Rapid Response

Legalizing Cannabis Cultivation: What we need to know & is Lebanon Ready?

A K2P Rapid Response responds to urgent requests from policymakers and stakeholders by summarizing research evidence drawn from systematic reviews and from single research studies. K2P Rapid Response services provide access to optimally packaged, relevant and high-quality research evidence for decision-making over short periods of time ranging between 3, 10 and 30-days.

Rapid Response

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K2P Rapid Response

Legalizing Cannabis Cultivation: What we need to know & is Lebanon Ready?

Knowledge to Policy Center K2P

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Contents

Key Messages

الرسائل الأساسية

السياق المحلّي

- ← في لبنان، يجرّم القانون 673، حصاد، أو إنتاج، أو تجارة، أو احتواز مواد مخدّرة غير مشروعة، من ضمنها الحشيش (القنب). وتشمل الاستثناءات إصدار تراخيص خاصة للزراعة من قبل مجلس الوزراء للمؤسسات الأكاديمية أو العامة لأغراض البحث العلمي أو الطبي (المادة 12 من القانون 673)، بالإضافة الى أذونات خاصة للاستخدام الفردي للمواد المخدّرة عبر الوصفات الطبية.
- ← لا يزال يشكّل تطبيق القانون تحدياً كبيراً، لا سيما من حيث إنتشار استخدام الحشيش على نطاق واسع بين اللبنانيين وإستمرار زراعته ،خاصة في منطقة البقاع، مما يفسح الطريق أمام الاتجار غير المشروع والتهريب.
- ← إن تشريع زراعة الحشيش للأغراض الطبية وقوننة سوقه يمكن أن يدر عائدات للحكومة تصل إلى مليار دولار أميركي.
- ← أدت النداءات المتزايدة للسياسيين اللبنانيين وأصحاب القرار والإعلاميين الهادفة لتشريع الحشيش إلى تسليط الضوء على إمكانية وضع حدّ لتجارة المخدرات والإدمان والتهريب غير المشروع، بالإضافة إلى فوائد اقتصادية وطبية.
- ← وتزامناً، تم الإعراب عن مخاوف خطيرة في ما يتعلق بالتطبيق الفعال للقانون وتنفيذه والتأكيد على الحاجة إلى الأطر القانونية والتنظيمية المناسبة للتخفيف من العواقب السلبية غير المقصودة جراء تطبيق القانون.

استخدامات الحشيش

- ← وافقت دول عدّة مثل كندا والدنمارك والولايات المتحدة على استعمال الحشيش في التطبيقات الطبية، خاصة في ما يتعلق بمعالجة حالات التقيؤ والأمراض العصبية.
- ← تمت الموافقة في 25 بلدا، على استعمال مزيج من مادة الـ Tetrahydrocannabinol (THC) والـ cannabidiol (CBD) المخدرة لعلاج الشلل التشنجي لدى مرضى التصلّب اللّويحي.
- ← أظهرت اثنا عشر دراسة منهجية أن للاستخدام الطبي للقنب فعالية في الحد من آلام الأمراض العصبية والألم والشلل التشنجي لدى مرضى التصلب اللويحي والغثيان والقيء لدى المرضى الذين يخضعون لعلاج كيميائي.
- ← إن للاستخدام الشخصي للقنب آثار ضارة على بنية الدماغ ووظيفته، وعلى عدد من اضطرابات الصحة العقلية، والتحصيل العلمي، ومعدلات حوادث السيارات.

نماذج تشريع الحشيش وتأثيراتها

- ← تشمل نماذج تشريعات الحشيش: الحظر، التشريع لأغراض طبية، إلغاء التجريم، وتشريع الاستخدام الشخصي.

- أظهرت تجارب البلدان السابقة أنه لا يوجد إطار عالمي موحد لتشريع الحشيش.
- الى جانب خلق أسواق سوداء ضخمة تحدّ من إيرادات الحكومة، وبالإضافة الى تطور فعالية الحشيش، لم تثبت سياسات الحظر فعاليتها في تخفيض الإستهلاك في العديد من السياقات.
- أظهرت الدراسات أن تشريع الحشيش لأغراض طبية تترافق مع ازدياد الإعتقاد في عدد من الولايات الأميركية أن احتواز الحشيش أصبح أكثر سهولة وإستعماله أكثر أماناً من الناحية الصحية.
- نتج عن عدد من الدراسات أدلة مختلطة من حيث تأثير تشريع الحشيش على نسب الاستهلاك، في حين أن غالبية الدراسات لم تظهر أي صلة مهمة بين التشريع والإستهلاك.
- قد يوفر تشريع الحشيش إيرادات وطنية كبيرة من خلال زيادة العمالة والدخل وعائدات ضرائب الضمان الاجتماعي عن طريق تحويل العمالة من أنشطة جنائية إلى أنشطة قانونية خاضعة للضريبة.
- إن استهلاك الحشيش يخضع لمرونة الأسعار، فانخفاض الأسعار قد يؤدي إلى زيادة الاستهلاك؛ مع تقديرات تشير الى أن كل انخفاض بنسبة 10٪ في السعر يؤدي إلى زيادة بنسبة 3 ٪ في العدد الإجمالي للمستخدمين وزيادة بنسبة 3-5٪ في عدد الشباب المستهل لإستهلاك الحشيش.

ما هي العوامل التي يجب أخذها بعين الإعتبار عند التطبيق العملي؟

- يلف عدم الوضوح العديد من الأدلة والخبرات للبلدان التي وضعت سياسات لاستخدام الحشيش. وهذا بدوره يجعل من الصعب استخلاص الاستنتاجات أو تكرار الخبرات في أطر مختلفة. على الرغم من عدم الثبات في الأدلة والتجارب، فإن اعتبارات التنفيذ التالية يجب أن تؤخذ بعين الاعتبار إذا قررت الدولة تعديل القانون 673 وتشريع زراعة الحشيش لأغراض طبية أو حتى ترويجية.
- **إجراء تقييم مفصّل للحالة الراهنة، من خلال التقييم والقياس الكمّي**:
  - لنسب استخدام الحشيش (مثل معدل تعاطي الحشيش)
  - لمعدل الجريمة المرتبط بالحشيش
  - لعدد ونوع الحالات الطبية التي تتطلب علاج الحشيش الطبي
  - لحجم سوق الحشيش وإمكانية التصريف
  - للتصورات والقيم والمواقف لدى مختلف أصحاب المصلحة الذين قد يتأثرون بسياسة الحشيش هذه
  - لتأثير أي سياسة أو إجراء يتعلق بتنظيم الحشيش
- **إشراك أصحاب القرار في حوار قائم على الأدلة العلمية يمكنهم من خلاله:**

- ← الموافقة على الهدف (أو الأهداف) لسياسة الحشيش المتبعة، مسترشدة بتقييم الوضع الراهن.
- ← الاستطلاع، الحكم، والإختيار، بعد الإستناد الى الأدلة العلمية والسياق الحالي، على الخيارات التي تضمن أعلى احتمالات لتحقيق الفوائد الصحية والاقتصادية المرجوة، مقابل أقل نسبة من العواقب االممكنة على الصعيد الصحي، الإقتصادي والإجتماعي.
- ← وضع إطار للتشريع وضمان توافر الإجراءات التنظيمية وأساليب الرصد والتقييم لتسهيل التنفيذ الفعال لقانون الحشيش.
- ← تقييم فوائد تشريع الحشيش، مثل الحرية الشخصية، والاستخدام الطبي، وعائدات الضرائب، والنمو الاقتصادي، مقابل الأضرار المحتملة المرتبطة بها مثل زيادة معدلات تعاطي المخدرات، ومعدل الإجرام المرتبط بالحشيش، والجهود والمصاريف الإدارية المطلوبة لوضع القواعد التنظيمية، والمراقبة، وآليات التحكم في إنتاج الحشيش والتجارة والضرائب والاستخدام.
- ← تقييم قدرة الحكومة اللبنانية على تنظيم القوانين والإشراف عليها وتنفيذها، لا سيما في مجال قد يؤدي فيه ضعف التنظيم إلى عواقب صحية واجتماعية مؤذية.

- ← **بعد الاتفاق بين أصحاب القرار المعنيين، ينبغي أن يشمل أي إطار لتشريع الحشيش الأبعاد التالية:**
  - ← الهيئات الحكومية المسؤولة عن إصدار التراخيص والإشراف على الزراعة والإنتاج والتوزيع والتصدير.
  - ← الأطر التنظيمية التي تعمل بموجبها تلك الهيئات.
  - ← قواعد وسياسات واضحة بشأن حصاد الحشيش، والتصنيع، والتجهيز، والتعبئة، ووضع العلامات الفارقة، ونقاط البيع بالتجزئة، والتوزيع، والتصدير، والتسويق، والكمية المنتجة، ووسائل الاستخدام.
  - ← طبيعة ونوعية وفعالية المنتجات التي يمكن إنتاجها وتوزيعها.
  - ← آلية تنظيم الأسعار لتجنب الأسواق غير القانونية وزيادة الاستهلاك.
  - ← آلية الضرائب واستخدام الضرائب والعوائد المالية.
  - ← آلية الرصد والتقييم التي تهدف إلى رصد وتخفيف أي تأثيرات ضارة غير مقصودة للقانون ومن ثم مراجعة القانون.
- ← ومن بين الشروط المسبقة للتنفيذ الفعال لأي إطار تنظيمي للحشيش، زيادة الوعي بين الشباب خصوصاً بشأن الأضرار الناجمة عن تعاطي الحشيش كمادة مخدّرة وكذلك تثقيف المجتمع فيما يتعلق بهدف تشريع الحشيش، والآليات التنظيمية وآليات التنفيذ، واستخدام الإيرادات.

Key Messages

Local Context

- In Lebanon, according to Law 673, it is illegal to harvest, produce, trade, or possess illicit drugs- including Cannabis. Exceptions include issuing special cultivation licenses by the council of ministers for academic or public institutions for scientific or medical research purposes (article 12 of Law 673). Special permissions are also issued for individual drug use through medical prescriptions.
- The implementation of the law remains a significant challenge as cannabis use is still widespread among the Lebanese populations and cannabis is still cultivated, mainly in the Bekaa' valley, paving the way to illegal drug trade and smuggling.
- Legalizing the cultivation of cannabis for medicinal purposes and moving it from an illicit to a legal market can release up to $1 billion in revenue for the government.
- Advocacy by local politicians, stakeholders, and media spokespersons for cannabis legalization increased, highlighting the potential for reducing illegal drug trade, addiction and smuggling, in addition to the economic and medical benefits.
- Simultaneously, critical concerns were voiced regarding the effective implementation and enforcement of the law and the need for appropriate legal and regulatory frameworks to mitigate unintended consequences.

Cannabis Utilization

- Several countries such as Canada, Denmark and the United States approved several cannabinoids for medical applications, particularly for the management of emesis and neurological conditions.
- A combination of Tetrahydrocannabinol (THC) and cannabidiol (CBD) has been approved for spasticity treatment in 25 countries.
- Twelve systematic reviews found that medical use of cannabis was effective in reducing neuropathic pain, pain and spasticity in multiple sclerosis patients and nausea and vomiting in patients receiving chemotherapy.
- Recreational use of cannabis was found to have deleterious effects on brain structure and function, various mental health disorders, educational attainment, and rates of motor vehicle accidents.

Cannabis Legislation Models and their Impact

- Cannabis legislation models include: prohibition, legalization for medical purposes, decriminalization, and legalization of recreational use.

- Shared experiences revealed that there is no universal framework for legalization.
- Besides generating huge black markets resulting in foregone revenues for the government and increasing potency of cannabis plant, prohibition policies, in many settings, were not found to significantly decrease consumption.
- Studies found that there was an increased perception of easy accessibility and enhanced safety in various US states after legalizing medical marijuana.
- Mixed evidence was found on the effect of cannabis legalization on consumption trends with the majority of studies negating any significant link.
- Cannabis legalization may provide significant national revenue through increasing employment, income, and social security tax revenues by shifting labor from criminal to legal and taxed activities.
- Cannabis consumption is price-elastic, with lower prices probably leading to higher consumption; with estimates that for each 10% drop in price, there would be a 3% increase in the total number of users and a 3-5% increase in youth initiation.

Implementation considerations for Lebanon

There are many uncertainties in the evidence and experiences of countries that have devised a cannabis use policy. This in turn makes it difficult to draw inferences or replicate practices across different settings. Despite these uncertainties, the following implementation considerations should be considered if the government chooses to amend Law 673 and legalize the cultivation of cannabis for medicinal or even recreational purposes.

- A priori to cannabis legalizing, a detailed assessment of the current situation is warranted through evaluating and quantifying:
  - Cannabis use such as the rate of cannabis abuse
  - Cannabis-related criminality rate
  - Number and type of medical conditions requiring medical cannabis treatment
  - Size of the cannabis market
  - Perceptions, values and attitudes of various stakeholders potentially affected by this cannabis policy
  - Impact projection of any policy or intervention regarding cannabis regulation
- Any attempt at cannabis regulation necessitates engaging stakeholders in an evidence-informed dialogue through which they can:
  - Agree on the objective(s) of the pursued cannabis policy, guided by the assessment of the status quo

- Explore, judge, and preferentially decide, guided by evidence and contextual factors, on options with the highest odds of achieving the pursued health and economic benefits, at the lowest possible trade-offs in health, economic, and social terms
- Set a framework for legalization and assure the availability of regulatory, monitoring, and evaluation procedures to facilitate the effective implementation of the cannabis policy.
- Weigh the benefits of cannabis legalization such as personal liberty, medical use, tax revenues, and economic growth against possibly associated harms such as growing substance abuse rates, cannabis-related criminality rate, and administrative efforts and expenses required to set regulatory, monitoring, and control mechanisms for cannabis production, trade, taxation, and use.
- Address the capacity of the Lebanese government to regulate, oversee and enforce laws, particularly in an area where poor regulation may result in deleterious health and social consequences.

- Following agreement by key stakeholders, any cannabis framework for legalization should encompass the following dimensions:
  - State bodies that are responsible for issuing licenses and overseeing cultivation, production, distribution and export
  - Regulations under which those bodies operate
  - Clear rules and policies regarding cannabis harvesting, manufacturing, processing, packaging, labelling, retail, distribution, export, commercialization, the quantity produced, and the means of usage
  - Nature, quality, and potency of the products that can be produced and distributed
  - Price regulatory mechanism to avoid a rise in consumption and illegal market.
  - Taxation and the use of tax returns
  - Monitoring and evaluation mechanisms aiming at monitoring and mitigating any unintended adverse effects and subsequently reviewing the policy
- Raising awareness particularly among the youth on the harms of cannabis use as well as education of the community regarding the goal of legalization, the regulatory and enforcement mechanisms, and the use of revenues generated are pre-requisites to effective implementation of any cannabis regulatory model.

Content

This Rapid Response document is structured as follows

1) Current Issue and Question
2) Background and Lebanese Context
3) Synthesis of the Evidence
4) What Other Countries are Doing
5) Implementation Consideration
6) Insights for Action

Current Issue and Question

For the past few years, legalizing the cultivation of cannabis for medicinal purposes has emerged as a controversial issue in Lebanon. In July 2018, the issue was again at the center of public debate and was brought to policymakers' agenda after the release of a report by the global consultancy firm McKinsey & Co. which suggested that legalizing the cultivation of cannabis would release up to $1 billion in revenue for the government (Al Joumhouria, 2018; The Daily Star, 2018a). Following this report, the Speaker of the Parliament appointed a committee to prepare a law proposal for cannabis cultivation (Al Akhbar, 2018; Al Joumhouria, 2018; The Daily Star, 201b). This was paralleled by increased advocacy for cannabis legalization by local politicians, stakeholders, and media spokespersons, highlighting the potential for reducing illegal drug trade, addiction and smuggling in addition to economic and medical benefits (Al Joumhouria, 2018a; Al Joumhouria, 2018b ; The Daily Star, 2018c). Farmers also welcomed the proposal for legalizing cannabis cultivation for medicinal purposes (Ismail, 2018). At the same time, critical concerns were voiced regarding effective implementation and enforcement of the proposed law and the need for appropriate legal and regulatory frameworks in order to

Background to K2P Rapid Response

A K2P Rapid Response responds to urgent requests from policymakers and stakeholders by summarizing research evidence drawn from systematic reviews and from single research studies. A systematic review is an overview of primary research on a particular question that relies on systematic and explicit methods to identify, select, appraise and synthesize research evidence relevant to that question.

K2P Rapid Response services provide access to optimally packaged, relevant and high-quality research evidence over short periods of time ranging between 3, 10, and 30-day timeframe.

This rapid response was prepared in a 10-day timeframe and involved the following steps:

1) Formulating a clear review question on a high priority topic requested by policymakers and stakeholders from K2P Center.

2) Establishing what is to be done in what timelines.

3) Identifying, selecting, appraising and synthesizing relevant research evidence about the question

4) Drafting the K2P Rapid Response in such a way that the research evidence is present concisely and in accessible language.

5) Submitting K2P Rapid Response for Peer/Merit Review.

6) Finalizing the K2P Rapid Response based on the input of the peer/merit reviewers.

7) Final Submission, translation into Arabic, validation, and dissemination of K2P Rapid Response

The quality of evidence is assessed using the AMSTAR rating which stands for A Measurement Tool to Assess Systematic Reviews. This is a reliable and valid measurement tool to assess the methodological quality of systematic reviews using 11 items. AMSTAR characterizes quality of evidence at three levels:

8 to 11= high quality

4 to 7 =medium quality

0 to 3 = low quality

mitigate unintended consequences (Al Mustaqbal, 2018; Al Joumhouria, 2018a).

This K2P rapid response aims to provide evidence to policymakers and stakeholders for informing any policy deliberation on critical considerations regarding the process of cannabis legalization in Lebanon. It also intends to disseminate knowledge regarding any potential cannabis regulatory framework with the aim of informing discussions among citizens and the media. This rapid response (1) describes the local context on cannabis policy, (2) presents the evidence surrounding impact of medical and recreational use of cannabis, (3) delineates the effect of legalizing cannabis mainly on consumption and the economy, and (4) outlines considerations and requisites for any potential cannabis policy in Lebanon. The intention of this document is not to advocate for specific policy elements or to close off discussions, but rather to inform and pave the way for an informed dialogue on this topic.

Local Context

In Lebanon, Law 673- signed in 1998 by President Elias Hrawi- makes it illegal to harvest, produce, trade, or hold illicit drugs- including Cannabis (article 11). Exceptions include issuing special cultivation licenses by the council of ministers for academic or public institutions for scientific or medical research purposes (article 12 of Law 673). Special permissions are also issued for individual drug use through medical prescriptions. Under the same law, charges may be dropped on drug abusers who submit to medical treatment and rehabilitation (Lebanese Ministry of Justice).

The law criminalizes the non-medical use and cultivation of cannabis (article 11 of law 673); however, its implementation remains a significant challenge. Cannabis use is still widespread in the Lebanese population, particularly among the youth. Nine percent of high school students reported ever trying any illegal drug, with slightly more than half of those using marijuana. Among university students, the proportion of lifetime use of marijuana in was 8.8%. Interestingly, although 95.3% of students perceived drugs as harmful, 15.6% advocated for legalizing marijuana for recreational use (Karam et al, 2010). A more recent study found that 12.3% of university students ever consumed cannabis (Salemeh et al, 2015). Non-medical cannabis use among university students (Ghandour et al, 2012), particularly for non-therapeutic reasons (Ghandour et al, 2013), was also more likely to coexist with other types of substance use and abuse. Additionally, cannabis abuse was associated with schizophrenia in 44.8% of patients admitted for cannabis abuse (Karam, Yabroudi, & Melhem, 2002). Moreover, marijuana use was a major cause for criminalization. According to the Internal Security Forces survey, marijuana ranked second to heroin as the most common substances behind arrest (Karam et al, 2010).

Furthermore, cannabis is still cultivated in Lebanon, particularly in the Bekaa valley, paving the way to illegal drug trade and smuggling (BBC news, 2016).

Cannabis cultivation is a major source of living in this impoverished area of Lebanon, where alternative crop programs have failed to meet the economic needs of farmers. As a result, cannabis cultivation became a major source of high quality cannabis. In 2016, the United Nations Office on Drugs and Crime ranked Lebanon as one of the world's top five sources of cannabis resin. Figure 1 below presents key events in cannabis policy and market in Lebanon.

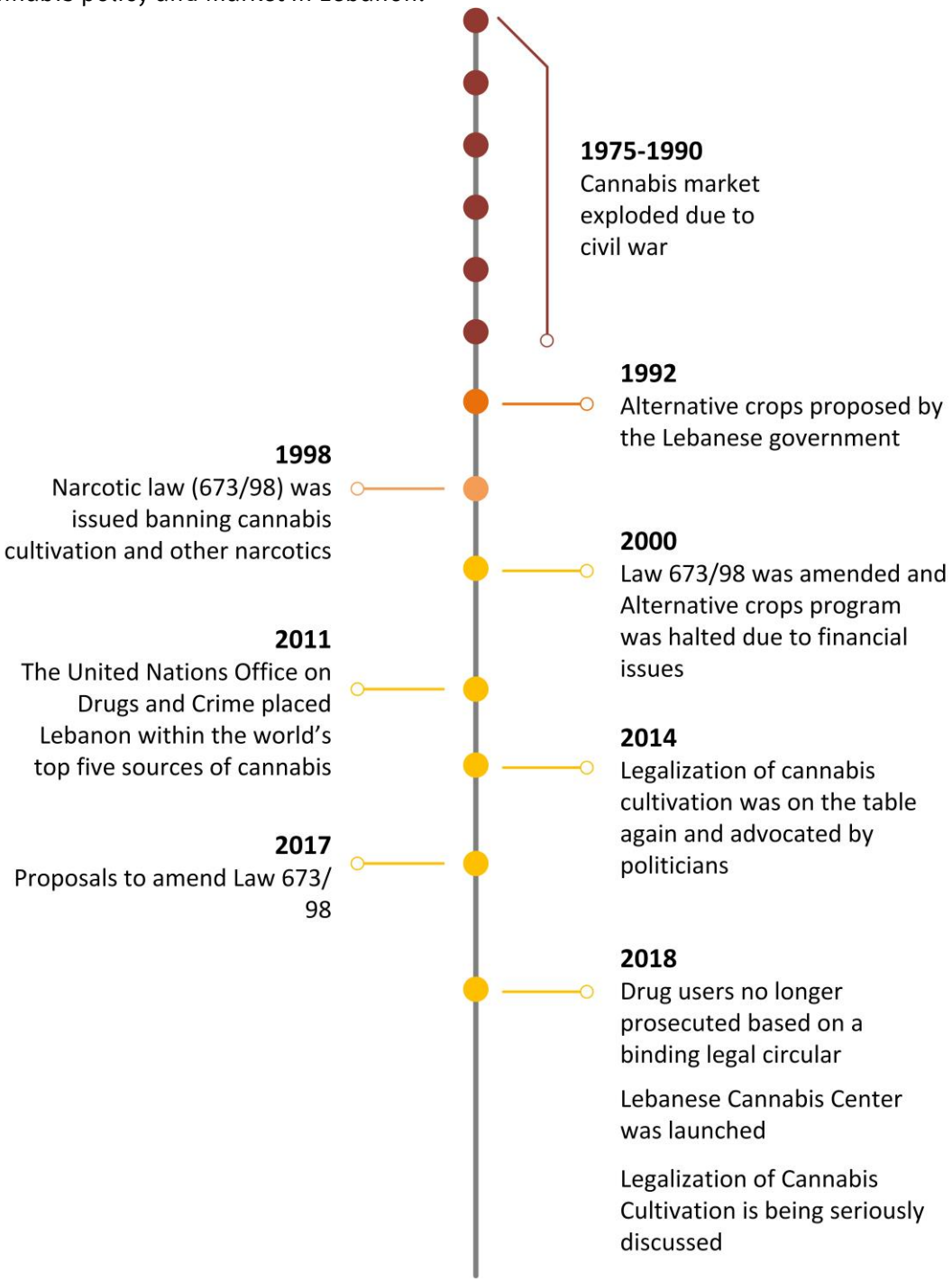

Figure 1 **Timeline**

Global Context

Several countries approved the use of cannabinoids for treatment of various medical conditions. Tetrahydrocannabinol (THC), for instance, is approved in Canada, Denmark and the United States as an anti-emetic, appetite stimulator, and for treatment of multiple sclerosis. Another formulation formed by a combination of THC and cannabidiol (CBD) is approved in 25 countries for spasticity treatment (Madras, 2015). FDA has also approved cannabinoids-based medications, Epidiolex, dronabinol and nabilone, for treating epilepsy, nausea and boosting appetite (FDA, 2016; FDA, 2018).

The following section presents findings from systematic reviews on the effects of medical and recreational use of cannabis on different clinical and health outcomes. It also presents the available evidence on the impact of cannabis legalization on consumption and the economy.

Medical Use of Cannabis

Twenty-one systematic reviews examined the effect of medical use of cannabis on different clinical outcomes. In summary, medical cannabis use was found to be effective in reducing:

- Neuropathic pain (Andreae et al, 2015; Martin-Sanchez et al, 2009; Lynch and Campbell, 2011; Whiting et al, 2015; Boychuk et al, 2015)
- Pain and spasticity in multiple sclerosis patients (Iskedjian et al, 2009; Koppel et al, 2014; Lakhan and Rowland, 2009; Whiting et al, 2015; Nielsen et al. 2018)
- Nausea and vomiting in patients receiving chemotherapy (Rocha et al, 2008; Whiting et al, 2015; Smith et al, 2015; Tramer et al, 2001)

It was also insignificantly associated with weight gain in patients with HIV (Lutge et al, 2013). In addition, limited evidence pointed towards a possible role of cannabis in treating some addiction disorders (Prud'homme et al, 2015). However, when used as a treatment option for schizophrenia, cannabis failed to demonstrate any superiority to psychoeducation (Rathbone et al, 2014). No reliable conclusions could be drawn regarding the efficacy of cannabinoids as a treatment for epilepsy, dementia, various rheumatic diseases, tics and obsessive-compulsive behavior in people with Tourette's syndrome (Gloss and Vickrey, 2013; Krishnan et al, 2009; Curtis et al, 2009).

Recreational use of cannabis

Sixty systematic reviews examined the effect of recreational use of cannabis on different clinical, health and socio-behavioral outcomes. All studies consistently reported findings of altered brain structure and function (Batalla et al, 2013; Batalla et al, 2014; Martin-Santos et al, 2010; Quickfall & Crockford, 2006; Lorenzetti et al, 2010; Rapp et al, 2012; Wrege et al, 2014; James et al, 2014; Rocchetti et al, 2013) among cannabis users. In addition, studies reported increased risk of depression (Lev-Ran et al, 2014), anxiety (Kedzior and Laeber, 2014), and psychosis (Semple et al, 2005; Moore et al, 2007; Marconi et al, 2016; Henquet et al, 2005; Kraan et al, 2016). Higher schizotypy scores (Szoke et al, 2014), exacerbation of manic symptoms in those previously diagnosed with bipolar disorder (Gibbs et al, 2015), earlier onset of schizophrenia (Myles et al, 2012), and increased risk of new manic symptoms (Gibbs et al, 2015) were also demonstrated. Some data pointed towards increased risk of adverse pregnancy outcomes (English et al, 1997; Gunn et al, 2015; Williams and Ross, 2007) and increased occurrence of caries, gingivitis, Candida albicans infection, and leukoedema (Veitz-Keenan and Spivakovsky, 2011). Nausea and dizziness were frequently reported side effects (Carbuto et al, 2012; Whiting et al, 2015) and were more likely to occur with faster infusion rates and higher doses (Carbuto et al, 2012).

Results on the effects of medical and recreational use of cannabis are summarized in the below table (more details can be found in Appendix 3).

Table 1 **Effect of medical and recreational use of cannabis**

Effects of medical use of cannabis	⇢ Effective in reducing neuropathic pain, spasticity in multiple sclerosis patients, and nausea and vomiting in patients receiving chemotherapy ⇢ Although non-significant, associated with weight gain in patients with HIV ⇢ Possible role in treating some addiction disorders
Effects of recreational use of cannabis	⇢ Altered brain structure and function ⇢ Increased risk of depression, anxiety, and psychosis ⇢ Higher schizotypy scores, exacerbation of manic symptoms in those previously diagnosed with bipolar disorder, earlier onset of schizophrenia, and increased risk of new manic symptoms ⇢ Increased risk of adverse pregnancy outcomes ⇢ Increased occurrence of caries, gingivitis, Candida albicans infection, and leukoedema ⇢ Increased risk for testicular non-seminoma germ cell tumor ⇢ Frequently reported nausea and dizziness ⇢ Lower educational attainment and poor school performance ⇢ Increased use of other illicit drugs ⇢ Increased risk of motor vehicle collisions including fatal collisions, homicide, and possibly suicide

Cannabis Legislation Models and their Impact

There are four distinctive legislation models on cannabis: (1) prohibition, (2) decriminalization, (3) legalization for medical use, and (4) legalization for recreational use (Ogrodnik et al. 2015). The table below presents examples of countries that have adopted such models and the impact of these models

Table 2 **Examples and Impact of models of cannabis legalization**

Models and Examples of Implementing Countries	Impact
Prohibition (Illegal use, possession, cultivation and supply)	
France ⇢ Cannabis use in France is almost strictly prohibited as only one cannabis derivative, Sativex, is legalized for use by patients with multiple sclerosis upon physician prescription ⇢ There is no distinction between different types of illegal drugs ⇢ The gravity of cannabis infraction is the same as that of heroin infraction (IDDA report, 2013). ⇢ Drug supply is sanctioned more severely than drug use.	**Consumption**: The rate of past-year use in the overall population is 9% in France with over 30% of the population has ever used cannabis (Van Laar, 2011). Other study demonstrated that cannabis prohibition policies have limited impact on consumption (Ogrodnik et al. 2015). **Potency** Average THC content in many countries has increased, and the THC:CBD balance deteriorated partially due of the illegality of cannabis production and the lack of regulations (Room et al. 2008; Caulkins et al, 2016). **Black market** Prohibition policies have generated a large black market resulting in foregone revenues for the government (Hall et al. 2009)
Legalization for medical use	
United States ⇢ 31 states allow for the medical use of marijuana. ⇢ 15 states allow use of 'low THC, high cannabidiol (CBD)' products for medical reasons (NCSL, 2018).	**Consumption** Most studies negated any significant association between legalizing cannabis for medical use and consumption of cannabis in the US (Choo et al, 2014; Gorman & Huber, 2007; Harper et al, 2012; Khatapoush & Hallfors, 2004; Lynne-Landsman et al, 2013; Wall et al, 2012; Reinarman et al. 2004).
United Kingdom ⇢ Distinctions are made between classes of drugs (DrugScope, 2015), with imposed sanctions differing accordingly. ⇢ Prohibition is the principal policy to prevent cannabis use. Cannabis use has been illegal in 1928, but it has been reclassified	One study found a paradoxical reduction in adolescent cannabis use after legalization for medical use in some US states (Choo et al, 2014), while 3 other studies found that legalizing cannabis medical use was associated with increased consumption in the US (Pacula, 2010; Cerdá et al, 2012; Wall et al, 2011).

Models and Examples of Implementing Countries	Impact
in 2002, resulting in the reduction of the maximum custodial sentence for possession to 2 years (Macleod & Hickman, 2010). ⇢ In July 2018, the government approved the use of medicinal cannabis by prescription (The Independent 2018, BBC 2018).	**Perception** There was an increased perception of easy accessibility (Schuermeyer et al, 2014; Jaffe & Klein, 2010; Schwartz et al, 2003) and enhanced safety (Schuermeyer et al, 2014; Jaffe & Klein, 2010; Wall et al, 2011) in various US states. **Economy** In the state of Colorado, monthly tax revenues from the retail and medical marijuana markets brought in over $8.5 million in the month of December alone. In revenue from sales, licenses and fees in both the medical and retail marijuana markets, the state revenues were to net approximately $76 million in the 2014 calendar year.
Decriminalization of cannabis use (Cannabis possession is sanctioned by a fine or allowed in a certain amount)	
Switzerland ⇢ An adult is fined for holding less than 10g with no criminal sentence. **Portugal** ⇢ Sanctions concerning drug use are administrative rather than criminal. For an amount of cannabis of less than 25g, the consumer receives a citation to appear before the Commission for the Dissuasion of Drug Addiction (Laqueur 2015). ⇢ If a consumer possesses more than 25g, the possessor undergoes the same judicial proceedings as a supplier. ⇢ Depenalization in Portugal did not affect drugs sales prices. **Australia** ⇢ Arrestees with less than 10g of cannabis receive a Citation Intervention Requirement (Government of Western Australia Drug and Alcohol Office, 2015).	**Consumption** In South Australia, cannabis decriminalization was associated with increased consumption, with similar increases noted in jurisdictions that prohibited cannabis use (Single et al, 2000). Early initiation and net increased consumption were adverse effects of cannabis decriminalization in Australia. Five years after the decriminalization policy, there was no significant effect on cannabis use initiation among youth or adults (Williams & Bretteville-Jensen, 2014). In Portugal, between 2001 and 2007, cannabis consumption remained stable and the rate of convictions decreased. Only lifetime use increased (IDDA report, 2013). **Use of other substances** In Portugal, decriminalization was associated with increased treatment referrals for cannabis abuse from 47% to 65%, decreased referrals for heroin abuse from 33% to 15%, and stable referrals for cocaine abuse at 4-6% (Hughes & Stevens, 2010). **Economy** Cannabis decriminalization modifies demand and supply. Expert analyses predicted that legalizing

Models and Examples of Implementing Countries	Impact
	cannabis would shift the demand curve upwards increasing the quantity demanded at a given price (Ogrodnik et al, 2015). Cannabis decriminalization is also expected to substantially reduce production costs, resulting in pre-tax retail price reduction of more than 80%; with the eventual consumer price depending on the tax-structure (Kilmer et al, 2010).
Legalization for recreational use	
State production and supply monopoly determines the price: **Uruguay** ⇢ Three forms of cannabis cultivation are allowed: private cultivation at home with up to six plants, cooperatives with up to 45 members, and licensed producers who supply the government. ⇢ Buyers of the commercially produced, over the counter sold cannabis are allowed a maximum purchase of 40 g per month (Ramsey, 2013). ⇢ The government is the primary cannabis supplier, allowing it to retain control over the quantity produced and the prices at which cannabis is sold(Musto, 2015). The institute for Regulation and Control for Cannabis is responsible to run the registry, issue and enforce regulations controlling the market and advise the government. ⇢ Advertisement and promotion of cannabis products is prohibited.	**Crime rate** In Uruguay, there was an increase in the number of persons charged for drug-related crimes from 739 in 2013, a year before cannabis legalization, to 1233 in 2015. However, the contribution of the new cannabis policy to this increase needs yet to be determined (Panampost, 2016). **Consumption** In the Netherlands, the effect of increased consumption was of late onset, observed several years after depenalization (MacCoun & Reuter, 1997; MacCoun, 2011). In Canada, after legalizing medical cannabis, there was an increasing demand from Canadians for medical cannabis, many of who were seeking a legal way to use cannabis recreationally (Health Canada). Through the same regulatory procedures, with a medical exemption, individuals became able to legally possess, use, grow and purchase cannabis; resulting in an exponential increase in medical cannabis users from 100 in 2001 to over 200,000 in 2017 (Government of Canada, 2018).
Legalization of consumption and trade. The price being determined by the market: **Netherlands** ⇢ Small-scale cannabis cultivation for private consumption is permitted. Authorities also tolerate the sale of cannabis for personal consumption in licensed coffee shops, which are allowed to detain a stock of 500g of cannabis. ⇢ Cannabis prices are low and determined by the market (United Nations Office on Drugs and Crime, 2009), with no set price or governmental interference.	**Economy** As a result of Cannabis legalization, it was stipulated that tax revenues from the sale of cannabis in Colorado provided $40 million, which were used for school construction (Brown et al, 2013).

Models and Examples of Implementing Countries	Impact
Colorado ⇢ Localities given autonomy to set marijuana regulations. As a result, municipalities' prohibition of local stores and cultivation operations (State of Colorado, 2012) led to the concentration of marijuana stores in about 20 cities or counties only (Ingold, 2013). Such stores are not allowed to sell other goods, with cannabis sale limited to 1 oz for Colorado residents and 1/4-oz for non-residents. ⇢ Product containers are also required to carry specified health warning statements. **Canada** ⇢ As of October 17, 2018, the recreational use of cannabis in Canada will officially become legal. ⇢ Throughout recent years, Canada has witnessed a marked policy shift in its stand towards cannabis cultivation and use. Medicinal cannabis has been legal since 2001 (Leung, 2011) at which time each person applying for a medical exemption was required to receive special access from Health Canada. Pricing schemes and the distribution of medical cannabis were regulated by the private industry.	

Lessons Learned from Shared Experiences of Countries

There are many uncertainties in the evidence and experiences of countries that have devised a cannabis use policy. This in turn makes it difficult to draw inferences and replicate practices across different settings. Acknowledging these challenges, shared experiences highlight key lessons learned for developing and implementing a cannabis policy.

- Different countries are driven by different objectives for designing and implementing a cannabis use policy

In the United States, for example, the explicit purpose of the cannabis policy is the prevention or cessation of use, while in Australia the focus is on minimizing harms associated with use (Single et al, 2000). Other goals of cannabis policies include raising tax revenues, eliminating arrests, undercutting black markets, reducing criminalization, assuring product quality, and controlling youth access (Caulkins et al, 2012). In Canada, moving from a prohibition model to legalization will allow the federal focus to shift to harm minimization, restricting youth access, social education, and maintaining public health and safety (Government of Canada, 2018b).

The impact of cannabis legalization should be assessed in accordance with the perceived goals and consequently the projected outcomes. Such diversity in goals and outcomes across countries limits the ability for performing cross-comparisons or drawing sound conclusions.

- Laws and policies governing cannabis use are considered to be part of recent history and still not very well studied

With the dearth of accumulated knowledge in this regard, it is uncertain how legalization will affect behaviour, consumption, economies, and other related outcomes in the short or long term. The expected positives and shortcomings of any policy, which are rather assumed, will need to be cautiously balanced (Caulkins et al, 2015a).

- Although cannabis use was shown to be correlated with many adverse health and social outcomes, it is cannot be ascertained whether the nature of the identified correlation is causation

The effects of cannabis use, under prohibition, might not accurately predict the effects of cannabis use in the future under some alternative legal regime. Furthermore, no one knows precisely how legalization will affect factors such as consumption, substance abuse rates, or products quality and potency. Thus, it is

difficult to ascertain whether the associations identified in the past are accurate predictions of those that will exist after legalization (Caulkins et al, 2015b). Similarly, the effects of cannabis legalization on economic parameters such as supply, demand, price, revenue, and cost remain postulates that need to be verified in different settings.

⇢ Cannabis laws or policies are not simply a binary choice between prohibition on one hand and legalization on the other

Cannabis regulation encompasses a wide range of possible regimes, with at least four dimensions: the kinds of organizations that are allowed to provide cannabis, the regulations under which those organizations operate, the nature of the products that can be distributed, and price (Caulkins et al, 2015b). Moreover, experiences have revealed that there is no universal framework for legalization. Any postulated legal framework in this field should have clear rules and policies regarding cannabis harvest, manufacturing, processing, packaging, labelling, retail, distribution, export, commercialization, age of retailers and users, permitted holding quantity, means of usage, price, quality, taxation, use of taxes and returns, and regulatory mechanisms (Caulkins et al, 2015a). Changing one variable under any of those dimensions potentially produces profound consequences on the outcomes of legalization in terms of health and social well-being, as well as for job creation and government revenue (Caulkins et al, 2015b).

⇢ Tax returns from retail cannabis sales may provide significant revenue (Daily Star, 2018)

Legalization may increase income and social security tax revenues by shifting labor from criminal to legal and taxed activities (UNODC, 2015; Ogrodnik et al, 2015).

⇢ Tradeoffs are inevitable

The benefits of cannabis legalization such as personal liberty, medical use, tax revenues, and economic growth may be offset by possibly associated harms such as increasing substance abuse rates and the administrative efforts and expenses to set regulatory, monitoring, and control mechanisms for cannabis production, trade, taxation, and use (Caulkins et al, 2015b). Significant costs will also be encountered through the establishment of programs and services for cannabis abuse prevention and treatment, as well as for the regulation of the new industry. In addition, consequences related to security, crime, legal and legislative issues, monitoring and enforcement, family problems, low performance, absenteeism, car and workplace accidents, and insurance should be accounted for, as they can incur significant costs (UNODC, 2015). Therefore, the success or failure of any cannabis policy is relative to the scale against which it is being measured.

- The price

Legalizing supply may shift the supply curve downwards, also reducing the selling price (Ogrodnik et al, 2015). Since cannabis consumption is price-elastic, the lower price will probably lead to higher consumption (Caulkins et al, 2012). For each 10% drop in price, it was estimated that there would be 3% increase in the total number of users (Kilmer et al, 2010) and a 3-5% increase in youth initiation (Pacula, 2010).

Implementation Considerations for Lebanon

Based on the experiences of other countries, the following implementation considerations should be taken into account if the government chooses to amend Law 673 and legalize the cultivation of cannabis for medicinal or even recreational purposes.

- A priori to cannabis legalizing, a detailed assessment of the current situation is warranted through evaluating and quantifying
  - Cannabis use such as the rate of cannabis abuse
  - Cannabis-related criminality rate
  - Number and type of medical conditions requiring medical cannabis treatment
  - Size of the cannabis market: size of the cannabis market: assessing the size of the market and the potential destination of export is crucial to avoid the misuse of cannabis produced
  - Perceptions, values and attitudes of various stakeholders potentially affected by this cannabis policy
  - Impact projection of any policy or intervention regarding cannabis regulation

- Any attempt at cannabis regulation necessitates engaging stakeholders in an evidence-informed dialogue through which they can
  - Agree on the objective(s) of the pursued cannabis policy, guided by the assessment of the status quo
  - Explore, judge, and preferentially decide, guided by evidence and contextual factors, on options with the highest odds of achieving the pursued health and economic benefits, at the lowest possible trade-offs in health, economic, and social terms
  - Set a framework for legalization and assure the availability of regulatory, monitoring, and evaluation procedures to facilitate the effective implementation of the cannabis policy.

- Weigh the benefits of cannabis legalization such as personal liberty, medical use, tax revenues, and economic growth against possible associated harms such as growing substance abuse rates, cannabis-related criminality rate, and administrative efforts and expenses required to set regulatory, monitoring, and control mechanisms for cannabis production, trade, taxation, and use.
- Address the capacity of the Lebanese government to regulate, oversee and enforce laws, particularly in an area where poor regulation may result in deleterious health and social consequences.

- Following agreement by key stakeholders, any cannabis framework for legalization should encompass the following dimensions
  - State bodies that are responsible for issuing licenses and overseeing cultivation, production, distribution and export
  - Regulations under which those bodies operate
  - Clear rules and policies regarding cannabis harvesting, manufacturing, processing, packaging, labelling, retail, distribution, export, commercialization, quantity produced, and means of use
  - Nature, quality, and potency of the products that can be produced and distributed: it is crucial to control quality and potency though setting the allowed THC content of the cannabis plant which determine its use
  - Price regulatory mechanism: Price is considered a key variable that needs to be regulated to avoid a rise in consumption and illegal market. State monopolization in supply will give it control in determining the price.
  - Taxation and the use of taxes and returns: Tax revenues from cannabis retail can be allocated to education sector, awareness and prevention of illicit drug use.
  - Monitoring and evaluation mechanisms aiming at monitoring and mitigating any unintended adverse effects and subsequently reviewing the policy

- Education of the community and information sharing regarding the goal of the legalization, the regulation and enforcement mechanisms, the use of revenues generated are pre-requisites to effective implementation of legalizing cannabis.
- Raising awareness, mainly among youth, on the deleterious effects of cannabis use is necessary to accompany any effort for legalization through national awareness and educational campaigns.

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Annexes

Annexes

Annex 1: Cannabis Composition

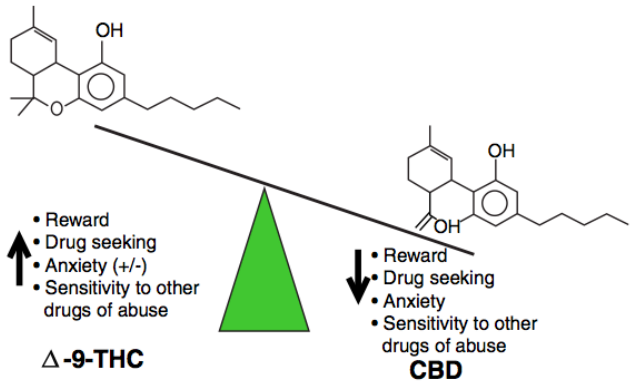
Cannabis is the accepted designation of the plant Cannabis sativa, Cannabis indica, and Cannabis ruderalis (Gloss; 2015). These species contains at least 400 distinct chemical moieties, with at least 85 isolated cannabinoids (Fischedick, 2009; Borrelli et al, 2009; Zanelati et al, 2010; Jones et al, 2011). Cannabis use for medicinal, ritual or recreational purposes results from the actions of cannabinoids.

Cannabinoids are derived from three sources:

- Phytocannabinoids, which are cannabinoid compounds produced by the cannabis plants such as nabiximol.
- Endocannabinoids, which are neurotransmitters, produced in the brain or in peripheral tissues, that act on the cannabinoid receptors
- Synthetic cannabinoids, such as dronabinol and nabilone, which are synthesized in the laboratory, are structurally analogous to phytocannabinoids or endocannabinoids, and act by similar mechanisms (Madras, 2015).

The main cannabinoids are tetrahydrocannabinol, which produce the majority of psychoactive effects (Taylor et al, 1967), cannabidiol and cannabinol, both of which significantly modify the effects tetrahydrocannabinol and have distinct effects of their own. Interestingly, tetrahydrocannabinol and cannabidiol have opposing effects on addiction-related behaviors. Whereas tetrahydrocannabinol is rewarding and promotes drug use, cannabidiol has low hedonic property and inhibits drug seeking (Hurd et al, 2015)

Figure 1 **Tetrahydrocannabinol and Cannabidiol Opposing Effects**
(Adopted from Hurd et al, 2015)



Annex 2: Systematic Reviews Addressing Health and Socio-behavioral Outcomes of Cannabis Use

Table 1: Neuropsychiatric Outcomes of Cannabis Use

Systematic Review	Number of studies	Countries	Intervention	Outcome	Impact
Neurological Diseases					
General Neurologic Effects					
Systematic review: efficacy and safety of medical marijuana in selected neurologic disorders: report of the Guideline Development Subcommittee of the American Academy of Neurology (Koppel et al, 2014)	34	NA	Medical marijuana	Symptoms of multiple sclerosis, epilepsy, and movement disorders	Spasticity: - Oral cannabis extract (OCE) was effective, and nabiximols and tetrahydrocannabinol (THC) were probably effective, for reducing patient-centered and objective measures at 1 year. Central pain or painful spasms: - OCE was effective; THC and nabiximols were probably effective. Urinary dysfunction: - Nabiximols were probably effective for reducing bladder voids/day; THC and OCE were probably ineffective for reducing bladder complaints. Pain: Central pain or painful spasms (including spasticity-related pain, excluding neuropathic pain): OCE is effective; THC and nabiximols are probably effective. Tremor: - THC and OCE were probably ineffective; nabiximols was possibly ineffective. Other neurologic conditions: - OCE was probably ineffective for treating levodopa-induced dyskinesias in patients with Parkinson disease. - Oral cannabinoids were of unknown efficacy in non–chorea-related symptoms of Huntington disease, Tourette syndrome, cervical dystonia, and epilepsy. Adverse events: - Risk of serious adverse psychopathologic effects was nearly 1%
Pain					

Systematic Review	Number of studies	Countries	Intervention	Outcome	Impact
Inhaled Cannabis for Chronic Neuropathic Pain: A Meta-analysis of Individual Patient Data (Andreae et al, 2015)	5	US	Inhaled cannabis	Pain reduction	Inhaled cannabis provided short-term relief for 1 in 5 to 6 patients with neuropathic pain.
The effectiveness of cannabinoids in the management of chronic nonmalignant neuropathic pain: a systematic review (Boychuk et al, 2015)	13	NA	Various formulations Cannabis-based medicinal extracts	Reduction in pain intensity and adverse events	Cannabinoids provided effective analgesia in chronic neuropathic pain conditions that are refractory to other treatments.
Systematic Review and Meta-analysis of Cannabis Treatment for Chronic Pain (Martin-Sanchez et al, 2009)	18	NA	Cannabis treatment	Efficacy and harm	This systematic review found evidence of efficacy in the use of cannabis therapy for patients with chronic pain. A high number of serious adverse events in the very short term, principally at the level of the central nervous system were found. Efficacy analysis performed using visual analog scales, displayed a difference in standardized means in favor of the cannabis arm of -0.61 (-0.84 to -0.37). For the analysis of harms: - For events linked to alterations to perception, OR was 4.51 (3.05–6.66), and number needed to harm (NNH) was 7. - For events affecting motor function, OR was 3.93 (2.83–5.47), and NNH was 5. - For events that altered cognitive function, OR was 4.46 (2.37–8.37) and NNH was 8.
Cannabinoids for treatment	18	NA	Smoked cannabis,	Chronic non-cancer pain	- Fifteen of the eighteen trials demonstrated a significant analgesic

Systematic Review	Number of studies	Countries	Intervention	Outcome	Impact
of chronic non-cancer pain; a systematic review of randomized trials (Lynch and Campbell, 2011)			oromucosal extracts of cannabis based medicine, nabilone, dronabinol and a tetrahydrocannabinol (THC) analogue		effect of cannabinoid as compared with placebo and several reported significant improvements in sleep. - There were no serious adverse effects.
Epilepsy					
Cannabinoids for epilepsy (Gloss and Vickrey, 2013)	4	NA	200 to 300 mg daily of cannabidiol (CBD)	The four reports only assessed the secondary outcome (adverse effects)	- No reliable conclusions could be drawn regarding the efficacy of cannabinoids as a treatment for epilepsy. - None of the patients in the treatment groups suffered adverse effects.
Dementia					
Cannabinoids for the treatment of dementia (Krishnan et al, 2009)	1	US	Cannabinoids use	- Clinical global impression of change - Cognitive function	Data in the study report could not be extracted for further analysis and there was insufficient quantitative data to validate the results
Sleep					
The effects of cannabinoid administration on sleep: a systematic review of human studies (Gates et al, 2014)	11	US, Canada	Various formulations for recreational or medical use	Impact on sleep	Cannabinoid use among recreational users: - May interrupt the normal cycles of sleep, particularly slow-wave sleep; and - Does not appear to consistently cause any significant change to the time spent asleep or the number of night time awakenings - May leave an impression of non-restful sleep Cannabinoid use among users with a medical condition known to disturb sleep: - Demonstrated some consistency across studies of improved sleep via reduced night time disturbances

Systematic Review	Number of studies	Countries	Intervention	Outcome	Impact
					- Demonstrated relatively inconsistent effects on sleep among studies with objective measures.
Multiple Sclerosis					
The Use of Cannabis and Cannabinoids in Treating Symptoms of Multiple Sclerosis: a Systematic Review of Reviews (Nielsen et. al. 2018)	11 systematic reviews	NA	cannabinoids		The clinical use of cannabinoids may have modest effects for spasticity and pain in multiple sclerosis. The findings were inconclusive on use to treat other common symptoms (e.g. bladder control, ataxia and tremor).
Delta-9-tetrahydrocannabinol + cannabidiol. A reasonable option for some patients with multiple sclerosis (unknown author, 2014)	3	France	Transmucosal spray of delta-9-tetrahydrocannabinol and cannabidiol	Anti-spastic efficacy	- Combined analyses showed response rates of around 35% with the mixture versus about 25% with placebo. - About 10% of patients in whom standard anti-spastic medications were unsatisfactory benefit from this oral spray.
Whole plant cannabis extracts in the treatment of spasticity in multiple sclerosis: a systematic review (Lakhan and Rowland, 2009)	6	NA	Tetrahydrocannabinol and cannabidiol extracts	Spasticity	- Although there was variation in the outcome measures reported in these studies, a trend of reduced spasticity in treated patients was noted. - Adverse events were reported, however combined TCH and CBD extracts were generally considered to be well-tolerated.
Meta-analysis of cannabis based treatments for neuropathic and multiple sclerosis-related pain	7	NA	Cannabidiol/ delta-9-tetrahydrocannabinol buccal spray, cannabidiol, and dronabinol	MS-related/ neuropathic pain	The CBD/THC buccal spray decreased pain by 1.7 ± 0.7 points, CBD by 1.0 ± 0.7 points, dronabinol by 1.0± 0.6 points, and all cannabinoids pooled together by 1.6 ± 0.4 points. - Placebo baseline-endpoint scores did not differ. At endpoint, cannabinoids were superior to placebo

Systematic Review	Number of studies	Countries	Intervention	Outcome	Impact
(Iskedjian et al, 2009)					- Dizziness was the most commonly observed adverse event in the CBD/THC buccal spray arms, across all cannabinoid treatments, as well as in the placebo arms.
Addiction					
Cannabidiol as an Intervention for Addictive Behaviors: A Systematic Review of the Evidence (Prud'homme et al, 2015)	14 (9 on animals and 5 on humans)	NA	Cannabidiol use	Impact on addictive behaviors	A limited number of preclinical studies suggest that CBD may have therapeutic properties on opioid, cocaine, and psychostimulant addiction, and some preliminary data suggest that it may be beneficial in cannabis and tobacco addiction in humans.
Tourette's Syndrome					
Cannabinoids for Tourette's Syndrome (Curtis et al, 2009)	2	Germany	Any cannabinoid preparation	Efficacy of treatment of tics and obsessive compulsive symptoms	Not enough evidence to support the use of cannabinoids in treating tics and obsessive-compulsive behavior in people with Tourette's syndrome.
Cognition					
Acute and Chronic Effects of Cannabinoids on Human Cognition—A Systematic Review (Broyd et al, 2016)	105	NA	Various formulation	Impact on cognition	Acute Effects of Cannabis on Cognition: - Impaired verbal learning, memory, attention, tasking, psychomotor function, and dose dependent Impaired inhibition. - Less impact on other executive functions Chronic Effects of Cannabis on Cognition: - Impaired verbal learning, memory, and attention. - Possible impaired psychomotor function - Mixed evidence for executive function and decision- making. - Likely persistent effects on attention and psychomotor function. - Possible persistent effects on verbal learning and memory
Non-acute (residual) neurocognitive effects of	15	NA	Cannabis use	Neurocognitive performance	- Decrements in the ability to learn and remember new information were noted in chronic users. - Other cognitive abilities remained

Systematic Review	Number of studies	Countries	Intervention	Outcome	Impact
cannabis use: A meta-analytic study (Grant et al, 2003)					unaffected.
Nonacute (residual) neuropsychological effects of cannabis use: a qualitative analysis and systematic review (Gonzalez et al, 2002)	40	NA	Non-acute cannabis use	Alteration in neuropsychological performance	- There was absence of consistent evidence for persisting neuropsychological deficits in cannabis users - 22 of the 40 studies reported at least some subtle impairments.
The effects of cannabis on memory function in users with and without a psychotic disorder: findings from a combined meta-analysis (Schoeler et al, 2016)	88	NA	Cannabis use	Memory function	- Cannabis use was associated with significantly impaired memory, verbal immediate and delayed recall as well as visual recognition in healthy individuals, but a better global memory, visual immediate recall, and recognition in patients with psychotic disorders. - Lower depression scores and younger age appeared to attenuate the effects of cannabis on memory. - Cannabis-using patients with psychotic disorders had lower levels of depression and were younger compared with non-using patients, whilst healthy cannabis-users had higher depression scores than age-matched non-users. - Longer duration of abstinence from cannabis reduced the effects on memory in healthy and patient users.
Residual Effects of Cannabis Use on Neurocognitive Performance After Prolonged Abstinence: A Meta-Analysis (Shreiner and Dunn, 2012)	33	NA	Cannabis abstinence	Residual effects on neurocognitive performance	- The effect size for all assessed cognitive domains indicated a significant negative effect, with effect size of –0.29 and CI 95% –0.46 to –0.12. - For studies with at least 1-month of abstinence, an effect size for all assessed cognitive domains was not significant, indicating absence of evidence for lasting residual effects on overall performance.

Systematic Review	Number of studies	Countries	Intervention	Outcome	Impact
Psychiatric Diseases					
Depression					
The association between cannabis use and depression: a systematic review and meta-analysis of longitudinal studies (Lev-Ran et al, 2014)	14	US, New Zealand, Columbia, Netherlands, Canada, Norway, Sweden, Australia	Cannabis use	Depression	- The OR for cannabis users developing depression compared with controls was 1.17 (95% confidence interval 1.05-1.30). - The OR for heavy cannabis users developing depression was 1.62 (95% CI 1.21-2.16), compared with non-users or light users. - Meta-regression revealed no significant differences in effect based on age of subjects and only marginal difference in effect based on the length of follow-up.
Mania					
Cannabis use and mania symptoms: a systematic review and meta-analysis (Gibbs et al, 2015)	6	NA	Cannabis use	Manic symptoms	- Studies supported an association between cannabis use and the exacerbation of manic symptoms in those previously diagnosed with bipolar disorder. - A meta-analysis of two studies suggests that cannabis use is associated with an approximately 3-fold increased risk for the new onset of manic symptoms.
Anxiety					
A positive association between anxiety disorders and cannabis use or cannabis use disorders in the general population- a meta-analysis of 31 studies (Kedzior and Laeber, 2014)	31	US, Australia, Columbia, Switzerland, France, Canada, New Zealand, UK, Netherlands, Germany	Cannabis use	Anxiety symptoms	- There was a small positive association between anxiety and cannabis use (OR 1.24)/cannabis use disorder (*OR* 1.68), and between comorbid anxiety + depression and cannabis use (*OR* 1.68). - Cannabis use at baseline was significantly associated with anxiety at follow-up in 5 studies (*OR* = 1.28).
Association of cannabis use with the development of elevated	10	US, Columbia, Sweden, Australia, New	Cannabis use	Elevation in anxiety	The main analysis (demonstrated an association of cannabis use with anxiety, with a very small but significant OR of 1.15.

Systematic Review	Number of studies	Countries	Intervention	Outcome	Impact
anxiety symptoms in the general population: a meta-analysis (Twomey, 2017)		Zealand, UK, Netherlands			
Schizotypal Disorder					
Association between cannabis use and schizotypal dimensions – A meta-analysis of cross-sectional studies (Szoke et al, 2014)	29	NA	Cannabis use	Schizotypal dimensions	The cannabis group (ever or current) had higher schizotypy scores.
Schizophrenia					
The Environment and Schizophrenia: The Role of Cannabis Use (Henquet et al, 2005)	7	NA	Cannabis use	Psychosis	The pooled odds ratio was 2.1 (95% CI: 1.7–2.5) and could not be explained by confounding or reverse causality, suggesting that cannabis is a component cause in the development and prognosis of psychosis.
The effects of cannabis use on neurocognition in schizophrenia: A meta-analysis (Rabin et al, 2011)	8	NA	Cannabis use	Cognitive functioning	Effect size differences in cognitive performance in the schizophrenia group as a function of cannabis use were in the small to medium range, denoting superior performance in cannabis-using patients.
Cannabis and schizophrenia (Rathbone et al, 2014)	1	Australia	Cannabis use	Change in mental state, relapse, change in general behavior	No significant differences were found between the 'Cannabis and Psychosis Therapy' intervention group and the 'Psycho-education' intervention in terms of objective measures, social functioning, mental state, cannabis use, and knowledge on mental health and cannabis.

Systematic Review	Number of studies	Countries	Intervention	Outcome	Impact
The Impact of Cannabis Use on Cognitive Functioning in Patients With Schizophrenia: A Meta-analysis of Existing Findings and New Data in a First-Episode Sample (Yucel et al, 2012)	10	NA	Lifetime history of cannabis use	Cognitive functioning	- Patients with established schizophrenia and a cannabis use history displayed superior cognitive abilities compared with non-cannabis-using patients. - Better cognitive performance was seen only in lifetime users but not in recent users.
The association between cannabis use and earlier age at onset of schizophrenia and other psychoses: meta-analysis of possible confounding factors (Myles et al, 2012)	NA	NA	Cannabis use	Age at onset of schizophrenia and other psychoses	Meta-analysis showed that the age at onset of schizophrenia for cannabis users was 32 months earlier than that for cannabis non-users
Cannabis abuse and brain morphology in schizophrenia: a review of the available evidence (Malchow et al, 2013)	16	NA	Cannabis use	Brain morphology	While there is some evidence that chronic cannabis abuse could alter brain morphology in schizophrenia in patients continuing their cannabis consumption, there is no convincing evidence that this alteration takes place before the onset of schizophrenia.
Psychosis					
Cannabis as a risk factor for psychosis: systematic review (Semple et al, 2005)	11	NA	Cannabis use	Schizophrenia, psychosis or psychotic symptoms	- Seven studies were included in the meta-analysis, with a derived odds ratio of 2.9 (95% confidence interval 2.4–3.6). - Early use of cannabis appeared to increase the risk of psychosis. - For psychotic symptoms, a dose-

Systematic Review	Number of studies	Countries	Intervention	Outcome	Impact
					related effect of cannabis use was seen.
Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review (Moore et al, 2007)	35	NA	Cannabis use	Psychotic or affective symptoms	- There was an increased risk of any psychotic outcome in individuals who had ever used with an OR 1.41 (95% CI 1.20–1.65). - Findings were consistent with a dose-response effect, with greater risk in people who used cannabis most frequently, with an OR 2.09, (95% CI 1.54–2.84).
Meta-analysis of the Association Between the Level of Cannabis Use and Risk of Psychosis (Marconi et al, 2016)	18	US, Australia, New Zealand, Sweden, Germany, England, Finland	Degree of cannabis consumption	Psychosis	- Higher levels of cannabis use were associated with increased risk for psychosis in all the included studies. - Compared to the nonusers, OR among the heaviest cannabis users was 3.90 (95% CI 2.84 to 5.34) for the risk of schizophrenia and other psychosis-related outcomes.
Effects of cannabis use on outcomes of psychotic disorders: systematic review (Zammit et al, 2008)	13	Australia, Canada, UK, US, Spain, Germany	Cannabis use	Outcome of psychotic disorders	Cannabis misuse was associated with a greater rehospitalization index, increased psychosis relapse, non-adherence to treatment, and inconsistently greater number of admissions.
Cannabis Use and Earlier Onset of Psychosis (Large et al, 2011)	83	NA	Cannabis, alcohol, and other psychoactive substances	Age at onset of psychosis	Meta-analysis found that the age at onset of psychosis for cannabis users was 2.7 years younger than for nonusers (standardized mean difference = –0.414).
Cannabis use in patients at clinical high risk of psychosis: impact on prodromal symptoms and transition to psychosis	11	NA	Cannabis use	Clinical risk for psychosis and transition to a first psychotic episode	- Mixed results were revealed whereby in some studies cannabis use was associated with more severe symptoms at baseline, increased pre-psychotic symptoms immediately after intoxication, and earlier onset of certain high-risk symptoms. - In other studies, no significant association between cannabis use and baseline symptomatology was found. - In one study, cannabis use was

Systematic Review	Number of studies	Countries	Intervention	Outcome	Impact
(Van der Meer et al, 2012)					significantly associated with a decrease in pre-psychotic negative symptoms, and with fewer symptoms of depression and anxiety. - Four out of 5 studies reported no significant effect of cannabis use on transition to psychosis.
Neurological Soft Signs in Patients with Psychosis and Cannabis Abuse: A Systematic Review and Meta-Analysis of Paradox (Ruiz-Veguilla et al, 2012)	5	NA	Cannabis use	Neurological Soft Signs	Four studies concluded that cannabis-consuming patients with psychosis, particularly those with first episode of psychosis, showed fewer neurological soft signs.
A systematic review of the antipsychotic properties of cannabidiol in humans (Iseger and Bossong, 2015)	29	NA	Cannabidiol use	Antipsychotic properties	- Results show the ability of CBD to counteract psychotic symptoms and cognitive impairment associated with cannabis use as well as with acute THC administration. - These effects are possibly mediated by opposite effects of CBD and THC on brain activity patterns in key regions implicated in the pathophysiology of schizophrenia, such as the striatum, hippocampus and prefrontal cortex.
Cannabis use and transition to psychosis in individuals at ultra-high risk: review and meta-analysis (Kraan et al, 2016)	7	Australia, US, Europe, UK, Canada	Cannabis use	Transition to psychosis	- Lifetime cannabis use was not significantly associated with transition to psychosis - A second meta-analysis yielded an OR of 1.75 (95% CI 1.135–2.710), indicating a significant association between current cannabis abuse or dependence and transition to psychosis.
Continued versus discontinued cannabis use in patients with psychosis: a systematic review and meta-analysis	24	Spain, UK, Italy, Germany, Netherlands, US, Canada, Pakistan, Norway, France,	Continued or discontinued cannabis use	Psychosis relapse	- Independent of the stage of illness, continued cannabis users had a greater risk of psychosis relapse and longer hospital admissions than did both non-users and discontinued users. - Cannabis discontinuation was not associated with relapse with meta-regression suggesting greater effects of continued cannabis use than discontinued use on relapse, positive

Systematic Review	Number of studies	Countries	Intervention	Outcome	Impact
(Schoeler et al, 2016)					symptoms, and level of functioning, but not on negative symptoms.
Structural and Functional Brain Changes					
Structural and functional imaging studies in chronic cannabis users: a systematic review of adolescent and adult findings (Batalla et al, 2013)	43	NA	Chronic cannabis users	Change in brain structure and function	- Neuroimaging studies provided evidence of morphological brain alterations in adolescents and adults, particularly in the medial temporal and frontal cortices, as well as the cerebellum. These effects may be related to the amount of cannabis exposure. - Functional neuroimaging studies suggested different patterns of resting global and brain activity during the performance of several cognitive tasks in both age groups, which may indicate compensatory effects in response to chronic cannabis exposure.
Neuroimaging studies of acute effects of THC and CBD in humans and animals: a systematic review. (Batalla et al, 2014)	24 in humans and 21 in animals	NA	Acute cannabis exposure	Impact on brain function	Functional neuroimaging studies provided evidence for the acute modulation of brain function by cannabinoids.
Neuroimaging in cannabis use: a systematic review of the literature (Martin-Santos et al, 2010)	41	NA	Chronic or acute cannabis exposure	Neuroimaging effects	- Functional neuroimaging studies suggest a modulation of global and prefrontal metabolism both during the resting state and after the administration of THC/marijuana cigarettes. - Minimal evidence of major effects of cannabis on brain structure has been reported.
Brain Neuroimaging in Cannabis Use: A Review (Quickfall & Crockford, 2006)	31	NA	Cannabis use	Structural and functional neuroimaging studies	- Regular users demonstrated reciprocal changes in brain activity globally and in the cerebellar and frontal regions. - Structural abnormalities have generally not been identified with chronic use. Chronic use and cannabis administration resulted in attenuated brain activity in task-activated regions or activation of compensatory regions.

Systematic Review	Number of studies	Countries	Intervention	Outcome	Impact
Structural MRI Findings in Long-Term Cannabis Users: What Do We Know? (Lorenzetti et al, 2010)	13	NA	Chronic cannabis use	Structural MRI changes	- No global structural changes were described in cannabis users, although six studies reported regional alterations. - Findings of changes in the hippocampus and parahippocampus were inconsistent across studies. - Available literature also provided some evidence that regional structural changes and psychopathology were associated with cannabis use patterns, suggesting that THC exposure affects brain morphology, especially in the medial-temporal regions.
Effects of Cannabis Use on Human Brain Structure in Psychosis: A Systematic Review Combining In Vivo Structural Neuroimaging and Post Mortem Studies (Rapp et al, 2012)	19	Netherlands, UK, US, Australia	Cannabis use	Effect on brain structure	- There was evidence for consistent brain structural abnormalities in cannabinoid 1 receptor enhanced brain areas - As these effects have not consistently been reported in studies examining non-psychotic and healthy samples, psychosis patients and subjects at risk for psychosis might be particularly vulnerable to brain volume loss due to cannabis exposure.
Effects of Cannabis on Impulsivity: A Systematic Review of Neuroimaging Findings (Wrege et al, 2014)	13	NA	Cannabis use	Neuroimaging	- Studies of acute administration of THC or marijuana reported increased brain metabolism in several brain regions during impulsivity tasks. - Functional imaging studies of impulsivity studies suggested that prefrontal blood flow is lower in chronic cannabis users than in controls. - Structural imaging studies of cannabis users found differences in prefrontal volumes and white matter integrity that might mediate the abnormal impulsivity and mood observed in marijuana users.
The brain effects of cannabis in healthy adolescents and in adolescents	24	NA	Cannabis use	Structural and functional brain changes	Healthy adolescents: There is a suggestion of greater memory loss and hippocampal volume changes. Adult-onset schizophrenia: - The studies of cannabis use in adolescent-onset schizophrenia differ,

Systematic Review	Number of studies	Countries	Intervention	Outcome	Impact
with schizophrenia: a systematic review (James et al, 2014)					with one study pointing to extensive grey matter and white matter changes. - There is a suggestion that the left parietal lobe may be more vulnerable to the effects of cannabis - Cognition does not appear to be adversely affected
Is cannabis neurotoxic for the healthy brain? A meta-analytical review of structural brain alterations in non-psychotic users (Rocchetti et al, 2013)	14	NA	Cannabis use	Structural brain changes	- Meta-analysis showed a consistent smaller hippocampus and amygdaloid in users as compared to non-users. - No significant differences were observed in intracranial volume and whole brain volume between cannabis users and non-users.

Table 2: Health (non-neuropsychiatric) Outcomes of Cannabis Use

Systematic Review	Number of Studies	Countries	Intervention	Outcome	Impact
General Health Effects					
Cannabinoids for Medical Use A Systematic Review and Meta-analysis (Whiting et al, 2015)	79	NA	Cannabinoids medical use	Disease-specific outcomes, activities of daily living, quality of life, global impression of change, and adverse events (AEs)	- Compared with placebo, cannabinoids were associated with a greater average number of patients showing a complete nausea and vomiting response, reduction in pain and improved spasticity. - There was an increased risk of short-term adverse events with cannabinoids such as dizziness, dry mouth, nausea, fatigue, somnolence, euphoria, vomiting, disorientation, drowsiness, confusion, loss of balance, and hallucinations.
Cardiovascular Disease					
What is the Current Knowledge About the Cardiovascular Risk for Users of Cannabis-Based Products? A Systematic Review (Jouanjus et al, 2017)	115	USA, France, New Zealand, Germany, Spain, Sweden, Turkey, Finland, Australia, UK, European countries	Use of cannabis-based products	Cardiovascular outcomes	-Data revealed an association between exposure to cannabis-based products and cardiovascular disease, with the evidence stronger for ischemic strokes -Results suggest that cannabis use may have negative cardiovascular consequences, particularly at large doses.
Cancer					
Head and neck cancer among marijuana users: a meta-analysis of matched case-control studies (de Carvalho et al, 2015)	9	UK, US, Latin America, North Africa	Marijuana smoking	Head and neck cancer development	The meta-analysis found no association between exposure and disease (OR=1.021, 95% confidence interval 95% 0.912-1.14)
Insufficient Evidence to Support or Refute the Association between Head and Neck	6	NA	Lifetime use of marijuana	Development of head and neck cancer	After adjusting for age, gender, race, and tobacco use, the odds for development of head and neck cancer after ever being exposed to marijuana was 1.02 (95% CI, 0.91-1.14).

Systematic Review	Number of Studies	Countries	Intervention	Outcome	Impact
Cancer and Marijuana Use (Osazuwa-peters et al, 2015)					
The Association Between Marijuana Smoking and Lung Cancer A Systematic Review (Mehra et al, 2006)	19	NA	Marijuana smoking	Lung premalignant findings and lung cancer	Premalignant findings: -Compared with tobacco smokers or nonsmoking controls, an association was found between marijuana smoking and increased tar exposure, alveolar macrophage tumoricidal dysfunction, oxidative stress, and bronchial mucosal histopathologic abnormalities Cancer: -After adjusting for tobacco use, studies of subjects with marijuana exposure failed to demonstrate significant associations between marijuana smoking and lung cancer.
Cannabis exposure and risk of testicular cancer: a systematic review and meta-analysis (Gurney et al, 2015)	3	US	Cannabis use	Testicular germ cell tumors	- When compared to never-use of the drug, current, chronic, and frequent cannabis use was associated with the development of testicular germ cell tumor. - The strongest association was found for non-seminoma development, whereby those using cannabis on at least a weekly basis had two and a half times greater odds of developing a non-seminoma testicular germ cell tumor compared those who never used cannabis (OR: 2.59, 95 % CI 1.60–4.19). - Inconclusive evidence was revealed regarding the relationship between cannabis use and the development of seminoma tumors.
Chemotherapy Induced Nausea and Vomiting					
Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review	30	NA	Oral nabilone, oral dronabinol, and intramuscular levonantradol	Antiemetic efficacy and adverse effects	- Cannabinoids were more effective antiemetics than prochlorperazine, metoclopramide, chlorpromazine, thiethylperazine, haloperidol, domperidone, or alizapride: relative risk 1.38 (95% confidence interval 1.18 to 1.62) - NNT 6 for complete control of nausea, whereas NNT 8 for complete

Systematic Review	Number of Studies	Countries	Intervention	Outcome	Impact
(Tramer et al, 2001)					control of vomiting. - Cannabinoids were not more effective in patients receiving very low or very high emetogenic chemotherapy. - Some potentially beneficial side effects occurred more often with cannabinoids such as 'feeling high', sedation or drowsiness, and euphoria. - Harmful side effects also occurred more often with cannabinoids. These include dizziness, dysphoria or depression, hallucinations, paranoia, and arterial hypotension. - Patients given cannabinoids were more likely to withdraw due to side effects 4.67 (3.07 to 7.09), NNT 11.
Therapeutic use of Cannabis sativa on chemotherapy-induced nausea and vomiting among cancer patients: systematic review and meta-analysis (Rocha et al, 2008)	30	NA	Therapeutic Cannabinoids use	Anti-emetic efficacy	- Studies demonstrated superiority of the anti-emetic efficacy of cannabinoids compared with conventional drugs and placebo. - Adverse effects were also more intense among patients who used cannabinoids.
Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy (Smith et al, 2015)	23	NA	Cannabis medical use	Effectiveness and tolerability	- A smaller proportion of people who received cannabis-based medicines experienced nausea and vomiting as compared to those who received placebo. - The proportion of people who experienced nausea and vomiting and who received cannabis-based medicines was similar to those who received conventional anti-nausea medicines. - Compared with those who received either placebo or other anti-nausea medicines, a greater proportion of those who received cannabis-based

Systematic Review	Number of Studies	Countries	Intervention	Outcome	Impact
					medicines experienced side effects such as 'feeling high', dizziness, sedation, and dysphoria; and eventually dropped out of the study.
Efficacy, tolerability, and safety of cannabinoids for chemotherapy-induced nausea and vomiting—a systematic review of systematic reviews (Tafelski et al, 2016)	6	NA	Herbal or pharmaceutical cannabinoids	Efficacy, tolerability, and safety	There was moderate quality evidence on the efficacy of cannabinoids compared to placebo and conventional antiemetics for chemotherapy-induced nausea and vomiting. There was moderate quality evidence that pharmaceutical cannabinoids were less tolerated and less safe than placebo and conventional antiemetics.
Lung Diseases					
Effects of Marijuana Smoking on Pulmonary Function and Respiratory Complications A Systematic Review (Tetraut et al, 2007)	34	NA	Marijuana smoking	Pulmonary function and respiratory complications	Short term: 11 of 12 challenge studies found an association between short-term marijuana administration and bronchodilation, manifesting as increases of 0.15-0.25 L in forced expiratory volume in 1 second. Long term: - No consistent association was found between long-term marijuana smoking and airflow obstruction measures. - All studies that assessed long-term marijuana smoking and respiratory complications noted an association with increased respiratory symptoms, including cough, phlegm, and wheezing
HIV/AIDS					
The medical use of cannabis for reducing morbidity and mortality in patients with HIV/AIDS	7	NA	Medical Cannabis use	Morbidity and mortality	- The evidence for substantial effects on morbidity and mortality is limited. - Data from only one relatively small study conducted in the period before access to highly-active antiretroviral therapy, showed that patients administered dronabinol were twice as likely to gain 2kg or more in body weight. However, the results were not

Systematic Review	Number of Studies	Countries	Intervention	Outcome	Impact
(Lutge et al, 2013)					significant. - The mean weight gain in the dronabinol group was only 0.1kg, compared with a loss of 0.4kg in the placebo group.
Diabetes Mellitus					
Cannabis Smoking and Diabetes Mellitus: Results from Meta-analysis with Eight Independent Replication Samples. (Alshaarawy & Anthony, 2015)	8	US	Smoked cannabis	Diabetes mellitus	Recently active cannabis smoking and diabetes mellitus are inversely associated. The meta-analytic summary odds ratio is 0.7 (95% confidence interval = 0.6, 0.8), suggesting a possible protective effect of cannabis.
Rheumatic Diseases					
Efficacy, tolerability and safety of cannabinoids in chronic pain associated with rheumatic diseases (fibromyalgia syndrome, back pain, osteoarthritis, rheumatoid arthritis): A systematic review of randomized controlled trials (Fitzcharles et al, 2016)	4	Canada, Germany, Israel	Various formulations used (medical use)	Efficacy, tolerability, and safety	- The findings of a superiority of cannabinoids over controls (placebo, amitriptyline) were not consistent. - Cannabinoids were generally safe and well tolerated despite some side effects
Cannabis-associated arteritis (Grotenhermen , 2010)	15	Morocco, UK, Switzerland , Germany,	Cannabis use	Association with arteritis	Clinical and pathological features of cannabis- associated arteritis do not differ from thromboangiitis obliterans. The major risk factor of thromboangiitis obliterans, tobacco

Systematic Review	Number of Studies	Countries	Intervention	Outcome	Impact
		France, Italy, US			use, was present in most, of these cases.
Oral Diseases					
Cannabis use and oral diseases (Veitz-Keenan and Spivakovsky, 2011)	7	NA	Cannabis use	Oral side effects	- The limited data reported about the increased occurrence of caries and gingivitis indicates a combination of factors such as lifestyle and dry mouth. - The effect on salivary function appears to decrease over time, possibly related to tolerance which develops during long term use. - Cannabis users demonstrated an increased prevalence of Candida albicans as compared to tobacco smokers. - No association was found between cannabis use and oral cancer. - Leukoedema appears to be more prevalent among cannabis users without any additional clinical relevance.
Geriatrics Population					
Efficacy and safety of medical cannabinoids in older subjects: A systematic review (Elsen et al, 2014)	5	NA	Oral THC and oral THC combined with cannabidiol	Indications, efficacy, safety and pharmacokinetics	- Results of studies showed no effect on dyskinesia, breathlessness, and chemotherapy induced nausea and vomiting. - Two studies showed that THC might be useful in treatment of anorexia and behavioral symptoms in dementia. - Adverse events, particularly sedation, were more common during cannabinoid treatment compared to control
Pregnancy Outcomes					
Maternal cannabis use and birth weight: A meta-analysis (English et al, 1997)	10	US, Canada	Various cannabis dosages used	Low birth weight	From the five studies of low birth weight, the pooled odds ratio for any use was 1.09 (95% CI 0.94-1.27), indicating that there is inadequate evidence that cannabis, at the amount typically consumed by pregnant women, causes low birth weight.
Consequences of prenatal toxin exposure for mental	100 (6 on marijuana)	NA	Various toxins	Neurodevelopment and mental	Children who had been exposed to marijuana prenatally were found to exhibit increased depressive

Systematic Review	Number of Studies	Countries	Intervention	Outcome	Impact
health in children and adolescents A systematic review (Williams & Ross, 2007)				health outcomes	symptoms and poor attentional skills at around 10-12 years of age.
Prenatal exposure to cannabis and maternal and child health outcomes: a systematic review and meta-analysis (Gunn et al, 2015)	24	US, Canada, Australia, Netherlands, Iran, Jamaica, Spain, Brazil	Cannabis use	Anemia, birth weight, neonatal length, placement in the neonatal intensive care unit, gestational age, head circumference, and preterm birth.	- Results of the meta-analysis demonstrated that women who used cannabis during pregnancy had an increase in the odds of anemia (pooled OR 1.36: 95% CI 1.10 to 1.69) compared with women who did not use cannabis during pregnancy. - Infants exposed to cannabis in utero had a decrease in birth weight (OR 1.77: 95% CI 1.04 to 3.01) compared with infants whose mothers did not use cannabis during pregnancy. - Infants exposed to cannabis in utero were also more likely to need placement in the neonatal intensive care unit compared with infants whose mothers did not use cannabis during pregnancy (OR=2.02: 95% CI 1.27 to 3.21).
Safety					
The safety of studies with intravenous Δ^9-tetrahydrocannabinol in humans, with case histories (Carbuto et al, 2012)	11	US	Intravenous THC	Safety of intravenous infusions	- 9.7% of subjects and 7.4% of infusions were associated with adverse events, mostly minor. - Nausea and dizziness were the most frequent side effects. - Adverse events were more likely to be associated with faster infusion rates (2-5 min) and higher doses (›2.1 mg/70 kg).
Adverse effects of medical cannabinoids: a systematic review (Wang et al, 2008)	31	NA	Medical cannabinoids	Adverse events	- Most adverse events (96.6%) were not serious. - Of the serious adverse events, the most common was relapse of multiple sclerosis (12.8%), vomiting (19.8%), and urinary tract infection (9.1%). - Dizziness was the most commonly reported non-serious adverse event (15.5%) among people exposed to cannabinoids.

Systematic Review	Number of Studies	Countries	Intervention	Outcome	Impact
Mortality					
Does cannabis use increase the risk of death? Systematic review of epidemiological evidence on adverse effects of cannabis use (Calabria et al, 2010)	19	Sweden, US, New Zealand, Australia, France, UK, Morocco	Various formulations	All-cause mortality, motor vehicle accidents, cancer, suicidal behaviors	- There is insufficient evidence, particularly because of the low number of studies, to assess whether the all-cause mortality rate is elevated among cannabis users compared to the general population. - Case-control studies suggest that some adverse health outcomes such as fatal motor vehicle accidents and respiratory and brain cancers may be elevated among heavy cannabis users. The evidence is as yet unclear as to whether regular cannabis use increases the risk of suicide.

Table 3: Socio-behavioral Outcomes of Cannabis Use

Systematic Review	Number of Studies	Countries	Intervention	Outcome	Impact
Educational Attainment					
A Systematic Review of the Relationship between High School Dropout and Substance Use (Townsend et al, 2007)	46 (16 on cannabis)	US, South Africa	Various toxins	Dropping out of high school	- Dropouts, students experiencing academic problems, and in-school students identified as being at risk for dropping out of school reported more current and lifetime cannabis use than in-school students and high school graduates, irrespective of gender or ethnicity. - Female dropouts reported more lifetime use than their male counterparts. - Three longitudinal studies provided evidence of a "reverse causal pattern" whereby the experience of dropping out of school led to an increase in marijuana use
Psychological and social sequelae of cannabis and other illicit drug use by young people: a systematic review of longitudinal,	48	New Zealand, Canada, Sweden, US, France, UK, Israel, Norway, Switzerland, Spain, Australia,	Cannabis and illicit drug use	Psychosocial harm	Fairly consistent associations were noted between cannabis use and both lower educational attainment and increased reported use of other illicit drugs.

Systematic Review	Number of Studies	Countries	Intervention	Outcome	Impact
general population studies (Macleod et al, 2004)		Germany, Spain, Columbia			
Motor Vehicle Accidents					
Acute cannabis consumption and motor vehicle collision risk: systematic review of observational studies and meta-analysis (Asbridge et al, 2010)	9	NA	THC	Death or injuries	- Driving under the influence of cannabis was associated with a significantly increased risk of motor vehicle collisions compared with unimpaired driving (OR 1.92, 95% confidence interval 1.35 to 2.73) - Acute cannabis consumption was associated with an increased risk of a motor vehicle crash, including fatal collisions.
Marijuana Use and Motor Vehicle Crashes (Mu-Chen et al, 2012)	9	Canada, New Zealand, US, Netherlands, France, Thailand	Marijuana use	Crash risk	Pooled analysis based on the random-effects model yielded a summary odds ratio of 2.66 (95% confidence interval: 2.07, 3.41), suggesting that marijuana use by drivers is associated with a significantly increased risk of being involved in motor vehicle crashes.
Neurocognitive Correlates in Driving Under the Influence of Cannabis (Busardo et al, 2017)	36	NA	Cannabis use	Acute and chronic neurocognitive effects induced by cannabis and the ability to drive	-Experimental and epidemiological studies have revealed that THC affects negatively both, psychomotor skills and cognitive functions. -Driving under the influence of cannabis doubles or triples the risk of a crash, spec through impairing critical-tracking tasks, increasing lane weaving, decreasing reaction time, and dividing attention.
Homicide					
Drug abuse and aggression between intimate partners: A meta-analytic review (Todd et al, 2008)	96 (15 on marijuana)	NA	Marijuana, cocaine, opiates, sedatives/anxiolytics/hypnotics, hallucinogen, stimulants, others, and	Aggression among intimate partners	Significant effect size was demonstrated in the relationship between marijuana use and intimate partner aggression

Systematic Review	Number of Studies	Countries	Intervention	Outcome	Impact
			and mixed drugs		
A meta-analysis of marijuana, cocaine and opiate toxicology study findings among homicide victims (Kuhns et al, 2008)	18	US, Sweden, Canada, Denmark, Norway	Marijuana, cocaine and opiate drug	Toxicology screen among homicide victims	On average, 6% of homicide victims tested positive for marijuana, 11% tested positive for cocaine, and 5% tested positive for opiates.
Suicide					
Can cannabis increase the suicide risk in psychosis? A critical review (Serafini et al, 2012)	45	NA	Cannabis use	Suicidal behavior	Most, but not all, studies reported an association between suicidal behavior and cannabis use both in psychotic and non-psychotic samples.
A literature review and meta-analyses of cannabis use and suicidality (Borges, Bagge, & Orozco, 2016)	19	New Zealand, Columbia, Norway, US, Sweden, Denmark, Canada, Ireland, Australia	Cannabis use	Suicide Suicide ideation Suicide attempts	The odds ratios for cannabis use and suicide, suicide ideation, and suicide attempts were 2.56, 1.43, and 2.23 respectively.

Appendix 3: Studies Addressing Effect of Cannabis Legalization on Consumption

Study	Country/City	Impact
Medical marijuana laws in 50 states: Investigating the relationship between state legalization of medical marijuana and marijuana use, abuse and dependence (Cerdá et al, 2012)	US	Residents of states with cannabis medical laws had higher odds of cannabis use and cannabis abuse/dependence.
The Impact of State Medical Marijuana Legislation on Adolescent Marijuana Use (Choo et al, 2014)	US states with medical marijuana law	There were no significant differences in adolescent cannabis consumption before and after legalization for medical use. In two states there was a reduction in adolescent cannabis use after legalization.
Do medical cannabis laws encourage cannabis use? (Gorman & Huber, 2007)	Three cities in California, one city in Colorado, and one city in Oregon	No statistically significant pre-law versus post-law differences were found in cannabis urine analysis among arrestees or in the proportion of emergency department visits.
Do medical marijuana laws increase marijuana use? Replication study and extension. (Harper et al, 2012)	US states with medical marijuana law	Legalization of medical use decreased past-month use among adolescents and had no discernible effect on the perceived riskiness of monthly use.
Did medical marijuana legalization in California change attitudes about and use of marijuana? (Khatapoush & Hallfors, 2004)	California	Although some cannabis-related attitudes changed after legalization for medical use in California, use did not increase.
Effects of state medical marijuana laws on adolescent marijuana use. (Lynne-Landsman et al, 2013)	Montana, Rhode Island, Michigan, and Delaware	No association was found between legalization for medical use and adolescent illegal cannabis use.
Do medical marijuana laws increase marijuana use? (Wall et al, 2012)	US states with medical marijuana law	Legalization for medical use was unrelated to past-month use among adolescents
Risks and prices: The role of user sanctions in marijuana markets (Pacula et al, 2010)	US	Legalization of use was associated with a reduction in the price of illegal cannabis.
Temporal trends in marijuana attitudes, availability and use in Colorado compared to non-medical marijuana states: 2003–2011. (Schuermeyer et al, 2014)	Colorado	Legalization after 2009 federal policy change was associated with lower cannabis risk perception and increased use.
Medical marijuana and adolescent treatment (Jaffe & Klein, 2010)	NA	Cannabis was perceived to be more beneficial and more available after legalization for medical use.
Medical marijuana: A survey of teenagers and their parents (Schwartz et al, 2003)	Virginia and Ohio	28% of the parent group and 55% of the teenagers believed that passage of legalization for medical use would make it easier for teens to smoke cannabis.

Study	Country/City	Impact
Adolescent marijuana use from 2002 to 2008: Higher in states with medical marijuana laws, cause still unclear. (Wall et al, 2011)	US states with and without medical marijuana law (comparison)	States that legalized cannabis for medical use had higher average adolescent cannabis use and lower perception of cannabis riskiness than states that did not legalize.
Impacts of Changing Marijuana Policies on Alcohol Use in the United States (Guttmannova, 2016)	US	Evidence existed for both substitution and complementary relationships in the context of liberalization of marijuana policies.
The effects of decriminalization of drug use in Portugal (Hughes & Stevens, 2010)	Portugal	Treatment referrals for cannabis abuse increased from 47% in 2001 to 65% in 2005, but referrals for heroin abuse decreased from 33% to 15%, and referrals for cocaine abuse remained stable at 4-6%.
Interpreting Dutch Cannabis Policy: Reasoning by Analogy in the Legalization Debate (MacCoun & Reuter, 1997)	Netherlands	No significant effect during the first 7 years after depenalization. An increase in consumption after legalization for the age group 18-20 was noted from 15% in 1984 to 44% in 1996; with past month prevalence rising from 8.5% to 18.5%.
The Impact of Cannabis Decriminalisation in Australia and the United States (Single et al, 2000)	Australia	Lifetime use of cannabis increased significantly in South Australia from 26% in 1985 to 36% in 1995, but similar increases were observed in jurisdictions with a total prohibition approach to cannabis, suggesting a limited impact of decriminalization on consumption.

Knowledge to Policy Center draws on an unparalleled breadth of synthesized evidence and context-specific knowledge to impact policy agendas and action. K2P does not restrict itself to research evidence but draws on and integrates multiple types and levels of knowledge to inform policy including grey literature, opinions and expertise of stakeholders.

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