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## **Does cannabis complement or substitute alcohol consumption? A systematic review of human and animal studies**

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**Key words:** Cannabis, alcohol, substitution, and complementarity.

## **ABSTRACT**

**Background:** Whether alcohol and cannabis complement or substitute each other has been studied for over two decades. In the changing cannabis policy landscape, debates are moving rapidly and spill over effects on other substances are of interest.

**Aims:** update and extend a previous systematic review, by; a) identifying new human behavioural studies reporting on substitution and/or complementarity of alcohol and cannabis, and b) additionally including animal studies

**Methods:** We replicated the search strategy of an earlier systematic review, supplemented with a new search for animal studies. Search results were cross checked against the earlier review and reference lists were hand searched. Findings were synthesised using a narrative synthesis.

**Results:** Sixty-five articles were included (64 in humans, one in animals). We synthesised findings into categories: patterns of use, substitution practices, economic relationship, substance use disorders, policy evaluation, others and animal studies. Overall, 30 studies found evidence for substitution, 17 for complementarity, 14 did not find evidence for either, and four found evidence for both.

**Conclusions:** Overall the evidence regarding complementarity and substitution of cannabis and alcohol is mixed. We identified stronger support for substitution than complementarity, though evidence indicates different effects in different populations and to some extent across different study designs. The quality of studies varied and few were designed specifically to address this question. Dedicated high quality research is warranted.

**Declaration of interest:** SB works at the Institute of Alcohol Studies which receives funding from the Alliance House Foundation. The other authors have no conflict of interest to declare.

## **BACKGROUND**

One aspect of the increasing liberalisation of medicinal and recreational cannabis taking place in many jurisdictions worldwide that remains poorly understood is the impact that potential increases in cannabis use will have on alcohol use, and whether alcohol and cannabis use substitute or complement one another. Substitution refers to the act of using something instead of another thing, and a complement is something which combines well with or improved something else.

A prominent argument in this issue is whether full or partial legalisation of cannabis will have beneficial or harmful effects on the population. Pro legalisation groups have highlighted the benefits of increased tax revenue, lower law enforcement costs, and the possible medical benefits of cannabinoids for the treatment of certain diseases (McGinty et al., 2017; Sznitman and Bretteville-Jensen, 2015). Contrarily, groups that favour criminalization argue on the harms caused to youth due to increased availability, increased motor vehicle accidents, and are sometimes also sceptical of the possible medical benefits (McGinty et al., 2017; Sznitman and Bretteville-Jensen, 2015).

A key component of the debate has been the harms due to these substances. By 2015, 63.5 million people were estimated to have alcohol use disorder worldwide, and 19.8 million cases of cannabis use disorder were estimated (Degenhardt et al., 2013; Peacock et al., 2018). Alcohol has been ranked as one of the most harmful psychoactive substances, and has been linked to a number of acute and chronic health harms such as cancer and cirrhosis, and is correlated with harms to others, as well as social and economic consequences (Nutt et al., 2010; Van Amsterdam et al., 2010). Some rank cannabis as a medium to low risk substance (Nutt et al., 2010; Van Amsterdam et al., 2010). However, research throughout the past

twenty years has evidenced that regular cannabis use is correlated to significant health and psychosocial harms, and has been linked to poorer school performance, psychosis and cognitive impairment in adulthood, and cardiovascular disease among vulnerable individuals (Hall, 2015).

Several reviews have looked at the relationship between cannabis and alcohol. While some have found evidence of increased co-use of cannabis and other substances upon cannabis liberalisation, they also concluded further research was needed on this subject (Yurasek et al., 2017). The current changing legal landscape has brought this debate to the forefront with some US states, Canada, and Uruguay, legalising recreational cannabis. Therefore, it is urgently pressing to better understand the relationship between alcohol and cannabis.

The present study is an update and extension of a systematic review completed by Subbaraman (2016), which concluded that alcohol and cannabis act as both complements and substitutes (Subbaraman, 2016). Given the rapidly changing policy landscape, a number of studies have been published since the previous was published. In the present study, we update and expand on the previous review on substitution and complementarity of alcohol and cannabis by identifying new behavioural studies in humans and adding a systematic review of experimental animal studies.

## **METHODS**

PRISMA-P 2015 Guidelines were used to report findings from this study.

## Search Strategy

MEDLINE, PsychINFO, and Embase were searched through OVID on the 28th of May 2018 replicating the search strategy of Subbaraman's 2016 review. The ISI Web of Science (WoS) was also searched using the Web of Science Core Collection. Additionally, articles found through hand searching reference lists on other sources that were found to be relevant were also included. Search terms were used as key words in the title and/or abstract, or as Medical Subject Heading Terms. The search terms used in OVID "alcohol.mp" OR "exp ALCOHOLS" AND "cannabis.mp" OR "exp CANNABIS" AND "complement\*.tw" OR "substitut\*.tw". For the ISI WoS, the search terms used were screened across titles and abstracts and where the following, "alcohol" OR "ethanol" AND "cannabis" OR "marijuana" AND "complement\*" OR "substitut\*"

For the additional review of animal studies, MEDLINE, PsychINFO, and Embase were searched through OVID on the 20th of May 2018. The search was performed simultaneously through the three databases. The search terms used were chosen because of their similarity to the ones used in the update of the Subbaraman review. The terms "complement" and "substitute" were not included. The search terms were filtered for title and abstract. The search strategy used in Ovid was "alcohol.tw" OR "ethanol.tw" AND "cannabis.tw" OR "marijuana.tw" and filters were used to limit the results to animal studies.

Additional records identified through hand searching and through expert recommendations were also included.

## **Inclusion Criteria**

In this systematic review, the inclusion criteria were the same as the Subbaraman (2016) review; (1) they had to be behavioural studies, (2) with a human population, and (3) if the independent variable was cannabis related, the dependent variable had to be alcohol related, or vice versa. For the animal studies, studies were eligible for inclusion if (1) they were experimental studies, (2) had an animal population, and (3) if the independent variable was cannabis-related, the dependent-variable had to be alcohol related, or vice versa.

## **Data selection**

All results were exported into Refworks ProQuest. Titles and abstracts were screened independently by two reviewers to assess eligibility for inclusion. The data extracted was; (a) country, (1) study design, (2) population, (3) sample size, (4) type of measure, (5) measurement tool, (6) independent variable, (7) dependent variable, (8) statistical analysis, (9) control variables, (10) conclusion (substitution, complementarity, both, or neither), and (11) quality assessment. The data was extracted into a data extraction template in Microsoft Excel.

## **Quality Assessment**

Quantitative studies were assessed using the Effective Public Health Practice Project Quality Assessment Tool for Quantitative Studies (EPHPP), as recommended in the Cochrane Handbook (Higgins and Green, 2011). However, the tool does not address individual limitations for each study, thus independent qualitative assessment was additionally

conducted by the reviewers to better assess the quality. Qualitative studies were assessed using the Critical Appraisal Skills Programme Checklist for Qualitative Studies (CASP). Animal studies were assessed using the SYRCLE's Risk of Bias tool for Animal Studies (Hooijmans et al., 2014).

### **Narrative Synthesis of Study Findings**

Due to the broad inclusion criteria in terms of study design and population, a meta-analysis was not feasible, and a narrative synthesis was more appropriate (Cheung and Vijayakumar, 2016; Jahan et al., 2016).

Findings were synthesised narratively under seven topics. Patterns of use; studies analysing how different populations use alcohol and cannabis in their daily life. Substitution practices; studies exclusively exploring self-reported substitution of cannabis for alcohol or alcohol for cannabis in specific populations. Economic relationship; Studies that evaluate if a monetary-related change in one substance affects the use or demand of another substance. Substance use disorders; studies evaluating changes in substance use in a population attempting to stop or reduce the use of another substance. Policy evaluation; studies that analyse the impact that a cannabis or alcohol related policy has in the use of alcohol or cannabis. Animal studies; experimental studies that analyse the relationship between alcohol and cannabis in animal models. Others; Studies that analyse substitution and complementarity between alcohol and cannabis but do not fit into any of the above-named groups



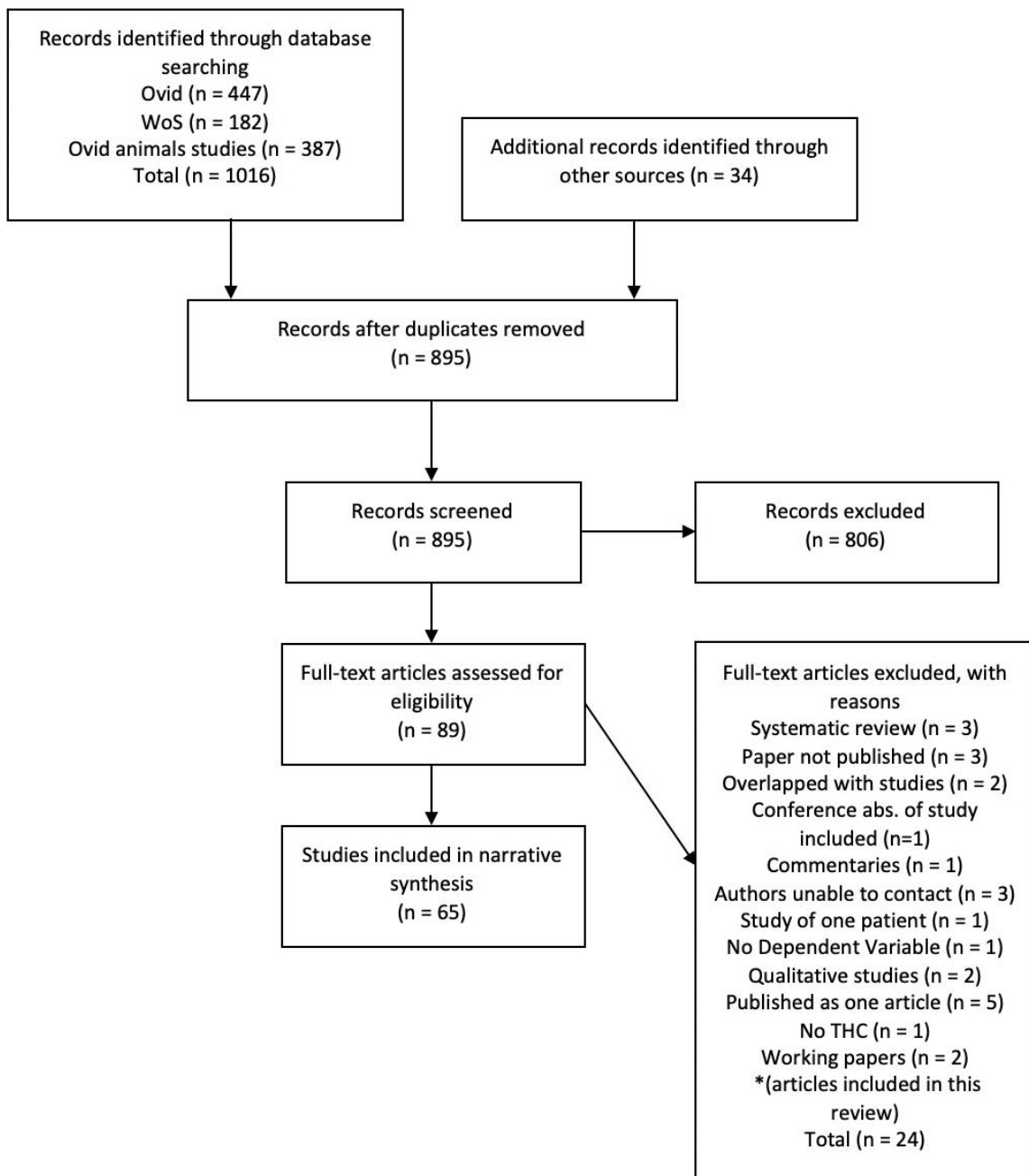
## **Terminology**

The word substitution and complementarity are used as shorthand throughout the article to describe the results of included studies. These terms are well suited to describing the majority of the individual-level data studies. However, they may be less adequate when addressing ecological studies which use population level data, where population level changes in alcohol or cannabis use do not necessarily reflect individuals switching from one substance to another, for example. However, for ease of understanding, and for consistency with the existing literature and search strategy, we use the same terminology for population-level studies.

## **RESULTS**

### **Included studies**

In total, 1046 articles were identified [FIGURE 1]. In total, 65 articles were included in the final review. Of these, 39 are the papers found in the Subbaraman (2016) review, and 26 additional articles were included in this review.



## General characteristics of the studies

Studies included were published between 1970 and 2019. Studies were conducted in USA (n=49), Canada (n=4), Australia (n=5), Norway (n=2), UK (2), Brazil (n=1), Sweden (n=1), and one was conjointly conducted in USA, The Netherlands, and Canada. The sample sizes ranged from 8 to 5,428,399. Twenty-six longitudinal studies, 34 cross sectional studies, one randomised controlled trial (RCT), one secondary analysis of an RCT, one experimental study in animals, one qualitative study, and one economic analysis study were identified.

Measures were also grouped into categories. The type of measure used was defined as the main unit or units of measurement explaining the dependent variable (outcome). Eight types of measure were identified (Table 1).

*Table 1. Types of measures*

Consumption	Units of quantity and/or frequency of alcohol and/or cannabis, or participation in use measured by a dichotomous variable
Toxicological	Toxicological measures
Self-reported use	Self-report of cannabis and/or alcohol use
Self-reported substitution	Self-report of substituting one substance for another
Fatalities	Quantity of traffic fatalities and of cannabis positive drivers involved in traffic fatalities
Monetary	Measures of drug prices
Qualitative interview	Reported through patient's interviews.
Locomotor activity	Distance moved by mice.
Unspecified	Does not specify the unit of measure used

## **1. Policy evaluation studies**

This section contains ecological studies on changes in cannabis policy. “Substitution” and “complementarity” are used as shorthand to describe any changes in alcohol use which were measured on a population level. Where studies used individual level data, this is noted in the text.

### *1.1 Minimum Legal Drinking Age (MLDA)*

Six studies looked at the effects of MLDA on cannabis and alcohol use, looking at the changes in substance use after a MLDA of 21 years had been applied in the USA. Two studies found evidence for substitution, one for complementarity, and three did not find evidence for either. Five studies used measures of consumption and one study used fatality measures. Four studies, and two were rated as moderate.

Regarding substitution, one study conducted in the 1980s in 43 US States, found that increased legal drinking age was associated with reduced alcohol use, but increased cannabis use (DiNardo and Lemieux, 2001). Another study using data from the early 2000s found that turning 21 years, and thus having legal access to purchase and drink alcohol, was linked to decreased cannabis use but increased alcohol use (Crost and Guerrero, 2012). This study analysed consumption data from individuals just below and above 21 years of age, therefore it did not rely on cross sectional state variations in alcohol prices and policies.

Contrarily, a study that used individual level data and also looked at cannabis and alcohol use just upon turning 21 years of age, found evidence for complementarity, with a 7% and 7.6% increase in cannabis and alcohol use respectively upon turning 21 in a MLDA-21 (Yörük and Yörük, 2011). Later on, the authors stated using a restricted sample in their original study, and

in a newer analysis found that in the full sample, the effect of the MLDA-21 was similar for alcohol but smaller and statistically insignificant for cannabis (Yörük and Yörük, 2013).

### *1.2 Medical Marijuana Laws (MML)*

Six studies assessed the impact of new MMLs on alcohol use. Four concluded substitution, one concluded complementarity, and one did not conclude either of the two. Four studies used measures of consumption and two used traffic fatality measures. Two studies were rated as strong, three as moderate, and one as weak.

Regarding substitution, a study looking at individual level data found that cannabis use and binge drinking decreased in 8<sup>th</sup> graders, but not in 10<sup>th</sup> and 12<sup>th</sup> graders, upon MML enactment, accounting for policies that could have affected the price of different substances (Cerda et al., 2018). Anderson (2013) conducted a study evaluating the impact of MMLs on traffic fatalities and alcohol use, and found that legalisation was associated with a decrease in alcohol involved traffic fatalities after a full the law came into effect (Anderson et al., 2013). Another study looked at border alcohol sales from Retail scanner data in 38 contiguous counties in Washington, and found that legalisation was associated with a 12% reduction in alcohol sales (Baggio et al., 2018).

One study found weak evidence for complementarity, stating that MMLs were associated with increased frequency of binge drinking in adults (21+), but this finding was not seen in adolescents (Wen et al., 2014). This study used individual level substance use and binge drinking.

### 1.3 Cannabis and alcohol related policies

Nine studies looked at cannabis related policies on alcohol and cannabis use. Seven studies found evidence for substitution and two for complementarity. Seven studies used consumption measures, one used a monetary measure, and one used fatality measures. Three studies were rated as strong, four as moderate, and two as weak.

Regarding substitution, one study that used a survey to simulate cannabis legalization on Australian college students found a 4% increase in cannabis use and a 1-4% reduction in alcohol use (Clements and Daryal, 2005). Another study evaluated the impact of cannabis decriminalisation in 11 US states, in an all-male sample, and found weak evidence that fewer individuals drank “*six or more drinks*” on a single drinking occasion (Thies and Register, 1993). Another study compared one London borough (Lambeth), where small quantities of cannabis were depenalised, to other London boroughs and found that cannabis depenalisation was associated with a reduction in alcohol-related hospital admissions in 15-24 years old, but no effect in older adults (Kelly and Rasul, 2014). A study that followed a small regional sample of two cohorts of 8<sup>th</sup> grade students in Tacoma, Washington, looking at individual-level alcohol and marijuana use, found that the cohort that did not experience recreational cannabis legalisation enactment had higher rates of cannabis use and the cohort that did experience the law enactment had higher rates of alcohol use (Mason et al., 2016).

In a study comparing different countries it was found that stricter alcohol policies were associated with reduced alcohol use among 6<sup>th</sup> and 10<sup>th</sup> graders but did not find evidence of changes in cannabis use (Simons-Morton et al., 2010). Another study found an increase in the price of alcohol was associated with a reduced probability of cannabis use in the youngest cohort (15-20 years), analysing individual level past month cannabis use (Farrelly et al., 1999).

## **2. Substance use disorders studies**

### *2.1 Cannabis cessation or reduction*

Twelve studies were identified. Four studies found evidence for substitution, one for complementarity, one for both, and six for neither. Seven studies used consumption measures, one used self-reported use of substance, one used toxicological data, and three did not specify the measure. One study was rated as strong, six as moderate, and five as weak.

Studies that found evidence for substitution were all conducted on non-treatment seeking cannabis users reducing their use (Allsop et al., 2014; Copersino et al., 2006a, 2006b; Peters and Hughes, 2010). One study found a 52% increase of alcohol use at follow-up (alcohol drinks/day), among participants with former alcohol abuse/dependence problems, when they abstained from cannabis use (Peters and Hughes, 2010). Another study identified a greater increase of alcohol use during cannabis abstinence among baseline light drinkers (21 Standard Units/week), compared to those who were heavier drinkers at baseline (Allsop et al., 2014).

### *2.2 Alcohol cessation or reduction*

Five studies were identified. One study found evidence for substitution and two studies concluded on complementarity and two did not conclude on neither. Four studies used measures of consumption measures and one used self-report use. Two were rated as moderate, and three as weak.

Regarding substitution, one study looked at records of 92 patients that reported using cannabis to treat their alcohol use problems and found that 83 patients reported cannabis as

effective, while nine said to use cannabis to achieve total abstinence (Mikuriya, 2004). As to complementarity, one study found that participants who used cannabis at post discharge from alcohol dependence treatment were associated with a higher risk of relapsing and returning to alcohol use (Aharonovich et al., 2005).

### **3. Economic relationship**

#### *3.1 General population*

Three studies were included in this group. One study concluded complementarity, and two studies found evidence for both complementarity and substitution. All studies used consumption measures and were rated as strong.

Comparing cross price effects in eight demographic samples, one study found that alcohol and cannabis were associated as economic complements in the full sample, in white-male-non-Hispanics, in blacks, and in Native Americans (Saffer and Chaloupka, 1999a). This study also found evidence of substitution in Hispanics, and no effect in women, Asians, and young people (Saffer and Chaloupka, 1999a).

A study conducted in Australia found that a 10% increase in the price of alcohol could be related to a 4.17% increase in the probability of cannabis use, suggesting economic substitution (Cameron and Williams, 2001). They also found that cannabis decriminalisation, as an indicator of price, could increase alcohol participation, suggesting complementarity (Cameron and Williams, 2001). In South Australia, the only state that decriminalised cannabis, individual-level alcohol drinking was 3% higher than in the rest of the country (Cameron and Williams, 2001).



### *3.2 Young people*

Two studies found evidence for complementarity, one for substitution, and one for both. All used measures of consumption and were rated as strong.

Regarding complementarity, a study from the USA among 14-21-year olds found that doubling beer tax could result in a 11.4% reduction in the probability of using marijuana and a 13.3% reduction in the demand for marijuana, compared to a 3.2% reduction in the probability of using alcohol and an 8.1% reduction in the demand for alcohol (Pacula, 1998).

Another study on college students found that higher beer tax was associated with lower prevalence of alcohol and cannabis use, and cannabis prices were negatively related to alcohol and marijuana participation (Williams et al., 2004). Results from Williams (2004) are difficult to weight as the tool used (CAS) is nationally representative of fulltime students in four-year colleges only, and provides self-reported data. Both studies rely on cross sectional data and price policies (Pacula, 1998; Williams et al., 2004).

A study from the 1980s that used decriminalisation as an indicator of cannabis price (cannabis in decriminalised states is expected to be cheaper) found that youth consumed alcohol less frequently and were less likely to engage in heavy drinking in decriminalized states (Chaloupka and Laixuthai, 1997). Furthermore, they found that a state that moved from criminalisation to decriminalisation, the number of drinking abstainers could increase by 12%, frequent drinkers could reduce by 11%, and heavy drinking episode could reduce by 12% (Chaloupka and Laixuthai, 1997). In a sample of 12th graders, one study found that a 1% increase in liquor prices was associated with reduced odds of frequent marijuana use by 2.4%

(complementarity), but decriminalisation of marijuana was linked to reduced odds of frequent drinking by 7% (substitution) (Yamada et al., 1996).

### *3.3 Drug users*

Of the two studies, one concluded on substitution and one on complementarity. One study used measures of consumption, and the other used monetary measures. One study was rated as strong, and the other as weak.

A study on a sample of 80 polydrug users found an increase in alcohol purchases when the perceived quality of cannabis dropped to average or poor (Cole et al., 2008).

A study in Australia found evidence for complementarity showing that the price of alcohol and the fine for exceeding the Blood Alcohol Concentration limit for driving was negatively related to cannabis use. This was stronger in participants that used alcohol and cannabis concomitantly (Williams and Mahmoudi, 2004).

### *3.4 Other*

This study analysed the changes in cannabis prices in Australia and found that, for the period of 1990, cannabis prices dropped an average of 20 percent, while cannabis consumption increased 2,8 percent and alcohol consumption dropped an average of 6,05 percent, supporting substitution (Clements, 2004).

## **4. Patterns of use**

### *4.1 General population*

This study found evidence for complementarity, used consumption measures, and was rated as moderate. The study compared the use and transition of substances in different types of cannabis users, in two periods of time, and found that participants who continued to use cannabis from Wave 1 to Wave 2 had higher odds of reporting alcohol use problems, compared to participants who stopped using cannabis (Choi et al., 2018).

### *4.2 Young people*

Four studies found evidence for complementarity, and one found evidence for neither. All studies used consumption measures. One study was rated as strong, one as moderate, and three as weak.

A Norwegian study on high school students found that those who drank more alcohol were more likely to use both substances, and that in 80% of cannabis events, drinking had also occurred (Pape et al., 2009). An earlier Norwegian study found that regular cannabis users showed greater alcohol use, compared to those who only tried cannabis occasionally (Hammer and Vaglum, 1992). A study that assessed a cohort of college students in the USA found that one more drink in the month duration of the study was associated with 40% increased odds of using cannabis (O'Hara et al., 2016).

## **5. Substitution practices**

### *5.1 Medical cannabis patients*

All studies found evidence of substitution. All studies used self-reported substitution as the main measure unit and were rated as weak.

The three studies conducted in Canada were funded by the dispensaries whose costumers made up the study populations, and found a 25%, 52%, and 41% substitution rate of medical cannabis for alcohol (Lucas et al., 2013, 2016; Lucas and Walsh, 2017). Another study was conducted across three dispensaries in USA and found that 42% of participants reported a reduction in alcohol use since they started using medical cannabis (Piper et al., 2017). The last study was conducted in the USA and found that 40% of the participants reported substituting alcohol for cannabis.

### *5.2 Cannabis users*

This was the only qualitative study identified in the review. The conclusion was substitution. Participants reported that they substituted alcohol for cannabis because it was “safer” and had less adverse effects.

## **6. Other**

Studies in this category did not fit within the other categories for the narrative synthesis. Two studies concluded substitution and two concluded complementarity. Three studies used consumption measures and one used self-reported substitution. One study was rated as strong, one as moderate, and two as weak.

Considering substitution, one study found that participants who reported no alcohol use were more likely to report cannabis use (Alter et al., 2006). Another study used a sub sample of

(Reiman, 2009), and found that 50% of participants reported substituting alcohol for cannabis (Reiman, 2007).

Regarding complementarity, one study analysing the impact of Methadone Maintenance Therapy (MMT) enrolment on the onset of heavy drinking, in injectable heroin users, found that cannabis use was related to heavy drinking onset, and not MMT (Klimas et al., 2016). Another study from the USA found that there were twice as many Simultaneous Users (using cannabis and alcohol concomitantly) as there were Concurrent Users (cannabis and alcohol use separately), and simultaneous users had higher levels of frequency and quantity of alcohol use, and had higher likelihood of drunk driving (Subbaraman and Kerr, 2015).

## ***7. Animal studies***

This study was conducted on a rodent model exploring the roll of cannabinoids in alcohol related problems using locomotor activity as the main unit of measurement. The study was rated with low risk of bias. It used a twelve-day acquisition period of daily ethanol injections, followed by four-days of injections of cannabinoid treatment, and found that THC or THC + CBD was effective at reducing alcohol sensitisation, but CBD alone was not effective (Filev et al., 2017).

## **DISCUSSION**

Sixty-five eligible articles were identified and included in this review. Thirty studies found evidence for substitution, 17 for complementarity, four found evidence for both, and 14 did not find evidence for either. Overall, the conclusions of this review and Subbaraman (2016) are very similar. However, whereas Subbaraman (2016) found that decriminalisation suggests some evidence of substitution, this review found mixed evidence for cannabis decriminalisation, depending on the population being studied. Our findings were synthesised into seven groups in a narrative synthesis. This showed that the evidence differs based on the population studied, on the type of study, and the quality of data.

### ***Main results***

The largest number of studies were on alcohol and cannabis related policies. This review found that in MML-jurisdictions, there is some evidence of a substitution effect among adolescents, which is similar to a review by Schlienz and Lee (2018). Other types of cannabis policies showed mixed findings. The evidence on the impact of alcohol related policies was inconclusive. However, there are studies that show that increasing the price of alcohol can result in a reduction of both, alcohol and cannabis use in adolescents. Overall, we find that a large number of policy studies address individual policies and are limited to cross sectional data and self-reported surveys, which makes analysis of results difficult as evidence may not be sufficiently strong.

Substitution of one substance for another has been a major concern among clinicians. One study found that even though the prevalence of co-use of alcohol and cannabis is high among

people in drug treatment, the literature does not show clear direction of substitution or complementarity (Yurasek et al., 2017). However, an interesting finding is that the few studies that show increased drinking during cannabis abstinence were all conducted on cannabis-users who were not seeking treatment, while those that showed evidence of reduced drinking during cannabis abstinence were all conducted on users who were seeking treatment. This shows there may be wider factors to additionally consider, such as motivation to stop substance use.

Regarding how cannabis and alcohol relate to each other economically, the findings were less consistent. Some studies suggested young people were more responsive to increased alcohol prices, compared to cannabis prices, given that two studies show that increased beer tax reduced alcohol and cannabis use in college students. Nevertheless, these studies are limited to cross sectional data and self-reported surveys, which could be highly biased.

There was some evidence that medical cannabis patients use cannabis to substitute alcohol. Still, these findings must be interpreted with caution, as most of these studies were funded by the same medical cannabis dispensaries who provided the cannabis to the study participants. These studies also did not assess complementarity, and therefore, the risk of bias is high in this group of studies.

Only one study in animals was identified. This study showed evidence of potential for cannabinoids in the treatment for alcohol use disorders, either in managing alcohol withdrawal or for relapse prevention.

This review has several strengths. Firstly, the quantity of papers included provides a large body of evidence which allows to expand our understanding as well as identifying gaps in the literature. Following the search strategy of the previous systematic review replicates and

expands on its findings. The addition of quality assessment tools provides more nuance of the studies included in this review, which allows for a greater understanding of the issue and highlights where more high-quality research is needed. The review of animal studies adds a new perspective to the debate and highlights potential medical benefits of cannabinoids in the treatment of alcohol use disorders. Finally, using a narrative synthesis of study allows for findings to be differentiated based on study design is another strength of the study as it may be the case that cannabis can be a substitute in some instances and a complement in others.

We also identified several limitations. First, most studies have been conducted on the impact of policies, leaving large gaps of evidence in other areas. Also, a large portion of the studies were assessed as weak, thus, much of the evidence is based on poor quality studies, making it difficult to draw strong conclusions. All studies on medical cannabis patients were found weak to be weak with a high likelihood of bias, thus providing little reliable evidence. Most studies also used self-report measures, which are known to be biased and somewhat less reliable. Some of the studies did not clearly state how they measured outcomes, making comparison to other studies difficult. Lastly, many studies have shown the potency of cannabis has drastically increased over the last few decades, which may lead different results between newer and older studies (Chandra et al., 2019; Freeman et al., 2019).

We identified a number of newer studies (17) published since the previous review, suggesting that ongoing monitoring of the literature would be of value. The evidence base may evolve as interest grows in this area and more studies are published. Comprehensive research of drug policy implementation across different populations should be subject of future studies. The recent enactment of cannabis legalisation in Canada will provide a natural experiment to



evaluate the changes in cannabis and alcohol use. Research into clinical populations is inconclusive with overall study quality being low.

Evidence from animal studies is recent and scarce and no early conclusions should be drawn. Also, these findings are difficult to generalise to humans as results from animal studies are often not replicated in humans.

Finally, most studies were conducted in the USA. Research is needed in other jurisdictions to study how findings vary in systems that differ politically, economically and culturally.

## **CONCLUSION**

This review found evidence for both, substitution and complementarity, between cannabis and alcohol. Across the different groups assessed in this review, we find that the largest amount of research has been conducted on policy studies substitution, with evidence leaning towards substitution. Otherwise, findings do not show a clear tendency to either substitution or complementarity, and suggest that alcohol and cannabis are used differently and have different effects in different populations. Moreover, to our knowledge, this is the first review that explores the effects of alcohol and cannabis use in animal models, with some novel findings. We find the evidence base on this topic expanding rapidly. Overall, there is a need of high-quality research designed to address the topic, for example, through experimental studies and capitalising opportunities to conduct ecological studies as a result of the current rapidly changing policy landscape around cannabis in some parts of the world.

**Table 2.** Policy Evaluation Studies (20 studies)

<i>Paper</i>	<i>Country</i>	<i>Study design</i>	<i>Population</i>	<i>Sample size</i>	<i>Measure Category</i>	<i>Measurement tool</i>	<i>Independent variable</i>	<i>Dependent variable</i>	<i>Conclusion</i>	<i>Quality assessment</i>
<i>Medical Marijuana Laws studies (7 studies)</i>										
Baggio, 2018 (Baggio et al., 2018)	USA	Pre/post	Nielsen Retail Scanner database 2006-2015	52 market areas in 48 contiguous states	Consumption	Nielsen Retail Scanner database	County-level MML	County-level alcohol sales	Substitution	Moderate
Cerda, 2018 (Cerda et al., 2018)	USA	Pre/post	MTF 1991-2015	1,179,372	Consumption	Monitoring The Future Data	State-level MML	Individual-level past 30-day cannabis use, and past two-week binge drinking	Substitution	Weak
Sabia, 2017 (Sabia et al., 2017)	USA	Repeated cross sectional	Behavioral RISK Factor Surveillance System 1990-2012 population	5,428,399	Consumption	Behavioral Risk Factor Surveillance System	State-level MML	Past 30-day alcohol consumption	Substitution	Moderate
Salomonsen-Sautel, 2014 (Salomonsen-Sautel et al., 2014)	USA	Longitudinal Pre/post	Fatality Analysis Reporting System (FARS)	36-six-month intervals of motor vehicle fatalities	Fatality	FARS	Indicator of commercial availability of medical cannabis in Colorado (2009)	State-level proportions of drivers in fatal crashes who were alcohol-impaired or cannabis-positive	Neither	Strong

Wen, 2014 (Wen et al., 2014)	USA	Cross sectional Survey	National Survey on Drug use and Health	183.600 (12-20), 219.400 (20+)	Consumption	National Survey on Drug Use and Health (NSDUH)	State-level MML indicator	Individual-level alcohol, cannabis, and other drug use, binge-drinking	Weak complements among those older than 21	Moderate
Anderson, 2013 (Anderson et al., 2013)	USA	Longitudinal Pre/post	National Survey on Drug Use and Health (NSDUH) and FARS BRFS	Varies by dataset	Fatality	NSDUH, High Price Magazine, FARS	State-level MML & cannabis decriminalisation indicators	State-level alcohol-related traffic fatality rate, monthly # drinks, prevalence of bingeing	Substitutes	Strong

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*Cannabis and alcohol related policies studies (7 studies)*

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Subbaraman, 2019 (Subbaraman and Kerr, 2019)	USA	Cross sectional survey	Washington residents aged 18 and over	5492	Consumption	Self-report survey	Legalisation of recreational cannabis	Individual-level past 30 days number of drinking days, number of drinks per drinking day, frequency of 5 or more drinks, alcohol related harms	Some evidence of substitution for (decrease in alcohol related harms)	Strong
Miller, 2018 (Miller and Seo, 2018)	USA	Longitudinal	Nielsen Retail Scanner database	37 Washington counties	Monetary	Nielsen Retail Scanner Dataset	State-level marihuana legalisation	State-level alcohol sales	Substitution	Moderate
Mason, 2016 (Mason et al., 2016)	USA	Cohort	Adolescents in Washington (two cohorts, before and	238	Consumption	Self-report surveys	State-level pre/post non-recreational marijuana law	Individual-level past 30 days rate of alcohol, marijuana and cigarette use	Substitution	Moderate

			after non-recreational marijuana law)							
Kelly, 2014 (Kelly and Rasul, 2014)	UK	Pre/post	Quarterly hospital admissions from 1997-2009 in London, England	<1 million public hospital admissions	Fatality	Hospital records	Depenalisation of cannabis possession in Lambeth, London, England	Hospitalizations related to alcohol use	Substitutes	Strong
Simons-Morton, 2010 (Simons-Morton et al., 2010)	Canada, USA, Netherlands	Cross sectional Survey	Health Behaviour in School Age Children (15 years old)	4858	Consumption	Health Behaviour in School-Aged Children Survey (HBSC)	Restrictiveness of country-level alcohol and cannabis prices	Country-level frequency alcohol, cannabis use	Complement	Strong
Clements, 2005	Australia	Cross sectional survey	First year college economics students	281	Consumption	Self-report survey	Hypothetical (simulation) cannabis legalisation	Individual-level beverage specific alcohol use	Substitution	Weak
Farrelly, 1999 (Farrelly et al., 1999)	USA	Cross sectional survey	National Household Survey on Drug Abuse (12-20 years old)	49,311	Consumption	National Household Survey on Drug Abuse (NHSDA)	State-level cannabis penalties, county-level # cannabis arrests	Individual-level past month cannabis use	Complement	Moderate
Thies, 1993 (Thies and Register, 1993)	USA	Cross sectional Survey	National Longitudinal Survey of Youth (1979)	12,686	Consumption	National Longitudinal Survey of Youth (1984 and 1988)	State-level cannabis decriminalisation indicator, MLDA arrests	Individual-level cannabis and alcohol use and frequency	Weak substitutes	Moderate

McGlothlin, 1970 (McGlothlin et al., 1970)	USA	Cross sectional survey	College students and free clinic patients	594	Consumption	Self-report survey	Occurrence of operation intercept (1969) (Marijuana blockage)	Prevalence of self-reported substitution of alcohol for cannabis	Substitution	Weak
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*Minimum Legal Drinking Age studies (6 studies)*

Keyes, 2015 (Keyes et al., 2015)	USA	Pooled cross sections	15-25-year olds from the 1999-2011 FARS	7191	Fatality	FARS	Turning MLDA of 21	Individual-level fatal injury due to alcohol use, marijuana use, or alcohol and marijuana use	Neither	Moderate
Krauss, 2015 (Krauss et al., 2015)	USA	Cross sectional Survey	NSDUH 2004-2012 (Born 1949-1972)	110,300	Consumption	National Survey on Drug Use and Health	State-level MLDA-21	Individual-level past month and past year cannabis use and meeting criteria for marijuana abuse/dependence	Neither	Strong
Crost, 2013 (Crost and Rees, 2013)	USA	Cross sectional panel survey	National Longitudinal Survey of Youth	28,089	Consumption	National Longitudinal Survey of Youth (1997)	Turning MLDA of 21	Individual level past 30-day cannabis use and frequency	Neither	Strong
Yoruk, 2013 (Yörük and Yörük, 2013)	USA	Cross sectional survey	National Longitudinal Survey of Youth (1997)	~9000	Consumption	National Longitudinal Survey of Youth (1997)	Turning MLDA of 21	Individual-level past 30-day cannabis and alcohol use and frequency	Neither	Moderate
Crost, 2012 (Crost and	USA	Cross sectional Survey	National Survey on	71 (State-level observations)	Consumption	National Survey of Drug use and Health	Turning MLDA of 21	Population level past month cannabis and alcohol frequency	Substitution	Strong

Guerrero, 2012)			Drug Use and Health							
DiNardo, 2001 (DiNardo and Lemieux, 2001)	USA	Cross sectional Survey	Monitoring the Future Study	>156,000	Consumption	Monitoring the Future Data	MLDA, State-level cannabis decriminalisation indicator, alcohol price	State level prevalence of past day 30-day cannabis & alcohol frequency	Substitution	Strong

Abbreviations for measurement tool: FARS (Fatality Analysis Reporting System)

**Table 3.** Substance use disorders studies (17 studies)

<i>Paper</i>	<i>Country</i>	<i>Study design</i>	<i>Population</i>	<i>Sample size</i>	<i>Measure Category</i>	<i>Measurement tool</i>	<i>Independent variable</i>	<i>Dependent variable</i>	<i>Conclusion</i>	<i>Quality assessment</i>
<i>Cannabis cessation or reduction studies (13 studies)</i>										
Hodgins, 2017 (Hodgins et al., 2017)	Canada	Cross sectional Survey	Individuals recovered from Cannabis Use Disorder through treatment-assisted or self-directed efforts	119	Consumption	Marijuana Problem Scale, Process of Change Questionnaire, researcher-led interview on substance use changes during recovery	Cannabis recovery (abstinence or moderation)	Self-reported changes in other alcohol use	Both	Weak
Allsop, 2014 (Allsop et al., 2014)	Australia	Prospective community-based cohort	Non-treatment seeking cannabis users	45	Consumption	Cannabis withdrawal Scale (CWS) and urine toxicology	Cannabis abstinence	Quantity of alcohol use	Substitution, especially among baseline light drinkers	Strong

Peters, 2010 (Peters and Hughes, 2010)	USA	Prospective cohort	Daily cannabis users not trying to stop or reduce cannabis	28	Consumption	MWC, MCQ, CPQ, and PACS	Cannabis abstinence	Drinks per day	Substitution	Moderate
Kadden, 2009 (Kadden et al., 2009)	USA	Prospective cohort	Cannabis treatment seekers	207	Consumption	Time-line Follow-Back (TLFB), Addiction Severity Index, Marijuana Problem Scale, Coping Strategies Scale	Past 90 days cannabis frequency	Indicator of increased (>10%) past 90-day proportion days using alcohol, drinks per drinking day	Neither	Moderate
Hughes, 2008 (Hughes et al., 2008)	USA	Prospective cohort	Daily cannabis users trying to stop or reduce on their own	19	Not specified	Questionnaire for cannabis use and intentions to use	Cannabis abstinence	Alcohol use	Neither	Weak
Copersino, 2006 (Copersino et al., 2006a)	USA	Prospective cohort	Non-treatment seeking cannabis users	104	Self-reported use	Marijuana Quit Questionnaire	None	Self-reported use of alcohol to relieve cannabis withdrawal during quit attempt	Substitution: Some evidence to relieve withdrawal	Weak
Copersino, 2006 (Copersino et al., 2006b)	USA	Cross sectional survey	Non-treatment seeking adult cannabis smokers	104	Consumption	Marijuana Quit Questionnaire	Cannabis abstinence	Alcohol use	Substitution	Weak

Budney, 2003 (Budney et al., 2003)	USA	Prospective cohort	18 cannabis users; 12 past users in parallel	30	Not specified	MWC, MCQ, Brief Symptom Inventory,	Cannabis abstinence	Alcohol use	Neither	Moderate
Budney, 2001 (Budney et al., 2001)	USA	Prospective cohort	Daily cannabis users	12	Not specified	Substance use diary, MWC, the Brief Symptom Inventory, MCQ	Cannabis abstinence	Alcohol use	Neither	Weak
Kouri, 2000 (Kouri and Pope, 2000)	USA	Prospective cohort	Current and former cannabis users	60	Toxicological	14-item daily withdrawal diary, Hamilton Depression Rating Scale, Hamilton Anxiety Scale	Cannabis withdrawal symptoms	Changes in alcohol use	Neither	Moderate
Stephens, 2000 (Stephens et al., 2000)	USA	Prospective cohort	Cannabis treatment seekers	291	Consumption	Follow up questionnaires	Past 90 days alcohol frequency	Monthly cannabis frequency	Weak complements	Moderate
Stephens, 1994 (Stephens et al., 1994)	USA	Prospective cohort	Cannabis treatment seekers	212	Consumption	DAST	Weekly alcohol use	Past 90 days cannabis frequency	Neither	Moderate

*Alcohol cessation or reduction (4 studies)*

Subbaraman, 2017 (Subbaraman et al., 2017)	USA	Secondary analysis of RCT	Newly alcohol-abstinent alcohol-dependant participants (COMBINE Study)	1383	Consumption	Follow-up medical assessments at week 8, 16, 26, 52, and 68	Cannabis use and quartiles of cannabis use	Post treatment percentage of days abstinent, Drinks Per Drinking Day, and	Weak evidence for complementarity	Moderate
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								Percentage of Heavy Drinking Days		
Peters, 2012 (Peters et al., 2012)	USA	RCT	8-week RCT of naltrexone for alcohol use	122 (18-21 years old)	Consumption	Young Adult Consequence Questionnaire, The Contemplation Ladder, The Barrat Impulsivity Scale, Drinking-Induced Disinhibition Scale, Medication Adherence Questionnaire	Cannabis user	Individual-level alcohol use and related problems	Neither	Weak
Aharonovich, 2005 (Aharonovich et al., 2005)	USA	Prospective cohort	Inpatient psychiatric/substance abuse treatment	250	Self-reported use	Longitudinal Psychiatric Research Interview for Substance and Mental Disorders	Post discharge cannabis use	Alcohol use post treatment	Complements	Weak
Mikuriya, 2004 (Mikuriya, 2004)	USA	Longitudinal cohort study	Seekers of physician's approval to use cannabis for alcohol treatment	92	Consumption	Examination of medical records follow up interview	indicator, alcohol	Efficacy of treating alcoholism with cannabis	Substitution	Weak
Rosenberg, 1978	Longitudinal Pre/post study	USA	Men experiencing difficulties with alcohol	44	Consumption	Not specified	Cannabis or cannabis and disulfiram	Alcohol use during	Neither	Moderate

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(Rosenberg et al., 1978)

alcohol treatment

Abbreviations for measurement tool: MTF (Monitoring The Future Survey), MWC (Marijuana Withdrawal Checklist), MCQ (Marijuana Craving Questionnaire), CPQ (Cannabis Problems Questionnaire), Penn Alcohol Craving Scale

**Table 4.** Economic relationship studies (ten studies)

<i>Paper</i>	<i>Country</i>	<i>Study design</i>	<i>Population</i>	<i>Sample size</i>	<i>Measure Category</i>	<i>Measurement tool</i>	<i>Independent variable</i>	<i>Dependent variable</i>	<i>Conclusion</i>	<i>Quality assessment</i>
<i>General population studies (3 studies)</i>										
Cameron, 2001 (Cameron and Williams, 2001)	Australia	Cross sectional survey	National Drug Strategy Household Survey (Australia)	9,744	Consumption	Australian National Drug Strategy's Household Survey	State-level cannabis decriminalisation indicator	Individual-level past 12 months cannabis and alcohol use	Both: Decriminalisation increases alcohol use suggesting complements, price effects suggest substitution	Strong
Saffer, 1999 (Saffer and Chaloupka, 1999a)	USA	Cross sectional survey	National Household Survey on Drug Abuse	49,802	Consumption	National Household Survey on Drug Abuse	State-level cannabis decriminalisation indicator	Individual-level alcohol frequency, cannabis use	Both Complements for full sample, white males and blacks: substitutes for Native Americans and Hispanics	Strong
Saffer, 1998 (Saffer and Chaloupka, 1999)	USA	Cross sectional survey	National Household Survey on Drug Abuse	49,802	Consumption	National Household Survey of Drug Abuse	State-level alcohol and drug prices	Individual-level alcohol frequency, cannabis use	Complements	Strong

*Young people studies (4 studies)*

Williams, 2004 (Williams et al., 2004)	USA	Cross sectional survey	Harvard School of Public Health's College Alcohol Study (CAS) (1993, 1997, 1999)	15,479 expands (Cameron 2001) to polysubstance users & adds control for drunk driving	Consumption	Harvard School of Public Health's College Alcohol Study (CAS)	State-level cannabis decriminalisation indicators, fines for drunk driving, price for cannabis and alcohol	Individual-level past year cannabis use	Complements, especially among polysubstance users & males	Strong
Pacula, 1998 (Pacula, 1998)	USA	Longitudinal panel	National Longitudinal Survey of Youth (1979)	8,008	Consumption	National Longitudinal Survey of Youth	State-level beer tax	Individual-level past 30 days # drinks, # of times used cannabis	Complement	Strong
Chaloupka, 1997 (Chaloupka and Laixuthai, 1997)	USA	Cross sectional survey	Monitoring the Future	25,430	Consumption	Monitoring the Future	State-level cannabis decriminalisation indicator	Individual-level alcohol frequency, heavy drinking accidents	Substitution	Strong

Yamada, 1996 (Yamada et al., 1996)	USA	Cross sectional survey	12th grade high school students in the academic year of 1981/1982	672	Consumption	National Longitudinal Survey of Youth	State-level liquor price / marijuana decriminalisation	Individual-level marijuana use / Individual-level alcohol use	Both	Strong
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*Drug user's studies (2 studies)*

Cole, 2008 (Cole et al., 2008)	UK	Cross sectional survey	Polydrug users who illegally use controlled drugs	80	Monetary	AUDIT, DAST-A, SDS, HADS, simulation purchase of alcohol and drugs	Changes in the quality of cannabis	Individual-level purchase	Substitution	Weak
Williams, 2004 (Williams and Mahmoudi, 2004)	Australia	Cross sectional survey	Australian National Drug Strategies Household Survey	48,174	Consumption	Australian National Drug Strategy's Household Survey	State-level cannabis decriminalisation indicator; cannabis price	State-level past month & past year alcohol and cannabis frequency	Complement	Strong

*Other (1 study)*

Clements, 2004 (Clements, 2004)	Australia	Economic analysis	Australian Drug market	NA	Monetary	Australian Bureau of Criminal Intelligence	Changes in marijuana prices	Alcohol consumption	Substitution	Unrated
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*Abbreviations for measurement tool: AUDIT (Alcohol Use Disorder Identification Test), DAST-A (Drug Abuse Screening Test for Adolescents, SDS (Severity of Dependence Scale for cannabis), SDS (Hospital Anxiety and Depression Scale)*

**Table 5.** Patterns of use studies (six studies)

<i>Paper</i>	<i>Country</i>	<i>Study design</i>	<i>Population</i>	<i>Sample size</i>	<i>Measure Category</i>	<i>Measurement tool</i>	<i>Independent variable</i>	<i>Dependent variable</i>	<i>Conclusion</i>	<i>Quality assessment</i>
<i>General population studies (1 study)</i>										
Choi, 2018 (Choi et al., 2018)	USA	Longitudinal panel	PATH study (wave 1 and 2) respondents	26,204	Consumption	Population Assessment of Tobacco and Health Study (PATH)	Past 12 months and 30 days of frequency of cannabis use	Past 12 months and 30-day frequency of alcohol use	Complements	Moderate
<i>Young people studies (5 studies)</i>										
Gripe, 2018 (Gripe et al., 2018)	Sweden	Cross sectional survey	Swedish Council for Information on Alcohol and Other Drugs Survey population	149,603	Consumption	Swedish Council for Information on Alcohol and other Drugs Survey	Individual-level alcohol use	Individual-level cannabis use	Neither	Strong
O'Hara, 2016 (O'Hara et al., 2016)	USA	Longitudinal cohort study	College students	876	Consumption	COPE inventory. Daily diary study: 2-3 weeks after baseline using an	Quantity of daily drinks and overall alcohol 30-day use	Evening cannabis use	Complement	Weak

						online website to report last night cannabis and alcohol use each day for 30 days.				
Deza, 2015 (Deza, 2015)	USA	Longitudinal panel	National Longitudinal Survey of Youth 1997	8,984	Consumption	National Longitudinal Survey of Youth (1997)	State-level medical marijuana laws	State-level traffic fatalities, alcohol and cannabis use	Complement	Moderate
Pape, 2009 (Pape et al., 2009)	Norway	Cross sectional survey	European School Project on Alcohol and Drugs	16,813	Consumption	Norwegian youth Survey and ESPAD	None	Proportion of cannabis/alcohol use occasions	Complement	Weak
Hammer, 1992 (Hammer and Vaglum, 1992)	Norway	Longitudinal cohort study	Sample extracted from the 1985 NSYPASW aged 17-20	1,997	Consumption	National Survey of Youngs People Adjustment to School and Work (NSYPASW)	Total past frequency of cannabis use and past year frequency of cannabis use	Past four weeks and past year of alcohol use, quantity of alcohol use in the last drinking incident	Complement in young groups and young adult females	Weak

*Abbreviations for measurement tool: ESPAD (European School Survey on Alcohol and Other Drugs)*

**Table 6.** Substitution practices studies

<i>Paper</i>	<i>Country</i>	<i>Study design</i>	<i>Population</i>	<i>Sample size</i>	<i>Measure category</i>	<i>Measurement tool</i>	<i>Independent variable</i>	<i>Dependent variable</i>	<i>Conclusion</i>	<i>Quality assessment</i>
<i>Medical Cannabis Patients (5 studies)</i>										
Lucas, 2017 (Lucas and Walsh, 2017)	Canada	Cross sectional survey	Patients registered to purchase cannabis from Tilray	271	Self-reported substitution	Online 107-item questionnaire available in French and English	Medical cannabis use	Participants reporting substituting cannabis for prescription drugs, alcohol tobacco, or illicit drugs	Substitution	Weak
Piper, 2017 (Piper et al., 2017)	USA	Cross sectional survey	Members of dispensaries in New England	1,513	Self-reported substitution	Online survey; items on self-reporting substitution of cannabis for alcohol and other drugs	Medical cannabis use	Prevalence of self-reported substitution of alcohol for cannabis	Substitution	Weak
Lucas, 2016 (Lucas et al., 2016)	USA	Cross sectional survey	Cannabis Access for Medical Purpose Survey (CAMPS)	473	Self-reported substitution	Cannabis access for Medical Purposes Survey (CAMPS)	Medical cannabis use	Prevalence of substituting cannabis for prescription drugs, alcohol tobacco, or illicit drugs	Substitution	Weak

Lucas, 2013 (Lucas et al., 2013)	Canada	Cross sectional survey	Medical cannabis patients from dispensaries in British Columbia	404	Self-reported substitution	Adapted version of medical cannabis survey from Reiman, 2009	None	Self-reported substitution of cannabis for alcohol	Substitution	Weak
Reiman, 2009 (Reiman, 2009)	USA	Cross sectional survey	Medical cannabis patients from Berkeley Patient's Group (BPG)	350	Self-reported substitution	Survey created by researcher with portions adapted from a Medical cannabis patient survey	None	Self-reported substitution of cannabis for alcohol	Substitution	Weak

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*Cannabis users (1 study)*

Lau, 2015 (Lau et al., 2015)	USA	Qualitative study	Baby Boomer marijuana users in San Francisco	97	Interview	Semi-structured in-depth life history interview, questionnaire and health survey	Recreational cannabis use	Self-reported substitution of cannabis for prescription drugs, alcohol, tobacco, or illicit drugs as a harm reduction measure	Substitution	Moderate (Assessed using CASP Tool)
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**Table 7. "Other" studies**

<b>Paper</b>	<b>Country</b>	<b>Study design</b>	<b>Population</b>	<b>Sample size</b>	<b>Measure category</b>	<b>Measurement tool</b>	<b>Independent variable</b>	<b>Dependent variable</b>	<b>Conclusion</b>	<b>Quality assessment</b>
Klimas, 2016 (Klimas et al., 2016)	Canada	Longitudinal prospective community-based cohort	Heroin users	357	Consumption	Self-report and 50.3 month follow up	Enrolment in Methadone Maintenance Treatment	Initiation of heavy drinking	Complement	Weak
Subbaraman, 2015 (Subbaraman and Kerr, 2015)	USA	Cross sectional survey	Current drinkers from the National Alcohol Study (NAS) 2005 and 2010	8,626	Consumption	National Alcohol Study (NAS)	Current alcohol use	Past 12 months cannabis use frequency, drunk driving, alcohol related social consequences, alcohol related harms	Some evidence of complementarity in concurrent users	Moderate
Reiman, 2007 (Reiman, 2007)	USA	Cross sectional survey	Medical cannabis patients	130	Self-reported substitution	Qualitative interview, adapted from of the RAND 36-item Health survey, Patient Satisfaction Questionnaire III	None	Self-reported substitution of cannabis for alcohol and other drugs	Substitution	Weak

Alter, 2006 (Alter et al., 2006)	USA	Cross sectional survey	Monitoring the Future, Midwest subsample	11,542	Consumption	Survey like Monitoring the future	Perceived access and harms of alcohol and cannabis	Individual-level past month alcohol and cannabis frequency	Substitution	Strong
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**Table 8. Animal studies**

<b>Paper</b>	<b>Country</b>	<b>Study design</b>	<b>Population</b>	<b>Sample size</b>	<b>Measure category</b>	<b>Measurement tool</b>	<b>Independent variable</b>	<b>Dependent variable</b>	<b>Conclusion</b>	<b>Quality assessment</b>
Filev, 2017 (Filev et al., 2017)	Brazil	Longitudinal experimental	DBA/2 Mice	84	Locomotor activity	Sensitisation context for 15 minutes (wooden box painted with white acrylic)	Photo cannabinoid treatment (THC, THC+CBD, CBD) by injection	Locomotor activity	Substitution in THC and THC+CBD treatment, no effect for CBD treatment alone	Low risk

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