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Is Cannabis a Gateway Drug? Key Findings and Literature Review

Wm. Nöel, MSc, Researcher
Judy Wang, PhD, Researcher

November 2018

A Report Prepared by the Federal Research Division, Library of Congress, Under an Interagency Agreement with the Office of the Director, National Institute of Justice, Office of Justice Programs, U.S. Department of Justice.

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70 Years of Research Services to the Federal Government
1948 – 2018

COMMITMENT TO UNBIASED RESEARCH

This report was conducted by the Federal Research Division (FRD) within the Library of Congress. FRD provides customized research and analysis on domestic and international topics to agencies of the U.S. government, the government of the District of Columbia, and authorized federal contractors on a cost-recovery basis. This report represents an independent analysis by FRD and the authors, who have sought to adhere to accepted standards of scholarly objectivity. It should not be construed as an expression of an official U.S. government position, policy, or decision.

Significant measures were taken to ensure that the topic was researched and written with a commitment to nonpartisan scientific integrity, and with as little bias as possible:

- Each researcher was selected and vetted by FRD. Potential contributors were screened and eliminated for factors that might introduce bias to the research. FRD interviewed approximately 25 PhD statisticians to identity the most qualified, and least biased, researchers.
- Each researcher was selected for having not previously researched/written on the topic.
- The identity of the client was never disclosed to the researchers. Each researcher signed a nondisclosure agreement, committing to not discuss the project outside of the project team. FRD's chief and business manager were the only individuals aware of the client's identity and acted as the communication channel between the client and research staff.
- FRD solicited feedback from outside experts and that feedback has been incorporated. None of the experts have written specifically on the topic of cannabis and do not have a vested interest in a particular outcome.
- As a nonpartisan cost-recovery government organization, FRD is free of the business and political drivers that could otherwise impact the integrity of its research.
- The funding agency owns the intellectual property developed by FRD while working under the agreement. FRD holds no rights to sell, share, or promote intellectual property.

The project team thanks the following experts for their contributions to this report:

- Dr. Mary Amanda Dew, professor of psychiatry, psychology, epidemiology, and biostatistics at the University of Pittsburgh, and
- Dr. Tomoko Steen, a research specialist in the Library's Science, Technology, and Business Division and an adjunct professor of microbiology and immunology at Georgetown University.

HOW TO READ THIS REPORT

The gateway hypothesis contends that using cannabis causes an individual to progress to using harder illicit drugs such as cocaine or heroin. FRD reviewed the existing corpus of literature on this hypothesis to evaluate the integrity of the scientific and statistical evidence used to conclude whether cannabis does indeed serve as a gateway drug.

Given the complexity of both substance abuse and statistics, as well as the specific terminology involved, a short primer precedes the main text of the report. This section outlines the overall structure of the report and defines the key statistical concepts that were used to examine the relationship between one's use of cannabis and other illicit drugs.

Structure

This report provides an analysis of 23 peer-reviewed research studies, including both human- and animal-based studies, on cannabis use and its association with the subsequent use of other illicit drugs. It details the methodological rigor of these studies (i.e., *how* they were conducted) to evaluate the statistical reliability of their findings.

The structure of the report includes the following sections:

The main text provides readers with a high-level summary of FRD's analysis, as well as general background information on the history of the gateway hypothesis and addictive drug laws in the United States. There is also an overview on association and causation, the two key measures that were considered for this report. This section provides real-world examples of the terms, as well as guidance on evaluating them in statistical research. After the key findings and conclusion, appendices detail the process through which FRD identified the relevant studies, along with how that relevancy was determined.

Terms and Definitions

To assist readers, FRD compiled a short glossary of the main references used in this report.

Statistical Terms

- **Association**: A relationship between two or more variables in which a change in one variable is accompanied by a change in another variable. Associations have several characteristics, including:
  - *Type*: The association between variables can be correlation, causation, or another kind of relationship.
  - *Form*: The association, if graphed, can be in the form of a straight line sloping upward or downward or in the form of a variety of curves.
  - *Strength*: Variables may have weak, moderate, or strong associations.
  - *Directness*: A change in one variable may be directly or indirectly associated with a change in another variable (e.g., the absence or presence of HIV [one variable] can be directly associated with immune-system functioning [a second variable] and indirectly associated with life expectancy [a third variable]).
- **Causation**: A type of association where a change in one variable produces a change in another variable. Causal relationships, like other types of association, are characterized by form, strength, and directness. In addition, causal relationships may be:
  - Necessary in nature, in which a change in one variable *must* occur for a change in another variable to transpire, or
  - Sufficient in nature, wherein a change in one variable alone is sufficient to produce a change in another variable.
- **Confidence Interval**: Statistics such as means (or averages) and medians are often calculated from data from a portion—or sample—of a population rather than from data for an entire population. Statistics based on sample data are called "sample statistics," whereas those based on an entire population are called "population parameters." A confidence interval is the range of values of a sample statistic that is likely to contain a population parameter, and that likeliness is expressed with a specific probability. For example, if a study of a sample of 1,500 Americans finds their average weight to be 150 pounds with a 95 percent confidence interval of plus/minus 25 pounds, this means that there is a 95 percent probability that the average weight of the entire American population is between 125 and 175 pounds.
- **Confounding Variable**: A factor or characteristic that influences another variable but which is not included in the statistical analysis. Not controlling for confounding variables reduces the validity of the experiment.

- **Correlation**: A type of association that measures the strength of a straight-line or "linear" relationship between two variables. Stated differently, if the variables are graphed and the points on the graph collectively assume the shape of a straight line sloping upward or downward, then there is evidence of a linear relationship between those variables. Correlations can be either positive or negative.
  - *Positive Correlation*: An association indicating that two variables change in the same direction. If one variable increases, the other tends to increase as well or as one variable decreases, the other also tends to decrease.
  - *Negative Correlation*: An association indicating that two variables change in different directions. If one variable increases, the other tends to decrease.
- **Covariate**: A variable that is related to a result (the result is often referred to as the "response variable"). Because covariates are associated with a result, that association should be examined; if the research does not examine this association, then it may make incorrect assessments about the relationship of other variables on the result. For example, if research on short-term memory loss among athletes only examined the influence of age and did not include covariates such as head trauma experience and gender, then the results could suggest that age has a stronger influence on memory loss than it actually does.
- **Hazard Ratio**: A hazard ratio is the ratio of two hazard functions, or the estimated probability of some "event" occurring over time for one group compared with another. Hazard functions measure the probability that an individual will experience a particular event given some personal characteristic (e.g., age or gender) and given that they have not yet experienced that event. For example, a hazard ratio could measure the estimated probability that individuals who receive a kidney transplant from a close, living family member will survive over time (e.g., day 1, day 2 . . . day 365) compared to individuals who receive a kidney transplant from a deceased, unrelated donor.
- **Model Types**: In statistics, models are equations or graphs that are used to describe or represent certain phenomena, such as the association between variables. To illustrate that association, regression models (a common type of statistical model) use mathematical equations for straight lines or curves, while path diagrams use graphs containing variable names and arrows.
- **Odds Ratio**: An odds ratio measures the magnitude of an association between two variables. In statistics, odds are the number of times an event occurs ("success") divided by the number of times it does not occur ("failure"), which is equivalent to the probability of the event occurring. For example, if medication A is given to 20 liver cancer patients, of whom 14 survive and 6 do not, then medication A has 2.33 times greater odds of success than of failure. If medication B is given to a separate but comparable group of liver cancer patients and has 1.4 times greater odds of success than of failure, then the odds ratio is 2.33 divided by 1.4, which equals 1.66. Thus, medication A has 1.66 greater odds of success than medication B.

- **P-Value**: A p-value is the estimated probability that a variable's value or other statistical result could have been produced by chance or random error. P-values can be interpreted as measures of the strength of evidence in support of a hypothesis that certain variables have some relationship or value. They are often expressed as $p<0.05$, which means that a statistical result (e.g., mean or median) has a less than 5 percent probability of resulting from chance or random error. The lower the p-value, the lower the probability that the result is due to chance or random error.
- **Significance**: An assessment of the meaningfulness or importance of any statistical findings; essentially, whether or not a variable's value or some other statistical result is significantly smaller or larger than would be expected by chance alone. Statistical significance is frequently determined by whether or not the *p*-value for some result is less than a pre-defined threshold (often 0.05). However, statistical significance does not necessarily mean that the result is practically or substantively significant. For example, if the odds of an event occurring increase by 1 percent, the finding may have little practical significance even though it is statistically significant.
- **Slope**: In regression models, slope is an estimation of how much change in one variable is associated with change in another. More specifically, it is an estimate of the average change in a response variable that is associated with a one-unit change in a predictor variable. For example, in a regression model where height is the predictor variable and weight is the response variable, a slope of 2.2 would indicate that a one-unit (i.e., one-inch) increase in height is associated with an average change in weight of 2.2 pounds.
- **Standard Error**: An estimate of the difference between a statistic result derived from a sample population and the true value for the entire population. For example, if a survey of 1,000 Americans found their average weight was 150 pounds and that around 67 percent of the sample was within 12.5 pounds of that average, the standard error would be 12.5 divided by the square root of the sample size (i.e., 12.5/31.6=0.4). Thus, the true weight of the entire American population would be 0.4 pounds more or less than the sample average of 150 pounds.
- **Validity**: The truth of statements about statistical results. In statistics, there a several types of validity, including internal and external validity.
  - Internal validity refers to the truth of a particular study's findings. It is based on the manner in which the research is conducted, the ways in which data are collected, and other aspects of the research.
  - External validity refers to the applicability of the research findings to other populations, places, and times. Stated differently, it refers to whether or not research findings based on one population, place, and time are repeated when tested against other populations, places, and times.
- **Variable**: A measurable characteristic of a population (e.g., age, gender, and weight) that varies in value among other components of that population. Measureable characteristics of population components that do not vary in value are called "constants."

Drug-Related Terms

- **Drug Abuse**: The excessive use of illicit substances that leads to an individual's failure to fulfill their responsibilities or gets them in legal trouble, or use that continues despite causing persistent interpersonal problems. According to the National Institute on Drug Abuse, this is an older diagnostic term "increasingly avoided by professionals because it can perpetuate stigma." More appropriate terms include "drug use (in the case of illicit substances), drug misuse (in the case of problematic use of legal drugs or prescription medications), and addiction (in the case of substance use disorder)."[1]

- **Drug Dependence**: The compulsive need for and use of a habit-forming substance that is characterized by well-defined physiological symptoms upon withdrawal. It is important to note that a person can be dependent on a substance without being addicted. Also, dependence can occur with the regular use of both licit and illicit drugs.

- **Illicit**: Illegal or forbidden by law. This report is focused on the potential relationship between illicit drugs like cannabis, cocaine, and heroin. Although cannabis is legal in many states and the District of Columbia, it is still illegal at the federal level.

- **Licit**: Legal or not forbidden by law. For example, while not necessarily healthy, alcohol and tobacco are both licit substances in the United States.

TABLE OF CONTENTS

TABLE OF FIGURES

TABLE OF TABLES

1. SUMMARY OF RESEARCH METHODOLOGY

The full research methodology can be found in section 7, appendix I.

1.1. Literature Selection Process

- To identify the most relevant research articles, the Federal Research Division (FRD) narrowed the existing corpus of statistical research to articles focused on the association between cannabis use and the subsequent use of other illicit drugs. The researchers discovered that though there are many articles on how the use of alcohol and tobacco may lead to cannabis use, there are fewer on the narrow topic of how cannabis use leads to harder illicit drug use.
- The only articles included in this report were peer-reviewed articles concerning statistical studies published between 2008 and 2018.
- To find scholarly publications that matched the narrow criteria, the project team used the JSTOR, ProQuest, PubMed, and Scopus databases.
  - Boolean logic and "wildcards" were used to capture the various spellings and terms used in describing cannabis, other illicit drugs, and the association between the two; different search terms were also used for the human- and animal-based studies.
- In addition to these databases, FRD looked for relevant, systematic reviews of cannabis-related research. These reviews were published by research institutions such as the National Academies of Sciences, Engineering, and Medicine, and the National Institute on Drug Abuse, as well as nonprofit organizations such as the Campbell and Cochrane Collaborations.
- After reviewing the study abstracts and browsing select articles' content, FRD established criteria to assess the relevancy of these articles to the topic of associations between cannabis use and the use of other illicit drugs (see section 7, appendix I, table 7).
- During the article selection process, relevant reports cited by the reviewed studies were also added to the list. Of the 466 articles FRD found, 66 were deemed to contain relevant information (see section 7, appendix I, table 8); 33 of those articles were published between 2008 and 2018. Of these 33 articles, 23 were profiled for the main report.

1.2. Literature Evaluation Methods

- **Bradford Hill Criteria**: To examine the validity of the gateway hypothesis, FRD applied modified Bradford Hill criteria to the 16 human-based studies.[2] Used to establish evidence of a causal relationship, the criteria consider the:

  - Strength of the observed associations,
  - Consistency of the results,
  - Specificity of the outcomes,
  - Dose-dependence of the biological gradients,
  - Temporality of the observed associations,
  - Plausibility of the observed associations, and
  - Coherence of the findings.

- **Maryland Scientific Methods Scale**: To develop a standardized evaluation of the human- and animal-based studies' internal validity, FRD adopted the Maryland Scientific Methods Scale (SMS). The scale runs from 1 to 5 and rates the studies' use of certain research designs; higher numbers indicate the use of research methods most likely to yield internally valid findings. Studies that randomly selected research subjects from a larger population and randomly assigned those subjects to control and experimental groups were rated higher than those that did not incorporate these methods into their research designs.[3]

- **Additional Analysis by FRD**: Since the SMS focuses on some aspects of internal validity, FRD also rated other features of the statistical methods used. In particular, the project team asked:

  - Was the statistical analysis appropriate?
  - Did the study have low statistical power to detect the effects because of small sample sizes?
  - Was there a low response rate or differential attrition?
  - Did the study narrowly focus on a specific high-risk population that limited the applicability of the conclusions to the general population?

  The study's SMS was then downgraded by one point for each problem that was identified in the additional analysis, resulting in a final score. For example, a twin study with serious flaws in the statistical analysis would receive a level rating of 3 rather than 4.

2. KEY FINDINGS: REPORT

1. **The existing statistical research and analysis show mixed results and do not clearly demonstrate scientific support for cannabis use leading to harder illicit drug use. As a result, FRD has determined that no causal link between cannabis use and the use of other illicit drugs can be claimed at this time.**

    - The inability to conclusively claim cannabis as a gateway drug is due to data-gathering limitations, failures to eliminate confounding variables, and questions about the applicability of findings from animal-based studies to human behavior.

    - Some studies found statistically significant associations between confounding variables, such as individual and peer drug use, mental health issues, and socioeconomic status, and the use of illicit drugs.

2. **The current state of research on this topic is very limited and existing studies suffer from difficulties in gathering information and applying the findings to a larger population.**

    - FRD found only one review of the current research on the gateway hypothesis in the existing literature—chapter 14 of a National Academies of Sciences, Engineering, and Medicine report. Published in 2017, it highlights several articles studying the associations among cannabis use and the use of other illegal substances, changes in the rates/use patterns of these drugs, and the development of substance dependence or abuse disorders. While the chapter does indicate that there is some evidence of a statistical association between cannabis use and the use of other illicit drugs, it also notes that there is not enough information, at the moment, to claim a causal link.[4]

    - Many studies of human cannabis use are based on self-reported data from longitudinal or retrospective studies. This collection method is known to be inaccurate and biased, as subjects often cannot recall the details requested by the researchers or the study participants attempt to provide answers they believe reflect most favorably upon themselves.

    - Some of the studies derived biased data by sampling from heroin users, street youth, and other at-risk populations. As such, the results can only be applied to narrow sections of the overall population.

    - Animal-based studies offer the ability to examine hypotheses using research techniques that cannot be legally used on humans. However, there are significant limitations to applying the results of this research to human behavior.

3. **While many of the studies reviewed in this report did find statistically significant associations between cannabis use and one's later use of other illicit drugs, there is not yet conclusive evidence to assert that cannabis is a gateway drug. Moreover, the practical significance of these findings was limited.**

   - According to statistics published in 2018 by the U.S. Department of Health and Human Services' Substance Abuse and Mental Health Services Administration (SAMHSA), an estimated 118.2 million Americans aged 12 and older have *used* cannabis at least once; nearly all of them (99 percent, 117.1 million) have also used alcohol or tobacco. Of those who have used cannabis, 32 percent have used cocaine, 12 percent have used methamphetamines, and 4 percent have used heroin.

   - When focused on the *abuse* of drugs, the SAMHSA data statistics reveal an even smaller percentage use cannabis and then abuse illicit drugs. Only 0.3 percent of those Americans who have used cannabis have abused heroin, 0.2 percent have abused cocaine, and 0.1 percent have abused methamphetamines.[5]

3. INTRODUCTION

Cannabis use and its perceived ability to drive individuals to the subsequent use of cocaine, heroin, or other illicit drugs has been studied and debated for decades. While the term "gateway drug" has no formal legal or medical definition, it suggests that cannabis users go on to use and become dependent on other illegal substances. Yet existing statistical research and analysis show mixed results and do not clearly demonstrate scientific support for this theory. **As a result, FRD has determined that no causal link between cannabis use and the use of other illicit drugs can be claimed at this time.**

Prior to the passage of the Controlled Substances Act (CSA), more formally known as Title II of the Comprehensive Drug Abuse Prevention and Control Act of 1970, the United States had over 200 laws concerning addictive drugs and other "public health and consumer protections."[6] The CSA, signed by President Richard Nixon, consolidated these federal regulations into a single statute, expanded their scope, and changed the government's management of controlled substances by dividing them into five different class schedules. Based on the drugs' potential for abuse, the categories descend in severity:

- **Schedule 1**: Drugs, substances, and chemicals with "no currently accepted medical use and a high potential for abuse." Examples include cannabis, heroin, LSD, and ecstasy.
- **Schedule 2**: Drugs, substances, and chemicals with "a high potential for abuse, with use potentially leading to severe psychological or physical dependence." Examples include cocaine, methamphetamine, oxycodone, fentanyl, and methadone.
- **Schedule 3**: Drugs, substances, and chemicals with "a moderate to low potential for physical and psychological dependence." Examples include anabolic steroids and ketamine.
- **Schedule 4**: Drugs, substances, and chemicals with "a low potential for abuse and low risk of dependence." Examples include Ambien, Valium, and Xanax.
- **Schedule 5**: Drugs, substances, and chemicals with a "lower potential for abuse than Schedule IV and consist of preparations containing limited quantities of certain narcotics." These drugs are generally used for antidiarrheal, antitussive, and analgesic purposes; examples include Lyrica and Robitussin AC.[7]

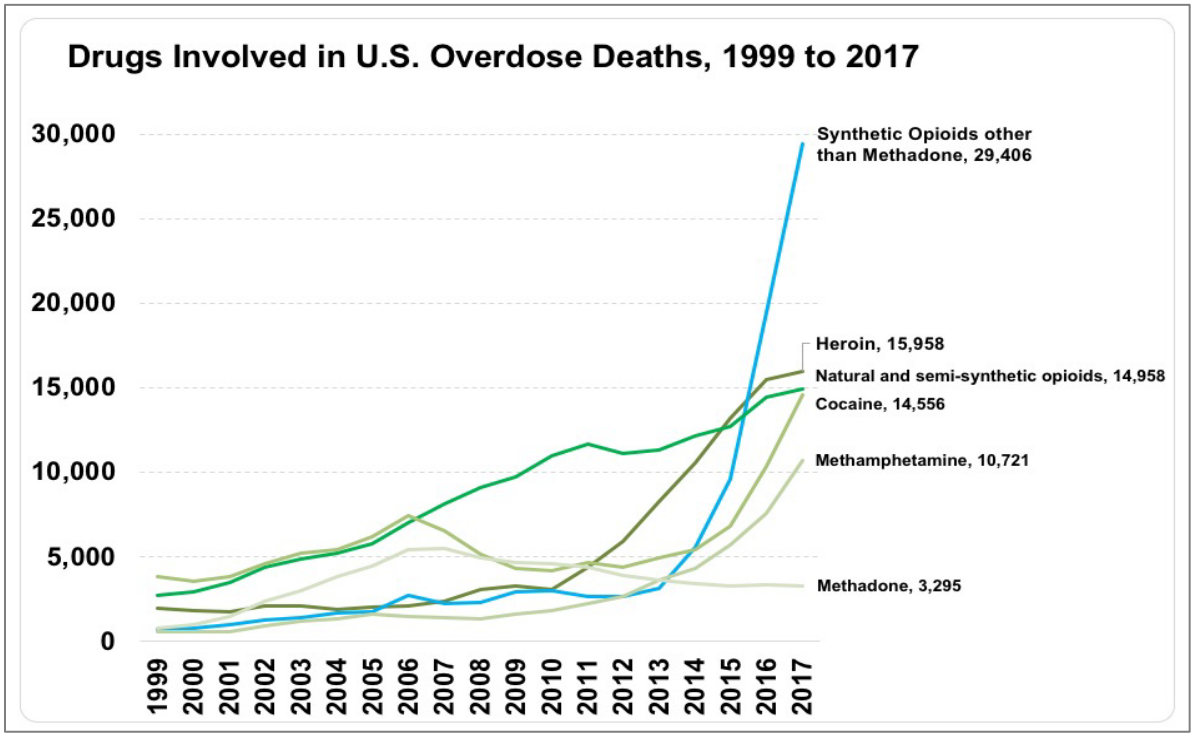
The CSA also established the National Commission on Marihuana and Drug Abuse, which examined the inclusion of cannabis as a Schedule 1 substance. Though the commissioners recommended using "a social control policy" instead of criminalization to discourage the use of cannabis, it is still categorized as an illicit substance by the federal government.[8] To date, ten states have legalized the recreational use of cannabis, while 30 states have legalized its use as a medical treatment.[9]

3.1. Cost of Substance Use and Abuse

While the concern that cannabis use leads one to use other illicit drugs has existed for decades, the idea has drawn more interest in the past few years given the current opioid epidemic in the United States. According to the U.S. Centers for Disease Control and Prevention (CDC), in 2016, 115 Americans died every day due to an overdose.[10] Additionally, it is estimated that between 21 percent and 29 percent of prescription opioid users misuse the drugs, with addiction rates ranging between 8 percent and 12 percent.[11] Moreover, it has been suggested that this misuse of prescription opioids may lead to later heroin use, as one study in 2016 found that 7.5 percent of nondependent illicit pharmaceutical opioid users transitioned to heroin.[12]

When including overdose deaths from other drugs, the CDC estimated that there were over 72,000 incidents in 2017, with the trends increasing rapidly. Of these incidents, synthetic, semi-synthetic, and natural opioids were responsible for the majority of deaths (44,364), followed by heroin (15,958), cocaine (14,556), and methamphetamine (10,721; see figure 1).[13]

Figure 1. Drug-Involved Overdose Deaths in the United States, 1999–2017



Source: National Institute on Drug Abuse, "Overdose Death Rates," revised August 2018, https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates; based on data from the CDC's WONDER database.

Along with its contribution to rising drug-addiction rates, prescription opioid misuse has been estimated to cost the United States nearly $80 billion a year.[14] When factoring in the abuse of nonprescription opioids and heroin, the White House Council of Economic Advisors estimated that the cost of the epidemic exceeded $500 billion in 2015 alone.[15] However, the current annual cost likely exceeds this amount as the rates of abuse have dramatically increased in the last several years.

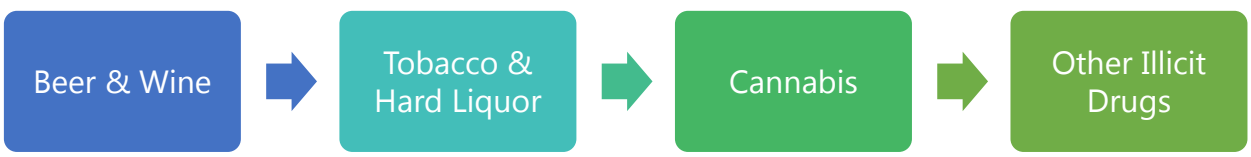
Due to the staggering human and economic costs of the opioid epidemic, the U.S. government has a vested interest in preventing the use and abuse of illicit drugs (as well as the misuse of prescription medications). As the gateway hypothesis postulates that using cannabis will increase one's chances of using more dangerous and costly drugs, determining the existence and magnitude of such an effect is all the more pressing given recent decriminalization efforts in several states.

3.2. Gateway Hypothesis

Numerous publications trace the genesis of the idea that using cannabis either leads to or increases one's drive to use other illicit drugs—commonly known as the gateway hypothesis—to Dr. Denise Kandel's 1975 article "Stages in Adolescent Involvement in Drug Use."

Using surveys of 5,468 public high school students in New York State in 1975, Kandel discovered a predominant temporal sequence involving four stages of drug consumption: beer and wine, tobacco and hard liquor, cannabis, and other illicit substances. The likelihood of progressing to the next stage increased based on the frequency of use at the current stage. However, she did not find this sequence to necessarily be causal; the evidence merely indicated that individuals who used one drug had an increased *chance* of progressing to the use of another drug. Further, her research did not find that all adolescents' drug use patterns go through all four stages or do so in the exact order. Rather, additional study by Kandel (in partnership with Dr. Richard Faust) on the patterns of adolescent drug use found that most individuals who use the aforementioned licit and illicit drugs are only *more likely* to do so in that order than in any other sequence (see fig. 2).[16]

Figure 2. Gateway Hypothesis Sequence



3.3. Drug Use vs. Drug Abuse

Though Kandel's hypothesis has been considered the standard drug use pattern for the past four decades—especially when considering the relationship between cannabis use and the use of other illicit drugs—recent evidence indicates that while a substantial number of Americans have used cannabis, relatively few have used it *and then used* other illegal substances.

As noted in section 2, according to statistics published in 2018 by SAMHSA, an estimated 118.2 million Americans aged 12 and older have used cannabis at least once; nearly all of them (99 percent, 117.1 million) have also used alcohol or tobacco. Of those who have used cannabis, 32 percent have used cocaine, 12 percent have used methamphetamines, and 4 percent have used heroin (see fig. 3). Yet when it comes to the *abuse* of other illicit drugs, the percentages are much lower: 0.3 percent of those Americans who have used cannabis have abused heroin, 0.2 percent have abused cocaine, and 0.1 percent have abused methamphetamines (see fig. 4).[17]

Figure 3. Number of People Who Have Used Alcohol, Tobacco, Cannabis, and Other Illicit Drugs

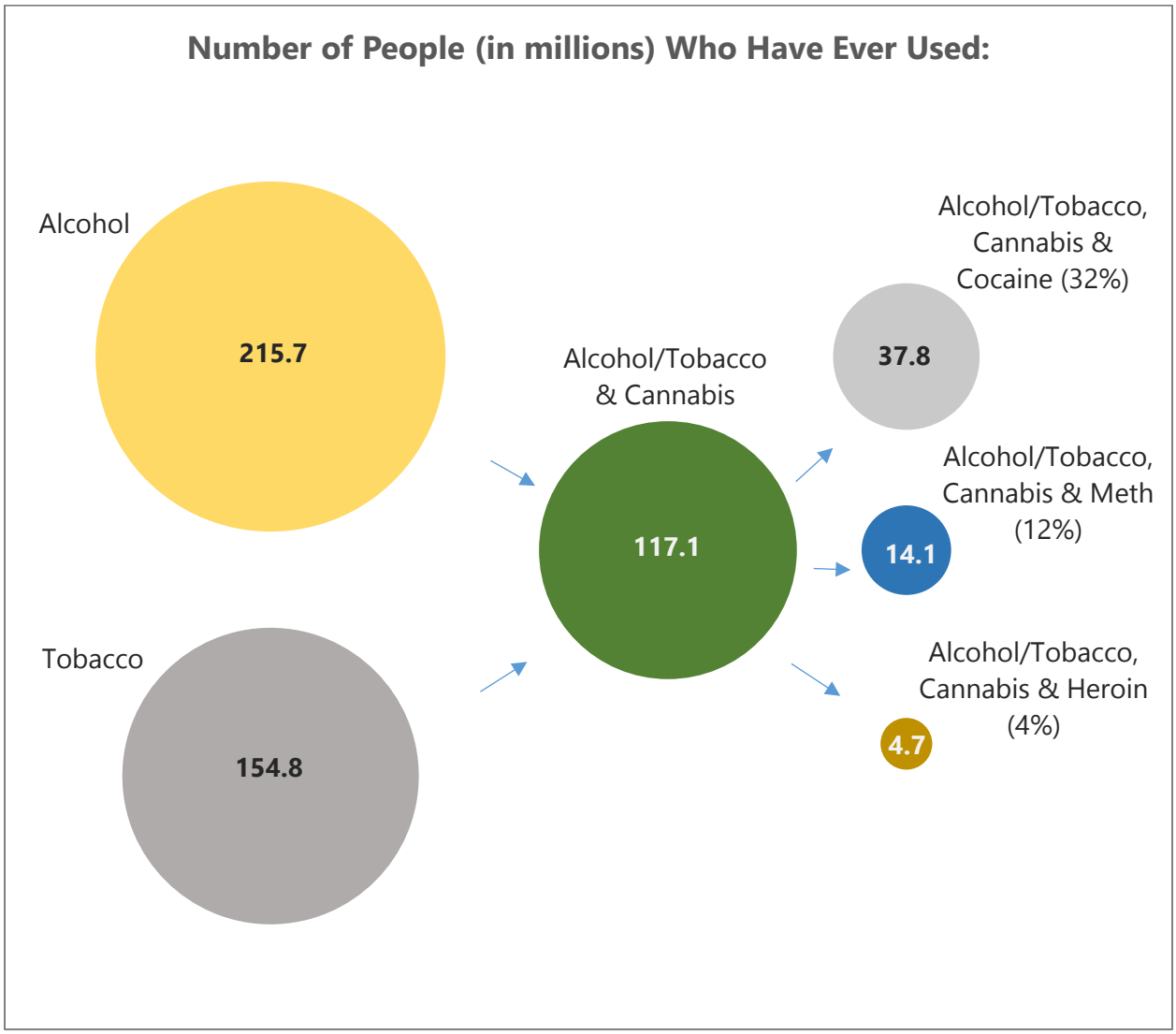
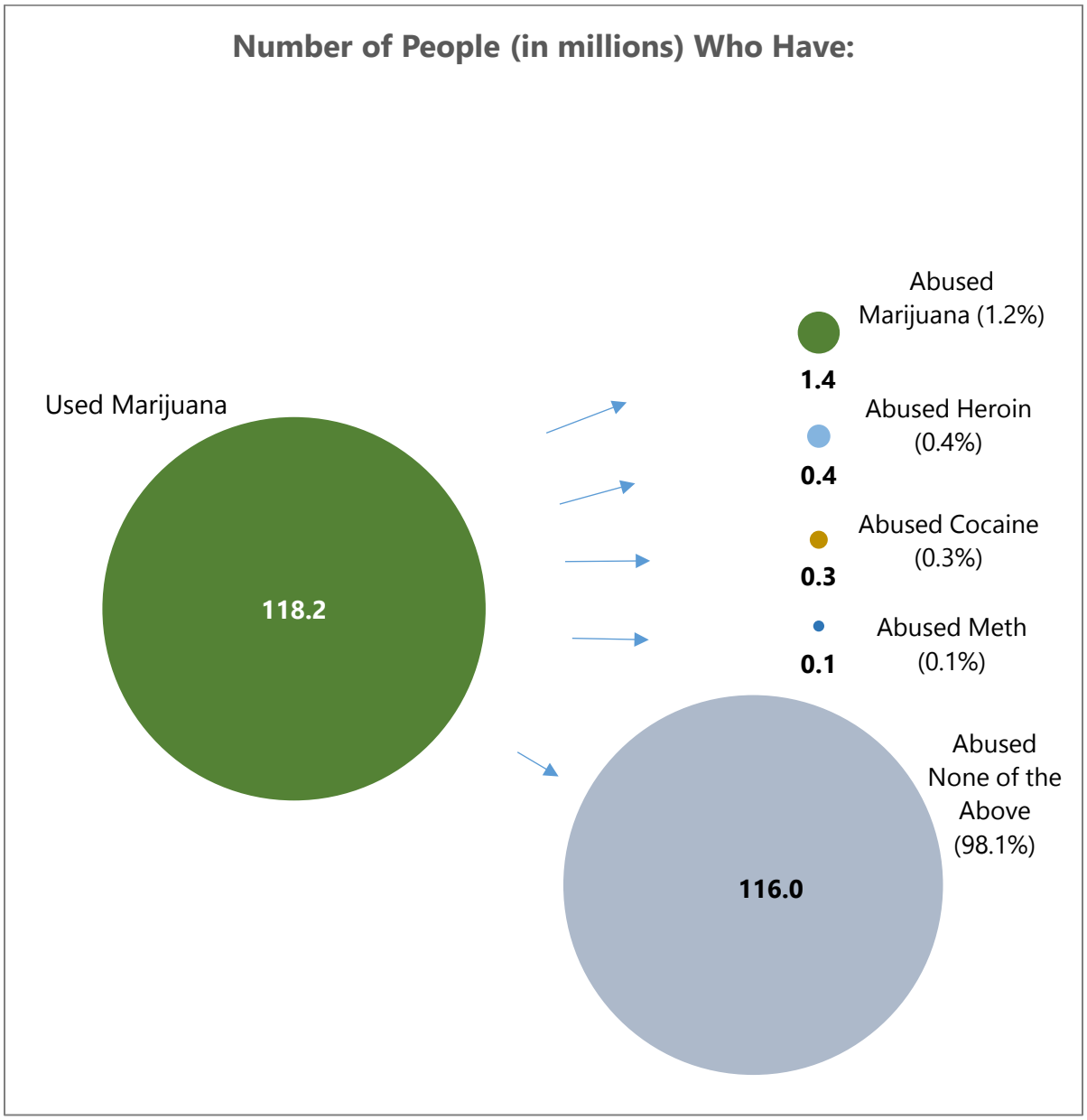


Figure 4. Number of People Who Have Used Cannabis and Abused Other Illicit Drugs



3.4. Cannabis as a Substitute for Other Illicit Drugs

While much of the existing research on this topic has focused on the gateway hypothesis, some studies have suggested that decriminalizing and providing greater access to cannabis products may actually decrease the consumption of other illicit drugs. That is, cannabis may act as a substitute for further drug use, rather than as a gateway for additional initiations or abuse.

For example, one study published in 2018 found that states with active medical cannabis dispensaries had 3.7 million fewer daily doses of prescribed opioids compared to those without medical dispensaries, while states allowing only home cultivation experienced 1.8 million fewer daily doses.[18] Another study showed similar findings, with opioid prescriptions decreasing by 5.9 percent in states that allow the medical use of cannabis and 6.4 percent in states that allow recreational use.[19] A third study found that states with medical cannabis laws experienced a 24.8 percent lower opioid mortality rate than states without such legislation.[20]

Similarly, another recent publication found that the association between legal medical cannabis use and decreased opioid deaths is dependent on how difficult cannabis is to obtain. Essentially, the association decreases as the level of medical dispensary regulation increases. Yet it is important to note that this study analyzed overdose deaths from 1999 through 2013, prior to recreational cannabis becoming available in any state.[21] As such, additional research is needed to determine the effects of recreational cannabis use on the use and abuse of other illicit drugs.

4. EXPLANATION/EVALUATION OF ASSOCIATION AND CAUSATION

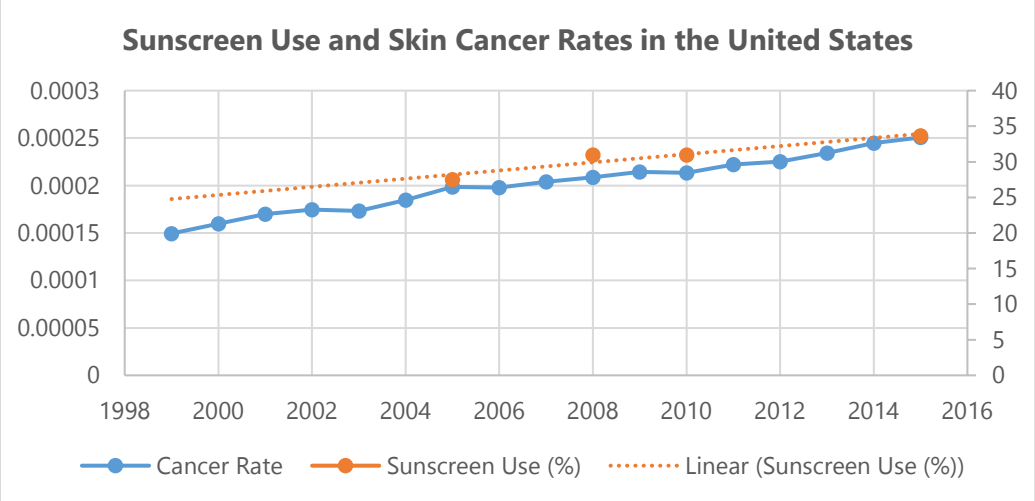
For this report, the two key variables of interest were cannabis use and the use of other illicit drugs. By conducting a systematic review of the existing literature, FRD sought to identify the association and causal relationships between those two factors to assess the validity of the gateway hypothesis. More detailed information about FRD's analysis is included in section 5.

4.1. Explanation of Statistical Association and Causation

Many statistical analyses focus on assessing the relationship between two variables. When two variables are found to be significantly positively correlated, this means the two events are likely to occur together. However, correlation often does *not* imply causation; that is, one event may *not* be the consequence of the other. Correlation is instead a statement about the mutual connection between the two events, while causality refers specifically to the cause-and-effect relationship.

Though these concepts seem relatively straightforward, the existence of confounding variables (e.g., social pressures, socioeconomics factors, personal habits, and education) can lead to a multitude of erroneous conclusions. For example, data from the CDC indicate that the use of sunscreen and incidents of skin cancer have both increased over the past few years (see fig. 5). This correlation may lead one to conclude that using sunscreen actually causes skin cancer, yet it ignores contributing factors such as the amount of time one spends in the sun, the popularity of tanning booths, and the improvement in skin cancer detection over the last several decades.

Figure 5. Sunscreen Use and Skin Cancer Rates in the United States



To determine the actual causation between using cannabis and using other illicit drugs, one needs to account for confounding variables. This can be accomplished by using a carefully designed study model, such as a randomized controlled trial, or by accounting for all of the potential outside factors in the statistical analysis. That said, both are challenging (if not infeasible) for experimental drug studies using human subjects.

4.2. Evaluation of Association and Causation

To examine the validity of the gateway hypothesis, FRD applied modified Bradford Hill criteria to the 16 human-based studies.[22] Used to establish evidence of a causal relationship, the criteria consider the:

- Strength of the observed associations,
- Consistency of the results,
- Specificity of the outcomes,
- Dose-dependence of the biological gradients,
- Temporality of the observed associations,
- Plausibility of the observed associations, and
- Coherence of the findings.

After reviewing these seven factors to determine the causality of using cannabis and using other illicit drugs, FRD determined that several criteria were not met. Most notably, the gateway hypothesis fails to show causation due to its inconsistent results across different populations, its lack of specific outcomes, and its lack of coherence. **At this time, an individual's use of other illicit drugs cannot be causally attributed to an initial use of cannabis.**

4.2.1. Strength

Strong, statistically significant associations are more likely to indicate causality, while weaker associations are more likely the result of confounding variables. Of the 16 human-based studies reviewed by FRD, 13 studies provided statistically significant evidence of an association between cannabis use and the use of other illegal substances. However, it is important to note that this evidence only suggests that cannabis use *may* play a causal role in later illicit drug use.

Table 1 provides a summary of the association strength and statistical significance—among other measures—of the 16 human-based studies. It includes:

- Column 1: The section number of the study's profile.
- Column 2: The study's Scientific Methods Score (SMS).
- Column 3: The number (n) of participants in the study.

- Column 4: The p-value for assessing the significant effect of cannabis use.
- Column 5: The estimated odds ratio (OR) and 95 percent confidence interval (CI).
- Column 6: The slope and standard error (SE), but only if a regression model was used in the statistical analysis.
- Column 7: The population to which the association applies.

Table 1. Association with Illicit Drug Use in Human-Based Studies*

Section	SMS	n	p-val	OR (95% CI)	Slope (SE)	Population
9.1	3	2,832	<.0001	7.80 (4.46–13.63)	—	Adolescents and young adults from Australia and New Zealand
9.2	3	900	<.0001	2.97 (2.60–3.41)	—	Adolescents and young adults from Christchurch, New Zealand
9.3	3	11,194	—	1.31 (0.49–3.55)	—	Americans using cannabis in adolescence (0–19) and other drugs in early adulthood (19–23)
			—	2.14 (1.30–3.52)	—	Americans using cannabis in young adulthood (24–33)
			—	7.79 (5.91–10.28)	—	Americans using cannabis in early adolescence (11–15) and other drugs in late adolescence (16–21)
			—	0.74 (0.50–1.07)	—	Americans using cannabis in early adolescence (11–15) and other drugs in early adulthood (19–23)
9.4	4	555	<0.05	—	0.13	American high-school student twin pairs
9.5	4	586	<.0001	3.57 (2.27–5.61)	—	American Vietnam War-veteran twins
9.6	2	1,984	0.0001	—	.710 (.185)	“Troubled youth" in Oslo, Norway
			0.0713	—	.294 (.163)	“Most youth” in Oslo, Norway
9.7	3	1,126	0.0004	2.24 (1.43–3.50)	—	Young adults who attended public school in Miami-Dade County, Florida in the 1990s
			0.6328	0.86 (0.47–1.60)	—	Young adults who attended public school in Miami-Dade County, Florida (21+)
			0.6449	1.20 (0.55–2.51)	—	Young adults who attended public school in Miami-Dade County, Florida (working)
9.8	1	9,282	<.0001	137.1 (94.8–198.3)	—	Individuals 18+ from 17 different countries
9.9	2	29,393	—	—	—	French youth
9.10	2	16,421	—	—	—	French residents (18–34)
9.11	1	245	<.0001	4.34 (2.17–8.7)	—	Unstably housed women in San Francisco using stimulants, but not cannabis
			0.0006	3.81 (1.78–8.15)	—	Unstably housed women in San Francisco using opioids, but not cannabis
			—	1.82 (0.87–3.97)	—	Unstably housed women in San Francisco using medical cannabis

Section	SMS	n	p-val	OR (95% CI)	Slope (SE)	Population
9.12	1	21,746	<.0001	4.26 (3.70–4.91)	—	Chronic pain patients in San Diego
9.13	1	562	—	—	—	Current heroin users
9.14	1	6,624	—	—	—	Lifetime cannabis users
9.15	3	711	—	—	—	Young adults in the Pacific Northwest
9.16	3	34,653	—	—	—	American adults abusing illicit drugs

* Other statistical measures are listed in the individual study profiles.

As the figures in table 1 attest, the vast majority of the evaluated studies found a statistically significant association between cannabis use and the use of other illicit drugs. However, finding such an association was not universal; some researchers even noted that it does not hold when controlling for certain life factors and characteristics. For example, the study profiled in section 9.7 found no significant association between the two variables after controlling for either age or working status (see table 2). Moreover, many of the populations included in the studies were very narrow (e.g., chronic pain patients) and, as a result, the findings are only applicable to similar groups.

Among the 16 human-based studies, five (including the one in sec. 9.7) investigated the association between cannabis use and illicit drug abuse or dependence. All of them found that using cannabis is significantly associated with a higher incidence of abusing other illicit drugs. Specifically, the studies highlighted in sections 9.3 and 9.5 found the significance to be modest (p-value<0.05), while two others found strong significance (p-value<0.01, see sec. 9.15–9.16).

Table 2. Association with Illicit Drug Abuse/Dependence in Human-Based Studies

Section	SMS	N	p-val	OR (95% CI)	Slope (SE)	Population
9.2	3	900	<0.0001	—	—	Adolescents and young adults from Christchurch, New Zealand
9.5	4	586	0.0173	2.13 (1.14–3.96)	—	American Vietnam War-veteran twins
9.7	3	1,126	0.0203	2.33 (1.14–4.76)	—	Young adults who attended public school in Miami-Dade County, Florida in the 1990s (covariates: gender, race, ethnicity, parents' socioeconomic status, and illicit drug use)
			0.1315	1.78 (0.84–3.76)	—	Young adults who attended public school in Miami-Dade County, Florida in the 1990s (covariates: life stressors)
9.15	3	711	<0.01	—	0.28 (0.07–0.59)	Young adults in the Pacific Northwest
9.16	3	34,653	0.0002	2.6 (1.6–4.4)	—	American adults abusing illicit drugs

4.2.2. Consistency

The second Bradford Hill criterion for determining causality is consistency—essentially, studies using different populations and methods should arrive at the same conclusion. No single study, regardless of its strength of association and statistical significance, should be seen as evidence of a causal relationship.

As depicted by the odds ratios in table 1, the association between cannabis use and other illicit drug use varies widely between the population types. Moreover, several target populations—such as those who are over 21 or working; youths *without* difficulties with their families, schools, or police; and medical cannabis users—did not exhibit any significant association between the two variables (see sec. 9.6, 9.7, and 9.11, respectively).

Similarly, a study focused on surveys conducted by the World Health Organization—profiled in section 9.8—specifically sought to study the patterns of drug use across different populations, including rarely-studied lesser developed countries. The researchers found that these patterns varied across countries, with departures from the gateway hypothesis reaching as high as 82.3 percent in Japan. With these different methods and source populations providing wide-ranging and varied results, the consistency factor was not adequately fulfilled in this analysis.

4.2.3. Specificity

Specificity dictates that a one-to-one association should exist between the input and outcome; if the outcome has multiple risk factors, causation is difficult to determine. Many of the human-based studies could not attribute the cause of one's use of other illicit drugs to any single factor, and determined that moving from cannabis to cocaine or heroin was due to a set of correlated variables, some of which may be unknown. For example, the association between using cannabis and other illicit drugs could stem from an individual's predisposition to drug use, which is driven by internal characteristics and external influences. These characteristics and influences include:

- Demographics (e.g., age, race/ethnicity, gender, income level, and employment status),
- Family history (e.g., parental criminality, parental socioeconomic status, disturbed family environment, and family substance abuse or dependence),
- General stressors (e.g., cognition and behavior disorders, mental health issues, and problems at school),
- Environmental factors (e.g., the availability of and opportunity to use drugs, and peer pressure), and
- Genetic differences.

The majority of the studies reviewed by FRD aimed to assess the association between cannabis use and other illicit drug use by accounting for these additional variables—providing evidence to both support and reject the influence of these factors. For instance, two sets of researchers conducting twin studies found that the association cannot be entirely attributed to household environment: Although twins were raised within the same household, those who used cannabis earlier showed increased odds of later illicit drug use (see sec. 9.4–9.5).[23] However, though both groups surveyed fraternal and identical twins, one study found that the association was similar across zygosities, while the other showed a stronger impact among fraternal twins, suggesting that the association could only be partly attributed to genetic difference.

4.2.4. Biological Gradient

The biological gradient states that the outcome of a study must be dose-dependent. That is, the larger the dose, the more likely the outcome. Several of the evaluated studies included an analysis of such dependence (i.e., the frequency of use) for the amount of cannabis consumed. For example, the study profiled in section 9.1 found that daily cannabis users had a higher chance of progressing to other illicit drugs than those who used cannabis less frequently. The study listed in section 9.2 likewise determined that the annual frequency of cannabis use is the strongest risk factor for using other illicit drugs.

With regard to probabilities, the study highlighted in section 9.9 noted that those who had never used cannabis had a 0.1 percent probability of moving on to other illicit drugs, while those who had initiated some cannabis use had a 1.7 percent probability; daily users, at 10.2 percent, had a much higher probability of using other illicit drugs. Based on the number of studies demonstrating a linkage between the frequency of one's cannabis use and the odds of progressing to other illicit drugs, this factor of the Bradford Hill criteria was met.

4.2.5. Temporality

Temporality is an essential factor to consider when evaluating associations, as one's exposure to the suspected cause must precede the observed outcome. In this case, that means cannabis use must precede the use of other illicit drugs, which holds for most of the human-based studies. There are, however, notable departures. For example, the study based on data from the World Health Organization found that neither Japan nor Nigeria follow the use sequence listed in the gateway hypothesis. Another study found that 20.3 percent of current heroin users deviate from the pattern, with African Americans more likely to not conform. Moreover, the researchers found that a greater proportion of participants began using multiple substances (i.e., alcohol, tobacco, and cannabis) within the same calendar year, rather than having a clear temporal progression from one to another (see sec. 9.13).

4.2.6. Plausibility

The plausibility factor requires the existence of an explanation, either biological or social, for the observed association. In this case, for the relationship between using cannabis and using other illicit drugs, researchers have proposed several plausible explanations. Based on the evaluated studies, there are three possible models to explain the association: biological effect, correlated vulnerabilities, and a combination of both. The biological effects model posits that cannabis use causes the future use of other illicit drugs, while the correlated vulnerabilities model attributes the effect to confounding variables. As such, to find evidence of causality, FRD focused on the biological effects model.

The notion of a biological effect of cannabis use requires "the pharmacological effects of cannabis [to] increase an adolescent's propensity to use other drugs."[24] The causal effect of this association can be confirmed by determining if the cannabis use:

- Induced changes in one's brain chemistry and functioning. These alterations may disturb the reward neural pathways that influence an individual's progression to future drug abuse.[25]
- Served as a learning process for the pleasurable effects of drugs. That is, the use of cannabis may sensitize one's brain to the rewards of psychoactive substances, therefore increasing the risk for using other illegal substances.[26]
- Increased one's incentive motivation (i.e., the sensitization of craving), thus leading to an increased intake of illicit drugs.[27]

When evaluating plausibility, and in turn causality, researchers must eliminate all relevant alternative influences.[28] This, however, is practically challenging, if not infeasible, for human-based studies. First, it is hard to control the effects of all confounding variables in a single study. Second, using sociodemographic variables cannot fully account for context effects (e.g., different sequences may exist in different regions and subpopulations). As a result, animal-based studies may provide more direct assessments of the causal effect of cannabis use on illicit drug use.

4.2.7. Coherence

The coherence factor, the final component of the modified Bradford Hill criteria FRD used to analyze the existing literature, demands an evaluation of the overall hypothesis to determine if it is well-defined and consistent. Yet, as noted earlier, there is no consensus definition or application of the gateway hypothesis or what is considered a gateway drug.

5. KEY FINDINGS: LITERATURE REVIEW

To examine the current literature for evidence concerning the gateway hypothesis, FRD turned to human-based and animal-based research efforts looking at cannabis use and its potential associations with the use of other illicit drugs. Though the findings of the animal-based studies are limited in their extrapolations to humans, restrictions on using human test subjects in drug research create the need for experimental research designs. In the United States (as in many countries), it is legally infeasible to involve humans in the direct testing of illicit drugs like cannabis, cocaine, and heroin. As such, in addition to the animal-based studies, researchers have used voluntary questionnaires and surveys to obtain retrospective and longitudinal information on individuals' drug use.

5.1. Human-Based Studies

The human-based studies reviewed by FRD had two types of design: retrospective cohort study and prospective longitudinal study. In the former, subjects' past behaviors (including a history of substance use) were reported retrospectively through recalls, and the incidence of illicit drug use was compared between cannabis users and nonusers after adjusting for covariates. In the latter, subjects were followed up with and assessed prospectively by questionnaires or interviews at multiple points in time. Table 3 provides a summary of each study's key findings.

Table 3. Summary of Key Findings from Human-Based Studies

Section	Key Findings
9.1	Compared to those who had never used cannabis, daily users younger than 17 had substantially increased odds of later cannabis dependence and illicit drug use. The authors suggest that this association supports a possible causal relationship between adolescent cannabis use and other illicit drug use in adulthood. However, they also note that the study was limited in its capacity to explain why there was such an association.
9.2	The annual frequency of cannabis use in late adolescence and early adulthood (16–25) emerged as the strongest risk factor for later illicit drug use. This development involves an accumulative process that includes exposure to adversity in childhood, childhood abilities to adjust, personality and individual factors, the use of cannabis, affiliations with substance-using peers, and alcohol use.
9.3	This study, finding inconsistent illicit drug use in adulthood by adolescent cannabis users, suggests that it may not have a determinative effect and that other factors may be involved in adults' use of illicit drugs.

Section	Key Findings
9.4	Examining the drug use of fraternal and identical twin pairs, this study notes that genetic differences may influence the relationship between cannabis use and later drug use. Evidence of this influence comes from the significant interaction effect regarding twin type and the later use of other illicit drugs.
9.5	After controlling for covariates, this study found that early cannabis users were at greater risk than their later-cannabis-using or never-cannabis-using cotwins for 8 out of 9 substance-related comparisons—providing strong evidence that cannabis use prior to age 18 is associated with higher risks of later drug use. Moreover, the results suggest that the association cannot be explained by genetic influence, but is more likely due to a third unmeasured environmental factor.
9.6	Recent cannabis use significantly increases the risk of subsequent drug use for individuals who have experienced childhood adversities, including problems related to family/friends, school, or police. By contrast, for most individuals with no such childhood traumas, it poses no significant risk.
9.7	The results of this study suggest that the effect of teen cannabis use on later drug use is short-term, and depends on life-course moderators: It is significant for unemployed adults younger than 21, while the effect is muted for those who are working and older than 21. As such, the authors suggest that the linkage between teen cannabis use and later illicit drug abuse may be spurious.
9.8	By examining drug use patterns in 17 different countries, this study found a variety of sequences regarding the use of alcohol, tobacco, and cannabis, and the subsequent consumption of other illicit drugs. In some countries, these patterns reflected differences in the availability of alcohol, tobacco, and cannabis, along with varying attitudes concerning drug use. One's age of first use and amount of exposure were more important predictors than the type of drug used.
9.9	As with the study in section 9.1, this research found that nondaily cannabis users were more likely than those who never used cannabis to subsequently use other illicit drugs, and that daily cannabis users are even more likely to use other illicit drugs later in life.

Section	Key Findings
9.10	Subjects who used substances early (under the 25th percentile for age) were more likely to use a series of substances, starting with tobacco, cannabis, or other illicit drugs. However, the likelihoods of many sequences suggests that the progression from one substance to another is more affected by an individual's environment than the substance they first use.
9.11	The manner in which cannabis is obtained affects the association between the use of cannabis and other illicit drugs. If it is obtained through a medical context, for example, cannabis is not associated with the use of other illicit drugs; yet if it is obtained through a nonmedical context, there is an association with other illicit drug use.
9.12	There is a significant association between the presence of tetrahydrocannabinol and other illicit drugs in the urine specimens of chronic pain patients.
9.13	The authors' principal conclusion is that the gateway hypothesis and substance-use chronologies provide clinically relevant findings and valid predictions of drug use sequences. However, they note that sociocultural differences or variations in the drugs' availability may also influence these patterns.
9.14	This study identified several characteristics that increase one's chance of progressing from using cannabis to other illicit drugs, including being a male between ages 30 and 44; born in the United States; in an urban environment; less educated (i.e., no high school diploma); mentally ill; divorced, separated, or never married; a young cannabis user; and from a family with a substance use/abuse history.
9.15	There is a social context to the gateway hypothesis. Specifically, the presence of friends who use other illicit drugs contributes to an individual's progression from using cannabis to using and depending on other illicit drugs themselves.
9.16	Within the general population, cannabis use is associated with an increased risk for several substance use disorders, including those connected to alcohol, nicotine, and other illicit drugs.

When viewed together, these key findings fall into four main categories: general association and support of the gateway hypothesis, age of first use, frequency of use, medical cannabis use, and other common liability factors.

5.1.1. General Association and Support of Gateway Hypothesis

In addition to the associations listed in table 1, several human-based studies made specific comments regarding their conclusions on the association and potential causality of cannabis use and the use of other illicit drugs. However, it is worth repeating that many of these relationships can only be applied to narrow populations.

- **Caution against assuming causality**. A number of researchers specifically advised against making causal connections between cannabis use and other illicit drug use. For example, while one group found a significant association between the two, it cautioned against the study's ability to demonstrate causality (see sec. 9.1). Another study explicitly stated that the relationship between adolescent/adult drug use cannot be explained by the gateway hypothesis alone (see sec. 9.3).

- **Inconsistent findings across disparate populations**. The studies also found that illicit drug use is inconsistent across different populations, which suggests that cannabis use may not be a determinative factor. In particular, by evaluating drug use patterns in 17 different countries, the study profiled in section 9.8 discovered that each country has its own unique sequence. For example, while only 11.4 percent of other illicit drug users in the United States have *not* used cannabis that percentage increases dramatically in other countries. Countries diverging from the gateway hypothesis include the Netherlands (20.4 percent), Columbia (33.4 percent), Nigeria (77.8 percent), and Japan (83.2 percent). Moreover, the association is insignificant for almost all age groups in Japan and has no significance for any age group in Nigeria.

- **Variations in drug use and abuse**. A study of current regular heroin users (using at least three times per week) within the United States found that 20.3 percent deviated from the gateway hypothesis. Those who were found to have initiated heroin use at an earlier age, used heroin for a longer duration and used it more frequently than those who followed Kandel's pattern (see sec. 9.13).

- **Unmeasured common causes**. In concluding their study, the researchers behind the multi-country analysis noted that the variations indicated an unmeasured common cause of drug use patterns. Some potential causes (i.e., common liability factors) are examined in section 5.1.5.

- **Practical significance**. One of the twin studies found that although there is a statistically significant association between one's cannabis use and the use of other illicit drugs, that association is not *practically* significant (see sec. 9.4).

5.1.2. Age of First Use

Several studies determined that the age of one's first use of cannabis was a strong predictor of future illicit drug use. For example, two studies found a significant negative association between age and the effects of cannabis use, with young users being more susceptible to those effects (see sec. 9.4 and 9.8). Similarly, as previously noted, one of the twin studies found that a twin using cannabis at an early age (i.e., younger than 18) had a significantly higher risk of using sedatives, opiates, and hallucinogens when compared to their later-using twin. Finally, another study determined that those who used substances early (i.e., under the 25th percentile for age) were more likely to use a series of substances, including other illicit drugs (see sec. 9.10).

5.1.3. Frequency of Use

The frequency of an individual's cannabis use was found across several studies to be a strong predictor of their subsequent use of other illicit drugs. One study found that the odds of using other illegal substances increased in relation to a rise in the frequency of cannabis use (see sec. 9.1). Another study, listed in section 9.2, asserted that the annual frequency of cannabis use in late adolescence and early adulthood (ages 16–25) emerged as the strongest risk factor for later illicit drug use.

5.1.4. Medical Cannabis Use

When considering the medical use of cannabis, one study found that recreational users have significantly increased odds of using stimulants and opioids; medical users do not. That is, how the cannabis is obtained drives the drug's association with other illicit drug use (see sec. 9.11).

5.1.5. Other Common Liability Factors

Several studies attributed the observed association between cannabis use and the use of other illicit drugs to internal or external characteristics. For example, one group of researchers only found an association for a subgroup of "troubled youths," which comprised 24 percent of youths who had experienced problems with their family/friends, school, or police. Among the remaining "most youth" group, prior cannabis use did not have a statistically significant impact on later illicit drug use (see sec. 9.6).

In 2016, another set of researchers came to a similar conclusion: that the progression from one substance to another is more affected by personality traits and environmental factors than the substance first used (see sec. 9.10). Six years earlier, a study found that the association between using cannabis and using other illicit drugs becomes insignificant after accounting for stress and various sociodemographic factors, such as age, education, employment, and family status (see sec. 9.7).

5.2. Animal-Based Studies

Unlike human-based studies, those involving animals enable researchers to create controlled environments to test the effects of cannabis use while reducing or eliminating confounding factors. However, these studies suffer from limitations as well, as their findings may not translate to human subjects.[29] Moreover, the created environments do not accurately reflect real-world scenarios, as the animals are given direct injections of cannabis components (rather than all of the ingredients included in cannabis products) and are often introduced to additional stressors such as food deprivation.

Despite the potential empirical benefits of research designs using animal subjects, all of the studies reviewed by FRD had statistical issues that undercut the reliability and validity of their findings. While specific limitations are discussed in the individual profiles, the most frequent issue was the use of small sample sizes, which led to inherently low statistical powers for distinguishing the effect of cannabis use from a random result.

The external validity of the seven animal-based studies is also doubtful due to the treatment of the test subjects. Whereas humans generally smoke or eat cannabis, the majority of the animal studies used injections of specific cannabis components, namely THC, WIN, and CBD. As a result, the applicability of these studies' findings to humans' cannabis use is unclear. The key findings for each of these studies are listed in table 4.

Table 4. Summary of Key Findings from Animal-Based Studies

Section	Key Findings
10.1	Rats injected with THC during adolescence voluntarily used more heroin doses and greater amounts of heroin in adulthood.
10.2	THC-induced changes in the endogenous cannabinoids in specific sections of the rats' brains provided supporting evidence of increased opioid reward-related behavior after adolescent THC exposure.
10.3	The effects of THC exposure on the rats' heroin use varied with genetic background.
10.4	THC-exposed rats self-administered more heroin injections than the control group when the heroin was freely available. However, these rats did not make more efforts than their nonexposed peers once the cost of obtaining heroin increased.
10.5	Under a fixed-rate schedule, THC exposure did not affect the rats' self-administration of cocaine when the cost remained constant. When the cost increased under a progressive ratio schedule, the rats exposed to THC "requested" fewer doses of cocaine than the control group. The THC-exposed rats also showed higher levels of locomotor activity when they were then treated with heroin, but not when they were treated with cocaine.
10.6	Cannabis may act as a gateway to other illicit drugs by reducing the levels of eIF2α—and other eukaryotic initiation factors—in the nucleus accumbens of adolescent brains.
10.7	CBD injections tend to reduce heroin-seeking behavior, an effect that remained significant even two weeks after treatment.

As with the human-based studies, these key findings can be grouped together in themes: cognitive changes, dose dependence, drug-seeking behavior, and genetic differences.

5.2.1. Cognitive Changes

The animal-based studies highlighted two cognitive changes that may occur when using cannabis or other illicit drugs:

- **Reward behavior**. A causal connection between cannabis use and the use of other illegal substances may be supported by studies that found cannabis-induced reward changes in the brain. For example, one study noted that rats exposed to THC during adolescence voluntarily used heroin in greater amounts in adulthood (see sec. 10.1). However, another study found that genetically different rats experience disparate reactions. Specifically, Lewis rats experienced increased dopamine levels in response to heroin, but Fisher 344 rats did not (see sec. 10.3).
- **Locomotor activity**. Several studies explored possible changes in the rats' locomotor activity following THC exposure—changes that may be indicative of abuse potential. A 2007 study, for example, found that rats exposed to THC experienced higher levels of locomotor activity than the control group for heroin but not for cocaine (see sec. 10.5). Eleven years later, a 2018 study took this analysis a step further by comparing the effect differences between adolescent rats and adult rats. The researchers used a cannabinoid similar in effect to THC, but with a different chemical structure: WIN. They concluded that while rats exposed to WIN in adolescence did experience increased locomotor activity, there was no cross-sensitization observed in adult rats exposed to WIN (see sec. 10.6). Similarly, a study examining the effects of CBD, another cannabis component, found that exposure did not alter the rats' locomotor activity (see sec. 10.7).

5.2.2. Dose Dependence

With regard to other illicit drug use, the study listed in section 10.1 found that lower doses of heroin did not increase the rats' self-administration of the drug following THC exposure, but higher doses did. However, they administered these doses during a period of food restriction, which may have affected the results. The equivalent dosage schedule for human subjects is unknown.

5.2.3. Drug-Seeking Behavior

Three of the reviewed studies specifically observed how cannabis components affected the test subjects' drug-seeking behavior. The one highlighted in section 10.4 found that THC-exposed rats consumed more heroin than the control group when the cost remained constant; however, there was no difference between the groups' drug use when the cost increased. The study

profiled in section 10.5 found a slight reversal of this when evaluating cocaine consumption: THC exposure did not increase the self-administration of cocaine under a fixed-cost scenario. However, when the cost increased, the THC-exposed rats actually consumed fewer doses than the control group. Finally, the study listed in section 10.7 found that CBD injections did not alter the rats' heroin-seeking behavior. They instead tended to reduce this behavior with the effect lasting two weeks.

5.2.4. Genetic Differences

As mentioned in the section on cognitive changes, genetic differences within the rat varieties resulted in inconsistent findings. Specifically, the 2013 study identified in section 10.3 found that while Lewis rats had an increased dopamine reaction to heroin following THC exposure, Fisher 344 rats did not.

6. CONCLUSION

While many of the studies reviewed in this analysis did find statistically significant associations between cannabis use and one's later use of other illicit drugs, **there is not yet conclusive evidence to say that cannabis is a gateway drug**, due to data limitations, failures to eliminate confounding variables, and questions about the applicability of findings from animal-based studies to human behavior.

6.1. Data Limitations

Many studies of humans' cannabis use are based on self-reported data from longitudinal or retrospective studies. Yet these data collection methods are known to be biased, as subjects often cannot recall many of the details asked by the researchers or they attempt to provide the answers they believe reflect most favorably upon themselves, regardless of their anonymity in the collection process. Additionally, some of the studies reviewed in this analysis derived their findings from biased data by oversampling from heroin users, street youth, and other at-risk individuals. As such, the results can only be applied to narrow sections of the population.

6.2. Confounding Variables

An additional complication is the fact that some studies found significant associations between confounding variables and illicit drug use, raising questions about whether a person's cannabis use contributes to, independently causes, or is in some way linked to their later use of other illegal substances. For example, some of the studies reviewed in this report found statistically significant evidence of associations between confounding variables, such as individual and peer drug use, mental health issues, and socioeconomic status, and the use of illicit drugs.

6.3. Applicability of Findings

As previously noted, animal-based studies offer an ability to examine hypotheses using research techniques that cannot be legally used on humans. However, there are reasons to be skeptical of the applicability of their findings. These studies randomly assigned living things to experimental groups that were given cannabis in the forms of THC, WIN, and CBD, and then offered cocaine or heroin. While such a design eliminates the influence of internal and external covariates, the potential influence of such factors on humans' use of cannabis and other illicit drugs raises some questions about the ability to extrapolate these studies' findings.

6.4. Recommendations for Future Research

Like other research on the harmful effects of drugs, an analysis of cannabis and its association with other illegal substances should be conducted as clinical trials often are: through research designs that randomly assign selected human participants to control and experimental groups, and that screen these potential participants for confounding variables, such as genetic predispositions to addiction. Baseline data on drug use and a range of socioeconomic covariates should be obtained from the study participants; researchers should also collect longitudinal data on these factors. Crucially, specific data on one's use of cannabis and other illicit drugs should not be obtained through voluntary responses to questionnaires, as prior research has found that people often underreport their own drug use in such self-reported formats.

7. APPENDIX I: Article Selection and Scoring

Before evaluating the relevant human- and animal-based studies, FRD had to narrow down the existing corpus of statistical research to articles focused on the association between cannabis use and the subsequent use of other illicit drugs. This criterion filtered out much of the material, which was further refined by focusing on statistical studies published between 2008 and 2018.

7.1. Article Searches

To identify scholarly publications that matched these criteria, the project team searched the JSTOR, ProQuest, PubMed, and Scopus databases—ProQuest and Scopus yielded the most results. During the initial searches, FRD perused book reviews, commentaries, and other types of content to gauge their usefulness. Based on this information, FRD limited its search to peer-reviewed journal articles and used terms synonymous with cannabis, other illicit drugs, and the relationship between them (see table 5).

Table 5. Search Terms Used for Human-Based Studies

Cannabis	Other Illicit Drugs	Association
cannabis	Drug	gateway
cannabinoid*	Narcotic	"stepping stone"
hash*	Illicit	"stepping-stone"
marijuana	illegal	associat*
marihuana	"controlled substances"	correlat*
"THC"	addict*	dependen*
—	"substance abuse"	Later
—	—	Subsequent
—	—	relation*
—	—	develop*
—	—	increase*
—	—	relate*

Additionally, FRD used Boolean logic and "wildcards" to capture spelling variations. The resulting search strings were used to find relevant articles published in ProQuest and Scopus:

> (cannabis OR cannabinoid* OR marijuana OR marihuana OR "thc") AND (drug OR narcotic OR illicit OR illegal OR "controlled substances" OR addict* OR "substance abuse") AND (gateway OR "stepping stone" OR "stepping-stone" OR associat* OR correlat* OR dependen* OR later OR subsequent OR relation* OR develo* OR increase* OR relate*)

(hashish) AND (drug OR narcotic OR illicit OR illegal OR "controlled substances" OR addict* OR "substance abuse") AND (gateway OR "stepping stone" OR "stepping-stone" OR associat* OR correlat* OR dependen* OR later OR subsequent OR relation* OR develo* OR increase* OR relate*)

While the results of these searches included some studies that featured animal test subjects, the terminology in those articles led the project team to use a different set of search terms to find animal-based research in peer-reviewed journals. Table 6 highlights the terms that were used to search ProQuest and Scopus.

Table 6. Search Terms Used for Animal-Based Studies

Cannabis	Other Illicit Drugs	Animals
tetrahydrocannabinol	Cocaine	Animal*
—	Heroin	Mice
—	"Illegal drug"	Mouse
tetrahydrocannabinol	"illicit drug"	Monkey*
—	"illicit substance"	Rat
—	—	Rats

As with the human-based studies, an additional search string was used to find relevant articles in ProQuest and Scopus:

tetrahydrocannabinol AND (mice OR mouse OR rat OR rats OR monkey* OR animal*) AND (cocaine OR heroin OR "illicit substance" OR "illicit drug" OR "illegal drug")

Along with these databases, FRD looked for relevant studies in expert and systematic reviews of cannabis-related research. These sources were published by research institutions like the National Academies of Sciences, Engineering, and Medicine, as well as the National Institute on Drug Abuse, and nonprofit organizations such as the Campbell and Cochrane Collaborations.

7.2. Article Relevancy and Selection for Further Review

After reviewing the study abstracts and browsing select articles' content, FRD established criteria to assess the relevancy of the articles to the topic of associations between cannabis use and the use of other illicit drugs (see table 7).

Table 7. Relevancy Criteria

Relevancy	Explanation
None	Does not study the association between cannabis use and the use of other illicit drugs or is commentary.
Somewhat	Studies the association between illegal substances but not the effect of cannabis use on subsequent illicit drug use, or does not involve quantitative analysis.
High (Human)	Uses data collected during human-based studies to examine the association between cannabis use and further illicit drug use.
High (Animal)	Uses animal models to examine the association between cannabis use and further illicit drug use.

During the selection process, relevant articles cited by the reviewed studies were also added to the list. Of the 466 articles FRD found, 66 were deemed to contain relevant information (see table 8); 33 of those articles were published between 2008 and 2018. Of these 33 articles, 23 were profiled for the main report.

Table 8. Relevant Articles by Publication Year

Source	Articles	Relevant Art.	2008–18	2000–7	≤1999
Animal Studies	17	7	4	3	—
National Academies	5	5	4	1	—
National Institute on Drug Abuse	15	8	5	3	—
ProQuest ProQuest_hash Scopus Scopus_hash	32 22 220 139	30	12	15	3
Cited References	16	16	8	8	—
TOTAL	**466**	**66**	**33**	**30**	**3**

7.3. Scientific Methods Scale

To develop a standardized evaluation of the studies' internal validity, FRD adopted the Maryland Scientific Methods Scale (SMS). The scale runs from 1 to 5 and rates the studies' use of certain research designs; higher numbers indicate the use of research methods most likely to yield internally valid findings. Studies that randomly selected research subjects from a larger population and randomly assigned those subjects to control and experimental groups were rated higher than those that did not incorporate these methods into their research designs.[30]

The five levels of the SMS are:

- **Level 1**: Conducts a cross-sectional comparison of treated and control groups without using any control variables to adjust for differences between the two.

- **Level 2**: Uses adequate control variables to compare treated and control groups. Most of the studies included at this level collected their data retrospectively (i.e., through recalls).

- **Level 3**: Uses adequate control variables to compare treated and control groups. Most of the studies included at this level collected their data prospectively (i.e., through longitudinal studies.

- **Level 4**: Compares treated and comparable control groups after accounting for control variables.

- **Level 5**: Compares treated and control groups, where the assignment of treatment and control conditions is random.

Since the SMS focuses on some aspects of internal validity, FRD also rated other features of the statistical methods used. In particular, the project team asked:

- Was the statistical analysis appropriate?

- Did the study have low statistical power to detect the effects because of small sample sizes?

- Was there a low response rate or differential attrition?

- Did the study narrowly focus on a specific high-risk population that limited the applicability of the conclusions to the general population?

The study's SMS was then downgraded by one point for each problem that was identified in the additional analysis, resulting in a final score. For example, a twin study with serious flaws in the statistical analysis would receive a level rating of 3 rather than 4.

8. APPENDIX II: Summary Tables for Human-Based Studies

As FRD began filtering its research findings, the project team catalogued various aspects of the relevant human-based studies, including region, population, study design, data source, collection method, and sample size. The results of that cataloging, as well as the related profile sections, are detailed in tables 9–14.

Table 9. Articles by Region and Section

Region	Articles	Sections
U.S.	11	9.3, 9.4, 9.5, 9.7, 9.8, 9.11, 9.12, 9.13, 9.14, 9.15, 9.16
Non U.S.	5	9.1, 9.2, 9.6, 9.9, 9.10

Table 10. Articles by Population and Section

Population	Articles	Sections
Adolescents (<18)	3	9.2, 9.4, 9.9
Young Adults (18–26)	4	9.1, 9.6, 9.7, 9.15
Adults or Mixed	6	9.3, 9.5, 9.8, 9.10, 9.14, 9.16
High-Risk Population	3	9.11, 9.12, 9.13

Table 11. Articles by Study Design and Section

Study Design	Articles	Sections
Retrospective Cohort	9	9.5, 9.6, 9.8, 9.9, 9.10, 9.11, 9.12, 9.13, 9.14
Prospective Longitudinal	7	9.1, 9.2, 9.3, 9.4, 9.7, 9.15, 9.16

Table 12. Articles by Data Source and Section

Data Source	Articles	Sections
Primary Data	6	9.2, 9.6, 9.7, 9.12, 9.13, 9.15
Existing Data	10	9.1, 9.3, 9.4, 9.5, 9.8, 9.9, 9.10, 9.11, 9.14, 9.16

Table 13. Articles by Collection Method and Section

Collection Method	Articles	Sections
Administered Interview	8	9.1, 9.3, 9.5, 9.8, 9.10, 9.11, 9.14, 9.16
Self-Administered Questionnaire	4	9.4, 9.6, 9.7, 9.9
Other	4	9.2, 9.5, 9.12, 9.13

Table 14. Articles by Sample Size and Section

Sample Size	Articles	Sections
200–500	1	9.11
501–1,000	7	9.2, 9.4, 9.5, 9.6, 9.8, 9.13, 9.15
1,001–10,000	3	9.1, 9.7, 9.14
>10,000	5	9.3, 9.9, 9.10, 9.12, 9.16

9. APPENDIX III: Literature Review of Human-Based Studies

As previously noted, this appendix includes detailed profiles for the 16 human-based studies FRD reviewed during the period of performance.

9.1. Young Adult Sequelae of Adolescent Cannabis Use

Edmund Silins et al. "Young Adult Sequelae of Adolescent Cannabis Use: An Integrative Analysis." *Lancet Psychiatry* 1, no. 4 (2014): 286–93. doi: 10.1016/S2215-0366(14)70307-4.

9.1.1. Scientific Methods Score

SMS: 3—Longitudinal study with covariates.

9.1.2. Summary and Purpose

This study examined the association between the frequency of one's cannabis use before age 17 and their drug use in adulthood; it also looked at outcomes such as educational attainment and psychological development. It used data from three different longitudinal studies of childhood, adolescent, and adult development conducted in Australia and New Zealand. According to the authors, the combined data was used to create a sample that could be statistically analyzed with sufficient power to examine multiple outcomes of adolescent cannabis use, rather than a single result, such as the use of other illicit drugs.

9.1.3. Results

- Individuals who reported using cannabis on a less than monthly basis prior to age 17 had higher odds of other illicit drug use by age 30 than those who never used cannabis (OR: 1.67, 95% CI: 1.45–1.92) and higher odds of cannabis dependence (OR: 2.06, 95% CI: 1.75–2.42).
- The odds of other illicit drug use increased with the frequency of cannabis use, and individuals who were daily cannabis users before age 17 had higher odds of illicit drug use by age 30 than those who had never used cannabis (7.80, 95% CI: 4.46–13.63), as well as substantially increased odds of later cannabis dependence (17.95, 95% CI: 9.44–34.12).

9.1.4. Conclusions

- The frequency of one's cannabis use during adolescence had a statistically significant association with other illicit drug use and cannabis dependence in young adulthood.
- The authors suggest that this association supports a possible causal relationship between the two. However, they also caution that their study was limited in its capacity to explain the why there was such an association between adolescent cannabis use and the later use of other illicit drugs.

9.1.5. Method, Source, and Sampling

- *Method*: Logistic regression with a study-specific random intercept for three different longitudinal studies and common slopes across all three studies.
- *Data Type*: Longitudinal (meta-analysis) study.
- *Data Source*: Existing data from the Australian Temperament Project, the Christchurch Health and Development Study, and the Victorian Adolescent Health Cohort Study.
- *Data Collection*: Existing data.
- *Sampling*: Original sampling plan.
- *Population*: Adolescents and young adults from Australia and New Zealand.
- *Sample Size*: For other illicit drug use, 2,832; for cannabis dependence, 2,675. The sample sizes varied due to the use of combined data from three different longitudinal studies, with sample sizes ranging from 2,537 to 3,765.
- *Age*: The three studies contained data on other illicit drug use between the ages of 23 and 25, and data on cannabis dependence between the ages of 17 and 25. The oldest age at which the three studies collected data from participants on cannabis use was 17; the oldest age on outcomes was 30. Hence, Silins and his coauthors express cannabis use frequency as before age 17 and state all outcomes as results by age 30.
- *Other Drugs*: Inhalants, hallucinogens, ecstasy, amphetamines, methamphetamines, heroin, cocaine, and the nonmedical use of prescription drugs.

9.1.6. Covariates

- A total of 52 covariates were considered, including:
  - Demographics (ethnicity, gender, and socioeconomic status),
  - Drug use (smoking, drinking, or illicit drug use before age 17),
  - Family history (parents who were smokers or criminals), and
  - Stressors (cognitive/behavioral issues and depression).
- The maximum frequency of cannabis use before age 17 (never, less than monthly, monthly or more, weekly or more, or daily).

9.1.7. Limitations

- The use of data from observational studies (thus confounding variables may be omitted).
- The variations in research design between the three longitudinal studies from which the authors drew their data.
- The possibility of response bias (self-reported data on drug use).
- The results may be limited in their extrapolation to other populations.

9.2. Developmental Antecedents of Illicit Drug Use

David M. Fergusson, Joseph M. Boden, and L. John Horwood. "The Developmental Antecedents of Illicit Drug Use: Evidence from a 25-Year Longitudinal Study." *Drug and Alcohol Dependence* 96, no. 1–2 (2008): 165–77. doi: 10.1016/j.drugalcdep.2008.03.003.

9.2.1. Scientific Methods Score

SMS: 3—Longitudinal study with covariates.

9.2.2. Summary and Purpose

This paper examined the extent to which childhood factors and adolescent adjustment may be related to later illicit drug use by analyzing a 25-year longitudinal study of nearly 900 children from New Zealand. The analyses were conducted by repeated-measures logistic regression to account for the effects of cannabis use and other covariates, including parental drug use and criminal behavior; physical/sexual abuse in childhood; gender; age at interview; time-dynamic measures such as peer influence; and the frequency of smoking and drinking.

9.2.3. Results

- The annual frequency of cannabis use in late adolescence/early adulthood (ages 16–25) emerged as the strongest risk factor for later illicit drug use (estimated coefficient: 1.09, SE: 0.07, p-value<0.0001).
- The association was both dose dependent (a higher dose had a larger impact) and age dependent. Young users were more susceptible to the effects of cannabis; the estimated interaction effect of annual frequency of cannabis use and age is -0.10 with an SE of 0.02.
- Novelty-seeking (p-value<0.01), alcohol use at ages 16–25 (p-value<0.01), and peers' substance use (p-value<0.0001) significantly elevated the risk of one's own illicit drug use.

9.2.4. Conclusions

The development of early illicit drug use and dependence involves an accumulative process that includes exposure to adversity in childhood, one's ability to adjust, personality and individual factors, alcohol and cannabis use, and an affiliation with substance-using peers.

9.2.5. Method, Source, and Sampling

- *Method*: Logistic generalized estimating equation (longitudinal data analysis with a random subject effect).
- *Data Type*: Longitudinal study.
- *Data Source*: Existing data from the Christchurch Health and Development Study.

- *Data Collection*: Self-reported information, parental interviews, reports from teachers, psychometric assessments, and data and medical and other records.
- *Sampling*: N/A.
- *Population*: Children from Christchurch, New Zealand who were born in 1977.
- *Sample Size*: Approximately 900 children. The study began with 1,265 children, but a combination of participant attrition and missing data reduced the sample size to around 900. The authors do not specify the exact figure.
- *Age*: Individuals were surveyed at ages 16, 18, 21, and 25.
- *Other Drugs*: Solvents (glue, petrol, and paint); stimulants, including methamphetamines; barbiturates; prescription medications that were illicitly obtained; opiates, including both heroin and morphine; cocaine (in any form); hallucinogens, including ecstasy, LSD, and PCP; and plant extracts, including mushrooms and datura.

9.2.6. Covariates

- Demographics (age at interview and gender),
- Drug use (annual frequency of cannabis use and the frequency of drinking/smoking),
- Family history (parents who used alcohol or illicit drugs, or were criminals or violent),
- Friend history (peers who used illicit substances), and
- Stressors (physical/sexual abuse in childhood, witness to inter-parental violence, conduct and attention problems between ages 7 and 13, and novelty-seeking behavior).

9.2.7. Limitations

- The use of data from observational studies (thus confounding variables may be omitted).
- The possibility of response bias (self-reported data on drug use).
- The results may be limited in their extrapolation to other populations.

9.3. "Gateway Hypothesis" and Early Drug Use

Stephen Nkansah-Amankram and Mark Minelli. "'Gateway Hypothesis' and Early Drug Use: Additional Findings from Tracking a Population-Based Sample of Adolescents to Adulthood." *Preventive Medicine Reports* 4 (2016): 134–41. doi: 10.1016/j.pmedr.2016.05.003.

9.3.1. Scientific Methods Score

SMS: 3—Longitudinal study with covariates.

9.3.2. Summary and Purpose

Using longitudinal data on drug use from the National Longitudinal Study of Adolescent to Adult Health, the authors test the existence of a relationship between drug use in adolescence and the use of other illicit drugs in adulthood, as well as the influence of depressive symptoms on such a relationship. They also analyze the influence of individuals' mental health status at various development stages on the relationship.

9.3.3. Results

- After adjusting for age, gender, and race, when compared to those who never used cannabis, individuals who used cannabis in adolescence (aged 18 or younger at the time of the first wave of data collection) were more likely to have used illicit substances in late adolescence (aged 16–21 during the second wave) and young adulthood (aged 24–33 at the fourth wave), but not in early adulthood (aged 18–26 during the third wave).
  - Specifically, subjects' use of cannabis in early adolescence (ages 11–15) was associated with significantly higher odds of illicit drug use in late adolescence (OR: 7.79, 95% CI: 5.91–10.28) and young adulthood (OR: 3.19, 95% CI: 2.65–3.84). Yet the association with such drug use in early adulthood was not significant (OR: 0.74, 95% CI: 0.50–1.07).
  - In comparison to those who did not use cannabis, individuals first using the drug between the ages of 16 and 18 were associated with significantly higher odds of using illicit drugs in late adolescence (OR: 5.98, 95% CI: 3.80–9.40) and young adulthood (OR: 3.59, 95% CI: 2.65–4.85). However, they had lower odds of using illicit drugs in early adulthood than did those who did not use cannabis (OR: 0.31, 95% CI: 0.15–0.67).

9.3.4. Conclusions

The finding of inconsistent illicit drug use in adulthood by adolescent cannabis users suggests that cannabis may not have a determinative effect on such use and that other factors may be involved.

9.3.5. Method, Source, and Sampling

- *Method*: Rao Scott Chi-squared tests for statistical significance of unadjusted comparisons, and a generalized estimating equation with cumulative logit link function to estimate the ORs and 95% CIs of baseline and later drug use.
- *Data Type:* Longitudinal study.
- *Data Source*: Existing data from the National Longitudinal Study of Adolescent to Adult Health, which spans a 14-year period.
- *Data Collection*: Self-reported information in questionnaires, followed by interviews.

- *Sampling*: There were two-stage stratified samples—in the first stage, 80 middle, junior high, and high schools were selected from a sample of 26,666 schools through stratified sampling, with strata including census region, level of urbanization, level of diversity, size, and school type (e.g., Catholic, private, and public). In the second stage, 20,745 students were selected through stratified sampling, with strata including ethnicity (e.g., Chinese, Cuban, and Puerto Rican) and "genetics" (e.g., fraternal twins, identical twins, full siblings, and half-siblings). Thus, the study's first sample was 20,745, and its last was 15,701.[31]
- *Population*: Adolescents from the United States who were in grades 7–12 during the first wave in 1994.
- *Sample Size*: 11,194; the authors' sample included adolescents who had participated in the first four waves of the study.
- *Age*: Wave 1, 9–19; Wave 2, 11–21; Wave 3, 18–26; and Wave 4, 24–32.
- *Other Drugs*: Amphetamines, crystal methamphetamine ("ice"), cocaine, heroin, ecstasy, LSD, PCP, and any other illicit psychoactive substance.

9.3.6. Covariates

- Demographics (age and race),
- Drug use (current substances: cannabis, cocaine, and other illicit drugs), and
- Stressors (mental health issues and indicators of depressive symptoms).[32]

9.3.7. Limitations

- The possible omission of confounding variables, such as education/income level, or genetic covariates, like a predisposition to addiction.
- The possibility of response bias (self-reported data on drug use).

9.4. Understanding the Association between Adolescent Marijuana Use and Later Serious Drug Use

H. Harrington Cleveland and Richard P. Wiebe. "Understanding the Association Between Adolescent Marijuana Use and Later Serious Drug Use: Gateway Effect or Developmental Trajectory?" *Development and Psychopathology* 20, no. 2 (2008): 615–32. doi: 10.1017/S0954579408000308.

9.4.1. Scientific Methods Score

SMS: 4—Longitudinal twin study with covariates.

9.4.2. Summary and Purpose

This study examines the influence of family environment and genetics on one's use of cannabis and other illicit drugs to see if cannabis use is a determinative factor or if other variables are involved. Drawing on data from the National Longitudinal Study of Adolescent to Adult Health, the authors focus on reported drug use by 555 pairs of same-gender twins, a sample including both identical and fraternal cotwins.

9.4.3. Results

- In a bivariate regression, the frequency of one's cannabis use is associated with the use of other illicit drugs when both fraternal and identical twins are in the sample (β=0.169, $p<0.05$). However, the adjusted regression ($R^2=0.029$) indicates that the model accounts for little variance in illicit drug use. Therefore, the association is statistically significant but not practically significant.
- In a bivariate regression, one's use of other illicit drugs is associated with the later use of additional substances when both fraternal and identical twins are in the sample (β=0.133, $p<0.05$). However, the adjusted regression ($R^2=0.018$) indicates that the model accounts for little variance in later illicit drug use. Therefore, the association is statistically significant but not practically significant.
- In a multivariate regression that accounts for one's early use of other illicit drugs and friends' cannabis use, the latter had significant positive effects on one's drug use later in life (β=0.215, $p<0.05$). In addition, the interaction effect of twin type (fraternal=0, identical=1) with early cannabis use was significant (β=-0.145, $p<0.05$), indicating that the effect of early cannabis use is stronger for fraternal twins than identical ones.
- Lastly, the adjusted regression ($R^2=0.054$) for the multivariate model indicates that it accounts for more variance in later illicit drug use than the bivariate model. Nonetheless, the relatively low value indicates that the interaction between cannabis use and twin type has a statistically significant association with one's later use of other illicit drugs but not a practically significant one.

9.4.4. Conclusions

The study results suggest that genetics influence the relationship between one's cannabis use and the later use of other illicit drugs. This evidence comes from the significant interaction effect between twin type and later drug use, as fraternal twins generally have different chromosome profiles while identical twins do not.

9.4.5. Method, Source, and Sampling

- *Method*: Regression of later drug use difference on early cannabis use difference (accounting for covariates).
- *Data Type*: Longitudinal twin study.

- *Data Source*: Existing data from the National Longitudinal Study of Adolescent to Adult Health.
- *Data Collection*: Self-reported information that was collected in 1995, 1996, and 2001.
- *Sampling*: Same-gender twin pairs (pulled from the study's sibling data).
- *Population*: American high school students.
- *Sample Size*: 555 twin pairs.
- *Age*: Cannabis use, ages 12–19 (the authors list the range as 12.64–19.64 years of age); later illicit drug use, ages 18–25 (specifically, 18.98–25.98).
- *Other Drugs*: Illicit drug use was divided into four categories: cocaine, including crack, freebase, or powder; crystal meth; drugs like ecstasy, LSD, PCP, mushrooms, inhalants, ice, heroin, and prescription medicines not prescribed to the user; and any injected drugs.

9.4.6. Covariates

- Demographics (gender),
- Drug use (age of first use, earlier hard-drug use difference, and within-pair difference of early cannabis use score [square root of frequency of uses]), and
- Peer history (amount of cannabis use among three closest friends).

9.4.7. Limitations

- The use of data from an observational study (thus confounding variables may be omitted).
- The use of difference scores shifts the question to assessing the impact of one's frequency of cannabis use on the use of other illicit drugs, rather than establishing a "threshold" measure between the two.
- As the age range of the sample was 12 to 19, the measure of cannabis use is "earlier" not adolescence.
- The possibility of response bias (self-reported data on drug use).

9.5. Cotwin-Control Analysis of Drug Use and Abuse/Dependence Risk Associated with Early-Onset Cannabis Use

Julia D. Grant et al. "A Cotwin-Control Analysis of Drug Use and Abuse/Dependence Risk Associated with Early-Onset Cannabis Use." *Addictive Behaviors* 35, no. 1 (2010): 35–41. doi: 10.1016/j.addbeh.2009.08.006.

9.5.1. Scientific Methods Score

SMS: 4—Twin study with covariates.

9.5.2. Summary and Purpose

This paper analyzes data on early cannabis use (before age 18) among discordant, male twin pairs that are veterans of the Vietnam War. The aim was to assess whether cannabis use remains a significant predictor of other illicit drug use and dependence after controlling for genetic and shared environmental influences. Two series of logistic regression analyses were conducted using two samples: 293 discordant pairs, where one twin was an early cannabis user and the other either used cannabis later or never; and a subset of 190 discordant pairs where one twin was an early cannabis user and the other used cannabis later in life.

In addition to accounting for covariates such as education, depression, post-traumatic stress disorder, early regular alcohol use, early regular nicotine use, and Southeast Asia military service, the logistic regression includes the interaction of zygosity and early cannabis use.

9.5.3. Results

- The difference between twins who use cannabis early in life and those who use the drug later in life is small (OR: 1.40, 95% CI: 0.87–2.24 for any other illicit drugs), though the early users still showed significantly higher risks of using sedatives (OR: 2.53, 95% CI: 1.19–5.36), opiates (OR: 2.33, 95% CI: 1.14–4.74), and hallucinogens (OR: 2.13, 95% CI: 1.10–4.14).
- After controlling for covariates, early cannabis users were at greater risk than their cotwins who used cannabis later or not at all for eight out of nine substance-related comparisons, including using other illegal drugs (ORs: 2.71–4.09), having illegal drug dependence (ORs: 2.02–2.13), and developing alcohol dependence (OR: 2.36).
- The interaction effect of twin type (i.e., fraternal or identical) and early cannabis use is not significant (p-value>0.10).

9.5.4. Conclusions

The results provide strong evidence that cannabis use prior to age 18 is associated with a higher risk of later drug use. Moreover, they suggest that the association between early cannabis use and later illicit drug use cannot be explained by genetic influence since it is not stronger for fraternal twins than identical ones. Instead, it is more likely due to a third unmeasured factor that is independent of familial influence.

9.5.5. Method, Source, and Sampling

- *Method*: Logistic regression on two discordant samples with an interaction of zygosity and early cannabis use.
- *Data Type*: Retrospective twin study.

- *Data Source*: Vietnam Era Twin Registry (VET-R), a database of 7,375 male twin pairs, both of whom served in the military between 1965 and 1975.
- *Data Collection*: Cotwin-control design and telephone interviews in 1992 to obtain data on various matters, including the use of other illicit drugs.
- *Sampling*: Nonrandom sample consisting of individuals in VET-R who had neither used other illicit drugs nor developed alcohol dependence prior to using cannabis for the first time.
- *Population:* Male twins who served in the U.S. military during the Vietnam War.
- *Sample Size*: 6,362 males from 3,181 twin pairs.
- *Age*: The mean age during the 1992 telephone interviews was 42.
- *Other Drugs*: Stimulants, cocaine, sedatives, opiates, and hallucinogens like PCP.

9.5.6. Covariates

- Demographics (education level [less than or equal to high school] and military service during the Vietnam War),
- Drug use (early cannabis use and early regular use of alcohol and nicotine), and
- Stressors (childhood conduct disorders, depression, and PTSD).

9.5.7. Limitations

- The use of data from an observational study (thus confounding variables may be omitted).
- The analysis is focused on discordant twin pairs so the study shares some same limitations as those discussed in section 9.4.
- The possibility of response bias (self-reported data on drug use).
- The results may be limited in their extrapolation to other populations.

9.6. Is Cannabis a Gateway to Hard Drugs?

Hans Olav Melberg, Andrew M. Jones, and Anne Line Bretteville-Jensen. "Is Cannabis a Gateway to Hard Drugs?" *Empirical Economics* 38, no. 3 (2010): 583–603. doi: 10.1007/s00181-009-0280-z.

9.6.1. Scientific Methods Score

SMS: 2—Retrospective study with covariates.

9.6.2. Summary and Purpose

The aim of this study was to test the hypothesis that cannabis use directly increases one's risk of consuming other illicit drugs. Focusing on young adults from Norway, the authors used a bivariate hazard survival model to study the onset of cannabis use and illicit drug use, with shared frailty estimated using a latent class approach. There were two distinct groups that were analyzed. One was "troubled youths," who had childhood problems with their families, friends, school, or local police forces. The other group was those without these problems (i.e., "most youths").

9.6.3. Results

- For the smaller group of "troubled youth," which consisted of about 24 percent of the population, the hazard of starting to use other illicit drugs is almost double that for "previous cannabis users." The coefficient of previous cannabis use for the hazard model is estimated as 0.710 (SE: 0.185).
- For the "most youth" group, which consisted of about 76 percent of the population, previous cannabis use had a smaller impact and the effect is not statistically significant (estimated coefficient: 0.294, SE: 0.163).

9.6.4. Conclusions

Recent cannabis use has a significant increased risk of subsequent drug use for individuals who experience childhood adversities. By contrast, for most individuals with no childhood traumas, recent cannabis use has no significant risk of later drug use.

9.6.5. Method, Source, and Sampling

- *Method*: Latent class bivariate hazard survival model.
- *Data Type*: Retrospective study.
- *Data Source*: Original data the authors collected from mailed questionnaires, and data on drug prices from the Norwegian Institute for Alcohol and Drug Research.
- *Data Collection*: The questionnaires were sent to a representative sample of 21- to 26-year-olds living in Oslo in 2002. The drug price data were obtained by the institute during face-to-face interviews with people visiting the Oslo needle exchange in 1994–97.
- *Sampling*: The authors do no explain their sampling methods for the questionnaires but describe it as "representative." The drug price data comes from a nonrandom convenience sample.
- *Population*: Young adults, living in Oslo, who have used cannabis.
- *Sample Size*: 811 young adults.
- *Age*: Questionnaire, 21–26; ages for the institute sample were not included.
- *Other Drugs*: Amphetamines, cocaine, and heroin.

9.6.6. Covariates

- Demographics (gender),
- Personal history (self-reported problems with parents, friends, school, and the police during childhood), and
- Miscellaneous (time [as a cubic function] and time-dependent covariates [prices of amphetamines, cocaine, and heroin]).

9.6.7. Limitations

- The use of data from an observational study (thus confounding variables may be omitted).
- The use of data from a mailed questionnaire, which leaves homeless/institutionalized individuals underrepresented in the sample. Moreover, people with various antisocial behaviors may be underrepresented as well.
- The possibility of response bias (self-reported data on drug use).

9.7. Life-Course Perspective on the "Gateway Hypothesis"

Karen Van Gundy and Cesar J. Rebellon. "A Life-Course Perspective on the 'Gateway Hypothesis.'" *Journal of Health and Social Behavior* 51, no. 3 (2010): 244–59. doi: 10.1177/0022146510378238.

9.7.1. Scientific Methods Score

SMS: 3—Longitudinal study with covariates.

9.7.2. Summary and Purpose

Using prospective longitudinal data from 1,286 young adults living in South Florida, the authors aimed to assess the association between teen cannabis use and subsequent illicit drug use, and to determine if the association is short-term or long-term. The analysis was conducted by fitting seven logistic regression models, each of which had an interaction term of teen cannabis use and a life-course variable, such as age, education, stress, and employment, marital, and parental status.

9.7.3. Results

- When no interactions are considered in the logistic regression model, teen cannabis use is associated with significantly higher odds of subsequent drug use (OR: 2.24, 95% CI: 1.43–3.5).

- The odds ratio of an interaction effect between teen cannabis use and respondents who were over 21 years of age at the time of the survey was 0.22 (95% CI: 0.09–0.56). Thus, the odds of recent illicit drug use—"recent" being in the 12 months prior to the survey—among individuals who used cannabis as teenagers declined with age, with those over 21 having lower odds than respondents under 21 of recently using other illicit drugs.
- Similarly, the odds ratio of an interaction effect between teen cannabis use and respondents who were employed at the time of the survey was 0.24 (95% CI: 0.09–0.60). This means that the odds of recent illicit drug use among individuals who used cannabis as teenagers was likely to be lower among survey respondents who were employed than those who were not.
- The authors found a significantly positive association between teen cannabis use and subsequent drug abuse when controlling for gender, race/ethnicity, the socioeconomic status of one's parents, and teenage illicit drug use (OR: 2.33, 95% CI: 1.14–4.76).
- After accounting for stress and life-course variables (age, education, and employment/family statuses), the effect of teen cannabis use on further illicit drug abuse becomes insignificant (OR: 1.78, 95% CI: 0.84–3.76).

9.7.4. Conclusions

The study results suggest that the effect of teen cannabis use on later drug use/abuse is short-term, and depends on life-course moderators: It is significant for young and unemployed adults, and muted for those older than 21 and working. As such, the authors note that a link between the two may be spurious.

9.7.5. Method, Source, and Sampling

- *Method*: Logistic regression models with an interaction of teen cannabis use and life-course variables.
- *Data Type:* Longitudinal study.
- *Data Source*: Young adults who attended public school in Miami-Dade County, Florida during the 1990s.
- *Data Collection*: Four waves of self-reported illicit drug use.
- *Sampling*: Random sample stratified by race/ethnicity.
- *Population*: Teens and young adults living in South Florida.
- *Sample Size*: 1,286 individuals.
- *Age*: 18–23.
- *Other Drugs*: Analgesics, cocaine, heroin, hallucinogens, inhalants, sedatives, stimulants, and tranquilizers.

9.7.6. Covariates

- Demographics (age, race/ethnicity, gender, education, and employment, marital, and parental status),
- Drug use (teenage use of illicit drugs),
- Family history (socioeconomic status of parents/guardians), and
- Stressors (general stress level).

9.7.7. Limitations

- The use of data from an observational study (thus confounding variables may be omitted).
- An insufficient sample of subjects to test for some covariates: 4 percent were married and 10 percent had children. Also, the stress index was underestimated.
- The possibility of response bias (self-reported data on drug use).
- The results may be limited in their extrapolation to other populations (study focused on one urban area so it did not examine regional, social, or cultural effects).

9.8. Evaluating the Drug Use "Gateway" Theory Using Cross-National Data

Louisa Degenhardt et al. "Evaluating the Drug Use 'Gateway' Theory Using Cross-National Data: Consistency and Associations of the Order of Initiation of Drug Use Among Participants in the WHO World Mental Health Surveys." *Drug and Alcohol Dependence* 108, no. 1–2 (2010): 84–97. doi: 10.1016/j.drugalcdep.2009.12.001.

9.8.1. Scientific Methods Score

SMS: 1—Retrospective study that only includes the age factor.

9.8.2. Summary and Purpose

This study investigated whether the gateway hypothesis's drug use sequence is due to the use of certain drugs or to variations in drug availabilities and social attitudes. In order to examine if the sequences vary across time and place, Degenhardt and her colleagues used data from the World Health Organization's World Mental Health Survey. This included data from adults in the United States and 16 other countries, including advanced industrial and developing nations.

9.8.3. Results

- Overall, the rates of cannabis use and other illicit drug abuse conformed to the hypothesized gateway sequence. In countries with relatively high rates of cannabis use, the gateway sequence was the predominant pattern. In countries with relatively lower cannabis use rates, it was not. For example,

  - In the United States, which had a relatively high rate of cannabis use, the association between cannabis and the use of other illicit drugs was statistically significant (OR: 137.1, 95% CI: 94.8–198.3). Moreover, 11.4 percent of those who reported using other illicit drugs had not used cannabis.

  - The association between cannabis use and other illicit drug use in Colombia, a major source of cocaine, was also statistically significant (OR: 64.3, 95% CI: 30–138). However, 33.4 percent of those who had used other drugs had not used cannabis.

  - Likewise, in the Netherlands, the association between cannabis use and the use of other illicit drugs was statistically significant (OR: 62.5, 95% CI: 9.6–406.5). Yet there too a number of other illicit drug users (20.4 percent) had not used cannabis.

  - On the other end of the spectrum, Japan had a relatively low rate of cannabis use and 83.2 percent of those who reported using other illicit drugs had previously not used cannabis. However, the association between the two was statistically significant (OR: 455.4, 95% CI: 37.5–5,522.9), largely because of the substantial risk for individuals aged 30–44 at the time of interview (OR: 593.1, 95% CI: 19.7–17,884.6). Yet the association was insignificant for all other age groups.

  - In Nigeria, cannabis use had no significant association with later illicit drug use for any age group, although the association was significant for the overall sample of Nigerians (OR: 22.2, 95% CI: 2.2–226.6). Furthermore, 77.8 percent of those who had used other illegal drugs had not used cannabis.

- Discrete-time survival analyses of the pooled data from all 17 countries in the study found that drug dependence among cannabis users was associated with:

  - Age: One's risk of drug dependence decreased as the age at which they first used cannabis increased (OR: 0.2, 95% CI: 0.2–0.3);

  - Gender: Female cannabis users had a lower risk of drug dependence than male cannabis users (OR: 0.7, 95% CI: 0.5–0.8);

  - Personal use: The overall risk of dependence decreased as the amount of time since one's first use of cannabis or other illicit drugs increased (OR: 0.8, 95% CI: 0.8–0.8); and

  - Mental health issues: One's risk for drug dependence increased along with higher numbers of mental health disorders before age 15 (internalizing disorders [OR: 1.6, 95% CI: 1.4–1.7]; externalizing disorders [OR: 1.4, 95% CI: 1.2–1.7]).

- The researchers also discovered that the risk of drug dependence increased as the number of illicit drugs used increased (two drugs [OR: 6.1, 95% CI: 4.5–8.3]; three drugs [OR: 15.4, 95% CI: 11.1–21.5]; four drugs [OR: 35.7, 95% CI: 24.6–51.8]).

9.8.4. Conclusions

- Different countries exhibit different associations between the use of alcohol, tobacco, and cannabis and the subsequent consumption of other illicit drugs. In some countries (e.g., Japan and Nigeria), these variations reflect differences in the availability of alcohol, tobacco, and cannabis. If the gateway hypothesis was consistent across these diverse countries, it would provide support for a causal relationship—it was not.
- The order of drug use and the likelihood of progressing from one drug to another also varied among countries. For example, cannabis users in the United States were more likely to progress to the use of other illicit drugs than those in the Netherlands.
- The gateway hypothesis partially reflects unmeasured factors, such as the availability of and local attitudes towards particular drugs, not causal effects. As such, efforts to reduce cannabis use may not lead to reductions in the use of other illicit drugs.
- Given that the age of first use and the amount of exposure are more important predictors of drug dependence than type of substance used, prevention efforts should likely focus on youth dealing with certain challenges (such as mental disorders) or risky behaviors.

9.8.5. Method, Source, and Sampling

- *Method*: Stratified multistage cluster sampling in the United States and all other countries, with the exception of Japan, which used a two-stage probability sample; Taylor series linearization methods to adjust for sample weights and clusters;[33] regression for the association of age, drug use, and "violations" of the gateway hypothesis (e.g., using illegal drugs before cannabis); and discrete-time survival analysis for associations of "gateway drug" use and later drug use.
- *Data Type*: Retrospective study.
- *Data Source*: WHO World Mental Health Surveys.
- *Data Collection*: Face-to-face interviews.
- *Sampling*: Probability household samples, specifically stratified multistage cluster sampling in the United States and all other countries, except Japan, which used a two-stage probability sample.
- *Population*: Individuals aged 18 years and older.
- *Sample Size*: 85,088 individuals (nearly 11 percent [9,282] lived in the United States).
- *Age*: For the United States and most other countries, the age was 18 years and older. The exceptions were Israel (21+ years), Japan (20+ years), New Zealand (16+ years), Colombia, and Mexico (both 18–65 years).
- *Other Drugs*: Cocaine, heroin, glue, LSD, opium, peyote, "or any other drug."

9.8.6. Covariates

- Demographics (age, country of origin, gender),
- Drug use (alcohol use; tobacco use; ages at which alcohol, tobacco, cannabis, and cocaine were first used; number of illicit drugs used; years since first use), and
- Stressors (mental health issues before age 15).

9.8.7. Limitations

- The use of data from observational studies (thus confounding variables may be omitted).
- The surveys were not designed to answer the researchers' question about the influence of local attitudes and the availability of illicit substances on drug use patterns.
- The possibility of response bias (self-reported data on drug use).

9.9. Cannabis Use Stages as Predictors of Subsequent Initiation with Other Illicit Drugs among French Adolescents

Aurélie Mayet et al. "Cannabis Use Stages as Predictors of Subsequent Initiation with Other Illicit Drugs among French Adolescents: Use of a Multi-State Model." *Addictive Behaviors* 37, no. 2 (2012): 160–66. doi: 10.1016/j.addbeh.2011.09.012.

9.9.1. Scientific Methods Score

SMS: 2—Retrospective study with covariates.

9.9.2. Summary and Purpose

By focusing on teenagers living in metropolitan France, Mayet and her colleagues aimed to examine the influence of cannabis use patterns on the initiation of other illicit drug use. The study accounted for covariates such as age, gender, alcohol use, and tobacco use.

9.9.3. Results

- The estimated probability of transitioning from never using cannabis to the initiation of other illicit drugs is 0.1 percent.
- The estimated probability of transitioning from using cannabis only to the initiation of other illicit drugs is 1.7 percent.
- The estimated probability of transitioning from the daily use of cannabis to the initiation of other illicit drugs is 10.2 percent.

9.9.4. Conclusions

The extent of one's cannabis use was associated with their subsequent use of other illicit drugs. Nondaily cannabis users were more likely than individuals who had never used cannabis to subsequently use other illicit drugs, while daily cannabis users were even more at risk.

9.9.5. Method, Source, and Sampling

- *Method*: Piecewise constant-intensities Markov State Model.[34]
- *Data Type*: Retrospective study.
- *Data Source*: 2005 ESCAPAD survey (Survey on Health and Consumption on Call-up and Preparation for Defence Day).
- *Data Collection*: Self-administered anonymous questionnaire; there was a 98 percent response rate.
- *Sampling*: 17-year-olds during a one-day military information session.
- *Population*: French teenagers living in mainland France.
- *Sample Size*: 29,393 individuals.
- *Age*: 17; survey participants were asked to recall events occurring at ages 7–17.
- *Other Drugs*: Cocaine, heroin, crack, ecstasy, amphetamines, ketamine, and LSD.

9.9.6. Covariates

- Demographics (age of progression from one drug to another [specifically before/after age 13, gender), and
- Personal history (tobacco use [never use, first use, daily use], drunkenness [never or at least once]).

9.9.7. Limitations

- The use of data from an observational study (thus confounding variables may be omitted).
- The study only focused on the short-term effect of cannabis use.
- The possibility of response bias (self-reported data on drug use).
- The possibility of selection bias (participation was voluntary).

9.10. Gateway Hypothesis, Common Liability to Addictions or the Route of Administration Model?

Aurélie Mayet et al. "The Gateway Hypothesis, Common Liability to Addictions or the Route of Administration Model? A Modelling Process Linking the Three Theories." *European Addiction Research* 22, no. 2 (2016): 107–17. doi: 10.1159/000439564.

9.10.1. Scientific Methods Score

SMS: 2—Retrospective study with covariates.

9.10.2. Summary and Purpose

Mayet and her colleagues sought to test the gateway hypothesis and two other substance use theories—the common liability and route of administration models—with data on one's first use of tobacco, cannabis, and other illicit drugs. Using data from French national health surveys, they examined multiple drug use progressions while adjusting for several covariates, including gender and "socioeconomic level" (a categorical variable for employment status and income).

9.10.3. Results

- The most likely pattern of additional substance use was the gateway hypothesis sequence of first using tobacco (probability [P]: 3.47%, 95% CI: 3.39–3.56%), then using cannabis (P: 3.02%, 95% CI: 2.81–3.27%), and then using other illicit drugs (P: 0.36%, 95% CI: 0.28–0.47%).

- Women were less likely than men to begin using cannabis after using tobacco (hazard ratio [HR]: 0.89, 95% CI: 0.85–0.93), but were more likely than men to proceed from tobacco to other illicit drugs (HR: 2.00, 95% CI: 1.44–3.65).

- Individuals with a lower socioeconomic status were less likely than those with a higher status to transition from tobacco to cannabis (HR: 0.89, 95% CI: 0.85–0.93). Yet, like women, they were more likely than their higher socioeconomic status counterparts to transition from tobacco to other illicit drugs (HR: 2.29, 95% CI: 1.44–3.65).

- An item response theory analysis of a latent variable of early drug use explained 85.8 percent of the variance for variables exploring early drug use. Additionally, other illicit drugs had higher propensity indices (propensity coefficient: 5.95–10.83, $p<0.001$) than alcohol, tobacco, or cannabis (propensity coefficient: 2.49–5.11, $p<0.001$). This latent variable was built on seven dummy variables: first using tobacco under age 13; first using cannabis and inhalants under age 15; first experiencing drunkenness under age 15; and first using a depressant (e.g., heroin and buprenorphine); stimulant (e.g., cocaine and ecstasy), and hallucinogen (e.g., mushrooms and LSD) under age 18.

- A second item response test of a latent variable of current substance use explained 88.6 percent of the variance for variables measuring current drug use. As was the case with the first latent variable, other illicit drugs had higher propensity indices (propensity coefficient: 5.76–9.75, $p<0.001$) than alcohol, tobacco, or cannabis (propensity coefficient: 0.21–4.28, $p<0.001$). This second latent variable was also based on seven dummy variables: current daily tobacco use; current alcohol use classified as "hazardous" according to an alcohol use disorder identification test;[35] cannabis use within the past month; and the use of inhalants, depressants, stimulants, and hallucinogens within the past year.

9.10.4. Conclusions

- Individuals who used substances early (under the 25th percentile for age) were more likely to use a series of substances, starting with tobacco, cannabis, or other illicit drugs.
- The likelihoods of many sequences suggest that the progression from one substance to another is more affected by an individual's environment than the substance of first use.
- While the most likely pattern of drug use was the gateway hypothesis sequence of tobacco, then cannabis, then other illicit drugs, there was evidence of other sequences. The findings from latent variable tests of early drug use and substance use propensities support an alternative theory, the common liability model of drug use. The model posits that using both licit and illicit drugs may be attributable to factors such as genetics, individual vulnerabilities, or family histories of addiction.
- Finding evidence of patterns where cannabis is used first, then tobacco, and vice versa indicates a reciprocal interaction effect between these drugs that does not support the gateway hypothesis. However, it does support the route of administration theory, which posits that a shared method of consumption (such as inhalation) can explain why a drug that is consumed in one particular manner, like tobacco, can precede the use of another substance, like cannabis, that is consumed in the same fashion. This suggests that individual (personality traits) and environmental (substance availability, peer influence) characteristics impacts one's use of drugs, as well as the order in which they are used.

9.10.5. Method, Source, and Sampling

- *Method*: Item response theory analysis of two latent variables and Markov State Model.
- *Data Type*: Retrospective study.
- *Data Source*: Existing data from nationwide surveys conducted among French residents aged 15–85 in 2005 and 2010.
- *Data Collection*: Telephone interviews.
- *Sampling*: Randomized two-stage sample (household/individual).
- *Population*: French residents aged 18–34.
- *Sample Size*: 16,421 individuals.
- *Age*: 18–34.
- *Other Drugs*: Cocaine, heroin, buprenorphine, methadone, GHB, ketamine, crack, ecstasy, amphetamines, MDMA, mushrooms, and LSD.

9.10.6. Covariates

- Demographics (gender, socioeconomic status [unemployment, low income, medium income, or high income),
- Drug use (age of first use for tobacco, cannabis, inhalants, depressants, stimulants, and hallucinogens; current/recent use of tobacco, cannabis, inhalants, depressants, stimulants, and hallucinogens; age of first episode of drunkenness; current use of alcohol classifiable as "hazardous"),
- Drug use sequences (e.g., no drug use prior to using other illicit drugs, no drug use prior to using tobacco and then using other illicit drugs), and
- Time period.

9.10.7. Limitations

- The use of data from an observational study (thus confounding variables may be omitted).
- The possibility of response bias (self-reported data on drug use).

9.11. Associations between Medical Cannabis and Other Drug Use among Unstably Housed Women

Meredith C. Meacham et al. "Associations Between Medical Cannabis and Other Drug Use among Unstably Housed Women." *International Journal of Drug Policy* 52 (2018): 45–51. doi: 10.1016/j.drugpo.2017.11.009.

9.11.1. Scientific Methods Score

SMS: 1—Retrospective study with covariates examining a high-risk population.

9.11.2. Summary and Purpose

Researchers studied the association between using cannabis (for medical or nonmedical purposes) and using stimulants and opioids by examining retrospective survey data from 245 HIV-positive women in California who used free meal programs or were "unstably housed" in homeless shelters or single-room occupancy hotels. The stimulants included crack cocaine, powdered cocaine, amphetamine, and methamphetamine ("crystal, speed, crank, glass or ice"), while the opioids included heroin and un-prescribed opioid painkillers.

9.11.3. Results

- Compared to those who had not used cannabis in the past six months, nonmedical cannabis users had significantly higher odds of using stimulants (OR: 4.34, 95% CI: 2.17–8.7) and opioids (OR: 3.81, 95% CI: 1.78–8.15).

- Conversely, medical cannabis use was not significantly associated with higher odds of using stimulants or opioids (OR: 1.82, 95% CI: 0.87–3.79).

9.11.4. Conclusions

The manner in which cannabis is obtained affects the associations between its use and the use other illicit drugs. When cannabis is obtained through a medical context, it is not associated with the use of other illicit drugs. When it is obtained through a nonmedical environment, however, cannabis is associated with use of other illicit drugs.

9.11.5. Method, Source, and Sampling

- *Method*: Chi-square tests, analysis of variance, and logistic regression for adjusted analysis.
- *Data Type*: Retrospective study.
- *Data Source*: Existing data that was collected in 2008 and 2010.[36]
- *Data Collection*: Interviewer-administered surveys; self-reported use in the past six months.
- *Sampling*: Women who were older than age 18 and participating in free meal programs, living in shelters or single-room occupancy hotels, and had a history of unstable housing.
- *Population*: Women living in San Francisco, California.
- *Sample Size*: 245 individuals.
- *Age*: Average was 47.5 years old.
- *Other Drugs*: Stimulants, such as crack cocaine, powdered cocaine, amphetamine, or methamphetamine, as well as opioids like heroin and un-prescribed opioid painkillers.

9.11.6. Covariates

- Demographics (age, race/ethnicity [white, nonwhite], health status, education level [at least high school], monthly income level),
- Drug use (cannabis use in the past 6 months [none, medical, nonmedical]),
- Personal history (experience with violence), and
- Stressors (recent homelessness, unmet subsistence needs).

9.11.7. Limitations

- The use of data from an observational study (thus confounding variables may be omitted).

- The small number of participants reporting medical cannabis use and opioid use may have reduced the statistical power of the association.
- The limiting classification of "medical" and "nonmedical" cannabis use.
- The possibility of response bias (self-reported data on drug use).
- The results may be limited in their extrapolation to other populations.

9.12. Marijuana Correlates with Use of Other Illicit Drugs in a Pain Patient Population

Amadeo Pesce et al. "Marijuana Correlates with Use of Other Illicit Drugs in a Pain Patient Population." *Pain Physician* 13, no. 3 (2010): 283–87. http://www.painphysicianjournal.com/current/pdf?article=MTM1Mg%3D%3D&journal=55.

9.12.1. Scientific Methods Score

SMS: 1—Cross-sectional study, with no covariates, examining a high-risk population.

9.12.2. Summary and Purpose

Pesce and his colleagues analyzed urine specimens from 21,746 chronic pain patients in San Diego, California, to determine if those who used cannabis had higher rates of cocaine or methamphetamine use than those who did not use cannabis. The study was intended to inform physicians treating chronic pain patients about those patients' risks of using other illicit drugs.

9.12.3. Results

The presence of cocaine or methamphetamine was positively associated with the presence of the acidic form of THC in the urine specimens (OR: 4.26, 95% CI: 3.70–4.91).

9.12.4. Conclusions

There is a significant correlation between cannabis use and the use of other illicit drugs for chronic pain patients.

9.12.5. Method, Source, and Sampling

- *Method*: Chi-square test (contingency table) and logistic regression.
- *Data Type*: Cross-sectional study.
- *Data Source*: Urine samples from chronic pain patients currently using opioids.
- *Data Collection*: Measurements from the urine specimens.
- *Sampling*: No exclusion criteria were used. The patients were selected as part of the usual practices of treating physicians.

- *Population*: Chronic pain patients in San Diego, California.
- *Sample Size*: 21,746 urine specimens.
- *Age*: Not stated.
- *Other Drugs*: Cocaine and methamphetamine.

9.12.6. Covariates

There was just one covariate, the presence of THC in the urine specimen.

9.12.7. Limitations

- The use of data from an observational study (thus confounding variables may be omitted).
- No information was provided to distinguish between medical and nonmedical cannabis use.
- The results may be limited in their extrapolation to other populations.

9.13. Progression to Regular Heroin Use

Eric A. Woodcock et al. "Progression to Regular Heroin Use: Examination of Patterns, Predictors, and Consequences." *Addictive Behaviors* 45 (2015): 287–93. doi: 10.1016/j.addbeh.2015.02.014.

9.13.1. Scientific Methods Score

SMS: 1—Retrospective study, with covariates, examining a high-risk population.

9.13.2. Summary and Purpose

Woodcock and his colleagues collected data from 562 current, regular heroin users to evaluate the predictors and patterns that led to that use. They examined the age of initial and regular use (at least three times per week) of cannabis as a predictor for one's age of initial and regular heroin use. They also studied the characteristics of individuals who followed or deviated from the gateway pattern sequence.

9.13.3. Results

- More individuals began using cannabis and alcohol or tobacco in the same calendar year (41.3 percent) than those who began using any single drug (alcohol, tobacco, cannabis, cocaine, or heroin) and then progressed to using one or more drugs.
- Most study participants (79.7 percent) reported having a substance use pattern that was consistent with the gateway hypothesis. Given the first result concerning poly-substance use, this second result appears to misstate the gateway sequence of drug use.

- Participants who deviated from the gateway hypothesis pattern (20.3 percent) were more likely to be African American, older, younger at the age of initial heroin use, heroin users for a longer period of time, and more frequent heroin users in the past month.
- Substance use progressions were heterogeneous, as a greater proportion of participants began using alcohol, tobacco, and cannabis around the same time (specifically, within the same calendar year).

9.13.4. Conclusions

- The authors' principal conclusion was that the gateway hypothesis and other substance use chronologies provide clinically relevant findings and valid predictions of drug use sequences.
- Sociocultural differences or variations in opportunities for substance use may influence the order of one's drug use.

9.13.5. Method, Source, and Sampling

- *Method*: Linear regression with stepwise variable selection.
- *Data Type*: Retrospective study.
- *Data Source*: Original data.
- *Data Collection*: Self-reported data on drug use with in-person urinalysis screening for opioid use, breathalyzer for alcohol use, and IQ test for cognitive functioning.
- *Sampling*: Volunteers recruited through media advertisements and word-of-mouth referrals.
- *Population*: Current, regular heroin users.
- *Sample Size*: 562 individuals.
- *Age*: 18–55.
- *Other Drugs*: Cocaine, heroin, buprenorphine, methadone, GHB, ketamine, crack, ecstasy, amphetamines, mushrooms, and LSD.

9.13.6. Covariates

- Demographics (age, race/ethnicity, gender, education level), and
- Drug use (age of initial use and regular use of alcohol, tobacco, cannabis, and cocaine; age of initial use and regular use of heroin; frequency of heroin use).

9.13.7. Limitations

- The use of data from an observational study (thus confounding variables may be omitted).
- The possibility of response bias (self-reported data on drug use).
- The results may be limited in their extrapolation to other populations.
- The possibility of temporal issues as "initial use" was limited to a calendar year.
- The linear regression used in the study is not an appropriate method for evaluating hypotheses of multi-stage sequences such as the gateway hypothesis.
- The authors' conclusion that the gateway hypothesis's drug use sequence was the most likely pattern was undermined by their finding that the near-contemporaneous use of alcohol, tobacco, and cannabis more commonly preceded the use of other illicit drugs. This poly-substance use at the initial stage of drug use supports the common liability model rather than the gateway hypothesis.

9.14. Probability and Predictors of the Cannabis Gateway Effect

Roberto Secades-Villa et al. "Probability and Predictors of the Cannabis Gateway Effect: A National Study." *International Journal of Drug Policy* 26, no. 6 (2015): 135–42. doi: 10.1016/j.drugpo.2014.07.011.

9.14.1. Scientific Methods Score

SMS: 1—Retrospective study, with covariates, examining lifetime cannabis users.

9.14.2. Summary and Purpose

This study aimed to identify the predictors of one's progression from cannabis use to illicit drug use among individuals with a lifetime history of cannabis use. Analyses were conducted on a subsample of data from the National Epidemiological Survey on Alcohol and Related Conditions (NESARC), which consisted of survey participants who reported that they started using cannabis before any other drugs during the first round of data collection in 2001–2.

9.14.3. Results

- Based on a survival analysis, 44.7 percent of the individuals with lifetime cannabis use progressed to other illicit drug use at some time in their lives.
- The characteristics that increased one's chance of progressing to other illicit drugs included being a man between the ages of 30 and 44; being born in the United States; living in an urban environment; having less than a high school education; having mental disorders; being divorced, separated, or never married; having started cannabis use at an early age; and having a family history of substance use disorders.

9.14.4. Conclusions

The results indicated that several demographic characteristics, psychiatric disorders, and severe substance use can predict the progression from cannabis use to illicit drug use.

9.14.5. Method, Source, and Sampling

- *Method*: Survival analyses with time-varying covariates.
- *Data Type*: Retrospective study.
- *Data Source*: National Epidemiologic Survey on Alcohol and Related Conditions.
- *Data Collection*: Administered interviews.
- *Sampling*: Multi-stage probability sampling—Stage 1: Stratified proportional-to-size sampling of counties; Stage 2: Stratified sampling of census blocks; Stage 3: Systematic random sampling of households; Stage 4: Systematic random sampling of individuals.[37]
- *Population*: U.S. citizens who are lifetime cannabis users.
- *Sample Size*: The authors report two different sample sizes with no explanation as to why they did so. They first state that they used a subsample of 6,624 survey participants who reported having used cannabis but never any other drug during the first round of data collection (NESARC's total sample consisted of 43,093 respondents). However, the sample size listed for the statistical analyses was 2,572.
- *Age*: 18 and older.
- *Other Drugs*: Cocaine or crack, heroin, inhalants/solvents, stimulants, hallucinogens, analgesics, sedatives, tranquilizers, and "other."

9.14.6. Covariates

- Demographics (age, race/ethnicity, country of origin, gender, educational level, employment status, marital status, location),
- Personal history (psychiatric disorders), and
- Family history (substance use disorder among first-degree relative).

9.14.7. Limitations

- The use of data from an observational study (thus confounding variables may be omitted).
- The possibility of response bias (self-reported data on drug use).
- The results may be limited in their extrapolation to other populations.

9.15. Social Exigencies of the Gateway Progression to the Use of Illicit Drugs from Adolescence into Adulthood

Roy Otten, Chung Jung Munc, and Thomas J. Dishion. "The Social Exigencies of the Gateway Progression to the Use of Illicit Drugs from Adolescence into Adulthood." *Addictive Behaviors* 73 (2017): 144–50. doi: 10.1016/j.addbeh.2017.05.011.

9.15.1. Scientific Methods Score

SMS: 3—Longitudinal study with covariates.

9.15.2. Summary and Purpose

This study used participants from a family counseling program to investigate the association between one's earlier use of substances like alcohol, tobacco, and cannabis; friends' reported use of illicit drugs; and the onset and abuse of illicit drugs.

9.15.3. Results

- One's use of alcohol at age 17 was associated with higher levels of cannabis use at age 22. This, in turn, was associated with an increased likelihood of dependence on other illicit drugs between ages 22 and 27.
- Participants' use of cannabis at age 17 was positively associated with perceptions that their friends used illicit drugs when they were 22 (b=0.18, 95% CI: 0.03–0.33, p<0.001). This perception then was positively associated with the participants' initial use of other illicit drugs between the ages of 22 and 27 (b=0.41, 95% CI: 0.17–0.65, p<0.01).
- Participants' perceptions that their friends used illicit drugs when the participants were 22 was also positively associated with their abuse of and dependence on various drugs between then and age 27 (b=0.36, 95% CI: 0.07–0.65, p<0.05).
- Participants who, at age 11, were assigned to participate along with their parents in a family counseling program had a modestly lower rate of cannabis use by age 22 than those whose engagement in the program was voluntary (R^2=-0.08, p<0.05).

9.15.4. Conclusions

- There is a social context to the gateway hypothesis's drug use progression. The availability and choice of friends who use other illicit drugs contributes to an individual's progression from using cannabis to using and depending on other illicit drugs.
- Although the authors do not emphasize their findings concerning tobacco, tobacco use at ages 17 and 22 was positively associated with use of and dependence on other illicit drugs. This sequence was independent of cannabis use.

9.15.5. Method, Source, and Sampling

- *Method*: Structural equation modeling.
- *Data Type*: Longitudinal study.
- *Data Source*: Family Check-Up, a family counseling program that is administered by the University of Oregon and designed to address problem behavior by children.
- *Data Collection*: A questionnaire administered through schools to study participants at age 17, and a second questionnaire administered by mail to those individuals at ages 22 and 27.
- *Sampling*: Randomized sample of individuals participating in the Family Check-Up program.
- *Population*: Young adults living in the Pacific Northwest.
- *Sample Size*: 711 individuals.
- *Age*: At enrollment: 11; Surveyed at: 17, 22, and 27.
- *Other Drugs*: Cocaine/crack, heroin/opioids, and speed/amphetamines.

9.15.6. Covariates

- Demographics (gender, income level),
- Drug use (alcohol use and tobacco use, cannabis use in the past three months at the time of the survey [8-point scale], attempts at intervention), and
- Friend history (use of illicit drugs).

9.15.7. Limitations

- The use of data from an observational study (thus confounding variables may be omitted).
- The possibility of response bias (self-reported data on drug use, as well as perception of friends' drug use).
- The results may be limited in their extrapolation to other populations.
- The study left out subjects who reported using other illicit drugs at age 22.

9.16. Cannabis Use and Risk of Psychiatric Disorders

Carlos Blanco et al. "Cannabis Use and Risk of Psychiatric Disorders: Prospective Evidence from a U.S. National Longitudinal Study." *JAMA Psychiatry* 73, no. 4 (2016): 388–95. doi: 10.1001/jamapsychiatry.2015.3229.

9.16.1. Scientific Methods Score

SMS: 3—Longitudinal study with covariates.

9.16.2. Summary and Purpose

Blanco and his colleagues examined the associations between cannabis use, mental health, and substance use disorders in the general adult population by analyzing two waves from a longitudinal study in the NESARC.

9.16.3. Results

- Cannabis use in wave 1 (conducted in 2001–2, n=1,279) was significantly associated with substance use disorders in wave 2 (conducted in 2004–5).
- The authors found that within the general adult population, cannabis use was associated with an increased risk for a separate drug use disorder (OR: 2.6, 95% CI: 1.6–4.4).

9.16.4. Conclusions

As noted, the results of the study indicated that within the general population, cannabis use is associated with an increased risk for several substance (alcohol, tobacco, and other illicit drugs) use disorders.

9.16.5. Method, Source, and Sampling

- *Method*: Logistic regression and propensity score matching (matching each case [i.e., cannabis users] with controls).
- *Data Type*: Longitudinal study.
- *Data Source*: NESARC wave 1 and wave 2.
- *Data Collection*: Administered interviews.
- *Sampling*: Multi-stage probability sampling—Stage 1: Stratified proportional-to-size sampling of counties; Stage 2: Stratified sampling of census blocks; Stage 3: Systematic random sampling of households; Stage 4: Systematic random sampling of individuals.
- *Population*: U.S. adults.
- *Sample Size*: 34,635 individuals.
- *Age*: 18 years and older; the average age was 45.1.
- *Other Drugs*: Simply listed as "other than cannabis."

9.16.6. Covariates

- Demographics (age, race/ethnicity, gender, education level, marital status),
- Drug use (using cannabis in the past 12 months),

- Family history (substance use disorders, disturbed environment, childhood parental loss), and
- Stressors (low self-esteem, social deviance, recent trauma, and past/present psychiatric disorders).

9.16.7. Limitations

- The use of data from an observational study (thus confounding variables may be omitted).
- The possibility of response bias (self-reported data on drug use).
- Researchers did not study the association between cannabis use and the onset of other illicit drug use.
- The follow-up period was limited to three years.

10. APPENDIX IV: Literature Review of Animal-Based Studies

As previously noted, this appendix includes detailed profiles for the 7 animal-based studies FRD reviewed during the period of performance.

10.1. Adolescent Cannabis Exposure Alters Opiate Intake and Opioid Limbic Neuronal Population in Adult Rats

Maria Ellgren, Sabrina M. Spano, and Yasmin L. Hurd. "Adolescent Cannabis Exposure Alters Opiate Intake and Opioid Limbic Neuronal Populations in Adult Rats." *Neuropsychopharmacology* 32 (2007): 607–15. doi: 10.1038/sj.npp.1301127.

10.1.1. Scientific Methods Score

SMS: 4—Longitudinal case-control with random sampling using a small sample size.

10.1.2. Summary and Purpose

Ellgren and her colleagues conducted a study using rats to assess the effect of adolescent exposure to THC on opiate consumption and opioid neural systems in adulthood. In this experiment, male Long-Evans rats received THC injections or a saline solution every third day during their adolescence (post-natal days [PND] 28–49); their self-administration of heroin was then examined from young adulthood into full adulthood (PND 57–102).

10.1.3. Results

- The THC-exposed rats had a tendency towards a higher intake of heroin with a 15 mg/kg/infusion (p-value=0.057), and significantly higher intakes at 30 mg/kg/infusion (p-value<0.01) and 60 mg/kg/infusion (p-value<0.05).
- Further analysis showed that this increase in self-administration may be associated with alterations in the endogenous opioid within the nucleus accumbens, which is known to mediate reward-related behavior. The study found such evidence by examining the pharmacological properties of cannabis and their neurological effects on rats.

10.1.4. Conclusions

- Rats injected with THC during adolescence voluntarily used more heroin doses and greater amounts of heroin in adulthood.
- THC exposure may affect parts of the rats' brains that mediate reward-related behavior.

10.1.5. Method, Source, and Sampling

- *Method*: One- and two-way ANOVA with repeated measures, planned comparisons, and Bonferroni corrections for multiple comparisons.
- *Data Type*: Longitudinal study.
- *Data Source*: Primary data.
- *Data Collection*: Random assignment of 11 rats to experimental and control groups. Experimental group received THC injections while the control group received a saline solution. The heroin acquisition behaviors of the rats were recorded and brain sections were studied.
- *Sampling*: Random sampling.
- *Population*: Male Long-Evans rats that were 21 days old when the experiment commenced; this age is early adolescence for this rat species.
- *Sample Size*: 11 rats, 6 in experimental group and 5 in the control group.
- *Other Drugs:* Heroin.

10.1.6. Covariates

THC exposure and food deprivation.

10.1.7. Limitations

- Small sample size and thus a low statistical power.
- Imbalanced design with no explicit modifications to account for the different group sizes.
- Results may be limited in their extrapolation to humans; the rats were involuntarily injected with THC and heroin whereas humans often voluntarily smoke cannabis and inject heroin.
- Possible measurement bias as the different heroin treatments resulted in contrasting findings. For example, during the provision of the 15-milligram heroin doses, none of the rats met the minimum threshold to be considered as "self-administrating". However, when the researchers increased the dosage to 30 milligrams of heroin, the rats did cross this threshold. Yet these doses were offered during a period of food restriction, which effectively introduced an uncontrolled confounding variable into the study, raising the question as to whether the rats were responding to the heroin alone or a combination of the heroin and a period of stress.

10.2. Dynamic Changes of the Endogenous Cannabinoid and Opioid Mesocortico-limbic Systems during Adolescence

Maria Ellgren et al. "Dynamic Changes of the Endogenous Cannabinoid and Opioid Mesocortico limbic Systems during Adolescence: THC Effects." *European Neuropsychopharmacology* 18, no. 11 (2008): 826–34. doi: 10.1016/j.euroneuro.2008.06.009.

10.2.1. Scientific Methods Score

SMS: 4—Case-control with random sampling.

10.2.2. Summary and Purpose

Designed as a follow-up study to the one listed in section 10.1, this research investigated the effect of THC exposure on potential neurochemical alterations during adolescent brain development. The aim was to better understand the alterations that could account for the opioid reward-related disturbances observed in the earlier study.

10.2.3. Results

THC exposure resulted in clear developmental fluctuations throughout the rats' endocannabinoid levels in the nucleus accumbens and prefrontal cortex, regions involved in cognition, reward, and motivation.

10.2.4. Conclusions

The THC-induced changes in the endogenous cannabinoids in specific areas of the rats' brains provide supporting evidence of increased opioid reward-related behavior after adolescent THC exposure.

10.2.5. Method, Source, and Sampling

- *Method*: Two-way ANOVA followed by Tukey post-hoc analysis and Pearson correlation for endocannabinoid levels.
- *Data Type*: Longitudinal study.
- *Data Source*: Primary data.
- *Data Collection*: Male Long-Evans rats were randomly assigned to an experimental group injected with 1.5 mg/kg of cannabis every three days or a control group injected with a saline solution. Three stages were recorded: after the first THC injection (PND 29), after the fourth THC injection (PND 38), and after the eighth injection (PND 50).
- *Sampling*: Random sampling.
- *Population*: Adolescent male Long-Evans rats (PND 28–49).

- *Sample Size*: Unstated, but may be 20 (15 rats for the experimental group and 5 for the control group).
- *Other Drugs*: None.

10.2.6. Covariates

THC exposure and age.

10.2.7. Limitations

- Small sample size and thus a low statistical power.
- The study did not test to see if the changes in the rats' brains were related to the subsequent "use" of other illicit drugs.
- Results may be limited in their extrapolation to humans.

10.3. Strain Dependence of Adolescent Cannabis Influence on Heroin Reward and Mesolimbic Dopamine Transmission in Adult Lewis and Fischer 344 Rats

Cristina Cadoni et al. "Strain Dependence of Adolescent Cannabis Influence on Heroin Reward and Mesolimbic Dopamine Transmission in Adult Lewis and Fischer 344 Rats." *Addiction Biology* 20, no. 1 (2015): 132–42. doi: 10.1111/adb.12085.

10.3.1. Scientific Methods Score

SMS: 5—Longitudinal case-control with random sampling.

10.3.2. Summary and Purpose

This study sought to examine the effect of genetics on the relationship between adolescent THC exposure and heroin. The research used two rat species: Lewis rats and Fisher 344 rats; the latter is regarded as addiction-resistant while the former is seen as addiction-prone. Aged PND 38–42, rats from both species were divided into two groups: a treated group receiving increasing doses of THC (2, 4, and 8 mg/kg) over a three-day period with two injections per day, and a control group that received 3 milliliters of a saline solution on the same schedule. When the rats were around 9–11 weeks old, their responses to THC and heroin were monitored and studied by conditioned place preference as well as cognitive and emotional functions.

10.3.3. Results

- The effect of THC exposure on heroin varied with the rats' genetic backgrounds. THC pre-treatment increased the Fisher 344 rats' preference for a portion of a cage in which the heroin was available (p-value<0.0001); there was no statistically significant difference in place preference for the Lewis rats (p-value >0.05). Administering heroin after an initial

cessation increased the Lewis rats' preference for the heroin-paired compartment, but only in the THC-treated group. For the Fisher 344 rats, this reinstatement of heroin only affected the control group; it did not further modify the preferences of the THC-treated group.

- Adolescent THC exposure potentiated dopamine levels in response to heroin in Lewis rats' shell and core, but only in the core of the Fisher 344 rats, suggesting that the exposure increased the Lewis rats' sensitivity to heroin reward.

10.3.4. Conclusions

The effects of THC exposure on heroin preferences varies with genetic background.

10.3.5. Method, Source, and Sampling

- *Method*: ANOVA for repeated measures.
- *Data Type*: Longitudinal, randomized study.
- *Data Source*: Primary data.
- *Data Collection*: The rats' responses to THC and heroin, as well as their cognitive and emotional functions, were monitored and recorded. The treated group received twice-daily injections of THC in increasing amounts every three days, while the control group received 3 milliliters of a saline solution on the same schedule.
- *Sampling*: Random sampling.
- *Population*: Lewis rats and Fischer 344 rats in mid-adolescence (PND 38–42).
- *Sample Size*: 54 rats.
- *Other Drugs*: Heroin.

10.3.6. Covariates

THC exposure (pre-treatment) and genetics (rat species).

10.3.7. Limitations

Results may be limited in their extrapolation to humans

10.4. Exposure to Delta-9-Tetrahydrocannabinol (THC) Increases Subsequent Heroin Taking but Not Heroin's Reinforcing Efficacy

Marcello Solinas, Leigh V. Panlilio, and Steven R. Goldberg. "Exposure to Delta-9-Tetrahydro cannabinol (THC) Increases Subsequent Heroin Taking But Not Heroin's Reinforcing Efficacy: A Self-Administration Study in Rats." *Neuropsychopharmacology* 29 (2004): 1301–11. doi: 10.1038/sj.npp.1300431.

10.4.1. Scientific Methods Score

SMS: 4—Longitudinal study with random sampling but a small sample size.

10.4.2. Summary and Purpose

This study evaluated the effect of THC exposure on the subsequent self-administration of heroin in rats. The rats were divided into two groups: the treated group received THC injections while the control group received a saline solution six times over three days. One week after the last THC injection, the rats were tested for the self-administration of heroin under a "fixed rate 1 (FR1) schedule" in which a response (one poke through a nose hole) was required for each injection, as well as a "progressive-ratio schedule" in which the response requirement increased exponentially with each successive injection.

10.4.3. Results

- Under the FR1 schedule, THC exposure did not significantly affect the rats' self-administration of heroin, but it did tend to increase the amount of heroin injections per session.
- Under the progressive-ratio schedule, there was no significant difference between the behaviors of the treated group and the control group.

10.4.4. Conclusions

- Rats exposed to THC self-administered more heroin injections than rats not exposed to THC when heroin was freely available.
- Rats exposed to THC did not make more efforts than their nonexposed peers once the cost of obtaining heroin increased.

10.4.5. Method, Source, and Sampling

- *Method*: Two-way ANOVA with repeated measures and post-hoc Bonferroni corrections for multiple comparisons; regression with log-transformed response/predictor variables.
- *Data Type*: Longitudinal study.
- *Data Source*: Primary data.
- *Sampling*: Case-control study with random sampling.
- *Data Collection*: Random assignment of 13 rats to experimental and control groups. The rats' self-administration of heroin was monitored under two schedules.
- *Population*: Sprague-Dawley rats that were experimentally naive at the start of the study.

- *Sample Size*: 16 rats; 26 rats. Both experiments had "data not missing at random" since the researchers removed some rats that did not meet the threshold for self-administering heroin.
- *Other Drugs*: Heroin.

10.4.6. Covariates

THC exposure.

10.4.7. Limitations

- Small sample size and thus a low statistical power.
- Ten rats were dropped from the study: five for developing blocked catheters during the self-administration of heroin, and five for not "acquiring" self-administration at all. The study did not discuss whether the dropout was completely at random, and if not, how to account for this issue in the statistical analysis.
- Results may be limited in their extrapolation to humans.

10.5. Previous Exposure to THC Alters Reinforcing Efficacy and Anxiety-Related Effects of Cocaine in Rats

Leigh V. Panlilio et al. "Previous Exposure to THC Alters the Reinforcing Efficacy and Anxiety-Related Effects of Cocaine in Rats." *Neuropsychopharmacology* 32 (2007): 646–57. doi: 10.1038/sj.npp.1301109.

10.5.1. Scientific Methods Score

SMS: 5—Longitudinal study with random sampling.

10.5.2. Summary and Purpose

Similar to the study listed in section 10.4, Panlilio and her colleagues wanted to see if prior THC exposure affected the subsequent self-administration of cocaine. To do this, they organized three experiments, all of which involved randomly assigning rats to experimental and control groups. The experimental groups were given increasing intraperitoneal injections of THC on a three-day schedule. The control groups received an unstated solution. All were Sprague-Dawley rats that were 3–4 months old and weighed 300–325 grams at the beginning of the study.

10.5.3. Results

- The association between THC exposure and other illicit drug use was found to be insignificant ($p>0.05$).

- Experiment 1: Thirty rats (15 pre-exposed to THC and 15 that were not) were given initial injections of cocaine and were later allowed to electively receive further injections, first with FR1 schedule in which one poke through a nose hole provided a fixed amount of cocaine, and then with a progressive-ratio schedule in which more pokes were required to receive varying amounts of cocaine. The researchers found that under the fixed rate schedule, THC exposure did not affect the rats' acquisition of cocaine or the amount of cocaine taken. However, under the progressive-ratio schedule, the THC-exposed rats emitted significantly fewer cocaine-seeking responses and took fewer injections than the rats in the control group.
- Experiment 2: The rats were evaluated to see if prior THC exposure would alter the locomotor effects of cocaine and heroin. The THC-exposed rats showed higher levels of locomotor activity than the control group rats when they were subsequently treated with heroin, but not when they were treated with cocaine.
- Experiment 3: The researchers used a light-dark test to confirm the anxiety-related effects observed in Experiment 2. They found that the THC-exposed rats did not exhibit higher levels of locomotor activity than the control rats when they were subsequently treated with cocaine.

10.5.4. Conclusions

- Prior exposure to THC was not found to affect the rats' self-administration of cocaine when the cost to obtain the drug remained constant.
- Prior exposure to THC was found to decrease the rats' self-administration of cocaine when the cost to obtain it increased.
- These findings indicate that THC exposure can produce long-lasting alterations in the behavioral effects of illicit drugs, but that these effects can differ for heroin and cocaine.

10.5.5. Method, Source, and Sampling

- *Method*: Two-way ANOVA with a post-hoc Tukey-Kramer analysis for pairwise comparisons.
- *Data Type*: Longitudinal study.
- *Data Source*: Primary data.
- *Data Collection*: The researchers conducted three experiments, all of which involved randomly assigning the rats to experimental and control groups. The experimental groups were given increasing intraperitoneal injections of THC on a three-day schedule (day 1: 2 mg/kg/injection, day 2: 4 mg/kg/injection, and day 3: 8 mg/kg/injection). The control groups received an unstated solution.
- *Sampling*: Random sampling.

- *Population*: Sprague-Dawley rats that were 3–4 months old and weighed 300–325 grams at the beginning of the study.
- *Sample Size*: 85 rats.
- *Other Drugs*: Cocaine and heroin.

10.5.6. Covariates

THC exposure.

10.5.7. Limitations

Results may be limited in their extrapolation to humans.

10.6. Cannabinoid Modulation of Eukaryotic Initiation Factors (eIF2α and eIF2B1) and Behavioral Cross-Sensitization to Cocaine in Adolescent Rats

Philippe A. Melas et al. "Cannabinoid Modulation of Eukaryotic Initiation Factors (eIF2α and eIF2B1) and Behavioral Cross-Sensitization to Cocaine in Adolescent Rats." *Cell Reports* 22, no. 1 (2018): 2909–23. doi: 10.1016/j.celrep.2018.02.065.

10.6.1. Scientific Methods Score

SMS: 3—Cross-sectional and longitudinal studies with random sampling.

10.6.2. Summary and Purpose

This study aimed to determine if cannabis use was associated with an increased sensitization to cocaine addiction. Using in vitro and in vivo experiments, it examined the relationship between a specific cannabinoid, WIN, and addiction sensitization on two eukaryotic initiation factors, eIF2α and eIF2B1, which are known to be involved in protein synthesis, memory formation, and drug sensitivity.

10.6.3. Results

- Among adolescent rats, WIN tended to affect the levels of both eIF2α and eIF2B1.
- WIN reduced the levels of eIF2α in the nuclear accumbens of adolescent rats, but not in adult rats. Conversely, WIN increased the levels of eIF2B1 in both adolescent and adult rats.
- Additionally, the rats exposed to WIN were more likely to show increased locomotor sensitization in response to cocaine; that is, when the cocaine was injected, the rats exposed to WIN had traveled significantly longer distances than unexposed rats. However, this cross-sensitization was not observed among the adult rats.

10.6.4. Conclusions

Cannabis may act as a gateway to other illicit drugs by reducing the levels of eIF2α—and other eukaryotic initiation factors—in the nucleus accumbens of adolescent brains.

10.6.5. Method, Source, and Sampling

- *Method*: Two-way ANOVA and a two-sample t-test.
- *Data Type*: Cross-sectional, longitudinal study.
- *Data Source*: Primary data.
- *Data Collection*: The rats were randomly assigned to receive WIN or a saline solution subchronically for 11 days. After the last WIN administration, the rats' locomotor behaviors were monitored and their brains were examined for various measurements, including the levels of eukaryotic initiation factors.
- *Sampling*: Random sampling.
- *Population*: Male adolescent rats and male adult rats (PND 42 and 77, respectively).
- *Sample Size*: 8 rats were used in one experiment, 20 were used in another (n=4–5/group for adolescent rats and n=5/group for adult rats).
- *Other Drugs*: Cocaine.

10.6.6. Covariates

WIN exposure.

10.6.7. Limitations

- Small sample size and thus a low statistical power.
- Imbalanced design with no explicit modifications to account for the different group sizes.
- The study did not directly assess the effect of cannabinoids like WIN on the subsequent use of other illicit drugs.
- Results may be limited in their extrapolation to humans.

10.7. Adolescent Cannabidiol, a NonPsychotropic Component of Cannabis, Inhibits Cue-Induced Heroin-Seeking and Normalizes Discrete Mesolimbic Neuronal Disturbances

Yanhua Ren et al. "Cannabidiol, a NonPsychotropic Component of Cannabis, Inhibits Cue-Induced Heroin-Seeking and Normalizes Discrete Mesolimbic Neuronal Disturbances." *Journal of Neuroscience* 29, no. 47 (2009): 14764–69. doi: 10.1523/JNEUROSCI.4291-09.2009.

10.7.1. Scientific Methods Score

SMS: 5—Longitudinal case-control with random sampling.

10.7.2. Summary and Purpose

This study aimed to assess the effect of CBD, a nonpsychoactive component of cannabis, on the self-administration of heroin and other drug-seeking behaviors. A total of 155 rats went through the experiment though 18 were excluded due to poor health, catheter patency loss, and failure to meet the self-administration threshold.

10.7.3. Results

- CBD did not alter the rats' heroin intake behavior, nor did it affect the cessation of this self-administration. There was also no impact to the rats' locomotor activities.
- However, CBD did tend to affect the expressions of the rats' CB1 and GluR1 receptors, mainly in the nucleus accumbens.
- When reinstatement sessions were initiated by exposure to the conditioned stimulus light cue, rats treated with CBD showed reduced drug-seeking activities. Yet the effect was not significant on behaviors induced by a prime injection of heroin.

10.7.4. Conclusions

CBD injections tend to reduce heroin-seeking behavior, an effect that remained significant even two weeks after treatment.

10.7.5. Method, Source, and Sampling

- *Method*: One- and two-way ANOVA with repeated measures, planned comparisons, and Bonferroni corrections for multiple comparisons.
- *Data Type*: Longitudinal study.
- *Data Source*: Primary data.
- *Data Collection*: This experiment randomly assigned 137 rats to treated and control groups. The treated group received CBD injections while the control group received a saline solution. The rats' self-administration of heroin was recorded and their brains were studied.
- *Sampling*: Random sampling.
- *Population*: Male adolescent Long-Evans rats that weighed 230–250 grams at the beginning of the experiment.
- *Sample Size*: 137 rats.
- *Other Drugs*: Heroin.

10.7.6. Covariates

CBD exposure.

10.7.7. Limitations

Results may be limited in their extrapolation to humans.

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