last two decades, neuroimaging has provided substantial insight into that question by: (i) allowing researchers to investigate the roles of different neural regions in drug-induced euphoria and subsequent craving; (ii) enabling the gathering of tremendous information regarding the neurochemical and physiological adaptations of the brain during the addiction process.

Brain imaging studies of subjects addicted to psychostimulants indicate that the NAc – known to play a fundamental role in goal-directed behaviors (74) – is organized into two functionally distinct sub-compartments termed the shell and core (33). The shell and the VTA are critical in inducing motivational salience and responding to novel rewarding stimuli (75). The core mediates the expression of learned behaviors, and receives glutamatergic afferents from the PFC (33, 75). DA release into the core occurs in response to cues predicting a motivating event (76, 77). The NAc receives information regarding motivationally relevant events from the VTA, amygdala, hippocampus, and PFC, and responds by providing output to brain circuits which modulate the expression of the behavioral response (e.g., to seek the drug or not) (78). Chronic exposure to psychostimulants leads to the dysregulation of the mesolimbic circuitry, which in turn enhances the motivation to take drugs and decreases the ability to regulate the behavioral response to drug cues (33, 74).

The numerous neuroimaging methods used to study the chronic effects of psychostimulants on the brains of drug-addicted individuals have consistently found abnormalities in both cortical and subcortical neural areas (37, 79). More specifically, chronic exposure to psychostimulants causes functional alterations within frontal brain areas, including the dorsolateral prefrontal cortex (DLPFC), the OFC, and the anterior cingulate cortex (ACC) involved in goal identification; selection (80); decision making; impulsivity; behavioral inhibition (81), and assessment of consequences (82), respectively. It has been proposed that abnormalities within these three PFC-striatothalamic circuits play a central role in emotional response to drug cues, craving, compulsive drug-seeking, and relapse (26, 35, 83–85). Moreover, structural magnetic resonance imaging (structural MRI) studies associate chronic use of psychostimulants with alterations in white-matter integrity and gray-matter volume, which are strongly correlated with lower abstinence-based outcomes (86) and drug-induced compulsivity, decision making, and attention impairments in cocaine-dependent subjects, respectively (85). Furthermore, exposure to emotional distress and aversive stimuli also activates the cortico-limbic circuits, including prefrontal, AC, middle frontal, and orbitofrontal regions, limbic and paralimbic structures such as the amygdala, hippocampus, parahippocampal gyrus, fusiform gyrus, and other midbrain areas, but not the ventral striatum (87, 88). Overall, the data shows that chronic use of psychostimulants modulates a set of neural regions implicated in stress, emotions, impulsivity, and reward processing control which precipitate relapse in drug-abstinent individuals.

THE ENDOCANNABINOID SYSTEM

Though the significant role played by various neurotransmitters, genetic factors and specific brain structures in reinforcing the properties of psychostimulants has been established, the common mechanisms underlying the development of addictive behaviors have yet to be fully elucidated. A growing body of evidence points to the involvement of the ECBS in the acquisition and maintenance of drug-taking behaviors and in various physiological, as well as behavioral processes associated with addiction. Interestingly, a characteristic of psychostimulants abuse is the concurrent consumption of other substances including delta-9-tetrahydrocannabinol (Δ^9-THC) – the main cannabinoid found in cannabis [reviewed in Ref. (89)]. This poly-substance pattern of use has prompted researchers to investigate the potential interaction with, and effect of, these drug on neuropsycho-biological processes related to addiction. For example, some studies reveal that cannabis consumption enhances the incentive to use cocaine in individuals dependent on both, while others suggested that cannabis reduced withdrawal symptoms in abstinent cocaine-addicted subjects (22, 90, 91). Although it is recognized that components of the ECBS are involved in cocaine-seeking behaviors, very few studies have focused on understanding the neural and behavioral effects of endogenous and exogenous cannabinoids on psychostimulant use. In this section, we will first provide an overview of the ECBS, and then focus on recent findings

pointing toward a role of the ECBS in the circuitry underlying psychostimulant addiction.

OVERVIEW

The ECBS consists of a family of lipid signaling molecules referred to as endocannabinoids, their cognate receptors and specific metabolic enzymes which are responsible for degradation of the endocannabinoids – anandamide (AEA) and 2-arachidonoylglycerol (2-AG). The neurobiological properties of endocannabinoids are complex, but it is now well established that they modulate a wide diversity of physiological processes including pain and inflammation, immune responses, food intake, synaptic transmission, cognition, reward, and motor activity (92). Endocannabinoids also influence mechanisms involved in addiction and relapse.

RECEPTORS

There are currently two well described subtypes of cannabinoid receptors, termed CB1 and CB2, which differ in their signaling mechanisms and tissue distribution. Even though CB1 receptors are considered the most abundant and widely distributed G-protein-coupled receptors found in the CNS, they are also present in peripheral organs and tissues (i.e., endocrine glands, leukocytes, spleen, heart, and gastrointestinal tracts, etc.) (93–97). CB1 receptors are localized in TH-expressing neurons, probably dopaminergic neurons of the NAc, VTA, striatum, and pyriform cortex, suggesting that the ECBS may directly influence dopaminergic reward mechanisms. In addition, CB1 receptors are expressed in other neural regions related to reward, motivation and memory processing (i.e., basolateral amygdala, hippocampus, and cerebral cortex), movement (i.e., basal ganglia, cerebellum), pain modulation (i.e., certain parts of the spinal cord, periaqueductal gray). Endocannabinoids induce LTD of the inhibitory synapses in the hippocampus, contributing to the synaptic plasticity involved in the learning processes related to addictive behaviors. CB1 receptors are confined at the terminals of central and peripheral nerves, where they inhibit the release of excitatory and inhibitory neurotransmitters (release on command, retrograde signaling) (98–100). Thus, the activation of CB1 receptors protects the nervous system from over-activation or over-inhibition by neurotransmitters and thereby promotes the latter's prominent role in anxiety, depression, cognition, addiction, motor function, feeding behavior, and pain (101). CB2 receptors are mainly found in immune cells (i.e., spleen, tonsils, and thymus gland) (102–104), although recent experimental data indicate CB2 receptors expression in the cerebellum, brainstem, and cortex (105–107) as well as activated microglial within the CNS (108–110). Simulation of CB2 receptors on microglia modulates the neuro-inflammatory response by regulating cytokines release in the brain (111–113).

Increasing evidence points toward the existence of additional cannabinoid receptors subtypes in the CNS. Indeed, recent preclinical studies suggest the persistence of cannabinoid-like properties after cannabinoid agonists have been administered to mice lacking CB1 and CB2 receptors ($CB1^{-/-}$ and $CB2^{-/-}$) in neuronal subpopulations. This indicates that these agonists recognize non-CB1/CB2 cannabinoid receptors (114–117). Among these receptors, the orphan G-protein-coupled receptors modulate the ECBS. GPR55 specifically is found in the striatum and to a lesser extent in the hippocampus, the thalamus and the cerebellum (118). GPR55 is phylogenetically different from CB1 and CB2 receptors, in that it is activated by the CB1 antagonists – rimonabant and AM251 – but blocked by the cannabinoid agonist CP55, 940 (119–121). Thus, GPR55 is considered as a non-CB receptor with a binding site for cannabinoid ligands [reviewed in Ref. (122)]. Though a recent study from Rusakov's group suggests that GPR55 enhances neurotransmitters release at central synapses (123), further studies are required to confirm its neurophysiological function.

The actions of endocannabinoids are not only restricted to the CB1, CB2, and GPR receptors. Transient receptor potential (TRP) receptors have also been identified as sites of endocannabinoid interaction. Exogenous and endogenous cannabinoids interact with at least five TRP receptors (124); AEA binds to the transient receptor vanilloid potential 1 (TRVP1) with low affinity. TRVP1 is found on sensory neurons, where they are partly coexpressed with CB1 receptor, but also in several central nuclei including the hypothalamus and basal ganglia, the hippocampus and cerebellum (125). The efficacy and potency of AEA at TRVP1 is increased when the AEA degrading enzyme FAAH (fatty acid amide hydrolase) is suppressed (126–128). Surprisingly, pharmacological or genetic inhibition of FAAH enhances AEA, but decreases 2-AG levels via TRVP1 receptors (129). Interestingly, both endocannabinoids AEA and 2-AG decrease the excitatory GLU and the inhibitory GABAergic inputs to striatal neurons (130, 131). Therefore, it is likely that the potential of AEA to reduce 2-AG levels by activating TRVP1 receptors might represent a mechanism to integrate excitatory and inhibitory inputs in the basal ganglia.

ENDOCANNABINOIDS AND THEIR METABOLIZING ENZYMES

In the CNS, endocannabinoids mediate forms of short-term synaptic plasticity known as depolarization-induced suppression of inhibition (DSI) (132, 133) and depolarization-induced suppression of excitation (DSE) (134). Thus, endocannabinoids are considered as retrograde messengers that neuromodulate diverse physiological processes. AEA and 2-AG are the two most characterized endocannabinoids (135, 136), although other studies have identified of additional endocannabinoids such as 2-arachidonylglyceryl ether (noladin ether) (137), *N*-arachidonoyl-dopamine (NADA) (128), and *O*-arachidonoyl-ethanolamine (virodhamine) (138). However, the physiological functions of these endocannabinoids are still being investigated. While 2-AG acts as a full agonist at CB1 and CB2 receptors, AEA behaves as a partial agonist at both receptors subtypes and can also interact with GPR55 and TRVP1 receptors.

Unlike other neurotransmitters, AEA and 2-AG are not synthesized and stored in the nerve cells. Rather, they are produced on an "as needed" basis by their membrane lipid precursors in a Ca^{2+} dependent fashion (133, 139). Although additional studies are needed to ascertain the exact role of the *N*-acylphosphatidylethanolamine phospho-lipase D in the ECBS, it has been proposed that this enzyme might play a significant role in the synthesis of AEA (140). The enzyme responsible for 2-AG synthesis is the diacylglycerol lipase alpha (141). Upon depolarization of post-synaptic neurons, the endocannabinoids released into the synaptic cleft bind to and activate the presynaptic CB1 receptors, which in turn suppress the release of both excitatory and inhibitory

different neurotransmitters [see for review (142)]. Then, AEA and 2-AG are rapidly deactivated by cellular reuptake into both neurons and glial cells and metabolized by specific enzymes (143). AEA can be metabolized by either the FAAH (144), or monoacylglycerol lipase (MAGL), which degrades specifically 2-AG (145). In addition to MAGL, recent studies have suggested that the enzymes ABHD6 and ABHD12 could also be involved in 2-AG metabolism (146, 147). FAAH is over-expressed in the CNS and FAAH-positive neurons are localized in proximity to CB1 receptor-containing terminals, underlining the role for this enzyme in endocannabinoids inhibition (148). Thus, selective inhibition of FAAH (149) and MAGL (150) can prolong the effects of endocannabinoids. Pre-clinical studies have demonstrated that pharmacological inhibition of FAHH with URB597 (149) or PF-3845 compounds (151) induced-anxiolytic-like effects (152, 153) and anti-nociceptive properties in mice (152, 154). Inhibition of MAGL with JZL184 inhibitor causes analgesia, hypothermia, and hypomotility (155). However, chronic exposure to JZL184 impairs endocannabinoid-mediated synaptic plasticity in mouse hippocampus and cerebellum via 2-AG upregulation. It also induces tolerance to the analgesic effects, physical dependence, and persistent activation as well as desensitization of brain CB1 receptors (156). Surprisingly, MAGL knockout mice show enhanced learning behavior and have normal locomotor activity, suggesting the possible role of MAGL in cognitive function (157, 158).

EXOGENOUS CANNABINOIDS: Δ^9-THC VS. CBD

Cannabis is the world's most commonly used illicit drug (159, 160). Between 119 and 224 million people are cannabis users worldwide (4). Cannabis contains over 85 different chemical substances unique to the plant and termed phytocannabinoids. Among them, Δ^9-tetrahydrocannabinol (Δ^9-THC) and CBD are the two main components of cannabis, which has been used for thousands of years for both recreational and medicinal purposes. Most studies regarding cannabis properties have focused on Δ^9-THC, which is the main psychoactive constituent in cannabis extracts (161). Although Δ^9-THC possesses a number of therapeutic effects (e.g., on pain, spasms, inflammation), its negative impact on the CNS has been highlighted in several clinical studies on subjects smoking cannabis, documenting impulsive behavior, cognitive impairment, consumption of addictive substances, and psychiatric disorders (e.g., schizophrenia, depression, and anxiety) (162–165). For example, Δ^9-THC has been shown to induce psychotic-like and anxiogenic effects when administered intravenously to healthy subjects (166, 167). Other experimental studies revealed that Δ^9-THC injection in animal models causes hypolocomotion, catalepsy, antinociception, and hypothermia (168).

Pharmacological studies in animal models suggest that not all therapeutic effects related to cannabis administration can be ascribed to Δ^9-THC [reviewed in Ref. (169)]. Indeed, CBD – the second most abundant cannabinoid found in cannabis – acts as an antidepressant and possesses anticonvulsant, antiemetic, anxiolytic, and sleep-promoting as well as neuroprotective properties in humans (160, 170–176). CBD mediates its neuropharmacological properties by acting as an inverse agonist on CB1 and CB2 receptors (177, 178); it also stimulates the TRVP1 and TRVP2 (179) which serve as so-called ionotropic cannabinoid receptors. In addition, CBD inhibits FAAH, the main catabolic enzyme that alters the hydrolysis of the endogenous cannabinoid neurotransmitter AEA (180) (see above section), and is also an antagonist at the putative GPR55 receptor. The clinical association of the modulation of the ECBS by CBD remains to be fully investigated; this effect could arguably be related to DA uptake inhibition (181). Interestingly, ECBS interacts closely with other neurobiological structures which are implicated in the neural adaptations observed during chronic use of drugs and vulnerability to addiction. For example, CBD plays a role in the modulation of extracellular levels of DA (182) as well as μ and δ opioid receptors (183); it increases adenosine signaling through inhibition of uptake (184). Moreover, μ opioid and CB1 receptors colocalized within neural regions are known to modulate reward, goal-directed behavior, and habit formation relevant to addiction including striatal output projection neurons of the NAc and dorsal striatum (185, 186). While further studies are required to better understand the impact of CBD on GLU neurotransmission, its protective effects on GLU toxicity (187) and its psychopharmacologic interaction with ketamine (188), a *N*-methyl-D-aspartic (NMDA) receptor antagonist, are well documented. CBD activates also the serotoninergic receptors 5-HT1A (5-hydroxytryptamine) (171, 176, 189–193), which in turn diminishes vulnerability to stress and has anxiolytic-like effects in animal models (170, 172, 189, 190, 192–195). Similar results were observed in humans, where CBD administration decreases autonomic arousal and subjective anxiety (196). Interestingly, these anxiolytic effects have been linked to the modulation of core regions involved in the "emotional brain," including limbic system structures such as the AMG and the ACC (197, 198). CBD's anxiolytic effects were further confirmed by a study indicating that the effective connectivity between ACC and AMG is attenuated during the emotional processing of fearful faces, while resting activity of the left parahippocampus gyrus is increased. (196, 199). Remarkably, these neural structures are activated during drug craving in cocaine addiction (197, 200). It also decreases compulsive behaviors in rodents, which is hypothesized to be related to CB1-related mechanisms (201, 202).

While CBD has neuroprotective properties (187, 203, 204) and Δ^9-THC administration have been shown to cause neurotoxic effects (205), these opposing properties have been highlighted in brain imaging studies where Δ^9-THC and CBD activate different brain regions during tasks engaging verbal memory (206, 207), response inhibition (208), and emotional processing (196, 209–211). When given at appropriate doses, CBD counteracts Δ^9-THC properties. Thus, CBD can modulate the functional effects of Δ^9-THC (177, 178). Pre-clinical studies demonstrate that CBD decreases Δ^9-THC-induced conditioned place aversion and social interaction of on operant behavior model (212, 213). In addition, CBD diminishes Δ^9-THC-induced anxiety and psychotic-like symptoms in humans (214, 215). Together, this data clearly suggests that CBD limits Δ^9-THC adverse effects. Thus, administered together, CBD might increase Δ^9-THC clinical efficacy (216, 217). It has been established that unlike, Δ^9-THC, CBD possesses therapeutic properties that could reduce withdrawal symptoms often present in individuals with addictive disorders (e.g., anxiety, psychotic, mood symptoms, insomnia, and pain). For example, a recent pre-clinical study from Hurd's group aimed at assessing

the effects of cannabinoids on opioid-seeking behaviors in rats indicates that while Δ^9-THC potentiates heroin SA, CBD inhibits cue-induced heroin-seeking behaviors for up to 2 weeks following the last administration (218). In addition, CBD is well tolerated and has no gross effects on motor function (such as locomotor activity). CBD is also protects against damages caused by various substances; it reverses binge ethanol-induced neurotoxicity (219) and mitigates the cardiac effects of Δ^9-THC (220, 221). Together this data illustrates the different, and sometimes opposite, neurobiological properties of the two main constituents of cannabis – CBD and Δ^9-THC – that are linked to neural circuits which might play significant roles in addiction disorders. However, while numerous studies have highlighted the participation of the ECBS in the rewarding and addictive properties of drugs of abuse such as opioids, nicotine, and alcohol over the last decades, relatively few studies have focus on the impact of this system on addiction to psychostimulants.

INTERACTION OF THE eCBS WITH BIOLOGICAL AND BEHAVIORAL CORRELATES OF PSYCHOSTIMULANTS ADDICTION

HUMAN STUDIES

Human studies aimed at understanding the interaction of the ECBS with biological and behavioral correlates of addiction to psychostimulants have mostly focused on ECBS-related risk factors leading to drug dependence. Interestingly, cannabis use is strongly associated with the abuse and/or dependence of several class of drugs including psychostimulants such as cocaine (222). Moreover, exogenous cannabinoids have been shown to modulate the acute rewarding effects of cocaine. These lines of evidence may suggest an association between ECBS and liability to psychostimulant by pointing toward a possible involvement of the ECBS in the motivational effects mediated by psychostimulants (223) [reviewed in Ref. (224)]. Based on these observations, scientific efforts have been devoted to investigate the influence of various genetic (e.g., ECBS-related genes) and environmental characteristics (e.g., previous or current exposure to cannabinoid agonists) in individual progression from occasional use to psychostimulant addiction.

"The gateway theory" and addiction to psychostimulants

Association of prior or concomitant cannabis consumption with other illicit drugs including psychostimulants such as methamphetamine and cocaine, forms the basis of a well-known hypothesis – " the gateway theory," which suggests a causal role for cannabis in the development of subsequent drug use and addiction (225). While data indicate that smoking cannabis is positively associated with cocaine consumption, it would be inappropriate to assume that cannabis *per se* leads to cocaine use. A study from Lynskey et al. in human twins reveals that early cannabis use in life increases the odds of subsequent cocaine use, supporting the causative model of the "gateway theory." However, results of this study have been refuted by Kandel et al. (226) which argues that several additional genetic, social, and environmental factors, such as life experiences, might link cannabis use with subsequent cocaine consumption (227, 228). Actual neurobiological causal mechanisms underlying this "gateway theory" remain mostly unidentified. Interestingly, Tomasiewicz and colleagues show that Δ^9-THC exposure induces epigenetic dysregulation of the endogenous opioid proenkephalin in adolescents; these findings indicate that cannabis exposure, in and of itself, can be considered as a risk factor that acts "above the genome" and can "write" on the existing epigenetic background of adolescent neurodevelopment. Thus, in adolescents, Δ^9-THC exposure-mediated epigenetic effects may act in concert with other environmental or social factors to augment future behavioral responses to drugs of abuse via stable and long-term regulation of genes at the transcriptional level. However, while these data establish a direct link between Δ^9-THC-induced changes in proenkephalin expression and susceptibility to opiate drugs, no studies have confirmed that this mechanism can be applied to psychostimulants (229).

Genetic determinants of the ECBS and psychostimulant addiction

It is worth mentioning that not every subject who experiences the pleasurable effects of psychostimulants will become a chronic user. Indeed it is more likely that additional factors such as: (1) genetic variabilities (e.g., polymorphisms in the catechol *O*-methyltransferase gene (Val158met) and in the serotonin transporter gene (5-HTTLPR) (230, 231); (2) monoamine receptors deficiency – either genetically or as a result of their drug excesses – also contribute to the psychostimulants addiction process (232–235) (see **Table 1**). In the ECBS, different genetic variants of the CB1 receptors – *CNR1* – and *FAAH* genes have been associated with increased susceptibility to drug addiction. Indeed, genetic analyses demonstrate that the *CNR1* gene exhibits elevated numbers of (AAT)n triplet repetition in a sample of 192 non-Hispanic Caucasian subjects. Interestingly, this *CNR1* polymorphism increases the risk of intravenous drug use in this population, with strongest correlation observed in cocaine, amphetamine, and marijuana dependence (236). Similarly, a study from Ballon and colleagues shows that detection of this *CNR1* polymorphism in a sample of 142 African-Caribbean individuals predisposed them to cocaine addiction (237). Unfortunately, while single sequence repetitions can alter transcriptional rates and thereby induced gene overexpression or silencing (238), the functional nature of the microsatellite polymorphism triplet repetition (AAT)n in modulating *CNR1* gene expression remains blurred (239). It has been hypothesized that the presence of long alleles with high numbers of AAT triplets alter *CNR1* transcriptional gene expression, ultimately leading to low levels of CNR1 protein synthesis (240). A recent meta-analysis of 11 studies aimed at investigating the contribution of three *CNR1* polymorphisms (rs1049353, rs806379, and the AAT triplet repetitions) to drug dependence vulnerability confirmed the presence of (AAT)n repeats, but only in the Caucasian population [reviewed in Ref. (239)]. Unfortunately, the effect of the three *CNR1* polymorphisms appeared to be insignificant and showed high heterogeneity. Important caveats have to be considered when looking at these studies. First, the ethnicity of the different subjects may prove important, as some studies included several ethnic groups in their samples, and in some cases, these groups were not even mentioned (241, 242). Some reports also examined *CNR1* gene polymorphisms in connection with a different phenotype or stage of drug addiction such as craving, drug consumption, dependence, or drug withdrawal

Table 1 | ECBS and factors contributing to vulnerability to psychostimulants in humans.

Aspect	Conclusion	Reference
Genetic risks factors	CNR1 (AAT)n repeat polymorphism associated with IV drug use, including amphetamine and cocaine, in a non-Hispanic Caucasian population and with cocaine dependence in an African-Caribbean population	Comings et al. (236), Ballon et al. (237)
	CNR1 gene single nucleotide polymorphisms associated with cocaine addiction in an African-American population	Clarke et al. (244)
	FAAH gene mis-sense mutation associated with drug dependence	Sipe et al. (245), Flanagan et al. (246)
Cannabis effect in addiction to psychostimulants	Self-reported of cannabis smoking by crack-cocaine abusers alleviates withdrawal symptoms and drug-craving	Labigalini et al. (90)
	Post-discharge use of cannabis by American cocaine addicts increases risk of relapse	Aharonovich et al. (91)
	Cannabis use correlates with syringe sharing in injection drug users	Jutras-Aswad et al. (22)
	Recent cannabis use decreases activation of frontal cortices area during emotional stress stimulation in cocaine-dependent individuals	Li et al. (247)

(243). Furthermore, a detailed description of the repercussions of *CNR1* polymorphisms on CB1 function from a neurobiological standpoint is lacking from the reviewed studies.

Polymorphisms in the gene coding for the endocannabinoid-inactivating enzyme *FAAH* may constitute another risk factor for problematic drug use, as described by initial reports identifying C385A, a mis-sense single nucleotide polymorphism (SNP) causing reduced FAAH enzymatic activity (245, 246). Indeed, a study from Sipe et al. reveals significant association between C385A SNP and street drug abuse in a sample of 1737 Caucasian subjects with addictive disorders. Neuroimaging studies combined with genetic analysis reveal that low FAAH activity enhances AEA protein expression levels which, in turn, modulate brain regions implicated in drug addiction and reward circuitry such as the OFC, AC gyrus, and NAc (242). Additional neuroimaging studies show that C385A carriers exhibit increased ventral striatal reactivity – a correlate for heightened impulsivity and reward sensitivity. C385A carriers display low threat-related amygdala reactivity – a pattern observed in individuals with high familial risk of alcoholism. Moreover, C385A polymorphism-reduced FAAH functional activity increases risk-taking behavior associated with addiction through abnormal impulsivity and threat perception [reviewed in Ref. (224, 243)]. Contribution of SNPs that modulate FAAH functions to stimulant addiction remain to be explored as the aforementioned data were not obtained in individuals specifically addicted to stimulants.

Effect of exogenous cannabinoids on psychostimulant reward

As mentioned previously (see The Endocannabinoid System), an intriguing characteristic of psychostimulants abuse is the concurrent consumption of cannabis. Parallel to studies on the long-term effects of cannabis exposure on subsequent psychostimulant use, researchers also examined the acute rewarding effects of cannabis use on concurrent psychostimulant addiction (91, 222). However, studies aimed at investigating such interactions are sparse. Conflicting results from Foltin et al. and Lukas et al. provide evidence that cannabinoids modulate cocaine-mediated euphoric actions. First, data from Foltin and colleagues show that human volunteers who smoked cannabis prior to intravenous cocaine experience a prolongation of the "high" sensation (248). Second, a study from Lukas and colleagues reveals that smoking Δ^9-THC, 30 min prior to intranasal cocaine decreases the latency to onset of cocaine-induced euphoria significantly, from 1.87 to 0.53 min, as well as the duration of cocaine-induced dysphoria, from 2.1 to 0.5 min (249). Interestingly, when both drugs are administered concomitantly, no changes are observed in cocaine- and Δ^9-THC-induced positive subjective properties. Furthermore, Δ^9-THC increases the peak plasma levels and bioavailability of cocaine considerably. This increase might be the result of Δ^9-THC-induced vasodilation of the nasal mucosa which, in turn, reduces cocaine-induced vasoconstriction, thereby increasing cocaine's absorption. In addition, the discrepancies between these two studies might be also due to pharmacodynamic mechanisms including differences in cocaine absorption or in the ratio of CBD/Δ^9-THC levels found in the type of cannabis used for each study.

Using fMRI technology combined with script-guided imagery paradigm in which subjects imagined being in a real-life stressful situation, Rajita Sinha's group found that cannabis abuse contributed to stress-induced blood-oxygen-level-dependent (BOLD) contrast in a group of cocaine-dependent individuals. More specifically, cannabis consumption decreases emotional stress cue-induced frontal and cingulate activation in cocaine-dependent individuals (247). These findings suggest an abnormal cognitive control mechanism during affective processing in association with heavy cannabis use. An important caveat to consider in the latter study is that cocaine-dependent individuals were abstinent for several weeks prior to the neuroimagery session and were not current users of cannabis. Thus the study did not allow to examine the acute effect of cannabis on neural and behavioral responses. However, the fact that this cannabis-induced alteration in stress-response can be translated to cocaine craving and relapse vulnerability has definitely piqued further interest, and initial data on this matter already exists. Indeed, the effects of cannabis consumption on abstinence and relapse to cocaine use have been provided in a

study from Labigalini and colleagues, in which 25 cocaine-crack dependent individuals reported to smoke cannabis in order to get relief from abstinence mediated-cocaine-withdrawal symptoms. From this sample, 68% of addicts achieved crack-cocaine cessation while using cannabis during the 9 months duration of the study (90). However, the self-reported nature of this study and its limited duration suggest cautiousness in interpreting its outcome. In a more recent study, Aharonovich et al. drew opposite conclusions on the consequences of smoking cannabis on cocaine relapse. In this study, researchers investigated whether cannabis use after the discharge of 144 drug-addicts from inpatient treatment program could help them to maintain abstinence and thereby preventing relapse to cocaine use. Results from this study suggest that smoking cannabis reduced the achievement of sustained remission and increased relapse to cocaine use (91) (see **Table 1**). Surprisingly, a study from Jutras-Aswad et al. supports the assumption that irregular cannabis use increases risky behaviors (syringe sharing) of cocaine and opioid users, as opposed to regular cannabis use, suggesting a complex dose-effect relationship between cannabis and addictive behaviors (22). The possibility that cannabis use by recently abstinent cocaine-dependent individuals influences relapse to drug and other related behaviors remains poorly documented.

ANIMAL STUDIES

Over the last decades, development of animal models have allowed a better understanding of psychostimulant effects and addiction-related behaviors. These studies would not be available through clinical studies for ethical and practical reasons. Notably, invasive measures such as catheter installation for drug administration and surgical brain procedures for assessment of drug-induced neurobiological changes, as well as strictly controlled conditioning protocols involving restrictive environments, have extended the knowledge of psychostimulants effect on neurotransmission. These methods have also allowed observations of specific behavioral aspects of psychostimulant addiction. Thus, studies on animal models of psychostimulants abuse have provided tremendous insights on the role of ECBS in various aspects of psychostimulant addiction, spanning from drug reward, acquisition, and relapse.

Influence of ECBS on psychostimulants-induced behavioral and reinforcing effects

As mentioned above (see Neurobiology of Psychostimulants), substantial evidence indicates that behavioral and addictive properties of psychostimulants come from the interactions of psychostimulants with brain monoamines. Specifically, increase of extracellular levels of DA through promotion of DA release by amphetamine and MDMA, as well as inhibition of DA reuptake by cocaine, represent the primary mechanisms involved in rewarding effects mediated by psychostimulants (224). In animal models of intracranial self-stimulation (ICSS), the rewarding properties of drugs of abuse typically translate into lowering of the so-called reward threshold established after operant training [see Ref. (250) for description]. Initial experiments showed no effect of CB1 antagonist SR141716A on cocaine's ability to lower ICSS threshold in rats (251), although careful data analysis suggests a tendency toward attenuation. However, different results were obtained when using a more potent antagonist – AM251. This antagonist proves CB1 blockade's effectiveness in inhibiting cocaine's action on brain stimulation reward (250). Paradoxically, the non-selective cannabinoid agonist – WIN55, 212-2 – and the endocannabinoid transmission enhancer – AM404 – are also able to abolish cocaine's reinforcing effects as assessed by ICSS (252). Whether these apparently contradictory findings may indicate an inverse U-shape effect of CB1 stimulation function on rewarding properties of stimulants is not entirely clear. However, these results clearly indicate that cannabinoids might interfere with brain systems responsible for psychostimulants rewarding effects, and the mechanism underlying this phenomenon should be further explored.

Li and colleagues recently found significant reductions in DA levels in striatum of mice lacking the *CNR1* gene, when compared to their wildtype counterparts following acute cocaine administration and during the basal state (253). This observation shows consistency with above-cited ICSS studies and with a previous report on the inhibition of cocaine-induced DA release in rats by CB1 antagonist SR141716A (254). In contrast, initial findings suggested that neither basal levels nor cocaine-induced increases in extracellular NAc DA of CB1 knockout mice differed from that of normal mice (255), and that CB1 inactivation by antagonists AM251 and SR141716A failed to alter the increase in extracellular NAc DA responsible for cocaine-mediated rewarding effects in rats (256, 257). Differences in experimental methods used to measure DA levels (voltammetry vs. *in vivo* microdialysis) and in the genetic background of the knockout animals (C57BL/6J vs. CD1) could account for such discrepancies. Notably, compensatory neurobiological changes due to lack of CB1 receptors could explain the subnormal basal DA levels observed in Li et al. study. This subnormal basal DA levels could also have contributed to apparent attenuation of DA levels enhancement produced by cocaine. Overall, the extent to which ECBS interaction with psychostimulants-mediated reward effects depends on DA transmission seems limited, especially when CB1 is targeted. It remains a controversial issue, with subsequent reports of attenuation of cocaine-enhanced extracellular NAc DA activity by CB2 agonists JWH133 and GW405833 in mice (258), but not by the pharmacological FAAH inhibitor URB597 in rats (259) adding to the complexity of the matter (see **Table 2**).

The increase of DA neurotransmission in the NAc and other striatal regions responsible for psychostimulant-induced rewarding parallels the stimulation of locomotor activity following acute drug administration. Sensitization to hyperlocomotor responses produced by psychostimulants occurs after chronic treatment, reflecting adaptive changes in DA transmission and potentially correlating with drug-seeking and reinstatement behavior (254, 262). In various studies, neither genetic deletion (262–264) nor pharmacological inhibition of CB1 receptors by SR141716A (265, 266) altered cocaine's ability to induce acute motor effects or behavioral sensitization in rats and mice. However, a comparable number of reports described contradictory results, showing attenuation of both of these outcomes in CB1 knockout mice (253, 267) (see **Table 3**) as well as impairment of sensitization

Table 2 | Pharmacological inhibition of FAAH inhibition and properties of psychostimulants.

FAAH inhibitors	Drug	Animal	Outcome	Effects	Reference
AM404	Cocaine	Rat	Drug-induced lowering of brain reward/self-stimulation threshold	Impaired	Vlachou et al. (252)
			Drug-induced acute hyperlocomotion	Attenuated	Vlachou et al. (252)
URB597	Cocaine	Monkey	SA – effect of agonist after drug-taking extinction	No effect	Justinova et al. (260)
			SA – drug-taking behavior	No change	Justinova et al. (260)
		Rat	Cocaine-induced increase in VTA DA activity	Preserved	Luchicchi et al. (259)
			Cocaine-induced alterations in firing of NAc shell spiny neurons	Attenuated	Luchicchi et al. (259)
URB597, PMSF	Cocaine	Rat	SA – drug-seeking responses/intake	No change	Adamczyk et al. (261)
			SA – drug-induced reinstatement	Attenuated	Adamczyk et al. (261)
			SA – cue-induced reinstatement	Attenuated	Adamczyk et al. (261)

in animals pretreated with SR141716A (254, 268) or AM251 (267). Interestingly, although chronic cocaine use still induced sensitization in mice with invalidated CB1 receptors, sensitized response appeared somewhat changed when compared to control animals. Corbille et al. also found that AM251, unlike SR141716A (269), only impaired sensitization to cocaine after a single exposure, but not upon repeated administration. Similar experiments with cannabinoid agonists showed mixed results, as non-selective WIN 55,212-2 reduced cocaine's motor effects, probably in a non-CB1 mediated fashion (252, 270). Likewise, CB2 agonists JWH133 and GW405833 decreased both acute hyperlocomotion and sensitization in rats (258), which parallels findings observed in mice genetically overexpressing CB2 (271). Δ^9-THC failed to alter cocaine's motor effects in rats (268, 272). Similarly, cannabinoid-amphetamine interactions studies demonstrate that acute cannabinoid exposure antagonizes amphetamine's locomotion effects in a dose-dependent manner in rats. On the other hand, chronic exposure to Δ^9-THC induces sensitization to the psychomotor effects mediated by amphetamine in rats (273). Taken together, these experiments suggest that the acute motor stimulant effects of psychostimulant and the induction of cocaine sensitization may not depend on endocannabinoid tone, even though CB1 receptors could play a minor modulating role in this regard [reviewed in Ref. (274)].

Overall, while some evidence of ECBS involvement in the neurobiological and behavioral correlates of psychostimulant reinforcing properties exists, influence of ECBS on acute psychostimulant reward is modest and probably involves a combination of mechanisms which may not directly involve DA activity in the NAc or CB1 receptors.

Influence of ECBS on acquisition and maintenance of psychostimulant-induced seeking behaviors

Models of conditioning such as the SA paradigm and the conditioned place-preference (CPP) procedure illustrate the reinforcing properties of drugs of abuse and demonstrate their ability to induce and maintain drug-seeking behaviors. Consistent with findings showing the limited involvement of the ECBS in the reinforcing properties of psychostimulants (see Influence of ECBS on Psychostimulants-Induced Behavioral and Reinforcing Effects), modulation of the ECBS appears to have a modest influence on acquisition and maintenance of psychostimulant-taking behavior in animals. In CPP experiments, while CB1 receptor deletion did not affect psychostimulant-induced place conditioning in mice, SR141716A impaired cocaine-, methamphetamine-, and MDMA-induced place conditioning in both rats and mice (262–265, 281, 286, 287). Difference in species, compensatory changes in the knockout animals due to the lack of CB1 receptors, as well as use of more intense conditioning and higher doses of drugs in the genetic deletion studies may have contributed to this discrepancy. This suggests that intensity of conditioning could overcome the effects of blocking ECBS signaling [reviewed in Ref. (274)]. It is important to note that the weaker cannabinoid antagonist CBD did not affect establishment of amphetamine-induced CPP in rats (290) and that the genetic overexpression of cannabinoid receptor CB2 impaired acquisition of both cocaine-induced CPP and SA (271). Thus the CPP model indicates that, although not directly interfering with the rewarding properties of psychostimulant drugs, ECBS could play a role in the perception and memory of psychostimulant reward, depending on environment-related factors.

In general, CB1 receptor invalidation does not seem to affect SA of psychostimulants. Experiments with genetic deletion of CB1 show conflicting results, as both knockout and SR141716A-treated mice still acquired amphetamine- and cocaine-taking behavior in restrained mobility conditions (266, 275), whereas knockout mice showed impaired SA behavior in other protocols (255, 258). Overall, results suggest that learning SA behavior might not require extensive ECBS involvement. Maintenance of such behavior may not depend on CB1 either, as drug-taking responses under a fixed-ratio schedule in animals that had already acquired cocaine SA remained unaffected after CB1 blockade by SR141716A in mice (266, 283), monkeys (280), and rats (250, 256, 269, 283) and by AM251 in rats (250, 277). Only one contradicting report exists in which AM251 decreased methamphetamine SA in conditioned rats (278). Cannabinoid signaling enhancement by the pharmacological FAAH inhibitors – URB597 and PMSF – also failed to affect maintenance of fixed-ratio drug-taking behavior in rats (261) and monkeys (260). On the other hand, cannabinoid stimulation by CB1 agonists had significant effects in several studies.

Table 3 | Effects of CB1 cannabinoid receptor deletion and properties of psychostimulants; CB1 receptor antagonists and properties of psychostimulants.

Genotype	Drug	Animal	Outcome	Effects	Reference
CB1 KO	Cocaine	Mouse	Drug-induced acute hyperlocomotion	Preserved	Martin et al. (262), Houchi et al. (263), Miller et al. (264)
			Drug-induced acute hyperlocomotion	Attenuated	Corbille et al. (267), Li et al. (253)
			Drug-induced motor sensitization	Preserved	Martin et al. (262)
			Drug-induced motor sensitization	Attenuated	Corbille et al. (267)
			Drug-induced increase in NAc DA levels	Preserved	Soria et al. (255)
			Drug-induced increase in NAc DA levels	Attenuated	Li et al. (253)
			CPP – behavior acquisition under chronic unpredictable stress exposure	Preserved	Martin et al. (262), Houchi et al. (263), Miller et al. (264)
				Enhanced	Miller et al. (264)
			SA – behavior acquisition in restrained mobility protocol	Impaired	Soria et al. (255), Xi et al. (258)
				Preserved	Cossu et al. (275)
			SA – breaking point under PR schedule	Decreased	Soria et al. (255)
	Amphet.		Drug-induced acute hyperlocomotion	Preserved	Houchi et al. (263)
			Drug-induced acute hyperlocomotion	Attenuated	Corbille et al. (267)
			Drug-induced motor sensitization	Attenuated	Corbille et al. (267)
			SA – behavior acquisition in restrained mobility protocol	Preserved	Cossu et al. (275)
Antagonist	**Drug**	**Animal**	**Outcome**	**Effects**	**Reference**
AM251	Cocaine	Mouse	Drug-induced acute hyperlocomotion	Attenuated	Corbille et al. (267)
			Drug-induced motor sensitization (induction)	Attenuated	Corbille et al. (267)
			Drug-induced motor sensitization (expression)	Preserved	Corbille et al. (267)
			CPP – drug-induced reinstatement	Preserved	Vaughn et al. (276)
			CPP – stress-induced reinstatement	Impaired	Vaughn et al. (276)
		Rat	Drug-induced lowering of brain reward/self-stimulation threshold	Attenuated	Xi et al. (250)
			Drug-induced increase in NAc DA levels	Preserved	Xi et al. (257)
			Drug-induced increase in NAc glutamate	Attenuated	Xi et al. (257)
			SA – drug-induced reinstatement	Attenuated	Xi et al. (257), Adamczyk et al. (277)
			SA – cue-induced reinstatement	Attenuated	Adamczyk et al. (277)
			SA – drug-seeking responses/intake	No change	Xi et al. (250), Adamczyk et al. (277)
			SA – breaking point under PR schedule	Decreased	Xi et al. (250)
	METH	Rat	SA – drug-seeking responses/intake	Decreased	Vinklerova et al. (278)
SR141716A	Amphet., cocaine	Gerbils	Drug-induced acute hyperlocomotion	Decreased	Poncelet et al. (279)
			Reinstatement of drug-seeking	Decreased	Poncelet et al. (279)
	Cocaine	Monkey	SA – drug-seeking responses/intake	No change	Tanda et al. (280)
		Mouse	Drug-induced acute hyperlocomotion	Attenuated	Gerdeman et al. (268)
				Preserved	Lesscher et al. (266)
			Drug-induced motor sensitization (induction)	Attenuated	Gerdeman et al. (268)
				Preserved	Lesscher et al. (266)

(Continued)

Table 3 | Continued

Antagonist	Drug	Animal	Outcome	Effects	Reference
			Drug-induced motor sensitization (expression)	Preserved	Gerdeman et al. (268)
			Drug-induced motor sensitization (maintenance – specific to a drug-paired environment)	Reversed	Gerdeman et al. (268)
			CPP – behavior acquisition	Impaired	Yu et al. (281)
			CPP – drug-induced reinstatement	Impaired	Yu et al. (281)
			SA – behavior acquisition	Preserved	Lesscher et al. (266)
			SA – "extinction burst responding"	Attenuated	Ward et al. (282)
			SA – time for behavior extinction	Decreased	Ward et al. (282)
			SA – cue-induced reinstatement	Attenuated	Ward et al. (282)
			SA – drug-seeking responses/intake	No change	De Vries et al. (283), Lesscher et al. (266)
			SA – breaking point under PR schedule	Decreased	Soria et al. (255)
		Rat	Drug-induced acute hyperlocomotion	Preserved	Chaperon et al. (265)
				Attenuated	Cheer et al. (254)
			Drug-induced motor sensitization (expression)	Attenuated	Filip et al. (269)
			Drug-induced lowering of brain reward/self-stimulation threshold	Preserved	Vlachou et al. (251), Xi et al. (250)
			Drug-induced decrease in VP GABA efflux	Preserved	Caille and Parsons (256)
			Drug-induced increase in NAc DA levels	Preserved	Caille and Parsons (256)
				Suppressed	Cheer et al. (254)
			Drug discrimination	Preserved	Filip et al. (269)
			SA – drug-seeking responses/intake	No change	De Vries et al. (283), Caille and Parsons (256), Filip et al. (269), Xi et al. (250)
			SA – breaking point under PR schedule	No change	Xi et al. (250)
				Decreased	Orio et al. (284)
			SA – drug-induced reinstatement	Attenuated	De Vries et al. (283), Filip et al. (269)
			SA – HU210-induced reinstatement	Attenuated	De Vries et al. (283)
			SA – cue-induced reinstatement	Attenuated	De Vries et al. (283), Filip et al. (269)
			SA – stress-induced reinstatement	Preserved	De Vries et al. (283)
			CPP – behavior acquisition	Impaired	Chaperon et al. (265)
			CPP – behavior expression	Preserved	Chaperon et al. (265)
	MDMA	Mouse	CPP – drug-induced reinstatement	Increased	Daza-Losada et al. (285)
			CPP – behavior acquisition	Impaired	Rodriguez-Arias et al. (286)
		Rat	CPP – behavior acquisition	Impaired	Braida et al. (287)
			SA – drug-seeking responses/intake	Increased	Braida and Sala (288)
	METH	Mouse	CPP – behavior acquisition	Impaired	Yu et al. (281)
			CPP – drug-induced reinstatement	Impaired	Yu et al. (281)
		Rat	Drug-induced reinstatement of drug-seeking behavior	Attenuated	Anggadiredja et al. (289)
			Cue-induced reinstatement of drug-seeking behavior	Attenuated	Anggadiredja et al. (289)

Indeed, WIN 55,212-2 increased acquisition of MDMA SA in mice (286) and exposure to CP55,940 enhances development of cocaine SA in female rats (291). THC failed to alter acquisition of cocaine SA and amphetamine SA in monkeys (272) and rats (290), respectively. In regard to maintenance of drug intake in animals with SA behavior, cannabinoid agonists decreased drug-taking responses in rats – CP55,940 diminished MDMA intake (288) and WIN55,212-2 decreased cocaine administration (292) – and in monkeys – Δ^9-THC also decreased cocaine intake (272). Fattore et al. first interpreted the shift in psychostimulant intake produced by CB1 agonists as indicative of a synergistic action of CB1 stimulation on reinforcing properties of the drugs, which, incidentally, could account for the frequent use of cannabis among human psychostimulants users (292). Complementary experiments using progressive-ratio schedules also reveal interaction of CB1 receptors with psychostimulant-induced reinforcing properties. In PR schedules, both genetic deletion and antagonist treatment of CB1 receptors produce a decrease in the maximal effort mice provided to self-administer cocaine, as made apparent by decreases in breaking point measures induced by SR141716A (255, 277, 284) and by AM251 (250) (SR141716A producing no effect in this specific report). This adds to the evidence that the CB1 receptors, while not indispensable for acquisition or maintenance of cocaine-seeking behavior, may exert a specific modulation on motivation and reward salience in psychostimulant addiction.

Role of ECBS in extinction and reinstatement of drug-taking behaviors

Although the mechanism used by endocannabinoid signaling to modulate psychostimulant reward and acquisition or maintenance is still the subject of debate, some form of consensus exists in the literature about the pivotal role of the ECBS in extinction and reinstatement in animal behavioral models of psychostimulant addiction [reviewed in Refs. (89) and (274)]. In conditioning procedures, extinction refers to the learning phase that follows the removal of the reinforcer (i.e., psychostimulant drugs), during which rates of conditioned responses (i.e., SA or CPP) progressively decline back to pre-conditioning levels. After drug-seeking behavior becomes extinct, several behavioral phenomena can reinstate drug-seeking behavior. These include not only re-exposure to the abused drug itself, but also exposure to contextual cues associated with previous drug administration and to environmental stressors (274, 293).

In a recent study from Ward et al. mice treated with SR141716 after removal of cocaine in a SA paradigm altered the burst in cocaine-seeking observed in the initial phase of extinction learning, while decreasing the time required to achieve complete extinction of cocaine-seeking behavior when compared to vehicle-treated mice (282). CB1 blockade by SR141716A also significantly decreases cue-induced reinstatement of cocaine SA behavior following extinction, supporting similar reports of attenuation of cue-induced reinstatement of cocaine-seeking by CB1 antagonism in rats (269, 277, 283). Evaluation of reinstatement of SA behavior induced by drug-priming produced similar results: SR141716A blocks cocaine-induced reinstatement (269, 283), and both AM251 (257, 277) and SR141716A inhibit methamphetamine-induced reinstatement (289). It is worth noting that CB2 antagonism also has an anti-reinstatement effect in cocaine-primed, but not in cue-exposed rats (277). In CPP models, CB1 blockade by SR141716A, but not by AM251 (276), impaired drug-induced reinstatement in cocaine-conditioned mice (281). SR141716A also impaired methamphetamine-induced reinstatement of CPP (281). Few studies focused on stress-induced reinstatement of psychostimulant-seeking. Vaughn et al. recently found that AM251 reverses stress-induced CPP (276). De Vries et al. could not find an impact of SR141716A on stress-induced SA reinstatement (283).

Stimulation of CB1 receptors produced opposite results to those obtained in pharmacological blockade experiments (see **Table 4**). WIN55,212-2 increases time for extinction of CPP and enhances drug-induced reinstatement in MDMA-conditioned mice (285, 286). Similarly, Δ^9-THC increases cue-induced reinstatement of methamphetamine SA in rats (289). However, studies from Parker et al. and Adamczyk et al. complexify the interpretation of these results (290). Indeed, Adamczyk's group showed that FAAH inhibition impairs cue- and drug-induced reinstatement of cocaine SA. Using the place-preference conditioning paradigm, Parker et al. have assessed the potential of both exogenous cannabinoids – Δ^9-THC and CBD – to potentiate the extinction of cocaine- and amphetamine-induced CPP (290). After the establishment of cocaine-induced and amphetamine-induced place preference, rats were given an extinction trial, 30 min prior to which they were injected with a low dose of Δ^9-THC, CBD, or vehicle. During conditioning trials, researchers also injected rats with cannabinoids, or vehicle, prior to an amphetamine injection, to determine the effects of Δ^9-THC or CBD on the establishment and expression of a place preference. Results indicate that Δ^9-THC and CBD potentiate the extinction of stimulant-CPP learning, which is not mediated by an alteration of learning or retrieval. CBD does not have a reinforcing or hedonic property on its own, suggesting that it does not have the addictive potential of Δ^9-THC, a significant advantage in terms of therapeutic use. The non-reinforcing aspect of CBD has been replicated in studies looking at the co-administration of CBD and Δ^9-THC (212, 294). These discrepancies probably result from the lack of receptor selectivity in the methods used to enhanced cannabinoid signaling. Nonetheless, these experiments support a significant involvement of ECBS in the extinction and reinstatement of behaviors related to psychostimulant addiction. Overall, the positive results of CB1 antagonists on extinction and prevention of reinstatement of psychostimulant SA, combined with their lack of reinforcing properties, suggest a therapeutic potential for CB1 modulation in treatment of psychostimulant addiction.

CONCLUSION

A growing number of studies have investigated the neurobiological and behavioral mechanisms leading to psychostimulants dependence. A key feature of drug dependence is the relapse to drug use even after long period of abstinence. While greatly improved in recent years, treatment strategies for psychostimulants have

Table 4 | CB1 receptor agonists and properties of psychostimulants.

Agonists	Drugs	Models	Outcome	Effects	Reference
CP55,940	Cocaine	Mouse	SA – effect of agonist after drug-taking extinction	No effect	Vaughn et al. (276)
		Rat	SA – behavior acquisition following exposure during adolescence in female specimen	Enhanced	Higuera-Matas et al. (291)
	MDMA	Rat	SA – drug-seeking responses/intake	Decreased	Braida and Sala (288)
HU210	Cocaine	Rat	SA – effect of agonist after drug-taking extinction	Reinstatement	De Vries et al. (283)
Δ^9-THC	Amphet.	Rat	CPP – behavior acquisition	Preserved	Parker et al. (290)
			CPP – behavior extinction	Potentiated	Parker et al. (290)
	Cocaine	Monkey	SA – effect of agonist after drug-taking extinction	Reinstatement	Justinova et al. (260)
		Mouse	Drug-induced motor sensitization	Preserved	Gerdeman et al. (268)
		Rat	Drug-induced acute hyperlocomotion	Preserved	Panlilio et al. (272)
			Drug-induced motor sensitization	Preserved	Panlilio et al. (272)
			Drug-induced anxiety	Increased	Panlilio et al. (272)
			SA – behavior acquisition	Preserved	Panlilio et al. (272)
			SA – drug-seeking responses under PR schedule	Decreased	Panlilio et al. (272)
			CPP – behavior extinction	Potentiated	Parker et al. (290)
	METH	Rat	SA – cue-induced reinstatement	Increased	Anggadiredja et al. (289)
			SA – drug-induced reinstatement	Attenuated	Anggadiredja et al. (289)
WIN-55	Cocaine	Rat	Drug-induced acute hyperlocomotion	Attenuated	Przegalinski et al. (270), Vlachou et al. (252)
			Drug-induced lowering of brain reward/self-stimulation threshold	Impaired	Vlachou et al. (251)
			SA – drug-seeking responses/intake	Decreased	De Vries et al. (283)
	MDMA	Mouse	CPP – behavior acquisition	Increased	Rodriguez-Arias et al. (286)
			CPP – time for behavior extinction	Increased	Rodriguez-Arias et al. (286)
			CPP – drug-induced reinstatement	Increased	Rodriguez-Arias et al. (286), Daza-Losada et al. (285)

yet to address effectively drug-seeking behaviors linked to high rates of relapse, persistent drug use as well as subsequent health, mental, and social problems. There is consequently an urgent need for researchers to identify compounds that might help patients (1) initiate abstinence and (2) avoid relapse. The ECBS appears to play a critical role in dependence to psychostimulants and experimental studies are now providing evidence that while it does not participate in the primary reinforcing properties of psychostimulants, it reliably modulates relapse to drugs. Interestingly, emerging human data supports a role for ECBS modulation in vulnerability to psychostimulant addiction, and more significantly in addictive behaviors among dependent individuals. Accumulating evidence thus points to the ECBS as a critical target for the development of pharmacotherapies for the treatment of addiction to psychostimulants. Given the various neuropharmacological actions of exogenous cannabinoids, and their ability to modulate the acute reinforcing effects of drugs, data on Δ^9-THC and CBD is particularly promising as to the potential use of cannabinoids in relapse prevention strategies for psychostimulant-dependent individuals. The effects of these compounds on stimulant use outcomes in humans remains to be clearly established and could be assessed with well-designed controlled trials. The neurobiological correlates of cannabinoids' impact on stimulant-seeking behaviors could also be examined with neuroimaging studies in stimulants dependent individuals. Among potential barriers, social and scientific acceptability of cannabinoid-based therapy, side effects profiles, as well as addictive potential of certain cannabinoid such as Δ^9-THC, have to be taken into consideration.

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OPINION ARTICLE
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Why should cannabis be considered doping in sports?

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Recent debate and cases involving elite athletes raised the question whether or not *Cannabis sativa* (cannabis) should be considered doping in sports. Results from a 2010 report in the United States (Substance Abuse and Mental Health Services Administration, 2011) showed that cannabis is the most used illicit drug, with 17.4 million users smoking cannabis and 6.9 million users smoking cannabis on a daily or near daily basis. The World Anti-Doping Agency (WADA) included cannabis in its Prohibited List in 2004, claiming that cannabis may improve performance in some sports and is an illegal drug in most countries (Huestis et al., 2011); however, the inclusion of a substance in the Code (World Anti-Doping Agency, 2009) is complex, requiring intense debate among delegates and the fulfillment of specific criteria. For instance, Section 4 of the Code establishes that a substance be considered for inclusion in the Prohibited List if it is a masking agent or meets two of the three following criteria: (i) potential to enhance performance in sports – smoked cannabis affects cognition and performance, causes memory loss, executive function, and motor impairment, among other undesirable effect (Saugy et al., 2006). Cannabis smoking can be helpful for some activities such as extreme sports, as it improves muscle relaxation, reduces anxiety, and extincts fear memories (e.g., negative experiences) leading to enhanced performance. It is also worthwhile to note that cannabis smoking improves sleep time and recovery, which may favor performance when an athlete is facing multiple competitions in a short period of time. In light of these positive effects, one can assume cannabis is a doping substance that relaxes the mind and improves recovery (Huestis et al., 2011); (ii) potential or actual health risk – cannabis' cognitive effects in chronic users are still unclear, but it may downregulate CB1 receptors, affect executive functions, and cause motor impairment, reversed only after weeks of abstinence (Hirvonen et al., 2012). It seems unlikely that athletes are chronic cannabis smokers due to the detrimental effects of chronic use including inconsistent performance, concentration, and motivation. Cyclists who smoked cannabis had a 1-min decrease in maximal exercise performance at 10 min after smoking (Renaud and Cormier, 1986). These negative effects on cognition and performance can impair critical skills (e.g., decision making, vigilance, alertness) required in high-risk sports to avoid accidents and/or injuries; or (iii) violation of the spirit of sport – doping is essentially contrary to the spirit of sport, which is the principle of Olympism, characterized by several values, such as ethics, fair play and honesty, health, respect for rules and laws, and respect for self and other participants (World Anti-Doping Agency, 2009).

Over 60 cannabinoids are present in cannabis, with Δ9-tetrahydrocannabinol (THC) the main psychoactive constituent and responsible for the observed toxic effects after smoking, while other cannabinoids are responsible for minor effects, such as cannabinol (CBN), which is 10% as psychoactive as THC (Huestis, 2005). THC is lipophilic and stores in several organs, especially in adipose tissue; this extensive body burden explains the prolonged cannabinoid detection rate in blood and urine for at least 4 weeks in chronic daily cannabis smokers (Lowe et al., 2009; Bergamaschi et al., 2013). The WADA (World Anti-Doping Agency, 2013) establishes a 15 ng/mL urinary 11-nor-9-carboxy-THC (THCCOOH) threshold; urine analyses involves THCCOOH-glucuronide conjugates cleavage, which significantly increases free THCCOOH concentrations and detection time. Urinary THCCOOH concentrations above the 15 ng/mL threshold are considered Adverse Analytical Findings and may be interpreted as a violation of anti-doping rules (World Anti-Doping Agency, 2009). Studies showed that even occasional and single cannabis smoking might yield a THCCOOH positive result (≥15 ng/mL) for up to 5 days (Huestis et al., 1996). Thus, consuming cannabis even weeks before a match may imply a considerable risk of being detected in a doping test. In light of this considerable risk, some users started using a new preparation of herbal smoking blends named "Spice." Such substances are highly potent cannabinoid analogs, with unknown and potentially harmful toxicological properties that may cause prolonged intoxication. These substances mimic or worsen cannabis' toxic effects provoking cognitive and motor impairment (UNODC, 2011).

The non-psychoactive cannabidiol (CBD) is anxiolytic in humans following a single dose (Zuardi et al., 1993; Bergamaschi et al., 2011); decreased anxiety and fear memories extinction after oral CBD intake may enhance sports performance with no "violation" of the Code, as no THCCOOH is detected in urine. One way to protect athletes' health and to promote health, fairness, and equality in sports is to include any illicit drugs, their constituents and analogs in the anti-doping program. The sports may assist to create educational program for youth and athletes as an alternative to keep them away from drugs and to preserve the intrinsic value about the "spirit of sport."

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METHODS ARTICLE
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Statistics on cannabis users skew perceptions of cannabis use

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Collecting information about the prevalence of cannabis use is necessary but not sufficient for understanding the size, dynamics, and outcomes associated with cannabis markets. This paper uses two data sets describing cannabis consumption in the United States and Europe to highlight (1) differences in inferences about sub-populations based on the measure used to quantify cannabis-related activity; (2) how different measures of cannabis-related activity can be used to more accurately describe trends in cannabis usage over time; and (3) the correlation between frequency of use in the past-month and average grams consumed per use-day. Key findings: focusing on days of use instead of prevalence shows substantially greater increases in U.S. cannabis use in recent years; however, the recent increase is mostly among adults, not youth. Relatively more rapid growth in use days also occurred among the college-educated and Hispanics. Further, data from a survey conducted in seven European countries show a strong positive correlation between frequency of use and quantity consumed per day of use, suggesting consumption is even more skewed toward the minority of heavy users than is suggested by days-of-use calculations.

Keywords: cannabis, marijuana, substance abuse research, drug use metrics, drug use trends

INTRODUCTION

In substance abuse research, "use" is operationalized in terms of prevalence (i.e., how many individuals used a drug within a given period of time). However, prevalence is neither the only nor the ideal metric available. Other metrics, such as quantity of drug consumed may provide more insights into behaviors associated with intoxication and health-related outcomes, contact with law enforcement, and flows of money into black markets.

Studying users is perhaps the norm in substance abuse epidemiological research. One can ask a sample of people (e.g., in households or students in classrooms) questions about their drug use in order to learn, for example, how many used a given drug in the past-year, and on how many days did they consume. This is undoubtedly a useful perspective. We might find out, for example, that most marijuana users did not purchase the marijuana they consumed most recently; instead, it was shared with them or given to them for free.

However, imagine we could instead sample on the drug or, equivalently, the episode of drug use, rather than on the user. That would be like taking a random sample of all the grams consumed over the past-year, and asking: what are the users of this drug like? As we report below, from that perspective 88% of marijuana is consumed by someone who most recently obtained marijuana by purchasing it (as opposed to sharing or receiving it as a gift). The two perspectives suggest very different conclusions concerning the relative importance of purchases vs. gifts in retail marijuana distribution.

If the goal is to understand the drug-using careers of users, we might prefer to study a sample of users. But if the goal is to understand market-related quantities like how demand is affected by price or the roots of systemic violence, following the drug could be more valuable.

Naturally it is not literally possible to sample on chunks of the drug. No one assigns each gram a unique identification number, let alone a phone number that survey researchers could call. However, we can approximate this by weighting respondents by the quantities they consume. The purpose of this paper is to use a variety of data sets describing cannabis consumption to highlight the sometimes substantial differences in inference that arise when focusing on consumption, not consumers.

Before proceeding let us illustrate the principle numerically with a simple, extreme, and stylized example. Suppose there are just two kinds of cannabis users, "light" and "heavy," who use 1 g and 1 ounce per month, respectively. Suppose further that 80% of users are light users, so there are four light users for every heavy user. Obviously when sampling on users, one would report that most cannabis users are light, few are heavy.

But since each heavy user consumes about 28 times as much as a light user (1 ounce = 28.35 g), the heavy users consume $28/(28 + 4 \times 1) = 88\%$ of the cannabis. Prior research has shown that different conclusions can be drawn when observing light vs. heavy users [e.g., (1)].

Furthermore, if over time there were no change in the number of cannabis users, but the ratio of light vs. heavy users switched

from 80/20 to 20/80, then consumption would increase by 250% even though there was no change whatsoever in the number of users.

Because there is actually a continuum of usage, the difference between studying cannabis users and studying cannabis use is not so extreme, but it is large enough to matter, as we demonstrate below with a variety of examples. The basic observation is that when a covariate is positively correlated with quantity consumed conditional on there being some use, then individuals with that covariate account for a greater share of use than they do of users. For example, male users consume more than female users, so males account for a larger share of consumption than they do of prevalence. Conversely, users who are college graduates consume less intensively than do less educated users, so college graduates account for a smaller share of cannabis consumption than they do of cannabis users.

DATA

The National Survey on Drug Use and Health (NSDUH) is a nationally representative survey consisting of interviews conducted with randomly selected individuals ages 12 and older. NSDUH contains data on the prevalence of the use and abuse of alcohol, tobacco, and illegal substances. The survey contains sample weights that were used for all analyses to provide national-level estimates. From 2002 through 2011, there is an annual series of comparable data on past-year and past-30-day cannabis use (which we will refer to as "past-month use" throughout this paper), the number of use-days in the past-month for those who used in the last month, the number of use-days in the past-year for others who used in the last year, whether cannabis was purchased in the last month, the number of purchases in the last month for those who bought cannabis in the last month, and information about the most recent purchase of cannabis (amount purchased, cost of purchase, location of purchase, etc.). Starting in 2004 NSDUH also contains information about use of blunts (hollowed out cigar shells filled with cannabis), which was used to refine counts of past-month cannabis users and use-days for those years the item was available. While the impact of including survey items about blunts is small, it should be noted that counts of cannabis users and use-days from 2002 to 2003 may be slightly underestimated. In addition, NSDUH contains demographic information for each respondent that can be used to characterize users. One limitation of NSDUH is that it relies on self-report, which may introduce social desirability or recall bias (2). Another limitation of NSDUH is that it does not collect data from some populations that are known to have higher rates of illicit drug use, such as the incarcerated and homeless who are not in shelters (SAMHSA), but this can be shown to be a relatively insignificant deficiency in the case of cannabis (3).

The EU Drugs Markets II (EUMII) web-survey conducted by van Laar et al. (4) gathered information from a convenience sample of 4,156 cannabis users in seven countries: Bulgaria ($n = 208$), the Czech Republic (522), Italy (1,104), the Netherlands (1,128), Portugal (150), Sweden (791), and the United Kingdom (283). We focus on 2,530 observations since 1,626 of the respondents did not sufficiently answer the questions about quantity consumed (days per month, units per day, and grams per unit). For additional analyses of the EUMII cannabis data, see Caulkins et al. (5). As survey respondents often have difficulty answering directly questions about quantity consumed per day, this survey's great innovation was to present respondents with picture cards, visually contrasting various amounts of cannabis with both a ruler and a credit card, to facilitate their ability to estimate how much they have consumed.

The EUMII survey has a number of limitations. Since it is an internet survey based on a convenience sample largely recruited on the web (i.e., no sampling frame), there is an obvious selection bias toward those who (1) use the internet, (2) are not concerned with sharing data about illegal behaviors online, and (3) think that volunteering to complete marijuana surveys is a good use of their time. van Laar et al. (4) report that while internet penetration in the EU is high (72% of the population), there was variation among the selected countries – 49% in Bulgaria, 51% in Portugal, 58% in Italy, 71% in the Czech Republic, 84% in the United Kingdom, 90% in the Netherlands, and 92.9% in Sweden (Internet World Stats 2011). Furthermore, recruitment methods differed by country and van Laar et al. note that most countries employed strategies that biased the sample toward attracting students and young adults.

Also some respondents may try to complete the survey multiple times or give unrealistic answers. Since incentives were not offered to complete the survey, we are less concerned about the former. As for the latter, which is not unique to web surveys, van Laar et al. (4) screened the data, setting unrealistic values to missing and dropping respondents "who indicated consuming more than 20 units (joints, pipes etc.) on an average use day" (68).

These limitations preclude using the EUMII data for estimating relative numbers of low- vs. high-frequency users, or for contrasting patterns across countries, but they should be of less concern when using the data as we do here to explore the correlation between use-days in the past-month and the average number of joints consumed per use day, particularly since the results are consistent with analyses from the U.S. (6) and Canada (7).

METHODS AND RESULTS

In the next three sections, we highlight (1) differences in inferences about sub-populations based on the measure used to quantify cannabis-related activity (past-year use, past-month use, past-month days of use, any past-month purchase, and number of past-month purchases); (2) how different measures can be employed to describe more accurately trends in cannabis usage over time; and (3) the correlation between frequency of use in the past-month and average grams consumed per day.

CROSS-SECTIONAL COMPARISONS OF USE VS. USE-DAYS IN NSDUH

National survey on drug use and health asks respondents whether they used cannabis in the last year, whether they used in the last month and, if so, how many days they used within the last month. It also asks whether they bought in the last month and, if so, how often. For any given subpopulation, say males, these variables let one define five proportions:

1. Males' share of past-year users.
2. Males' share of past-month users.
3. Males' share of past-month days of use.
4. Males' share of those who purchased within the last month.
5. Males' share of past-month purchases.

Sometimes the proportions are all very close. Often they vary, sometimes substantially. As a general rule, for any attribute that is positively associated with cannabis use, the strength of that association grows as one moves through the list of the five proportions. For example, males use more cannabis than females. That is apparent even in simple past-year prevalence; males account for 60% of past-year cannabis users identified by the 2011 NSDUH. That proportion grows to 64% of past-month users, 69% of past-month days of use, 70% of past-month purchasers, and 72% of past-month purchases. **Table 1** shows these five proportions for a variety of groups.

Variation across some rows is striking. Only 14% of past-year cannabis users meet the criteria for cannabis abuse or dependence, but they account for 26% of past-month days of use and 37% of past-month purchases. Perhaps the most striking contrast concerns blunts. Only 27% of past-year cannabis users report using a blunt within the last month, but those individuals account for 73% of cannabis purchases. On the protective factors side, the affluent, married, and college grads tend to use moderately; for example, college graduates account for 19% of past-year users, but only 13% of days of use and just 5% of purchases.

There is literature examining disparities in criminal justice sanctioning of drug users [e.g., (8–10)]. With varying degrees of sophistication, these studies compare for given groups (e.g., African-Americans) the share of some measure of sanctioning (arrests, convictions, incarceration, etc.) with their share of use or a use-related proxy. If the groups' shares of all use-related measure were the same, then it would not matter much which measure was used. But figures for those who were ever arrested and booked (see **Table 1**) show that is not the case. Hence, to get a more complete picture of disparities, such studies should probably do the comparison with the full range of measures considered in **Table 1**. This is not a novel idea; Brownsberger (11) noted something similar with respect to alternate measures of crack use. But it is important.

To give one example, consider the distinction between using and purchasing. Possession and use *per se* carry relatively little risk of arrest. As Nguyen and Reuter (10) show, the probability of arrest per episode of cannabis use in the United States is only about 1 in 3,000. Purchasing by contrast may carry a greater risk of arrest, although there is some question about the proportion of drug arrests attributable to purchase transactions (12). If the number of purchases per day of use were the same across all groups, this would be a distinction without a difference. However, as **Figure 1** shows, young people collectively report making more purchases per day of reported use than do older users. For example, 12–17-year-olds report fewer past-month days of use than do 50–64-year-olds (21 vs. 33 million), but many more past-month purchases (7.6 vs. 3.2 million).

Statistics indicating that the burden of arrest falls disproportionately on youth relative to their share of all *users* (9) may not be *prima facie* evidence of discrimination if making more purchases per day of use increases the risk of arrest per year of use. For example, 18–25-year-olds account for 49% of NSDUH respondents reporting having been arrested for a drug offense, even though they

Table 1 | Various populations' shares of cannabis-related activity by five different measures of participation, 2011 NSDUH.

	Past-year users (%)	Past-month users (%)	Past-month days of use (%)	Past-month purchasers (%)	Past-month purchases (%)
Risk factors					
Males	60[a]	64	69[a]	70[a]	72[a]
Used an illegal drug other than cannabis in					
Past-year	35[a]	40	47[a]	46[a]	51[a]
Past-month	15[a]	20	24[a]	24[a]	29[a]
Past-month use of					
Cocaine	4	5	7[a]	6	7[a]
Cigarettes	53[a]	59	66[a]	67[a]	76[a]
Alcohol	77[a]	80	79	81	81
Blunts	27[a]	42	54[a]	57[a]	73
Met criteria in past-year for					
Cannabis dependence	9[a]	12	18[a]	19[a]	27[a]
Cannabis abuse or dependence	14[a]	19	26[a]	26[a]	37[a]
Abuse of dependence, any substance	33[a]	37	42[a]	43[a]	52[a]
Bought cannabis used last time	45[a]	56	70[a]	85[a]	88[a]
Ever arrested and booked	36[a]	40	47[a]	47[a]	53[a]
Drove under influence of drugs (past-year)	29[a]	37	47[a]	46[a]	47[a]
Adult with less than high school education	14	16	19	19	24[a]
Protective factors					
College graduate	19	17	13[a]	11[a]	5[a]
Married	22	21	21	19	13[a]
Family income > $75,000	25	23	20	20	15[a]

[a] *Indicates that proportion is statistically significantly different from proportion of past-month users ($p < 0.05$).*

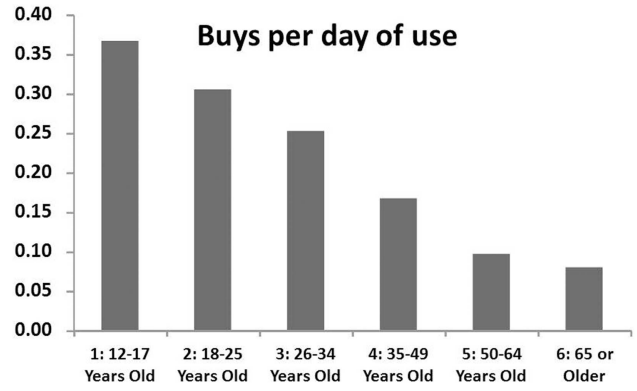

FIGURE 1 | The reported number of purchases per day of use varies dramatically with age in U.S. household survey data, 2011 NSDUH.

account for only 35% of past-year cannabis users. That appears to be a disproportionate arrest burden, but 18–25-year-olds account for 46% of buys reported in the past-month.

Likewise, the rate of arrest among past-year adult cannabis users is considerably higher for those with less than a high school education than overall (3.6 vs. 2.5 arrests per 100 users), but they make more buys per day of use, so the number of arrests per 100 buys is actually slightly below average (1.1 vs. 1.2 for adults overall).

Table 2 illustrates patterns for race and educational status. Non-Hispanic blacks represent 13% of past-year cannabis users vs. 23% of drug arrests reported by those users, but they report making 24% of the buys. Thus, some of their higher arrest rate may be a consequence of their purchase patterns. Indeed, Ramchand et al. (13) suggest that African-Americans may not only make more buys but also make riskier buys (e.g., more likely to buy outdoors).

In sum, the measure of use matters. Therefore when drawing inferences about use one should consider which measure of use is appropriate in any given context and/or test to see if the conclusions are robust with respect to the measure of use employed.

COMPARING USE VS. USE-DAYS IN NSDUH OVER TIME

The analysis above pertains to snap-shots based on the 2011 NSDUH, yet trends over time provide another interesting perspective. In this section, we explore trends in cannabis use from years 2002 through 2011 of NSDUH and show how studying past-month use-days provides additional information about changes in cannabis usage not apparent when merely studying prevalence of use.

Figure 2 shows the change since 2002 in four measures of cannabis use: past-year prevalence, past-month prevalence (past-month users), number of daily/near-daily users (those who used cannabis 21 days or more in the last month), and past-month days of use. All four measures show an increasing trend, but the growth in usage (proxied by past-month use-days) outstrips the growth in consumers because of the increase in daily/near-daily use. That is, consumption grew primarily because of an increase in the average frequency of use, not just because of an increase in the overall number of users.

Table 2 | Past-year use, number of drug-related arrests, and number of monthly purchases by education level and racial-ethnic group, 2011 NSDUH.

	Proportion of past-year users (%)	Proportion of those arrested for drug offenses (%)	Proportion of buys (%)
(AMONG ADULTS)			
Less than high school	16	23	27
High school graduate	31	39	37
Some college	32	34	30
College graduate	31	3	6
(AMONG ALL USERS)			
Non-Hispanic white	67	53	55
Non-Hispanic black	13	23	24
Hispanic	14	18	15
Other	6	7	6

Proportion who are daily/near-daily users

We calculated the total number of past-month use-days for each year from 2002 through 2011 and divide this total across four frequency of use categories: those who used 1–3 days, those who used 4–10 days, those who used 11–20 days, and those who used 21 days or more in the last month (daily/near-daily users). **Figure 3** shows the growth in the total number of users and total number of use-days for all four groups. Although daily/near-daily users represented less than one-quarter of past-month cannabis users in 2002 and roughly one-third of past-month users in 2011, they account for the vast majority of use-days and are thus are presumably responsible for the majority of consumption.

To understand more about the daily/near-daily users who are driving the increase in consumption, we explored their demographic characteristics over this 10-year time period. Examining the age distribution of the daily/near-daily users shows that youth's share of consumption plummeted by almost 50%, and more generally consumption shifted to older adults (see **Figure 4**). In 2002, 12–17-year-olds represented 13% of daily/near-daily users; in 2011, that had dwindled to 7%. The proportion of daily/near-daily users attributable to young adults (ages 18–21 years) also decreased from 26% in 2002 to 21% in 2011. The proportion aged 22 years and older increased from 62 to 73%. In other words, the age distribution of daily/near-daily users shifted so that the average age of daily/near-daily users is higher in 2011 than it was in 2002.

There was a notable inversion of the ratio of youth (ages 12–17) to older adults (ages 50 and up). In 2002, there were more than three times as many youth as older adults using cannabis on a daily/near-daily basis; in 2011 there were 2.5 times more older adults than youth using on a daily/near-daily basis.

We found a similar shift in the age distribution of daily/near-daily users of alcohol and cigarettes; however, it was not as dramatic and we did not see the same inversion that was observed for cannabis use (see **Table 3**). There was disproportionate growth in older populations over this time due to the aging of the "baby

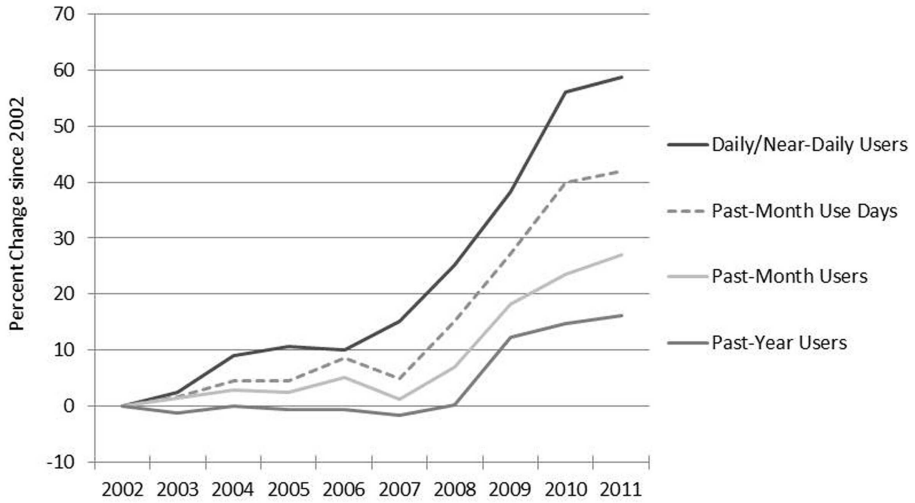

FIGURE 2 | Past-month use-days and daily near-daily users increased more rapidly from 2002 to 2011 than past-year and past-month users, NSDUH. Note: because NSDUH did not collect data about blunts in 2002 and 2003, use-days may be underestimated for these years.

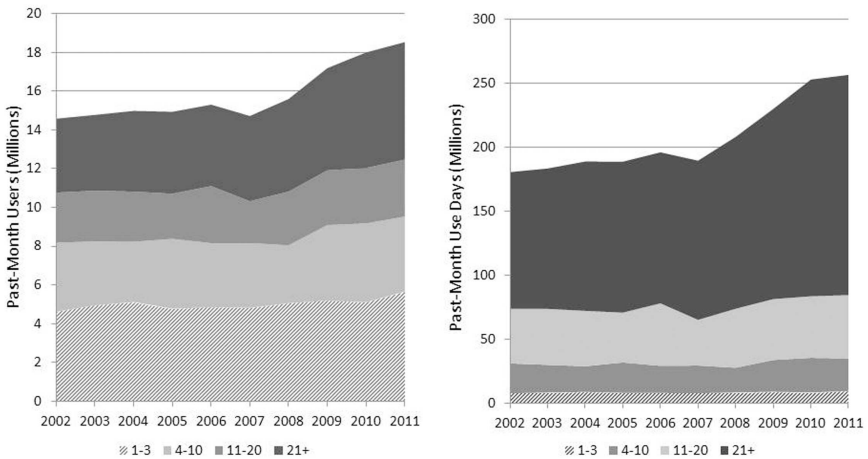

FIGURE 3 | Daily/near-daily users (21 days or more in the past-month) represent a minority of users yet are responsible for the majority of past-month use-days. Note: because NSDUH did not collect data about blunts in 2002 and 2003, use-days may be underestimated for these years.

boom" generation (14, 15), which explains most of the growth in older daily/near-daily users of alcohol and most of the growth in older daily/near-daily users of cigarettes. However, the increase in the proportion of older daily/near-daily users of cannabis was much greater than the increase in the proportion of older individuals in the population, suggesting an increase in heavy cannabis use among older individuals.

We also examined the distribution of race/ethnicity and found an increase in the proportion of Hispanic daily/near-daily cannabis users (from 8% in 2002 to 14% in 2011). While the proportion of the population identifying as Hispanic increased over this time period (16, 17), the relative increase in the population was not as large as the relative increase in daily/near-daily cannabis users. We also found a decrease in the proportion of non-Hispanic white daily/near-daily cannabis users (from 75% in 2002 to 66% in 2011) and little change in the proportion of non-Hispanic black daily/near-daily users, who represented 14% of daily/near-daily cannabis users in 2002 and 16% in 2011. There was not a parallel change in the distribution of race/ethnicity among daily/near-daily users of cigarettes or alcohol (see **Table 3**).

Educational attainment was relatively stable from 2002 to 2011 for daily/near-daily users of cannabis and cigarettes, but there was a shift in the proportion of daily/near-daily alcohol users, so that the group was more educated at the end of the time period (86% had more than a high school education in 2002, while 92% had more than high school education in 2011 – see **Table 3**).

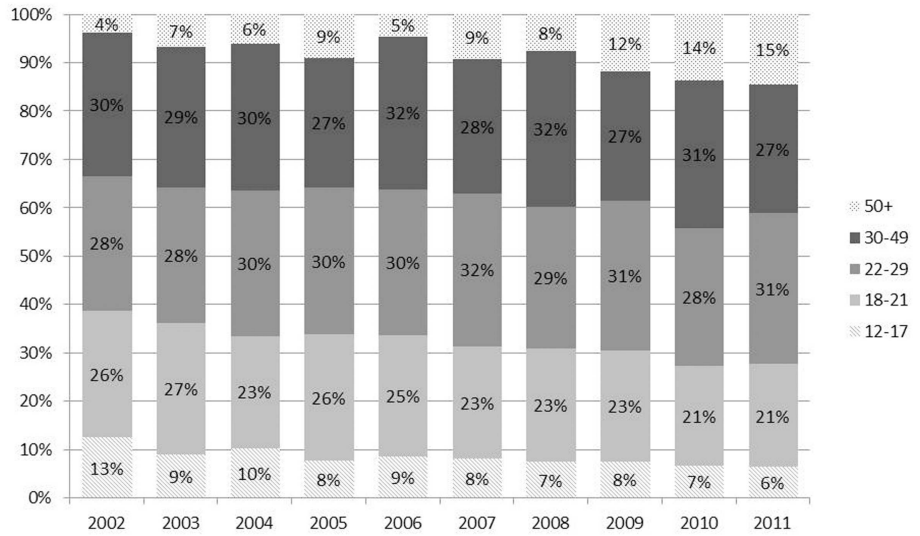

FIGURE 4 | Age distribution of daily near-daily cannabis users shifts over time so that older adults are responsible for an increasing proportion of consumption. Note: because NSDUH did not collect data about blunts in 2002 and 2003, use-days may be underestimated for these years.

Table 3 | Change in demographic profiles of daily/near-daily users of cannabis, cigarettes, and alcohol, 2002–2011.

	Cannabis (%)			Cigarettes (%)		Alcohol (%)	
	2002	2004	2011	2002	2011	2002	2011
AGE (AMONG ALL USERS)							
12–17	13	11	6	3	2	1	0
18–21	26	25	21	9	7	4	2
22–29	28	32	31	16	18	8	9
30–49	30	32	27	46	40	35	29
50+	4	7	15	25	33	53	60
RACE/ETHNICITY (AMONG ALL USERS)							
Non-Hispanic white	75	73	66	79	77	85	88
Non-Hispanic black	14	13	16	10	10	7	5
Hispanic	8	10	14	7	8	6	5
Other	3	4	4	5	6	2	3
EDUCATION (AMONG ADULTS)							
Less than high school	25	25	22	22	21	14	8
High school graduate	34	34	37	41	39	29	25
Some college	32	27	29	26	28	25	24
College graduate	9	13	12	11	13	32	43

Because NSDUH did not collect data about blunts in 2002 and 2003, use-days may be underestimated for these years.

Past-month use-days

For the most part, demographic changes in daily/near-daily users are also reflected in past-month use day trends. We explored changes in the past-month use-days since 2002 and found that consumption among adults over 50 grew sharply over the past 10 years while past-month use-days among those less than 18 years of age remained relatively stable (see **Figure 5** – note that base rates for older users in 2002 are relatively low).

From 2002 to 2011, all race/ethnicities experienced growth in the number of cannabis use-days, particularly after 2008. Hispanics and other races had the largest relative increases (130 and 105%, respectively); however, despite the relatively slower growth, non-Hispanic white users continue to be responsible for the majority of use-days (see **Table 4**).

An exploration of use-days by education level shows less dramatic change than the change in age distribution (see **Table 4**). There was growth in the number of use-days among all adults regardless of education level; overall, use-days among adults increased by 49% over this time period. However, the largest relative increase was among those with a college degree, whose use-days increased by 72% from 2002 to 2011.

The shift in the distribution of use-days and daily/near-daily users from a younger to an older population is noteworthy. For comparison, we display the age distribution of alcohol, cigarettes, and cocaine use-days to determine whether a similar shift occurred with other substances (see **Figure 6**). Adults over the age of 30 were already responsible for the majority of alcohol, cigarettes, and cocaine use-days in 2002; however, there was a similar shift in the percent of cocaine, cigarette, and alcohol use-days attributable to those older than 50 and away from those 21 and under.

CONTRASTING USE-DAYS WITH AMOUNTS USED

Although use-days provide more information about consumption than does prevalence alone, weighting respondents by days of use may still understate the skew in the distribution of use. This is due to an apparent positive correlation between *intensity* of use (grams consumed per day) and the *frequency* of use (days of consumption per month). Zeisser et al. (7), for example, observe a positive correlation between the reported number of joints consumed per day and self-reported days of use per month. Their data suggest that those using on 30 days per month consumed about three times as many joints per day as did those using only 1–4 days per month.

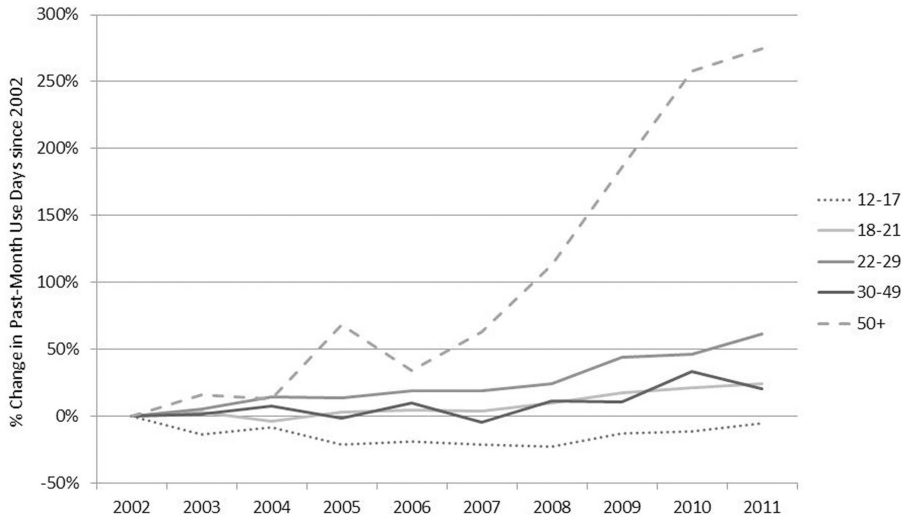

FIGURE 5 | Past-month use-days among older adults (50 and over) increased dramatically over this 10-year time period while use-days among youth (12–17) remained fairly stable. Note: because NSDUH did not collect data about blunts in 2002 and 2003, use-days may be underestimated for these years.

Table 4 | Cannabis past-month use-days (millions) by demographic groups over time.

	Use-days (millions)		
	2002	**2004**	**2011**
AGE (AMONG ALL USERS)			
12–17	23.2	21.3	21.9
18–21	44.0	42.1	54.6
22–29	47.5	54.2	76.5
30–49	56.6	60.7	68.1
50+	9.5	10.7	35.6
RACE/ETHNICITY (AMONG ALL USERS)			
Non-Hispanic white	133.0	134.6	169.7
Non-Hispanic black	26.2	27.2	39.2
Hispanic	15.4	19.9	35.3
Other	6.1	7.3	12.4
EDUCATION (AMONG ADULTS)			
Less than high school	36.4	37.9	48.9
High school graduate	53.4	57.6	83.8
Some college	48.6	48.4	69.0
College graduate	19.1	24.0	33.0

Because NSDUH did not collect data about blunts in 2002 and 2003, use-days may be underestimated for these years. We have included data from 2004 when the questions about blunts were introduced for reference.

Zeisser and colleagues' analysis does not consider the possibility that joint or unit *size* might also be positively correlated with frequency of use, but the EUMII web-survey (4) described above did gather information about quantity consumed per use-day (in grams) by using picture cards. The EUMII data suggest that when denominating by quantity (weight) consumed instead of number of units, that ratio may be closer to 4:1 (see **Figure 7**).

This relationship has important implications for what one might term "equivalence ratios." Naturally it takes multiple light users to consume as much as one heavy user, but how many? That depends on the measure of use. In particular, since it appears that those who use frequently also consume more per day of use, the ratios are considerably higher when the equivalence is one in terms of units or grams used rather than days of use.

If one focuses on days of use, it would take about 10–12 people using 1–5 times per month to match one daily user, but it would take more than three times that many (>40) to match a single daily user in terms of grams consumed per month. **Figure 8** shows these equivalence ratios for each of the categories of users, and with equivalence expressed in terms of both days of use (striped bars) and grams per month (solid bars).

Consider what this means for daily users' share of the market. The one-in-five past-month users who consume daily account for almost 60% of consumption, while the one-third of past-month users who consume less than four times per month account for just 2% of consumption.

DISCUSSION

The best metric for studying cannabis clearly depends on the objective of the research. For those interested in the prevalence of cannabis use, the number of users is likely sufficient. However, to obtain a more accurate portrayal of cannabis use and users' behavior or to better understand the market, one should look to frequency and amount of consumption. Likewise, those interested in drug-related criminal justice outcomes should focus on behavior that increases risk of arrest, such as the number of drug purchases and location of these purchases (e.g., indoor vs. outdoor).

Examining frequency of use over time provides a picture of not only changes in who is using but also how individuals are using. Beginning in 2007, there were increases not only in the number of

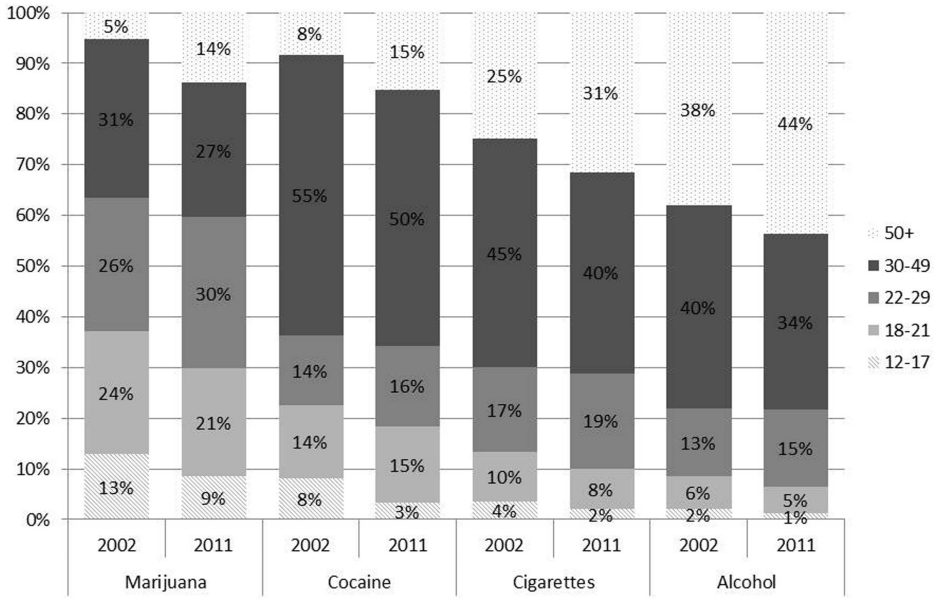

FIGURE 6 | A greater proportion of cannabis, alcohol, cigarettes, and cocaine use-days are attributable to older adults in 2011. Note: because NSDUH did not collect data about blunts in 2002 and 2003, cannabis use-days may be underestimated for these years.

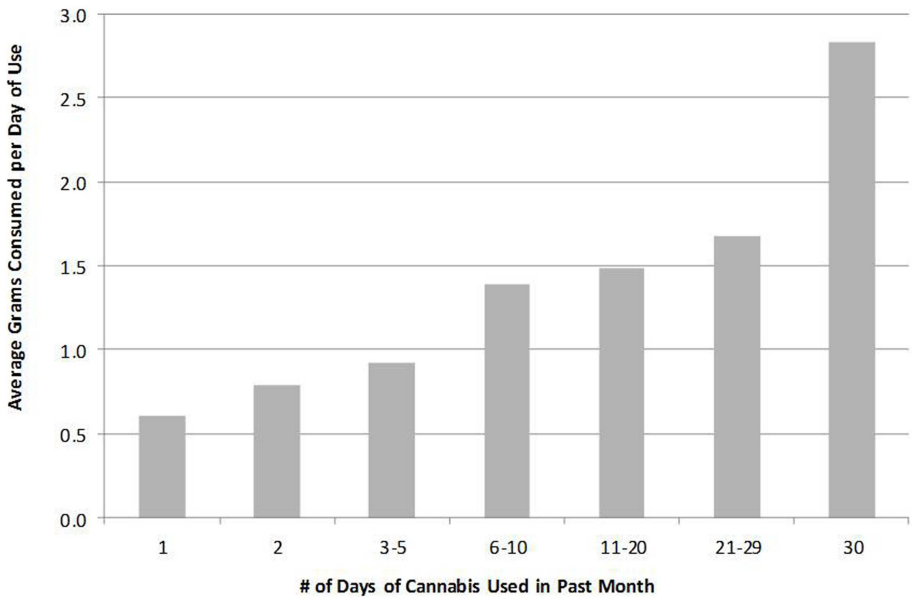

FIGURE 7 | Average quantity of cannabis consumed per day increases with frequency of cannabis use.

users but also in the number of use-days per user and the number of daily/near-daily users, suggesting heavier use over this time period. Some may wonder if this increase might be attributable to more honest reporting about cannabis use. (One way to assess this would be to examine how support for legalization in the Gallup poll changed over this period, but the lack of poll data between 2005 and 2009 complicates this exercise (18)]. However, there are supply side indicators which suggest a large increase in domestic and Mexican production post-2005 [El Paso Intelligence Center (19)].

The demographic shifts in cannabis use-days and daily/near-daily users (particularly the shift from a younger to an older population) are intriguing and raise additional questions. Given our knowledge of drug use cycles and awareness that initiation of

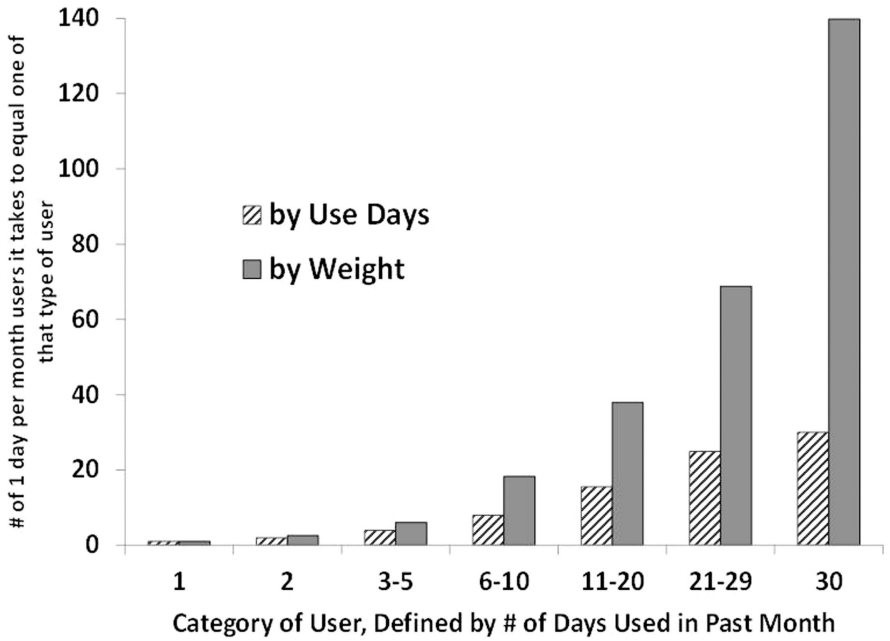

FIGURE 8 | The number of 1 day per month users required to match usage of more frequent users is higher when measuring usage in terms of grams per month rather than past-month use-days.

drug use typically happens at a young age (20, 21), can the increase in use among older individuals be attributed entirely to carrying drug use habits over time (which seems unlikely given the increase in use with respect to the relative increase in the older population) or something else? Are these older users using for medicinal or recreational purposes? Are these trends reflected in arrest or treatment datasets? Are users replacing cannabis use with use of another substance? Why did use-days among Hispanics increase so dramatically over this time period relative to other racial-ethnic groups? Does the increase in use-days among college-educated individuals indicate greater social acceptability or something else?

Zeisser et al. (7) and the EUMII web-survey (4) indicate that in Europe amount consumed per day is positively correlated with frequency of use, and thus, heavy users are responsible for a greater share of consumption than of days of use. A logical next question might be whether that pattern holds also for U.S. cannabis users and whether that means the average amount consumed per past-month user has increased along with frequency of consumption, at least in potency-adjusted terms. Preliminary analyses of data from Arrestee Drug Abuse Monitoring (ADAM) suggest there was not a statistically significant change in the average size of a joint over the 2000s (Kilmer et al., in preparation), but this is not a settled question. Further, future analyses must also account for the fact that cannabis is consumed in a variety of ways other than smoking joints (e.g., pipes, vaporizers, edibles) and that there may be substantial variation in potency as well.

In summary, by sampling on use-days and amount used, we find that most of the consumption and, hence, most of the associated intoxication and flow of money into the black markets, comes from people who use frequently. Examining the number of users can be enlightening but does not fully capture the dynamics of cannabis usage. In order to understand market-related quantities like demand, and to better assess implications for crime, health, and productivity, researchers should analyze cannabis usage indicators like use-days and quantity consumed.

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GENERAL COMMENTARY
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Erratum: Statistics on cannabis users skew perceptions of cannabis use

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An Erratum on

Statistics on cannabis users skew perceptions of cannabis use
*by Burns RM, Caulkins JP, Everingham SS and Kilmer B (2013). Front. Psychiatry **4**:138. doi:10.3389/fpsyt.2013.00138*

The authors would like to submit a correction to **Table 2** of the above article. The proportion of past-year users that are college graduates should be listed as 22 percent. The corrected table is printed here.

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Table 2 | Past-year use, number of drug-related arrests, and number of monthly purchases by education level and racial-ethnic group, 2011 NSDUH.

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Some college	32	34	30
College graduate	22	3	6
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Non-hispanic black/Afr Am	13	23	24
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