

# **International Covenant on Economic, Social and Cultural Rights (ICESCR)**

Article 3.12.13

2020

## **The parallel (shadow) report For the Third International Review**

NGOs:

**Taiwan Association of Gender/Sexuality Rights Protection**

**R.O.C. Association of HIV/AIDS and Child Care**

台灣性別人權維護促進協會

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**Article : ICESCR 3**

**Topic: The ambiguous definition of the term “sex” has made disturbance in execution of laws, and public opposition.**

<b>Article</b>	<b>International Covenant on Economic Social and Cultural Rights 3</b>
<b>Topic</b>	The ambiguous definition of the term “sex” has made disturbance in execution of laws, and public opposition.
<b>Situation</b>	1. Indistinction of Sex (biologic differences) and gender (social and culture differences) causes confusion and damage of children in education ° 2. The ambiguous definition of the term “sex” causes public opposition. 3. The Ministry of Education made a wrong definition of “sex” from the origin of teacher training.
<b>Suggestion</b>	Clearly defined “Sex” and “Gender” according to the definition of WHO 「性別」 should be translated and defined as “ (biologic) sex” , Gender should be translated and defined as “(social) gender”

**Situation**

- I. The definition of **Sex/Gender is clear in the documents of UN, however, the errors in translation caused confusion of definition of Sex/Gender in Taiwan.**

Regarding to the definition of “sex/gender” in Taiwan, the Concluding Observations and Recommendations of the third CEDAW International Review have clearly pointed out that “...inappropriate conceptual and practical use of the terms “sex” and “gender” in Taiwan.” and recommended the government to review it.

**Meaning and use of the terms “sex” and “gender”**

10. The IRC is concerned with the inappropriate conceptual and practical use of the terms “sex” and “gender” in Taiwan. In the CEDAW jurisprudence the Convention refers to sex based discrimination, but also covers gender-based discrimination against women. The term “sex” refers to biological differences between men and women. The term “gender” refers to socially constructed identities, attributes and roles for women and men and society’s social and cultural meaning for these biological differences resulting in hierarchical relationships between women and men and in the distribution of power and rights favoring men and disadvantaging

women.

11. The IRC recommends the Government to align all the legislative texts and policy documents and promote the correct and consistent understanding of the terms “sex” and “gender” in line with CEDAW Convention and the Committee’s General Recommendation No. 28.

Although Canadian government extended the “gender equality” to socially constructed identities, attributes and roles of gender on the official website since 1998,<sup>1</sup> “gender equality” is still based on men and women. It just reminded us that we should see gender and intersectional discrimination from a social perspective. CEDAW Convention and the Committee’s General Recommendation No. 28) ◦

Internationally, it is obvious that sex (biologic differences of women and men) and gender (socially constructed identities, attributes and roles of women and men) are different. However, they are confused in translation in Taiwan. Originally, the Chinese term-「性別」 was regarded as biological sex in all of our major fundamental laws and passports. However, under the policy of Gender Mainstreaming and the Gender Equity Education Act, all the related laws have never defined the term-sex/gender. As a result, the term-「性別」 used in each law has its own meaning and very often means sex, gender or even sexual orientation. Even more, we Taiwan has created a term “multi-sexes/genders” (lesbian, gay, bisexual, transgender, and the queer (LGBTQ), excluding men and women), which causes people confused and harms the health of people.

For example ,

1. The unclear definition of sex/gender causes the students confusion and harms their health. It is found that soaring numbers of adolescents want to change gender in England and some other countries. Therefore, UK Dept. of Ed. issued guidance against 'born in the wrong body' gender lessons in sex-ed, and the new government guidelines instructed educators not to "reinforce harmful stereotypes" or promote the idea that children might be the opposite sex based on their choice of clothing or personality. (News on Sep. 29,2020)

The above news revealed that this kind of education caused negative effect to children's sex/gender development, so UK Dep.of Ed. made new instructions disclosed as above.

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<sup>1</sup> <https://cihr-irsc.gc.ca/e/48642.html>

In Taiwan, similar gender ideology content appeared in the fifth grade textbook of elementary schools (Fig. 1).

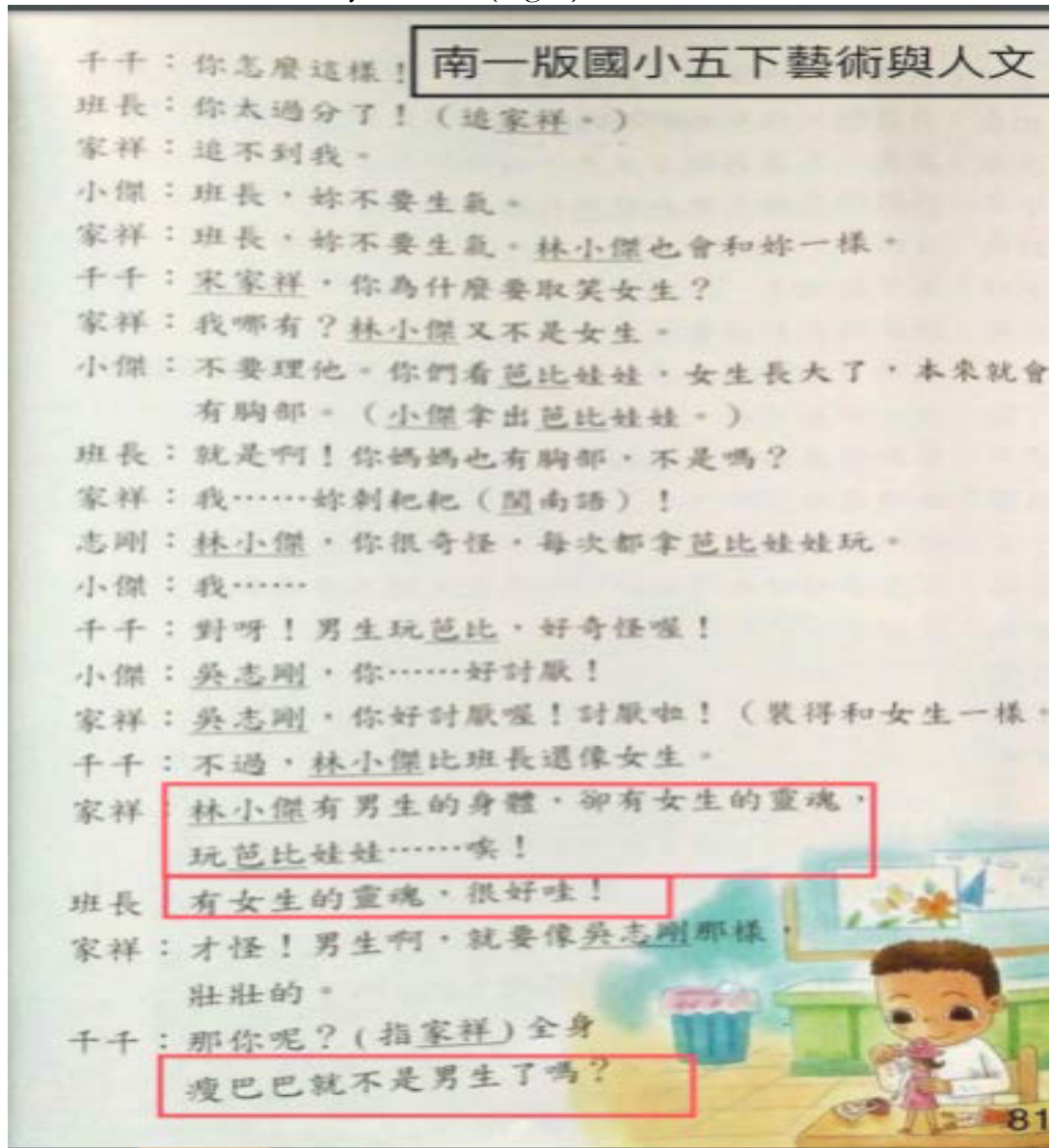


Fig. 1 Arts and Humanities, 5th grade, elementary school P.81 (Nani)

2. Our sex/gender definition is against that in the UN, EU and most of the countries. causing arguments in Gender Equity Education Act, and public opposition ( Attachment 1 [What is the definition of sex/gender ? They argue about the Gender Equity Education Act](#)<sup>2</sup> ) 。
3. The Ministry of Education made a wrong definition of “sex” from the origin of teacher training. Education is a very important aspect in the promotion of gender mainstreaming, but there are also incorrect definitions in the teacher training course :

(1) "Gender Human Rights and Citizen Action" lesson plan, p.178, in the book “How to teach sex well”  
.... Teaching "gender diversity" means " Gender Equity Education Act setting up, legislation and implementation...to throw away the traditional gender dichotomy, to recognize and understand the various possibilities of gender diversities and sexual orientations" (Fig. 2)

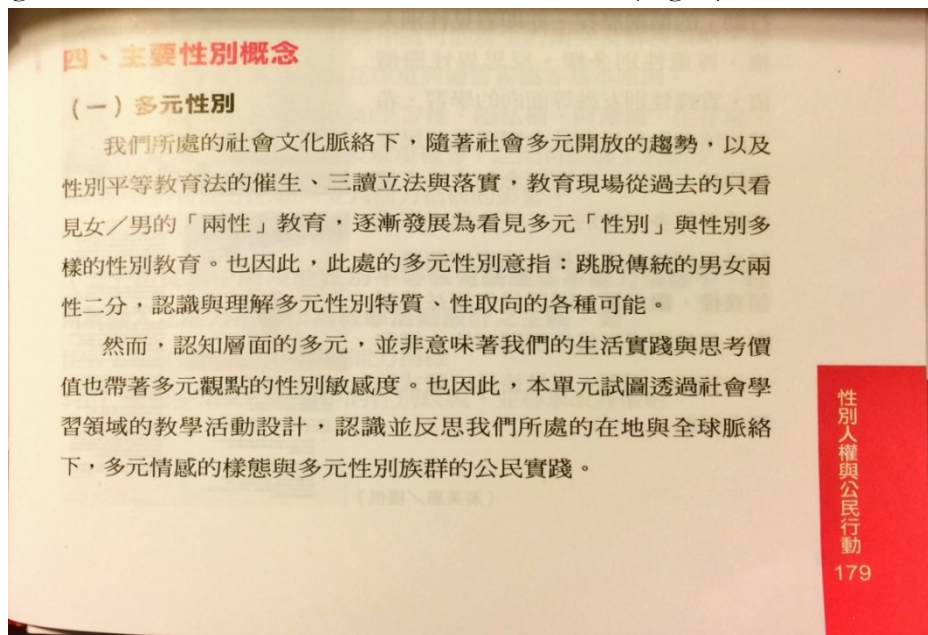


Fig. 2

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<sup>2</sup> <https://forum.ettoday.net/news/1220387>



(2) "Gender awareness grows". It said "gender" gradually replaces the term "two sexes" in this book. It also mentions "seeing multiple and intertwined genders" (Fig.3)



Fig. 3

**4. The medical statistics will be in a mess in “gender diversity”.**

The top ten cancers, life span, body mass index (BMI) or waist circumference for men and women are different in medical statistics. If we can decide "gender" by ourselves, or including sexual orientation, then the statistics will be in a mess in “gender diversity”.

**5. In public security, the crime rate of men and women will also be a question.** When studies point out that male-to-females had a significantly increased risk for crime compared to female controls but not compared to males.<sup>3</sup> Should male-to females (transgender women) be attributed to male or female criminals? It will cause great doubts and problems in gender statistics.

**II. Obvious facts show that the translation is wrong but the government insisted on going it alone.**

1. In Third National Report of the International Review Conference of the CEDAW on July 20, 2018, there was a proposal from a NGO -- The concept and usage of "biological sex" (sex) and “social gender” (gender) should be defined and used according to the definition of CEDAW. The terms "female" and "male" should not be replaced with the ambiguous term "multiple gender" by the government. This proposal was approved

<sup>3</sup> Dhejne C, Lichtenstein P, Boman M, et al. (2011) Long-Term Follow-Up of Transsexual Persons Undergoing Sex Reassignment Surgery: Cohort Study in Sweden. PLoS ONE 6(2): e16885.

by the CEDAW International Review Committee.<sup>4</sup>

2. However, the government ignored the opinions in the concluding observation and recommendations of the International Review Committee, and still used the words that caused misunderstandings in the Chinese-English translation (see the table below).

the concluding observation and recommendations of the third National Report CEDAW international committee	
English	Chinese translation
Meaning and use of the terms “sex” and “gender”	「性」與「性別」的意義與運用
10. The IRC is concerned with the inappropriate conceptual and practical use of the terms “sex” and “gender” in Taiwan. In the CEDAW jurisprudence the Convention refers to sex based discrimination, but also covers gender-based discrimination against women. The term “sex” refers to biological differences between men and women. The term “gender” refers to socially constructed identities, attributes and roles for women and men and society’s social and cultural meaning for these biological differences resulting in hierarchical relationships between women and men and in the distribution of power and rights favoring men and disadvantaging women.	10. 審查委員會關切「性」(sex)與「性別」(gender)二詞在概念上與實際上的不當運用。在 CEDAW 法理中, 公約提及基於性的歧視, 但亦涵蓋對女性基於性別的歧視。「性」意指男女生理上的差異; 「性別」意指社會建構的男女身分、歸屬 和 角色, 以及社會賦予這些生理差異的社會文化意義, 導致男女之間的階層關係以及權力和權利的分配有利於男性而不利於女性。

<sup>4</sup> In the discussion at the Review and Presentation of the ROC (Taiwan) CEDAW 3rd National Report 2018, The Italian IRC Bianca specifies that In the CEDAW jurisprudence the Convention clearly defined that "The term “sex” refers to biological differences between men and women. The term “gender” refers to socially constructed identities, attributes and roles for women and men and society’s social and cultural meaning for these biological differences resulting in hierarchical relationships between women and men and in the distribution of power and rights favoring men and disadvantaging women. The core of CEDAW is to eliminate all of the sex and gender discriminations as well as race, ethnicity, religion or belief, health, status, age, class, also sexual orientation and gender identity, as multiple factors of intersecting discrimination against women.

<p>11. The IRC recommends the Government to align all the legislative texts and policy documents and promote the correct and consistent understanding of the terms “sex” and “gender” in line with CEDAW Convention and the Committee’s General Recommendation No. 28.</p>	<p>11. 審查委員會建議臺灣政府依照 CEDAW 和 CEDAW 委員會第 28 號一般性建議統一所有法律和政策文件用詞, 並促進對「性」與「性別」正確、一致之認知。</p>
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**3. The Executive Yuan held a "closed-door meeting" and ignored the NGO which originally proposed redefinition of sex/gender**

In response to the concluding observation and recommendations of CEDAW international committee, Minister of state, Bing-Cheng Luo of the Executive Yuan, held a "closed-door meeting" of Report No. 10 and No. 11 on February 6, 109. However, he didn't invite the NGO which originally proposed redefinition of sex/gender, so it was unable to fully present various opinions. This meeting did not carefully examine the review committee's recommendations and ignored the UN's definition of 'sex' and 'gender'.

4. In the end, the wrong definition of sex/gender was interpreted as only the translation problem (attachment 2 - The Magic of Disappearing Women in Taiwan). So the government made a comparison table of "Chinese comparing to English" (see attachment 3) and asked all the Chinese 「性別」 translated into "gender". The term “sex” was disappeared!
5. In addition, the closed-door meeting did not provide a comparison table of "English to Chinese" at the same time. As a result, the "sex" was completely eliminated.
6. 「性別」 referred to "the sexes –men and women" in many laws and regulations originally. If it is changed to "gender", it will be unclear and confusing, because "gender" includes the meaning religion, age.....
7. In addition, the inspection itself presents a contradictory problem. The Chinese term- 「性別」 was regarded as biological sex in all of our major fundamental laws and passports, rather than the fluid social or psychological gender (gender). Therefore, does the term 「性別」

refer to social gender or biological sex? It caused logical confusion in the definition of the same term.

8. The confusion of 「性別」 definition caused by such translation can easily cause confusion in the implementation of laws and policies, and may lead to problems in subsequent government document processing and personal identity.
9. Finally, "multiple gender", which is authoritative and appeared in many policies and conferences in Taiwan, has neither Chinese-English translation, nor English-Chinese translation, nor its definition and explanation of its usage.

### **Suggestion**

1. Clearly defined "Sex" and "Gender" according to the definition of WHO "Gender is used to describe the characteristics of women and men that are socially constructed, while sex refers to those that are biologically determined."<sup>5</sup> – WHO
2. There should be a clear distinction between sex and gender. 「性別」 should be translated into "biological sex" (consistent with the long-term perception of the public). Gender should be translated as "social gender". The laws and the Gender Equity Education Act should be amended to clearly define "(biological) sex" and "(social) gender".

Then, Gender-related policies, gender statistics, and gender-equal education can be promoted without causing confusion, conflict or even affecting health. Finally, the substantially equality of men and women, and ultimate goal of gender equality of the United Nations gender mainstreaming could be achieved.

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<sup>5</sup> <https://www.euro.who.int/en/health-topics/health-determinants/gender/gender-definitions>

## Attachment

Attachment 1 [What is the definition of sex/gender ? They argue about the Gender Equity Education Act](https://forum.ettoday.net/news/1220387)  
<https://forum.ettoday.net/news/1220387>

Attachment 2 [The Magic of Disappearing Women in Taiwan](https://feminist-original.blogspot.com/2020/07/discussions-on-definition-of-sex-and.html)  
<https://feminist-original.blogspot.com/2020/07/discussions-on-definition-of-sex-and.html>

Attachment 3 A comparison table of Chinese and English nouns involving "sex" and "gender"  
<https://gec.ey.gov.tw/File/AC4C8F503D05AE3F/5d73b833-4b8c-45e2-a58b-ee299eab6863?A=C>

Article : ICESCR 12

Topic : Improper sexual education and PrEP policies violate people's right of health

Article	International Covenant on Economic Social and Cultural Rights 12
Topic	Improper sexual education and PrEP policies violate people's right of health
Situation	1. The numbers of sexual transmitted diseases increased annually in teens and in all ages in Taiwan 2. Promotion of "pre-exposure prophylaxis HIV (PrEP)" by public expense. Although the number of HIV infections decreased, the number of gonorrhea increased in August this year.
Suggestion	1. More emphasis (resources) should be put on Primary Prevention 2. The value of "Health First" should be cultivated in students, and they should be fully informed by correct knowledge about healthy development. 3. Sexuality education should be age-appropriate and "holistic" 4. Textbooks should be carefully reviewed 5. Teachers for sexuality education should be professionally trained and qualified 6. PrEP should not be the main policy to prevent HIV

**Situation**

(1) The numbers of sexual transmitted diseases increased annually in teens (Fig. 1 right) and in all ages (Fig. 1 left) in Taiwan

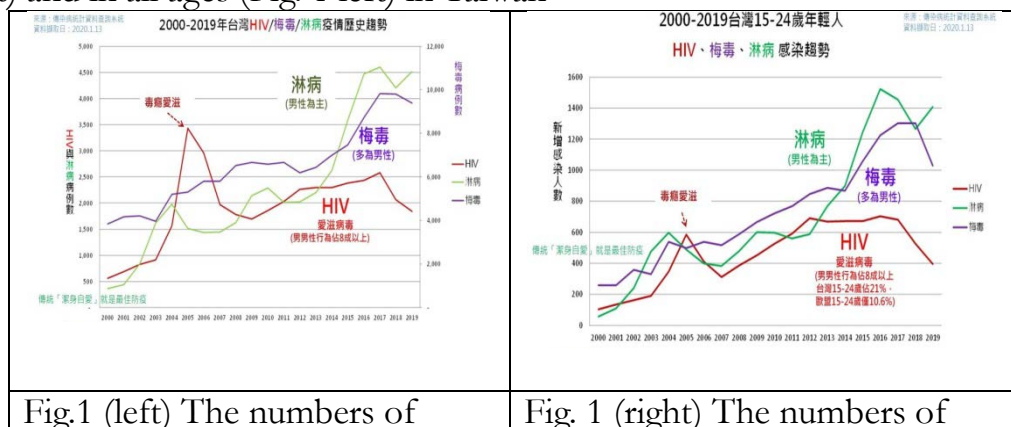


Fig.1 (left) The numbers of

Fig. 1 (right) The numbers of

STDs (syphilis, gonorrhea, and HIV) in Taiwan (2000-2019)	STDs (syphilis, gonorrhea, and HIV) in 15-24 year old in Taiwan (2000-2019)
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Source: Taiwan CDC

Promotion of "pre-exposure prophylaxis HIV (PrEP)" by public expense. There were about 1,000 people taking PrEP last year (Attachment 1). We estimated It would be about 2,000 people taking PrEP this year. Although the number of HIV infections decreased, the number of gonorrhea increased in August this year. (fig. 2)

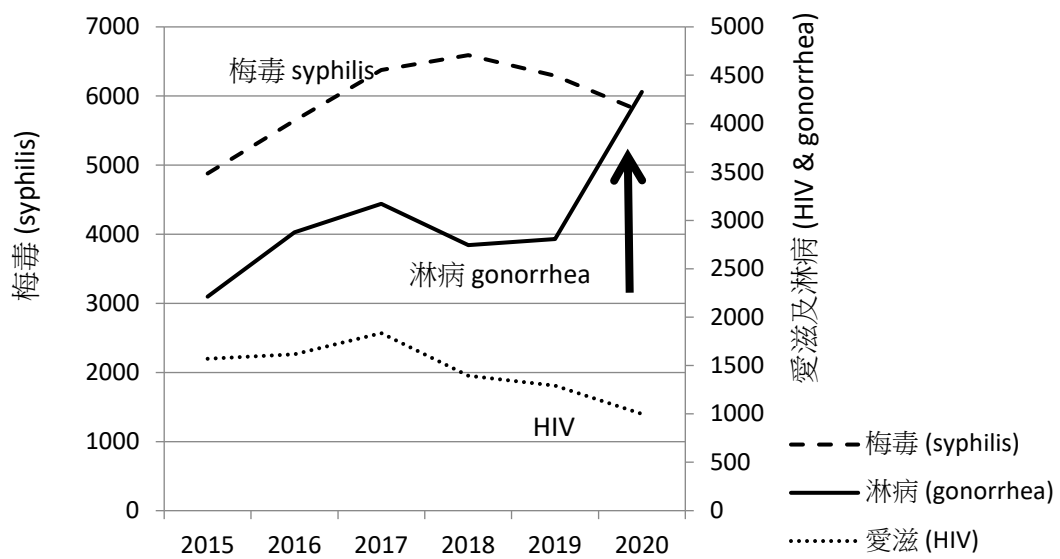


Fig.2 The numbers of syphilis, gonorrhea and HIV in August in 2016-2020 (Source: Taiwan CDC)

### Discussion

- (1) The sex education in school doesn't give students whole pictures of sexually transmitted diseases (STDs). "Condom Sex equals Safe Sex" are taught in schools. However, it is a myth and misleads the students to a risk situation in getting sexually transmitted diseases (STDs). In fact, for HIV/AIDS, there's only up to 80% protection with condoms (Weller & Davis-Beaty, 2012). However, the pathogens of other STDs may grow on the skin hair, and they can transmit to sex partners through the skin uncovered by the condoms (Figure 3). For gonorrhea, there is only 51-62% protection with condom use (Boily et al., 2009; Grossman, 2009). They don't teach students about these facts.

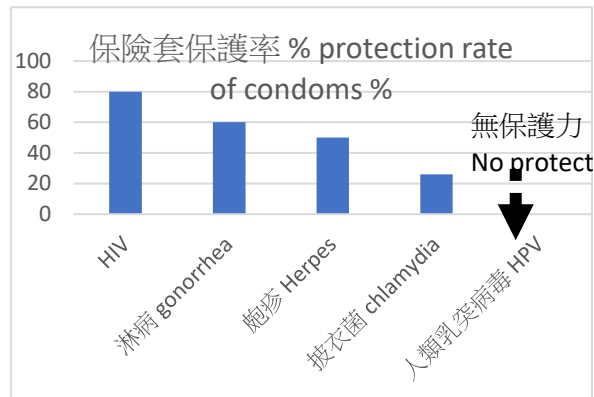


Figure 3 The protection rate of condoms in HIV and STDs

- (2) The AIDS prevention policy was wrong. The promotion of PrEP is expensive (NT345/pill) and PrEP may have renal and skeletal toxicity). PrEP may hurt young people. In addition, from the success in treating HIV to the advent of PrEP, some PrEP users are having more risky sex — and are being diagnosed with more sexually transmitted infections. (Traeger et al. 2018) Therefore HIV declined, while gonorrhea increased significantly.

### Suggestion

- (1) More emphasis (resources) should be put on Primary Prevention, that is, developmentally appropriate sexuality education for whole school, which can at least taking care of the needs of 80% students, as the WISER model<sup>6</sup> suggested (Figure 4).

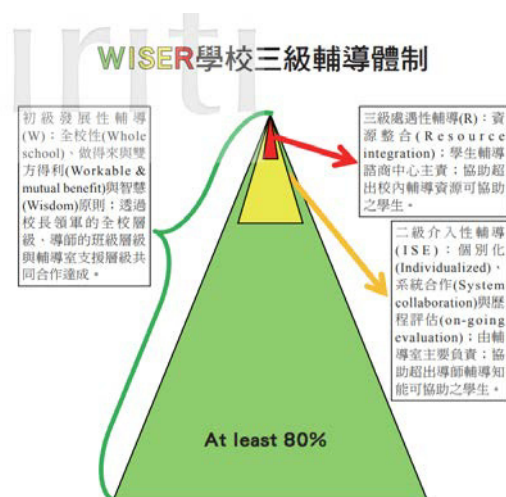


Figure 4. WISER model for consultation system in school  
**WISER** represents **W**hole Principle (whole school), **I**ndividualized, **S**ystem collaboration, **E**valuation, **R**esource Integration.

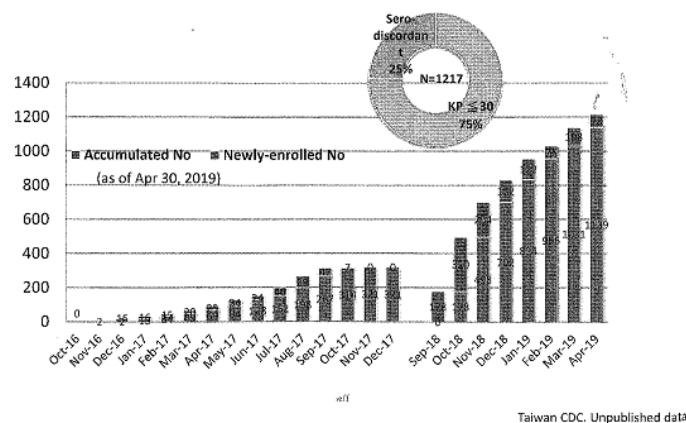
<sup>6</sup> WISER represents **W**hole Principle (whole school), **I**ndividualized, **S**ystem collaboration, **E**valuation, **R**esource Integration.



- (2) The value of "Health First" should be cultivated in students, and they should be fully informed by correct knowledge about healthy development. The school should also provide students with accurate information on STDs, HIV and protection. The school should promote family values and the key message that "Abstinence as best choice for teenagers", empowering students to make wise decisions about sex.
- (3) Sexuality education should be age-appropriate and "holistic"--including aspects of physical, psychological, and social aspects (ethics, morale, value, law), etc. It should include the 15 goals of the WHO. Students should be taught skills such as decision-making, assertiveness and the courage to say "no" to sexual exploration even under peer pressure.
- (4) Textbooks should be carefully reviewed. The Textbook Review System should include indicators like age-appropriateness, reasonable proportion (contents for all should be more than that for individual or special groups of students), and evidence-based knowledge
- (5) Teachers for sexuality education should be professionally trained and qualified, and should respect that they are in a position of trust with respect to students and ensure that schools are not used as arenas for advocacy on controversial issue.
- (6) In "ABC strategy" for HIV and STD prevention, we over emphasized C ---the use of condoms. A and B were neglected. We should teach young students: abstinence, be faithful, and avoid casual sex. PrEP should not be the main policy to prevent HIV. As a result, HIV seems decreased, but other STDs have increased, and the overall sexual health problems became more serious.

Attachment 1 The number of people taking PrEP (2019 by Taiwan CDC)

### 疾管署公費PrEP計畫: 收案趨勢



## References

1. Boily MC, Baggaley RF, Wang L, Masse B, White RG, et al. (2009) Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies. *Lancet*, 9: 118–129.
2. Grossman, M. (2009). *You're teaching my child what: a physician exposes the lies of sex Ed and how they harm your child*. Washington, DC: Regnery Publishing Inc.
3. Weller, S. C. & Davis-Beaty, K. (2012). *Condom effectiveness in reducing heterosexual HIV transmission*. New York: John Wiley & Sons.
4. Traeger MW, Schroeder SE, Wright EJ, Hellard ME, Cornelisse VJ, Doyle JS, Stoové MA. (2018) Effects of Pre-exposure Prophylaxis for the Prevention of Human Immunodeficiency Virus Infection on Sexual Risk Behavior in Men Who Have Sex With Men: A Systematic Review and Meta-analysis. *Clin Infect Dis*.16;67(5):676-686

**Article : ICESCR 12**

**Topic : Project-application of CBD (Cannabidiol) for medical usage - protecting rare-diseased children and preventing cannabis (marijuana) abuse**

Article	International Covenant on Economic Social and Cultural Rights 12
Topic	<b>Project-application of CBD (Cannabidiol) for medical usage - protecting rare-diseased children and preventing cannabis (marijuana) abuse</b>
Situation	<ol style="list-style-type: none"><li>1. Politicians promoted legalizing "medical marijuana", but their ultimate goal is legalizing "recreational marijuana".</li><li>2. Project-application of CBD for medical usage can prevent abuse of cannabis (marijuana).</li><li>3. Cannabis is addictive and affects brain function</li></ol>
Suggestion	<ol style="list-style-type: none"><li>1. The CBD application process should be improved to benefit patients who really need to use it.</li><li>2. The mechanism of CBD in treating intractable epilepsy is still unclear, so medical use of CBD should not be fully open.</li></ol>

**Situation**

**1. Politicians promoted legalizing "medical marijuana", but their ultimate goal is legalizing "recreational marijuana".**

It seems that only "legalizing medical marijuana" is being promoted, however, the ultimate goal is legalizing "recreational marijuana" (1) and "full open of marijuana" (2), regardless of the health risks of marijuana. They promoted "medical marijuana" in the name of health, but the truth is this is a cheating behavior.

**2. Project-application of CBD for medical usage can prevent abuse of cannabis (marijuana).**

Children with Dravet syndrome and Lennox-Gastaut syndrome with intractable epilepsy have the need to use CBD (Cannabidiol, cannabis extract). There are about 40 people being diagnosed Dravet syndrome in Taiwan (3). The incidence of Dravet syndrome is about 1 in 100,000, and Lennox-Gastaut syndrome is 1 in 10,000. That is, there are more than 200 Dravet syndrome patients and more than 2,000 Lennox-Gastaut syndrome in Taiwan. (4). The Ministry of Health and Welfare said that these patients can apply the drugs after the doctor's diagnosis. The application should be submitted by doctors in teaching hospitals according to "controlled drug act" and the "Regulations for Approval of Specific Medical Products'

Manufacturing or Importing as a Special Case " (5). However, no agency has imported the drugs, and patients must be approved and import the drugs by themselves. It is difficult to be approved, and only 33 people have successfully approved in the past three years (4). Therefore, they called for legalizing "medical marijuana" again.

### 3. Cannabis is addictive and affects brain function

The use of marijuana has adverse effects on the body and mind according to the data from the National Institute on Drug Abuse (NIDA) (5).

Marijuana is addictive and affect brain function (6), not as harmless as everyone thinks.

### Suggestion

1. **The CBD application process should be improved to benefit patients who really need to use it.**

2. **The mechanism of CBD in treating intractable epilepsy is still unclear, so medical use of CBD should not be fully open.**

Though CBD can treat some intractable epilepsy, dyskinesia and pain, the mechanism is still unknown. (7). The side effects may be unpredictable and un-controllable if we do not fully understand the mechanism of CBD.

Therefore, the UK is conservative about medical usage of CBD (8).

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### Attachment

- (1) Legislator 3Q thanked for supporting legalizing marijuana.  
<https://www.facebook.com/events/s/3q%E6%94%AF%E6%8C%81%E5%A4%A7%E9%BA%BB%E5%90%88%E6%B3%95%E5%8C%96%E3%84%98%E6%B0%B4%E9%A4%83%E6%84%9F%E8%AC%9D%E7%A5%AD/1100012473685211/>
- (2) [Cannabis is a magic but also a medicine 5] It is a second-class drug as amphetamines. It is difficult to legalize medical marijuana  
<https://www.mirrormedia.mg/story/20200717cul006/>
- (3) [Cannabis is a magic but also a medicine 1] Girl with rare disease had seizures 300 times a week before using cannabis oil, but now only once a week after using cannabis oil.  
<https://www.mirrormedia.mg/story/20200717cul002/>
- (4) Children with rare diseases, such as intractable epilepsy, can use THC (cannabis drugs), announced by Ministry of Health and Welfare.  
[https://www.twreporter.org/a/cannabis-for-medical-use-taiwan?fbclid=IwAR3DalzhWLSJz0AxpunOh7iA7JAML-3T4bjk253gP9KMyLin\\_afVtgJv4NE](https://www.twreporter.org/a/cannabis-for-medical-use-taiwan?fbclid=IwAR3DalzhWLSJz0AxpunOh7iA7JAML-3T4bjk253gP9KMyLin_afVtgJv4NE)
- (5) Legalizing Medical marijuana? Ministry of Health and Welfare answered.

<https://news.tvbs.com.tw/life/1320504>

- (6) Cannabis Addiction and the Brain: a Review J Neuroimmune Pharmacol. 2018; 13(4): 438–452.
- (7) Therapeutic potential of medicinal marijuana: an educational primer for health care professionals Drug Healthc Patient Saf. 2018; 10: 45–66.
- (8) Cannabis: the facts <https://www.nhs.uk/live-well/healthy-body/cannabis-the-facts/>

**Article : ICESCR 13**

**Topic : CDC, please don't use parents' money to harm kids- so called "gender-equal clubs" are wolves in sheep clothing**

Article	International Covenant on Economic Social and Cultural Rights 13
Topic	<b>CDC, please don't use parents' money to harm kids- so called "gender-equal clubs" are wolves in sheep clothing</b>
Situation	1. CDC uses parents' money (tax) to subsidize gender-equal clubs, which promote having sex with minors 2. Gender-equal clubs promote controversial and potentially lethal BDSM content in the university 3. Gender-equal clubs in the university mislead the students with the speaking - BDSM is "sex education".
Suggestion	1. Governments should protect the students, and parents' money (tax) should not be spent on clubs that promote "potentially lethal and controversial issues.", such as BDSM. 2. The Ministry of Education should ask the universities to remind the students, that they should not cross the red line or violate the law (such as having sex with minors) 3. The Ministry of Education should urge universities to promote the quality of students, and establish a self-review mechanism

**Situation**

**1. Taiwan CDC (Center for Disease Control) used parents' money (tax) to subsidize gender-equality clubs, which promote having sex with minors**

CDC used parents' money (tax) to subsidizes the gender equal clubs (1), however, the clubs promote illegal issue in the university. The gender equal club had a speech - "Can minors have SM (Sadism & Masochism)?", and talking about the sexual rights of minors on June 6, 2020 in National Sun Yat-sen University (Fig. 1 left and right). This violates the laws of Taiwan (It is illegal to have sex with minors) (Criminal Law 227). Having sex with minors is illegal in many countries. Did they encourage college students to break the law and harming the human rights (rights of health) of minors?

【活動分享】

- 講題：年齡政治大問哉：「未成年人士可以參加 SM 活動嗎」—探討未成年性權
- 時間：6/12(五) 19:00-21:00
- 地點：中山大學雨樹藝文空間
- 講師：縛生 講師 小林繩霧 老師
- 單位：國立中山大學性別友善社
- 報名表單：<https://forms.gle/WAU7gtUNYDsvgziA6>

這次中山大學性別友善社主辦的講座將探討台灣自90年代到今日對「#性」的態度，以及對「#未成年人」的態度的演變，從中理出性政治與年齡政治中的權力運作。有興趣的同學趕快點進粉專報名吧><



講題：年齡政治大問哉：「未成年人士可以參加 SM 活動嗎」—探討未成年性權

6月12日週五  
 未成年人能接觸sm活動嗎？談我所知的性與年齡政治



← 未成年人能接觸sm活動嗎？談我所...

講題：年齡政治大問哉：「未成年人士可以參加 SM 活動嗎」—探討未成年性權

時間：6/12(五) 19:00-21:00

地點：國立中山大學雨樹藝文空間

講師：縛生 小林繩霧 Nawakiri Shin 老師

12日 6月 未成年人能接觸sm活動嗎？談我所知的性與年齡政治  
 公開·活動·由中山大學性別友善社-Gender Friendly

Fig. 1 "Can minors have SM?", and talking about the sexual rights of minors on June 6, 2020 in National Sun Yat-sen University

**2. Gender-equal clubs promote controversial and potentially lethal BDSM (Bondage , Discipline , Dominance, Submission, Sadism and Masochism) content in the university**

The National Tsing Hua University gender-equal Club, which was just established this year in 2020, is going to teach BDSM (Figure 2). BDSM is known to be potential lethal (2), controversial, and criminal in certain countries (such as the United Kingdom and certain parts of the United States) (3).

【歡迎來到愛慾實務社，今天來晚愛慾吧！】

清華大學愛慾實務社在 2020 年的夏天正式成立了。我們希望能在清大創造討論性、情慾和親密關係的友善空間，去補足過去沒有完整上到的性教育。在成員的努力之下，在清大我們終於有大方談性的空間，一嘗愛慾的滋味。

下學期，我們會計劃針對【身體、情慾和性】、【性協商】、【BDSM】三個主題，邀請社師和講師來上課，並舉辦聊天會交流、安排期初期末派對聯絡感情。我們期待能透過演講和聊天會，對社員有興趣的主題深入探討（主題在社員大會與社員再行討論，目前暫定），讓清大可以形成固定討論性和情慾的社群，去讓我們在面對性的時候能夠做好準備，在享受性的時候也能保護自己與對方。

我們邀請了兩位相當專業的社團指導老師，針對主題規劃相應課程。

一位是清大心諮系的葉致芬老師，開設有性議題探討與思辯通識課，專長領域包含性與性 / 別議題諮商 (LGBTSQQ-Friendly、同志伴侶諮商、性平行為人諮商)、情感教育與輔導....等諸多領域。

另一位是 BDSM 實務經驗豐富的黛拉，是禁羈創作者、表演者及講者，現為《縛·生》編輯，並協助管理《皮繩愉虐邦》，演講內容豐富而表演令人驚豔。

我們明天將會公布社員招募表單，大家按讚分享搶先看本粉專，讓清大和我們一起來晚愛慾吧！

---

社員招募表單來了！快點一起加入我們吧！

<https://www.facebook.com/kuh10>

Fig. 2 Tsing Hua University's gender-equal club advocates BDSM, and believes that BDSM, "desire" and "enjoying sex" are ways to complement sex education.

### 3. Gender-equal clubs in the university mislead the students with the speaking - BDSM is “sex education”.

Sexual abuse and BDSM content are not related to sex education in any country. BDSM is extremely risky and may be fatal. They advocate BDSM as one part of sex education (Figure 2 and 3). It is cheating and misleading the students.

Fig. 3 Gender-equal clubs taught BDSM in different universities.



**輔仁大學**  
繩若成河 願為室縛

陸仁賈同志文化研究社

皮繩愉虐邦

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五月十四晚上七點入場七點半開始  
陸仁賈系列活動

東海大學同儕社  
【社課宣傳】

**東海大學 皮繩愉虐**

日期：4/21  
時間：19:00-21:00  
講者：小林繩霧  
地點：SS206 (東海大學社會科學院)

**國立台灣大學**

情愛抽鞭的秘辛  
探討你所不知道的BDSM

講者 台大BDSM社 社長版版  
副社小籬  
文書傑尼

5/25  
(三)  
19:00  
(18:30換場)  
G502

主辦  
台大BDSM  
世新 台大  
飛魚 BDSM

# 性虐待!!

逢甲大學【性別友善社】  
2015年11月21日 23:19 - 台中市 · 逢

【社課】 **逢甲大學**

就算沒玩過，你也肯定聽過 BDSM 這個詞  
電影《格雷的五十道陰影》上映後更是成為熱門詞彙  
但我們真的知道 BDSM 是什麼嗎？  
BDSM 只能在性關係中進行嗎？

皮繩愉虐邦

**BDSM**

宜大原色思潮  
2015年10月17日

【思潮分享】 **宜大原色**

這幾天，原色思潮都在多元性別展覽擔任解說員  
在展覽間有關於BDSM文化的議題  
有些人可能會想要了解什麼是BDSM  
現在就藉由這篇文章來為大家解惑吧！

25 THINGS EVERYONE SHOULD KNOW ABOUT **BDSM**

【翻譯】關於BDSM，格雷的五十道陰影不會教你的25件……

**國立台灣大學 皮繩愉虐社**

## Suggestion

**1. Governments should protect the students, and parents' money (tax) should not be spent on clubs that promote "potentially lethal and controversial issues.", such as BDSM.**

CDC subsidizes the gender-equal clubs in Public and private universities in Taiwan. However, these clubs advocate "freedom of sexual desire" and teach BDSM, or " Minors should explore sex". These contents are not related to research, are not healthy, and may violate the law. They should not use the classrooms or taxpayers' money to harm our children!

**2. The Ministry of Education should ask the universities to remind the students, that they should not cross the red line or violate the law (such as having sex with minors)**

**3. The Ministry of Education should urge universities to promote the quality of students, and establish a self-review mechanism**

Don't let children misled by these gender-equal clubs with wrong information (such as BDSM related to sex education) and make the universities inferior. These schools should have self-review mechanism. These odd information make people worry about the future of students in Taiwan.

## References.

- (1) Center for diseases Control subsidizes civil organizations and colleges for HIV prevention and control, and colleges should help to set up gender-equal clubs.

六、大專院校愛滋友善環境營造計畫 <b>【大專院校僅限定申請此項】</b>	大專院校教職員生	1.大專院校辦理安全性行為、愛滋防治及愛滋去歧視相關宣導活動，新申請的每所學校最高以補助 <u>5萬元為上限</u> 。102年至104年度已申請過之學校，補助 <u>1萬元為上限</u> 。 2.大專院校辦理申請本項計畫，需於年底前完成：(1)於校園「設置保險套販賣機至少1台」、或(2)「輔導成立學生同志社團」。 3.辦理愛滋病、性病防治、性教育及娛樂性用藥減少危險性行為，保險套使用推廣、愛滋去歧視等衛生教育活動，並可利用校園 PTT 聊天室、大型活動等方式，納入愛滋病防治衛生教育工作。亦可結合衛生局之同志健康中心，轉介並提供大專院校學生健康諮詢與篩檢服務。
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- (2) Lena Bunzel, Sarah C Koelzer, Barbara Zedler, Marcel A Verhoff, Markus Parzeller. Non-Natural Death Associated with Sexual Activity: Results of a 25-Year Medicolegal Postmortem Study] Sex Med . 2019 Oct;16(10):1547-1556
- (3) Julie Marks (2019) Is BDSM Legal in the US and Other Places?  
<https://www.everydayhealth.com/sexual-health/bdsm-legal-u-s-other-places/>

# **Attachments**



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**Article : ICESCR 3**

**Topic: The ambiguous definition of the term “sex” has made disturbance in execution of laws, and public opposition.**

**Attachment 1 What is the definition of sex/gender ? They argue about the Gender Equity Education Act**

<https://forum.ettoday.net/news/1220387>

「性別」定義是什麼？台灣性平教育吵翻天

ETtoday 新聞雲 > 雲論 2018 年 07 月 25 日 14:30

文/MAX

台灣性別平等教育吵翻天，一方說，國中小學要適齡性平教育，不要同志教育，一方說，沒有同志教育，就不是性別平等教育。照這種吵法，性平教育似乎只容一把量尺，就是支持同志、LGBTQ 教育與否？但問題是，性別平等的「性別」，究竟指男女還是 LGBTQ？

這番爭論，日前也搬上了在台北市舉行的聯合國《消除對婦女一切形式歧視公約》(CEDAW) 第三次國家報告審查會議（我國已簽署聯合國 5 項人權公約，CEDAW 為其一）。受邀來台的 5 位國際委員從官方及 NGO 提交的報告中觀察出端倪，原來台灣並沒有一條法令明確定義「性別」。

生理與社會性別分開看

為此，16 日義大利籍委員 Bianca 特別為 300 多名官員與 NGO 代表上了一堂課。她說，聯合國 CEDAW 公約中有清楚定義，「生理性別」(sex) 是指男女生理上的差異，「社會性別」(gender) 是指社會建構男女身份認同、特質和角色，以及社會賦予這些生理差異的社會文化意義導致男女之間的階層關係和權力與權利分配偏袒男性，且不利於女性。



CEDAW 的核心為，消除對婦女的生理性別及社會性別歧視，還有其他因種族、族裔、宗教或信仰、健康狀況、年齡、階級、種姓、性取向和性別認同等交叉因素，對婦女產生的多重及交叉歧視。

我國與聯合國定義不一

為確認我國法令究竟有沒有「性別」定義？國際委員再三追問下，僅教育部明確回應，《性別平等教育法》將性別從生理男女擴及到社會性別男女，並納入性別傾向與性別認同。「定義最清楚的是在第 14 條：學校不得因學生之性別、性別特質、性別認同或性傾向而給予教學……等之差別待遇。」

這番詢答，解開了藏在台灣性平教育爭議中最核心的疑惑，原來上路 14 年的《性平教育法》中的「性別」，與聯合國公約中定義的生理性別的男女、社會性別的男女，並不一致，且把性別認同、性傾向一起混淆進來。

回顧《性平教育法》立法時空背景，其前身為《兩性平等教育法》，後因「葉永鋕事件」發生，不同性別特質學生遭霸凌議題引起社會高度關注，政策才轉彎，特別將性別特質、性別傾向、性別認同納入，全部打包入「多元性別」一詞裡。

政策不再聚焦弱勢女性

《性平教育法》上路 3 年後，我國簽署 CEDAW，全面推動性別平等政策，亦援用「多元性別」概念。如今看來，「多元性別」一詞，應了港人一句俚語「好心作壞事」，為了多元性別，性平教育內容變得

無邊無界，多元性別也使得部分性平政策或措施，不再聚焦於婦女議題，尤其是弱勢女性。

姑且不論，國人近年性健康惡化、家庭暴力及離婚率攀高、情殺事件頻傳，與施行多年的性平教育及性平政策關連為何，可以確定的是，台灣社會已因性別定義與性傾向及性別認同混淆不清，陷入意識型態之爭，付上莫大代價。

### 籲盡速統一定義弭衝突

台灣政府縛力簽署各項聯合國人權公約，並將公約予以國內法化，全力保障兒童、婦女、身障者之權益。如今，面對導致社會嚴重分歧的性平教育爭議，政府當務之急，應是統一所有法律和政策文件的性別用詞及歧視定義，與有 193 個成員國的聯合國公約定義一致，以期迅速平息社會衝突。

原文網址：「性別」定義是什麼？台灣性平教育吵翻天 | 雲論 | ETtoday 新聞雲

<https://forum.ettoday.net/news/1220387#ixzz6ap8Bqb6F>

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## Attachment 2 The Magic of Disappearing Women in Taiwan

<https://feminist-original.blogspot.com/2020/07/discussions-on-definition-of-sex-and.html>

親愛的，我們在台灣把女人變不見了

The Magic of Disappearing Women in Taiwan

2020-07-04

### 「生理性別」與「社會性別」的國家討論 **Discussions on the Definition of Sex and Gender at the National Level, 2018-2020**

The series of discussions on the definition and usage of "sex" and "gender" in national policies in Taiwan initiated by NGOs at the Review and Presentation of the ROC (Taiwan) CEDAW 3rd National Report in July, 2018 will be shown in the following order.

1. Presentations of Association of HIV/AIDS and Child Care with 3 other NGOs, urging the government to use "sex" and "gender" according to the CEDAW definitions and not to leave out women
2. Request by the CEDAW International Review Committee (IRC) for the government to review and correct the use of "sex" and "gender" in "all the legislative texts and policy documents and promote correct understanding of these terms in line with CEDAW"  
(The IRC specifies that "The term "sex" refers to "biological differences between men and women" .See 2. in the following.)
3. The Executive Yuan issuing commands to all government agencies to review and correct the use of "sex" and "gender"
4. My letter to the Executive Yuan pointing out the missing of "Taiwan" (regarding the misuse) in the official translation and the vagueness of the government's instructions
5. Reply from the Executive Yuan, which promised to make corrections
6. **The closed-door meeting ( to which none of the initial NGOs was invited) on the definition and usage of "sex" and "gender" at the Executive Yuan**
7. The Executive Yuan issuing a shortlist of Chinese to English translations concerning the use of "gender" (**without any definition and without "sex"**) to all government agencies and instructing them to examine "all the legislative texts " accordingly

### 消歧公約第三次報告國際審查委員會有關"生理性別"及"社會性別"之討論過程

1. 民間團體發言，要求政府正確使用”生理性別”及”社會性別”，不應以定義不明的"多元性別"取代消歧公約中的男女
2. 國際委員建議行政院更正 sex and gender 的定義與使用
3. 行政院指示各單位更正 sex and gender 的定義與使用
4. 我寫信給行政院，因為在部會的性平會議中看不懂行院所下的指令
5. 行政院回信，表示會討論
6. 行政院召開閉門會議討論"sex"及"gender"的定義與使用
7. 行政院發給各級政府中翻英名詞對照表並要求檢視所有法規之英譯，對照表中完全沒有"sex"；沒有英翻中；也沒有有關"sex"及"gender"之定義或說明

1. Presentations of NGO's , urging the government to use these terms according to the CEDAW definitions and not to leave out women

CEDAW 第三次國家報告國際審查會議 NGO 場次發言單 (英文)

NGO 名稱(中文) : 中華兒少愛滋關懷協會

NGO 名稱(英文) : Association of HIV/AIDS and Child Care with 3 other NGOs

場次 :  7/16 下午     7/17 上午     7/17 下午  
2018

CEDAW: Article 3

Issue: Definitions of Sex/ Gender (and Equality)

一、英文

Dear committees,

In represent of my own and other three Associations, I would like to talk about the issue of definitions.

There are no clear definitions of sex/gender in our laws (the Enforcement Act of CEDAW and the Gender Equity Education Act), and they are confusing in the policies. Partly because both sex and gender are translated as the same Chinese term "性別"。Without clear definitions, it initiates a misdirecting progress.

At first, the terms in our legal documents are in accordance with the UN definition-(Sex means women/men, gender means female/male). However, the definition was latter expanded and shifted to multi-sexes and multi-gender (多元性別), and in the end, it becomes the synonym of LGBT.

"Women" simply disappeared! It ends up with ignoring women in the policies.

For example:

1.The theme of photo competition on "Seeing gender diversity" were restricted to LGBT. Women are not included.

2.In the Government supported radio program Gender Equality Eazy Go, LGBT topics are about doubled than the Women topics.

3. In the universities, all Women study were renamed as Multi-gender study.

Women are no longer the focus of gender equality policy or education, it's replaced by LGBT. Many women's issues are now ignored.

Therefore, we suggest that:

1. There should be clear definitions of sex/gender in the laws, and they should be consistent with UN CEDAW.
2. All the laws should include clear definitions of gender as female and male (woman & men), and distinguishing them from sexual orientation or gender identity.
3. Sex should be translated as 「性別」 - as it is showed on our ID and Passport. And, gender should be translated in a different term, as 「社會性別」.
4. Stop using the confusing term- 多元性別 (multi-gender) in all legal documents. Delete Article 2 in the Gender Equity Education Act.
5. Follow UN's suggestion, the Gender Equity Education Act should be corrected as Gender "Equality" education Act.
6. The factors for intersectional discrimination, including religion or belief, race, ethnicity, health, age, status, class, should also be included in the law to ensure that all women are equally treated.

### CEDAW 第三次國家報告國際審查會議 NGO 場次發言單 (中文)

NGO 名稱(中文): 中華兒少愛滋關懷協會

場次:  7/16 下午       7/17 上午       7/17 下午  
2018

**關切議題 (Issue): CEDAW 第三條: 關於性別定義**

二、中文

委員好:

我代表中華兒少愛滋關懷防治協會發言, 我們有三個協會都關注到性別定義的議題。

在 CEDAW 國內施行法以及性別平等教育法當中, 性別定義是令人混淆的。因為英文文件當中的 Gender 以及 Sex 都使用同一個中文詞“性別”做翻譯, 因此產生混淆。缺乏明確的定義, 將

導致錯誤的性別觀念與錯誤的政策方向。

原本我國法律中的性別定義跟聯合國 CEDAW 的定義是相同的，但是後來性別的定義被擴張成為「多元性別」，甚至多元性別成了 LGBTQ 的同義詞。

舉例來說：

1. 行政院所舉辦的多元的性別攝影比賽，比賽主題與方向限定為 LGBTQ。女人根本被排除在外。
2. 政府經費支持的電台節目性別平等 Easy go 節目中，與 LGBTQ 相關的話題是女性的兩倍。
3. 大專院校原本名為婦女研究的計畫或是課程，被迫更名為性別研究課程。

女性不見了，而女性的權益因為定義寬鬆而無法被完全的保障。

所以，我們建議：

1. 在法律條文中明確定義 Sex 與 Gender 的不同，並且符合聯合國 CEDAW 以生理性別（男女）為基礎。
2. CEDAW 國內施行法以及性別平等教育法及所有法令應該清楚的定義 Sex 以及 Gender，並與性傾向及性別認同加以區別。
3. Sex 應該翻譯成「性別」—與我國身份證及護照上的翻譯一致。而 Gender 翻譯成「社會性別」。
4. 不要再使用多元性別一詞，刪除性平法第二條。避免繼續造成混淆
5. 性別平等教育的英文名（Gender Equity Education Act）應該更名為 Gender Equality Education Act，以符合聯合國委員對於法律達到實質平等的要求。
6. 將其他會造成交叉歧視的要素，例如種族、部落、宗教或是信

仰、健康、社經地位以及年紀等條件都納入性別平等教育法案中。

### Meaning and use of the terms “sex” and “gender”

10. The IRC is concerned with the inappropriate conceptual and practical use of the terms “sex” and “gender” in Taiwan. In the CEDAW jurisprudence the Convention refers to sexbased discrimination, but also covers gender-based discrimination against women. The term “sex” refers to biological differences between men and women. The term “gender” refers to socially constructed identities, attributes and roles for women and men and society’ s social and cultural meaning for these biological differences resulting in hierarchical relationships between women and men and in the distribution of power and rights favoring men and disadvantaging women.

11. The IRC recommends the Government to align all the legislative texts and policy documents and promote the correct and consistent understanding of the terms “sex”



and “gender” in line with CEDAW Convention and the Committee’ s General Recommendation No. 28.

消除歧視公約國際審查委員會對政府的建議 2018/07/20 (官方中譯)

### 「性」與「性別」的意義與運用

10. 審查委員會關切「性」(sex)與「性別」(gender)二詞在概念上與實際上的不當運用。在 CEDAW 法理中，公約提及基於性的歧視，但亦涵蓋對女性基於性別的歧視。「性」意指男女生理上的差異；「性別」意指社會建構的男女身分、歸屬和角色，以及社會賦予這些生理差異的社會文化意義，導致男女之間的階層關係以及權力和權利的分配有利於男性而不利於女性。

11. 審查委員會建議臺灣政府 審查委員會建議臺灣政府依照 CEDAW 和 CEDAW 委員會第 28 號一般性建議統 號一般性建議統 一所有法律和政策文件用詞， 一所有法律和政策文件用詞，並促進對「性」與「性別」正確、一致之認知。

3. My letter to the Executive Yuan  
yenlin ku 2019/07/20

A. I point out that the Chinese translation left out the very important words "in Taiwan". The inappropriate conceptual and practical use of the terms “sex” and “gender” actually takes place here in Taiwan and needs to be addressed immediately.

B. The instructions sent out by the Executive Yuan were so vague that most officials failed to understand its intentions.

收件人：羅政務委員秉成、性平處吳處長秀貞、勞動部林常務次長三貴

送件人：顧燕翎

主旨：有關 **第 3 次國家報告**（審查委員會結論性意見與建議第）1011-00-02、序號 2、點次 10 及 11）國際委員指出之重要名詞誤用

日期：2020/07/20

說明：

一、 本人為勞動部性平委員，在參與第 17 次性平會議（108 年 7 月 16 日 10 時）時，討論消歧公約第 3 次國家報告結論性意見與建議之辦理情形追蹤管考，其中案號 1011-00-02、序號 2、點次 10 及 11，指出在台灣對於 sex 及 gender 的概念及使用均不恰當，需對政府所有文件及法律名詞做統一修正，事關重大，但與會之性平處代表及勞動部同仁均未能清楚說明事由，亦未能提出具體、清晰之措施，本人甚感困惑。

二、 經查性平處網站上述消歧會議之中英文會議紀錄及錄影檔，並比對聯合國官網上中英文消歧公約條文以及委員會第 28 號一般性建議，發現會議紀錄之中文翻譯可能未能掌握國際委員建議之重點，以致結論和建議無法被理解和有效執行。請慎重考查此事，避免政策方向混亂。

三、 以下將結論性意見與建議案號 1011-00-02、序號 2、點次 10 及 11 分別說明，紅色部分為本人之修改，括號部分是本人之加註，英文原文亦附於後，以幫助了解：

10. 審查委員會關切台灣在「性」(sex)與「性別」(gender 在法理中，公約提及基於 sex 的歧視，但亦涵蓋對女性基於 gender 的歧視。sex 意指男女生理上的差異；gender 意指社會建構的男女身分、歸屬和角色，以及社會賦予這些生理差異的社會文化意義，導致男女之間的階層關係以及權力和權利的分配有利於男性而不利於女性。

(委員特別指出此二名詞在台灣使用不當，刪去台灣二字便失去所指。)

11. 審查委員會建議臺灣政府依照 CEDAW 和 CEDAW 委員會第 28 號一般性建議統一所有法律和政策文件用詞，並促進對「性」與「性別」正確、一致之認知。

審查委員會建議台灣政府根據消歧公約的條文以及委員會第 28 號一般性建議，校正所有法律和政策文件用詞，提升對「生理性別」(sex)與「社會性別」(gender)這兩個名詞正確、一致之理解。

附原文：

10. The IRC is concerned with the inappropriate conceptual and practical use of the terms “sex” and “gender” in Taiwan. In the CEDAW jurisprudence the Convention refers to sex based discrimination, but also covers gender-based discrimination against women. The term “sex” refers to biological differences between men and women. The term “gender” refers to socially constructed identities, attributes and roles for women and men and society’ s social and cultural meaning for these biological differences resulting in hierarchical relationships between women and men and in the distribution of power and rights favoring men and disadvantaging women.

11. The IRC recommends the Government to align all the legislative texts and policy documents and promote the correct and consistent understanding of the terms “sex” and “gender” in line with CEDAW Convention and the Committee’ s General Recommendation No. 28.

四、以上建議敬請卓參。

4. Reply from the Executive Yuan 2019/07/29

They will convene a meeting to discuss this issue.

行政院性平處的回覆

Mon, 29 Jul 2019 09:56:00

顧老師好，

有關您所提 CEDAW 第三次國家報告結論性意見與建議第 11 點次，審查委員會建議臺灣政府依照 CEDAW 和 CEDAW 委員會第 28 號一般性建議統一所有法律和政策文件用詞，並促進對「性」與「性別」正確、一致之認知。老師建議中文應譯為「校正」所有法律和政策文件，根據 CEDAW 的條文以及第 28 號一般性建議，提升對「性」與「性別」這兩個名詞正確、一致之理解。

查第 11 點次中文翻譯意旨與老師意見相符，本處未來將採「校正」為原則，於後續邀集相關部會召開諮詢會議討論「性」與「性別」之涵義及釐清中英文翻譯後，請相關部會全面檢視法律和政策文件用詞。另外，未來視其必要，亦請相關部會運用妥適方式對外說明或解釋。感謝老師提供此寶貴意見！

行政院性別平等處 敬啟

5. The closed-door meeting was held at the Executive Yuan. The original NGOs that raised this issue was neither invited to the meeting nor informed of the conclusion. 2019/02/06

**The major points made in this meeting:**

1. There should be no discrimination based on gender, sexual orientation or gender identity.
2. There is no need to separate sex from gender. The concept of intersectionality is introduced in CEDAW General Recommendation 28 (2010). These NGOs need to catch up on CEDAW.
3. These NGOs are not gender groups. They want to focus on women and men, not multi-gender.
4. The IRC was only "lost in translation". (expressed in English) There is no need to change the legislative texts and policy documents .

**CEDAW 第 3 次國家報告結論性意見與建議第 10 點及第 11 點次研商會議紀錄**

**壹、時 間：**109 年 2 月 6 日（星期四）下午 2 時

**貳、地 點：**行政院第七會議室

**參、主 席：**羅政務委員秉成

紀錄：蔡

宏富

肆、出（列）席人員：詳如簽到表

伍、主席致詞：略。

陸、討論事項：

案由：校正我國法律和政策文件用詞有關「性」與「性別」之用法，並促進對「性」與「性別」正確、一致之認知案，請討論案。

決議：

一、就法規之文字「性」與「性別」英譯內容進行檢視：

（一）請本院性別平等處（以下簡稱性平處）提供各部會法規英譯檢視原則及優先處理之法律。

（二）請各部會依檢視原則自行檢視後，須修正之條文適時提報性別平等專案小組，並於本(109)年10月底前提報性平處。

（三）請性平處邀集專家學者成立諮詢小組，就各部會提報之修正內容提供意見。

二、未來民眾如對法規、計畫及文件之「性」與「性別」提出疑義，請各該主管機關主動向民眾澄清及說明。

三、請性平處就「性」與「性別」之相關專有名詞提供中英對照表，並上傳至本院性平會網站。

四、有關CEDAW第4次國家報告涉及「性」與「性別」英譯內容應明確，審查現場口譯人員應加強訓練及要求，避免翻譯錯誤。

柒、散會。(下午3時30分)

**發言紀要**

許秀雯委員：

本審查意見來自第3次CEDAW國家報告審查，部分團體認為性與性別應限定在兩性，進而想要排除性傾向及性別認同。中文語境

的「性」除了有生理性別的意思，還有性行為的意思。而英文則有 sex, gender, sexuality 這三個單字，在學術上的中文翻譯也有不同意見。但重要的是，這裡所指的性別是融合憲法平等權的精神，也就是不能因性別、性傾向及性別認同有所歧視，而不只是指生理性別。

伍維婷委員：

依 CEDAW 第 28 號一般性建議，可以知道性與性別是不可完全分割，所以不太需要完全區分是針對生理還是社會性別的歧視，且依第 28 號一般性解釋第 18 點還提到交織性歧視的部分，包含 sexual orientation (性傾向) 及 gender identity (性別認同)，所以部分團體應該是曲解 CEDAW 的內容，我們應該要求這些團體必須對 CEDAW 條文有基本認識才對。

何碧珍委員：

大眾目前可能真的還不清楚了解「性」跟「性別」的意思，本人認為除了議程所提的 3 點辦法之外，應該增加第 4 點，從教育著手，行政機關應教育大眾相關知識，尤其在學校教育就要開始，因此，我不知道教育部是否有確實推動這方面的教育，尤其是在課綱上。

官曉薇委員：

本人認為國外審查委員會有這樣的意見，問題主要來自於 lost in translation (翻譯的迷失)。Sex 一方面有性行為的意思，另一方面還有不同生理性別的意思，所以早在翻譯其他國家的法規，針對不能因為 sex 的歧視，我們就翻譯為「性別」，現在不可能改回去，因為最早的時候 sex 我們已經翻譯成性別。所以如果我們要機關去檢視及修正，以及重新教育民眾的話，可能社會的認知跟



法律的落差會更大。另外，其他國家在最開始反歧視法可能都是寫 sex，可是慢慢的會藉由司法及行政機關的擴張變成 gender、sexual orientation 及 sexual identity，如果現在透過函示的話，則我們過去的司法實務擴張到性傾向及性別認同的案件，會再限縮回去，這就跟過去的司法實務不同，原本進步及保障的空間也就跟著限縮。最後，自解嚴來所推動的性別平等一直都是 gender equality，這是我們的歷程，而且當初 CEDAW 第 28 號一般性建議的講義及教育訓練也都已經確認這些字詞。

黃淑玲委員：

國外在講 sex based 的 discrimination (歧視) 時，有其演化的過程，可能一開始 CEDAW 用 sex based，可是後來發現 sex based 跟 gender based 的意涵已經不一樣，gender based 包含的意涵更廣，包含性傾向、性別認同或跨性別。本人建議可以參考 CEDAW 的中文翻譯，雖然是中國翻譯的，但是 sex 他們翻為生理性別，而不是性，在醫學的研究也要特別區分 sex difference 及 gender difference，在醫學脈絡下就會凸顯這兩個字的差異。本人也不建議現在去大張旗鼓地請各部會全面盤點檢視法規，重要的是他們有沒有真的了解性與性別的意涵。

游美惠教授：

在審查會議時部分團體提出意見，這些部分團體其實並不是真的性別團體，而且在許多場合的辯論，這些團體都主張性別平等教育要回到兩性教育，否決多元性別這個詞。建議應該要商討出策略防止下次國家報告審查這些團體又上演同樣的戲碼。

官曉薇教授：

中文的法規如果在實務運用上沒有問題則不用修改，但是在國家

報告的文件，法規的英譯可能很有問題，因為我們要定期提國家報告，所以有英譯上的需求，在法規的英譯上仍有檢視的需要。

教育部：

有關民眾對性別平等教育法有關性的字詞疑義，本部均有在法規中做名詞定義，另外也有在本部的性別平等教育資源網定期放一些性別教育實施澄清的新聞稿或懶人包給民眾，教育部的粉絲專業也會不定期地提供名詞解釋給民眾參考。

卓春英委員：

法規的英譯檢視進度為何？哪個單位認可？建議可能由性平處統籌，成立小組，邀集外部專家學者審議。

林春鳳委員：

建議先由各部會自主檢視主管的法規，自己的法規自己清楚，再把檢視出有問題的內容提報性平處。

何碧珍委員：

建議各部會將檢視出有問題的法規先提報自己的性平專案小組。

郭素珍委員：

建議是否由 CEDAW 相關的諮詢委員協助審議，可能比較能符合 CEDAW 的要求。

黃淑玲委員：

有關翻譯的問題同樣也發生在 gender equality 跟 gender equity，實質平等跟齊頭式平等也要特別去區分。建議參考 UN women 官網上的中文版翻譯，將一些涉及性別的詞彙彙整一個參考

表放在性平會的網頁。

許秀雯委員：

回應游美惠老師的問題，為避免下次國家報告部分國內團體繼續誤導國外專家委員，行政機關應該在審查現場或跟國外委員溝通時，清楚說明性別在中文的語境脈絡其實就包含 sex, gender 及 sexuality，而我們早就在行政及司法實務上依據憲法第 7 條的精神，在相關法規例如性別平等教育法、性別工作平等法等落實交織性歧視的處理。

衛生福利部：

在 105 年至 106 年有做過類似的法規盤點，當時有給各部會檢視原則，建議這次的檢視也能請性平處提供原則給各部會，以利部會有所依據檢視。

6. The guidelines (a shortlist of Chinese to English translations) issued to all government agencies afterwards:

以下為性平會發給各政府單位的檢視原則：

**CEDAW 第 3 次國家報告結論性意見與建議第 10 點及第 11 點有關「性」與「性別」英文檢視原則**

一、本檢視原則依本(109)年 2 月 6 日 CEDAW 第 3 次國家報告結論性意見與建議第 10 點及第 11 點研商會議決議辦理。

二、有關「性」及「性別」定義及解釋詳如 CEDAW 委員會第 28 號一般性建議全文，並請特別注意該號建議第 5 點及第 18 點如下：

(一)General recommendation No. 28 (CEDAW 第 28 號一般性建議) 5. Although the Convention only refers to sex-based discrimination, interpreting article 1 together with articles 2 (f) and 5 (a) indicates that the Convention covers gender-based discrimination against women. The term “sex” here refers to biological differences between men and women. The term “gender” refers to socially constructed identities, attributes and roles for women and men and society’ s social and cultural meaning for these biological differences resulting in hierarchical relationships between women and men and in the distribution of power and rights favouring men and disadvantaging women. (雖然《公約》僅提及性歧視，但結合對第 1 條和第 2 條(f)款和第 5 條(a)款的解釋表明，《公約》也涵蓋對婦女的性別歧視。這裏的「性」指的是男性與婦女的生理差異。而「性別」指的是社會意義上的身分、歸屬和婦女與男性的作用，以及社會對生理差異所賦予的社會和文化含義，正導致男性與婦女之間的等級關係，亦造成男性在權力分配和行使權利

時處於有利地位，婦女則處於不利地位。)

(二)General recommendation No. 28 (CEDAW 第 28 號一般性建議) 18. Intersectionality is a basic concept for understanding the scope of the general obligations of States parties contained in article 2. The discrimination of women based on sex and gender is inextricably linked with other factors that affect women, such as race, ethnicity, religion or belief, health, status, age, class, caste and sexual orientation and gender identity. Discrimination on the basis of sex or gender may affect women belonging to such groups to a different degree or in different ways to men. States parties must legally recognize such intersecting forms of discrimination and their compounded negative impact on the women concerned and prohibit them. They also need to adopt and pursue policies and programmes designed to eliminate such occurrences, including, where appropriate, temporary special measures in accordance with article 4, paragraph 1, of the Convention and general recommendation No. 25.

(交叉性為理解第 2 條所載列締約國一般義務範圍的根本概念。以性和性別為由而對婦女的歧視，與其他影響婦女的因素息息相關，如：種族、族裔、宗教或信仰、健康狀況、年齡、階級、種姓、性取向和性別認同等。以性或性別為由的歧視，對此類婦女的影響程度或方式可能不同於對男性的影響。締約國必須從法律上承認該等交叉形式的歧視，以及對婦女的相關綜合負面影響，並禁止此類歧視。締約國亦需制訂和實施消除此類歧視的政策和方案，包括根據《公約》第 4 條第 1 項和第 25 號一般性建議，酌情採取暫行特別措施。)

### 三、檢視範圍：

- (一) 檢視涉及「性」與「性別」相關之法規。
- (二) 檢視上述法規有關「性」與「性別」英文翻譯。
- (三) 《性別平等教育法》、《性別工作平等法》、《性騷擾防治法》、《性侵害犯罪防治法》及《家庭暴力防治法》須優先檢視。

### 四、涉及「性」及「性別」之中英文名詞對照表如下：

中文	英文
性別	Gender
性傾向	Sexual orientation
性侵害	Sexual assault
性騷擾	Sexual harassment
性霸凌	Sexual bullying
性別認同	Gender identity
性別特質	Gender traits
性別歧視	Gender discrimination
任一性別 <sup>11</sup> 人數(代表)不得少於三分之一	Neither gender should occupy less than one-third of the seats of the committee/commission

<sup>11</sup> 包含性別比例、任一性別、單一性別比例、任一性別比例、任一性別人數等文字。

<sup>12</sup> 本項英文翻譯以委員會之委員為例，任一性別人數(代表)不得少於三分之一，原則為「性別」英譯成「gender」，其他依法遴聘(派)學者專家、民間團體及相關機關代表提供諮詢所辦理之相關諮詢會議亦同。此處性別之認定以身分證件之性別欄位為認定原則。

**Attachment 3 A comparison table of Chinese and English nouns involving "sex" and "gender"**

<https://gec.ey.gov.tw/File/AC4C8F503D05AE3F/5d73b833-4b8c-45e2-a58b-ee299eab6863?A=C>

**涉及「性」及「性別」之中英文名詞對照表<sup>1</sup>**

中文	英文
性別	Gender
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性別認同	Gender identity
性別特質	Gender traits
性別歧視	Gender discrimination
任一性別 <sup>2</sup> 人數(代表)不得少於三分之一	Neither gender should occupy less than one-third of the seats of the committee/commission <sup>3</sup>

<sup>1</sup> 本對照表係依據 CEDAW 第 3 次國家報告結論性意見與建議第 10 點及第 11 點辦理。

<sup>2</sup> 包含性別比例、任一性別、單一性別比例、任一性別比例、任一性別人數等文字。

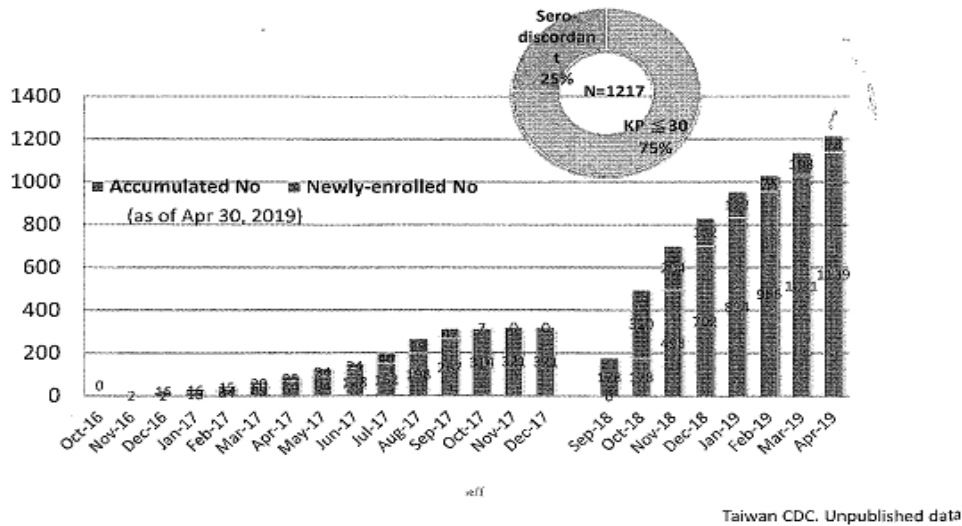
<sup>3</sup> 本項英文翻譯以委員會之委員為例，任一性別人數(代表)不得少於三分之一，原則為「性別」英譯成「gender」，其他依法遴聘(派)學者專家、民間團體及相關機關代表提供諮詢所辦理之相關諮詢會議亦同。此處性別之認定以身分證件之性別欄位為認定原則。

Article : ICESCR 12

Topic : Improper sexual education and PrEP policies violate people's right of health

Attachment The number of people taking PrEP (2019 by Taiwan CDC)

### 疾管署公費PrEP計畫: 收案趨勢





Attachments

**Article : ICESCR 12**

**Topic : Project-application of CBD (Cannabidiol) for medical usage - protecting rare-diseased children and preventing cannabis (marijuana) abuse**

**Attachment 1 Legislator 3Q thanked for supporting legalizing marijuana.**

3q 支持大麻合法化水餃感謝祭

Legislator 3Q thanked for supporting legalizing marijuana.

<https://www.facebook.com/events/s/3q%E6%94%AF%E6%8C%81%E5%A4%A7%E9%BA%BB%E5%90%88%E6%B3%95%E5%8C%96%E3%84%98%E6%B0%B4%E9%A4%83%E6%84%9F%E8%AC%9D%E7%A5%AD/1100012473685211/>



**Attachment 2 [Cannabis is a magic but also a medicine 5] It is a second-class drug as amphetamines. It is difficult to legalize medical marijuana**

【大麻是魔更是藥 5】和安非他命同列二級毒品 藥用大麻合法  
難度高

<https://www.mirrormedia.mg/story/20200717cul006/>

大麻事關疾病療效的認定問題，同時也事關國家治理的意識型態問題。

台灣綠黨在今年初立委大選時，提出「藥用大麻合法化」政見，包括：開放大麻萃取油、膠囊，並依濃度分列食品和藥品管理，也希望開放更多病症適用此類藥物。

在藥用大麻之後，還隱含更激進的政治主張。張竹苓不諱言：「藥用大麻合法化是對大麻去汙名化，才有機會推動大麻全面合法化的可能。」大麻的全面合法是各國綠黨追求的目標之一。2020 年立委選舉選後，綠黨內部研究發現，這是台灣綠黨有史以來最受注意的政見，並獲得大部分年輕選民的支持，「這個政見對選舉是正面的效果。」

不過，大麻是歐美青少年第一個接觸的「毒品」，他們普遍對大麻沒有戒心，這也反映到他們對大麻的態度：美國蓋洛普民調長期針對美國民眾調查對大麻的態度，2017 年，已有 66% 的人支持開放；加拿大在 2017 年的民調也有 53% 的人支持開放。

相比之下，台灣人對大麻很陌生，近 5 年台灣大麻查獲量占所有毒品僅 0.2 至 7.7%。台灣社會對成癮物質的態度也很保守，例如 2013 年研考會的委託民調顯示，有 7 成 5 的台灣民眾反對毒品施用者《刑法》除罪，而僅施以戒癮治療。不論是美國還是加拿

大，合法過程皆有強大的民意做後盾，促使政治人物和倡議者以政治力量促成開放，這個路線在台灣似乎難度頗高。

從衛福部 5 月聲明的會議紀錄看來，官方決定開放程度及如何開放的關鍵依然仰賴醫療科學意見，而目前關於大麻的科學討論仍落後一般使用者的經驗。比如一般大麻的使用經驗都有助眠和放鬆鎮定的效果，但連這個普遍基礎的「大麻效用」也尚無醫療臨床的支持。而開放派的倡議者，訴諸的仍是國家治理與個人自由的政治觀點，面對的則是還無法取得主流民意支持的困境。這二股力量的消長，將決定日後台灣開放大麻的樣貌。

**Attachment 3 [Cannabis is a magic but also a medicine 1] Girl with rare disease had seizures 300 times a week before using cannabis oil, but now only once a week after using cannabis oil**

**附件三 【大麻是魔更是藥 1】罕病小女孩一週痙攣 3 百次 用了大麻油只剩一次**

<https://www.mirrormedia.mg/story/20200717cul002/>

葉爸爸有個卓飛症的小孩，常要面對小孩突發的痙攣，大麻萃取油可望改善發病狀況。

大麻，這個在《本草綱目》即有記載的植物，自 1930 年代起，就在美國的主導下，成為禁忌的毒品，當時美國人認為，吸食大麻會使人喪失心神而殺人。這個毒品卻在近 5 年間，從十惡不赦的毒品逐漸蛻變，甚至成為一些罕病患者家屬眼中的神藥。一些原本藥石罔治的病症，彷彿都在這昔日的魔物裡，看到了希望。

毒品不必然十惡不赦，藥物也不只是藥物，所謂的「毒品」，更多是由社會脈絡來定義，這既是醫療和科學問題，同時也是國家治理的政治問題。我們企圖在「魔物」與「神藥」這 2 種極端形象裡，還原大麻做為「毒品」和「藥品」各自的樣貌，並進一步梳理爭議背後的各種思考衝突。

大麻這個出現在社會新聞裡的「毒品」，近年來被發現也是極具醫療潛力的植物。(翻攝畫面)

葉爸爸不時注意桌上的手機，因為 5 歲的兒子偉偉正在學習發展中心上課，隨時都可能癲癇發作，「我以前是不帶手機的，現在手機不離身。」人生的改變不只手機，為了照顧孩子，他甚至把全職工作改為兼職，還打算將來兒子入學了，要修習相關課程，擔任兒子的

教學助理，我稱讚他如此愛孩子，他卻說：「不是的，是他愛我比較多。」

那些我們習以為常的生活變化，對像偉偉這樣的罕見疾病卓飛症（Dravet syndrome）患者來說，卻是不可承受之重。他一歲前就發病，對環境特別敏感，一點細微變化就會引起不自主的全身痙攣、抽搐，若碰到其他物體，恐造成嚴重傷害。好比偉偉晚上搭車上高速公路、車窗外的路燈因車速而產生的移動視覺效果，搭手扶梯、階梯透出來的光都會引起腦部不正常放電而全身痙攣；有的患者則是家裡有客人，太高興，抽筋；體溫超過攝氏 38 度，抽筋；玩得太累，也是抽筋。

偉偉每日小發作大約 50 次，一個月大發作 4 次。遇上流感季節，一個月有超過 10 天的時間要住院。家住台北的葉家，「小孩 3 歲半之前，我們不敢帶小孩跨過濁水溪以南，怕發作，臨時找不到醫生。」

另一位患者、卓飛症協會祕書長徐婉馨的女兒歡歡已經 13 歲了，因為太常發作，教室桌椅還特別訂製、包裹泡棉，以防她發作時撞傷。徐婉馨形容這種痙攣的可怕：「我不怕她抽（筋），小發作幾分鐘會停下來的都還好，最怕是一個小時以上的大抽，腦部會錯亂，醒過來會突然什麼都看不到。」

這個病的難處在起因於基因異常，終身無法痊癒，又因是幼兒，無法動腦部手術減緩症狀，偏偏連治療藥物也不多，面對日復一日痙攣發作，家長們束手無策，只能各自發展一套 SOP，隨時快速打包，準備送小孩掛急診。全台目前已確診人數約 40 人；目前台灣最

常用的藥是法國藥廠的 Diacomit，一個月藥費 3 萬到 4 萬元，但會造成流口水、四肢無力、走路搖晃等副作用。

2013 年，CNN 擁有神經外科醫師背景的醫藥記者古普塔 (Sanjay Gupta)，採訪了一位卓飛重症女童夏洛特 (Charlotte)，夏洛特的父母讓她用了大麻萃取油，夏洛特從一週發作 300 次，減輕為一次，原本需用鼻胃管餵食，也因沒有其他癲癇藥物的副作用和頻繁的痙攣，可以自己進食並下床走動。

CNN 報導女童夏洛特使用大麻油後，從癱瘓在床到可以走動，神奇療效引起討論。(翻攝 CNN YouTube)

夏洛特的故事對患者家屬來說，是漫漫長夜裡的一盞明燈。本身也在醫藥界工作的葉爸爸一直關注這個消息。2018 年，美國食品藥物管理局 (FDA) 通過一款由 GW 藥廠出產的大麻萃取藥物 Epidiolex，專用於卓飛症和葛雷氏症的小兒癲癇 (今年 2 月 FDA 通過此款藥也適用多結節硬化症引發的癲癇)。葉爸爸得知消息後，馬上向台灣衛福部食藥署提出進口申請。

葉爸爸說：「我兒子一輩子不能晒太陽 (體溫過高會發作)，我不會企望用了這款藥病就好了、就能晒太陽，只希望一個月能減少一次大發作，只要一次，我就很滿意了。」

CNN 報導女童夏洛特 (右) 使用大麻油後，從癱瘓在床到可以走動，神奇療效引起討論。(翻攝 CNN YouTube)

但 2 週後，葉爸爸的申請被食藥署退件，一般認為退件的理由是該藥含有 0.1% 的 THC，即四氫大麻酚，它是一種由大麻提煉出的化學物質，是大麻中會使人成癮、產生幻覺的成分。

葉爸爸沒有氣餒，他召集親友在網路上的公共政策參與平台，連署要求政府開放藥用大麻。連署很快達標，今年 5 月 7 日，衛福部針對這項網路倡議回應：這款治療小兒癲癇的大麻萃取物，將可透過教學醫院專案申請。

幽暗無光的疾病之路，終於有光了嗎？葉爸爸說：「高興就只有一下而已。」他攤開一張紙，上面記載了各種藥物名稱和價格，其中這款被媒體吹捧的「神藥」，25 天的藥價高達 10 萬元。「像我們這種家庭，為了照顧小孩，通常其中一人要犧牲工作，這種價格真的負擔不起，雖然開放了，真的付得起這個價格的人也很少。」

葉爸爸在紙上記載兒子各種可能用藥及藥價，其中 1 款美國通過的大麻萃取油，25 天就要價近 10 萬元。

通過 FDA 認證的藥品因涉及大規模的實驗和研發成本，因此價格昂貴。葉爸爸希望政府能開放其他和 Epidiolex 類似、也含有低劑量 THC 的大麻萃取油，像是 CNN 報導中，女童夏洛特所使用的大麻油，沒有 FDA 認證，價格也便宜許多：「但是我知道不可能，不可能啦。」

為什麼不可能？這要從大麻的爭議說起。

**Attachment 4 Children with rare diseases, such as intractable epilepsy, can use THC (cannabis drugs), announced by Ministry of Health and Welfare**

附件四 大麻 THC 成分藥物罕病先行，衛福部公告頑固型癲癇病兒可專案使用

[https://www.twreporter.org/a/cannabis-for-medical-use-taiwan?fbclid=IwAR3DalzhWLSJz0Axpun0h7iA7JAML-3T4bjk253gP9KMyLin\\_afVtgJv4NE](https://www.twreporter.org/a/cannabis-for-medical-use-taiwan?fbclid=IwAR3DalzhWLSJz0Axpun0h7iA7JAML-3T4bjk253gP9KMyLin_afVtgJv4NE)

醫療用大麻的使用，在台灣有了新進展。2019 年 10 月，「醫療用大麻製劑合法」在公共政策網路參與平台展開連署，訴求「開放合法進口大麻藥物，用於罕見疾病、化療等治療」，該連署 3 個月內突破 5,100 人，成功達標。衛生福利部食品藥物管理署（簡稱食藥署）隨即召開專家會議討論，今（5 月 7 日）正式公告，大麻二酚

（CBD）藥品中內含四氫大麻酚（THC）成分者、或以大麻成熟莖及種子所製成之製品，THC 含量超過 10ppm 者，可由醫院專案申請進口，用於治療頑固型癲癇罕病患者。至於化療止痛上，專家認為效果不佳，暫不開放。由於 THC 是大麻中具成癮性的成分，因而此次討論格外受到矚目。

大麻在台灣仍屬第二級毒品。事實上，2017 年台灣也曾因民間連署，促使政府通過使用大麻中不具成癮成分的「漢麻」（Hemp）大麻二酚萃取物（CBD）；CBD 不具成癮性、未列管制藥品，但台灣尚無廠商正式進口相關產品，患者經專案審查通過須自行由國外帶藥使用，近 3 年來僅 33 人成功通過審核。

食藥日今日發出公告說明，目前台灣對醫療使用的大麻素製劑，因所含成分不同，有不同管理規定，僅以大麻二酚（CBD）為成分者，不屬於管制藥品。但目前國內未核准任何含 CBD 成分之藥品，若民眾經醫師診斷評估後開立此類藥品處方，可依「藥物樣品贈品管理



辦法」申請供個人自用 CBD 藥品專案進口。至於，藥品內含四氫大麻酚（THC）成分或以大麻成熟莖及種子所製成之製品，若 THC 含量超過 10 ppm 者，則屬於第二級管制藥品，3 月 30 日，食藥署回應公民提案召開專家會議，與會專家就現有臨床文獻所提專業評估意見，認為僅卓飛症候群（Dravet Syndrome, DS）跟雷葛氏症候群（Lennox-Gastaut Syndrome, LGS）兩種小兒頑固型癲癇罕病患者有使用此類大麻素製劑之需求，建議經醫師診斷評估後，得依「管制藥品管理條例」及「特定藥物專案核准製造及輸入辦法」，由區域醫院以上之教學醫院、精神科教學醫院提出申請。

至於用於止痛部分，則未開放。食藥署管制藥品組科長劉佳萍表示，疼痛醫學會的代表專家，認為大麻素製劑對於止痛的效果並不明確，暫不推薦。台灣疼痛醫學會代表指出，疼痛程度以 0 到 10 分計算，藥物止痛效果下降 3 分都能算有效，但大麻類藥物只能降 0.4 分，且副作用不少，許多國際文獻基本上都不推薦。

未來用於罕病治療上，醫師須先提治療計畫。劉佳萍解釋，區域醫院以上教學醫院、精神科教學醫院提出病人病歷資料及治療計畫的申請，由中央主管機關審核是否符合法規要求，准通過的話，可建議藥廠正式引進，或透過專案申請由藥廠輸入。

「這次公告不是首度開放醫療用大麻，而是因為民眾提案，發現大家都不清楚醫療用大麻製劑的管理方式，透過公告給大家多一點資訊，」劉佳萍認為，過去只是沒有單位提出申請，不是沒有開放。

然而，3 月 30 日專家會議，部分專家醫師仍是抱持著「使命」赴會，希望爭取官方更明確的政策進展。特別是想爭取美國食品藥物管理局（FDA）首個核可上市的大麻萃取純化藥物、已用於治療頑固

型癲癇的「Epidiolex」，也能讓台灣病兒使用。Epidiolex 主要成分是不具成癮性的 CBD，但也含有少量具成癮性的 THC。

這場專家會議中，包含神經醫學會、小兒神經、成癮、疼痛醫學會等相關 9 名專家，共同來討論這款醫用大麻藥物進口的必要。神經醫學會與癲癇醫學會代表、台北榮總神經內科主治醫師關尚勇說，與會的專家幾乎都贊成進口，因為這款藥物已通過 FDA 合格上市，也有明確安全性與有效性。

關尚勇提到，30 多年來，他見過許多頑固型癲癇患者，並為他們不斷嘗試新的治療方式，「我是抱著很大的希望過去的，我們很希望能夠促成這件事情（讓 Epidiolex 進口）。」

Epidiolex 是一款英國 GW 製藥公司的藥物，美國 FDA 於 2018 年 6 月核准上市。而台灣之所以對這款藥物特別小心翼翼，是因為此藥是由大麻純化後提煉。

讓全台 2 千多名頑固型癲癇患者的治療，多一個希望

Epidiolex 是美國食品藥物管理局（FDA）首個核可上市的大麻萃取純化藥物，已用於治療頑固型癲癇。（取自 GB Epidiolex 官網）

Epidiolex 是美國食品藥物管理局（FDA）首個核可上市的大麻萃取純化藥物，已用於治療頑固型癲癇。（取自 GB Epidiolex 官網）

「這款藥物（Epidiolex）的適應症，認為對罕見疾病卓飛症候群、雷葛氏症候群的病人有效，尤其針對後者，我也認為可以試試看，」關尚勇說。

卓飛症候群與雷葛氏症候群都屬於罕見的頑固型癲癇。國際上統計，前者發生機率約為 10 萬分之一，後者則為萬分之一；這代表台灣約有 2 百多位卓飛症候群患者、2 千多位雷葛氏症候群患者。

治療頑固型癲癇 30 多年的關尚勇，至今手上仍有超過 20 位 LGS 的病人。「很多小朋友我看了 15 年、20 年甚至 25 年，從小看到大。他們多數在 2 到 6 歲發病，也有一出生就發病的，不只有癲癇，多數都有智力障礙，發作起來也常反覆受傷，牙齒、下巴、鼻樑、骨頭摔斷都很常見。」

針對這些病人，關尚勇說，癲癇科醫師都會嘗試 4 種正規治療，包含加起來將近 15 種的抗癲癇藥物、手術、酮體飲食及電刺激，但效果都不佳。「少數幸運的，長大之後也許能到庇護工場上班、可以跟著爸媽，甚至自己來診間看病，但多數還是因為常常發作，只能待在家裡讓家長照顧。」

專家一致認同，但「大麻」二字讓人緊張

根據美國 FDA 的報告指出，Epidiolex 是一款大麻純化後的大麻二酚藥物，用於治療 2 歲以上的卓飛、雷葛氏症候群患者的癲癇問題，「這意味著 FDA 認為，此藥是安全、有效的。」

近幾年，關尚勇說，全球的癲癇醫學會都開始討論使用醫用大麻的經驗，他也接觸到幾個家長，曾看到相關報導而來詢問，這款藥物是否能給頑固型癲癇的孩子一個新希望？。

就算這款藥物主要成分是不具成癮性的 CBD、極少的成分是會造成上癮的 THC；但因是從「大麻植物」純化出來，多少讓政府有些疑慮與考量

雖然美國各州對於大麻合法的解禁程度不一，聯邦至今仍將大麻視為一級管制藥品，相較台灣列在二級來得嚴格。但美國 FDA 卻在 2018 年就核可這款藥物，肯定大麻在醫療上的潛力。

最重要的是，對罕見疾病的患者來說，多一種選擇，就是多一個希望。

#### 醫用大麻、合法化、台灣、大麻類罕藥

台北市聯合醫院昆明防治中心副主任、台灣成癮學會祕書長陳亮好表示，針對罕病的藥物，醫師不但不會隨便開，過去研究也沒有發生過濫用問題。對於漢麻萃取物 CBD 申請，她認為法規應與時俱進。(攝影／楊子磊)

台北市聯合醫院昆明防治中心副主任、台灣成癮學會祕書長陳亮好也贊成這款藥物進口，她表示，這種針對罕病的藥物，醫師不但不會隨便開，過去研究也沒有發生過濫用問題。

「在會中的代表也有說，希望食藥署一定要促成 (Epidiolex 合法進口)，不要最後不了了之、開個會發表一下公告就結束了。我記得當時負責主持的科長也答應，說一定會有後續的，會交給相關單位一定要研究執行，」關尚勇指出。

會有這樣的叮嚀，是因為台灣對於大麻的管理一向甚嚴，這次也比預定公告時間延後了一個月。劉佳萍解釋，3 月 30 日才召開專家會議，科內必須將討論內容整理、與專家來回確認，再將資料提供給食藥署，層層傳至衛福部審核，因此才無法如期在 4 月 8 日公告。

劉佳萍說，此案茲事體大，也有不少民眾在關切，「處理上會更謹慎小心，從食藥署到衛福部，多一些眼睛去看回應內容、決策是否妥適，每一層單位都會把關審視。」

關尚勇說，一旦醫用大麻藥物進口後，一定會討論如何管控，及臨床使用準則，如在國內現有的抗癲癇藥物使用過都無效之後，再將這款藥物作為最後一樣武器嘗試。「既然目前知道這款藥可能對部分病人有效，只要對某一些人有效，就可以試試看。」

為什麼大麻二酚（CBD）可以治療頑固性癲癇？

癲癇是腦部異常放電所造成，且有各式各樣的發病型態，例如肌肉僵直、失去意識，出現陣攣、口吐白沫等。而為什麼大麻二酚可以治療頑固型癲癇，關尚勇說，治療的作用機轉至今仍然未明，不過多半認為大麻二酚可以調整神經細胞的傳導功能，降低興奮性，進而減少癲癇發作。

為何大麻好壞討論兩極？

與其他成癮性物質或毒品相較，大麻的好處與壞處討論最為兩極，主要是「大麻屬」的植物，因栽種方式、生長環境等差異，有不同成分比例及作用的種類。如許多國家合法使用的漢麻（Hemp，亦稱工業用麻），它就是麻繩、麻線、麻布等原料，也可做為食用油等，且其中成癮性物質四氫大麻酚（THC）含量低，也有醫用潛力；而長年列入非法毒品的大麻，THC 含量高，過去多被用在娛樂使用，引發爭議。

正因為大麻成分不同、但外觀難辨識，也令其合法化及醫療用的討論，十分複雜。不過，其實關鍵重點在於具有療效的 CBD 及具有成癮性的 THC 濃度比例如何界定拿捏。

在台灣，2017 年食藥署已核可漢麻萃取物 CBD 使用，這類型的藥物，在美國被歸類在保健食品。若其中 THC 濃度在 10 ppm 以下，也不列管制藥品。劉佳萍解釋，因為如果是大麻種子、成熟莖做成的製品，如中藥的火麻仁，也會有天然微存 10 ppm 以下的 THC，所以製訂 10 ppm 標準，是為了讓原先就存在的相關製品，可以繼續合法使用。

但若是由大麻葉子、大麻花提煉出來的產品，不論 THC 濃度多少，都會直接歸在管制藥品類。

CBD 與 THC、大麻跟漢麻，差別是什麼？

在美國紐約布魯克林大麻藥局執業的藥師林筱莉表示，一株大麻植物裡，有超過 500 種的化合物成分。最普遍的分類標準，是不會成癮的大麻二酚（CBD）與有精神活性的四氫大麻酚（THC）的含量。

1971 年，加拿大科學家斯摩爾（Ernest Small）發表報告，若 THC 的成分高於 0.3%，就是一般人既定印象中，會上癮的二級毒品大麻（Marijuana）；小於 0.3%，則為工業大麻或漢麻（Hemp），沒有成癮性。

這是因為大麻跟漢麻雖然是同屬不同種的植物，但因為種植上常相互交配，因此有時從外表上分不出來兩者差異。0.3%的比例也是人為訂出，若沒有透過實驗室測量成分，就可能出現種植者難知道自己種出了大麻或漢麻的情況。

醫用大麻、合法化、台灣、大麻類罕藥、REUTERS、達志影像

若四氫大麻酚（THC）的成分高於 0.3%，就是一般人既定印象中會上癮的毒品大麻（Marijuana）；小於 0.3%，則為工業大麻或漢麻（Hemp），沒有成癮性。（攝影／REUTERS／Elijah Nouvelage／達志影像）

2017 台灣首波解禁，是開放漢麻萃取物 CBD 使用

3 年前開始在美國紐約州大麻藥局擔任諮詢藥師的林筱莉，2019 年 10 月專程返台，受邀在立法院公聽會中講解漢麻。她指出，在美國，CBD 製品因為不具成癮性，屬於保健食品等級，在一般藥局就可以購買。臨床上認為，CBD 製品有增加食慾、舒緩焦慮、噁心嘔吐、慢性疼痛等，也對帕金森氏症、癲癇有療效；CBD 相關製品還有美白效果，因此漢麻油、護手霜、面膜等產品亦大量問世。

台灣 2017 年前從未明確定義大麻、CBD 製品的差別，都是一概全禁。陳亮妤說，CBD 製品不會讓人「嗨」，且都是以錠劑或護膚油等方式呈現，和一般大眾對呼大麻的既定印象差別不小。但因 CBD 名字「大麻二酚」有大麻二字，相關藥品的審核較為嚴格。

直到 2017 年台灣出現連署訴求 CBD 藥品解禁，列入帕金森氏症、癲癇病患的醫療適應症處方，18 天內超過 5,100 人響應，食藥署才正式回應，將 CBD 列為非管制藥品，但因其多種醫療用途，正式歸類在「處方藥」。

申請自用 CBD 關卡多，近 3 年 62 人僅半數成功

不過，台灣目前並沒有藥廠拿到 CBD 製品的進口藥證，意即市面上仍買不到相關產品。食藥署藥品組科長張連成接受《報導者》電訪時，引述「藥物樣品贈品管理辦法」第 2 條第 4 款、第 14 條指出，病患可以在國外購買 CBD 藥品，但需向食藥署申請 CBD 藥品自用，

出具身分證影本、藥物外盒、說明書、仿單、醫師處方簽等，CBD 藥品就能合法入境使用。

這些規定看似合理，但難度其實頗高。

網路上甚至有民眾分享〈病患 CBD 個人自用專案進口完全失敗攻略〉，指出食藥署要求反覆，作者與之斡旋數月，依然沒有成功。

張連成說，自 2017 年 6 月連署至今年 3 月，有 62 人提出申請，但僅有 33 人通關拿到藥品。

此外，知道這項專案申請自用的規定的人並不多。4 月 20 日「國際大麻日」當天，綠黨與大麻合法支持團體「綠色浪潮」，更在立法院前召開記者會，其一訴求就是希望能放寬對 CBD 製品的管制，讓這些合法規定被看見，也能真正落實。

對實際需要的病患來說，要能夠真正使用到 CBD 藥品，有兩大難關得先過。

難關 1：成癮物質含量規定較國際嚴格，藥品進口認證不易通過  
醫用大麻、合法化、台灣、大麻類罕藥、REUTERS、達志影像  
在美國核可的 CBD 製品種類繁多，不只藥品，還有 CBD 製成的糖果、護手霜、面膜等產品。(攝影／REUTERS／Mike Segar／達志影像)

國外普遍定義 CBD 製品中的 THC 成分須低於 0.3%，但台灣「管制藥品分級及品項」CBD 產品中的 THC 濃度規定於「小於 10ppm (0.0001%)」。許多在美國核可的 CBD 製品，至多只測到小數點後兩位，包



裝上雖常標示 0%，但不代表小於 10 ppm，台灣食藥署就不會予以通過。

藥品難找，市場不大，也是台灣一直未有藥商申請合法藥證上市的原因之一；不只藥品，保養品中如護手霜、面膜等 CBD 製品，若 THC 驗出超過 10 ppm，也一律違法。

陳亮妤認為法規應該與時俱進，「含有大麻二酚的面膜、乳霜等，被認為是保養品，國外完全沒有被濫用的前例，是應該檢視一下現行法規是否適用現在的台灣。」

打過不少大麻官司的喆律律師事務所律師、綠黨黨員李菁琪也舉例，曾接獲販賣 CBD 製品的民眾求救，指自己被警察控訴販毒，只因在該批 CBD 產品中驗出「14 ppm」。「護手霜能吃嗎？而且檢驗機器究竟能不能驗出這麼細微的標準？我甚至認為 14 ppm 根本是誤差。」

對此，張連成解釋並非刻意刁難。「CBD 藥品申請自用，前提是民眾要用來治病。政府在還沒有合格藥證情況下，先給一個機會使用。但食藥署也應對民眾申請的藥物品質、安全、療效確定有保障。」

衛生福利部嘉南療養院成癮暨司法精神科主治醫師李俊宏也持保守態度，他認為，國外 CBD 產品可能混用 THC，種植過程可能受到農藥、重金屬污染。「(民眾)很可能在對製品不了解的狀況下，誤用品管不好的製品，因此食藥署的規定雖然嚴苛，也算是為國民健康品質把關。」

難關 2：醫師對 CBD 藥品了解不多，不願開處方簽

對大麻有研究、抱持同意態度的尹書田診所精神科主治醫師孔繁錦認為，隨著愈來愈多產品符合國內 10 ppm 的規定，接下來就差臨門一腳，只要有國內廠商申請合法藥證，就不再需要辛苦進口。（攝影／許菁倩）

尹書田診所精神科主治醫師孔繁錦是國內極少數對大麻有研究、抱持同意態度的醫師，他為不少有需求的病患開出 CBD 藥品處方簽。但除他之外，國內醫師對於大麻的理解，落差仍很大。

陳亮妤在美國 4 年，正好經歷美國各州陸續醫療大麻合法化的過程。「大麻的醫療用途涉及神經科、內科、外科、疼痛科、精神科、麻醉科……，在美國當時的電視辯論會，各科醫師都會參與，討論是很寬廣的，」陳亮妤回憶。

但相較之下，台灣的醫師並沒有跟上。不少討論大麻的論壇、Facebook 專頁中都發現，民眾抱怨醫師「根本沒聽過 CBD」，不願意開處方簽；《報導者》記者也曾致電麻醉科等其他科醫師，也收到「沒有研究」等理由被婉拒採訪；線上有在關注並發表意見的醫師，幾乎全為精神科醫師。

孔繁錦也表示，「民眾到診間會來說，以前願意開的醫師現在不開了，可能是被院方警告……。」他會在處方簽上寫下「病人適用 CBD」7 個字，讓民眾去申請攜帶相關產品入關。

劑量限制逐漸寬鬆，仍須等藥商申請藥證進口  
3 年下來，孔繁錦說，相較一開始，政府對 CBD 製品入關的管制已經愈來愈寬鬆。

2019年12月，《報導者》自食藥署取得CBD藥品的申請人數為30多人、10多人申請成功。僅僅3個月，申請且通過的人數都增加了一倍。

不僅如此，孔繁錦說，2017年CBD藥品剛通過時，民眾帶藥品入關時，被刁難的情況時有所聞。「但警方取締後發現，CBD藥品既不算毒品不能銷毀，也沒有非法疑慮，忙了一場，最後還是得發還給民眾，何苦？」

因此，近期都是在民眾進海關時「技術性地卡一下」，「先扣著，要求看診斷書、身分證，海關也可能打電話給我確認。也有民眾說，甚至只看了身分證就能領到，」孔繁錦說。

不只入關變容易，10 ppm的CBD產品雖然少，但隨著廠商技術精進，不再是強人所難的規定。孔繁錦說，目前國外已有幾家廠商，能將3,000 ppm再精煉到10 ppm以下，「不是為了台灣，純粹是對CBD產品而言，THC是雜質，當然愈低愈好。」

孔繁錦說，隨著愈來愈多產品符合國內10 ppm的規定，接下來就差臨門一腳，只要有國內廠商申請合法藥證，就不再需要辛苦進口，國內就能買到。只是，CBD仍非多數醫師會使用的藥物，若順利申請藥證上市，是否有足夠的醫師願意嘗試、市場效益如何，都還是目前藥商躊躇的原因。

大麻合法議題複雜，未來辯論仍是漫漫長路

醫用大麻、合法化、台灣、大麻類罕藥

國內上百位醫師連署醫用大麻合法化過關，但仍有許多實務面向有待解決。(攝影／許薈倩)

在大麻合法化的全球浪潮下，台灣已開始討論醫用療效，從沒有任何成癮性的 CBD 製品作為開端，到核可治療罕病的藥物使用，未來也會有更多討論。要如何制定規則，讓大麻的醫療好處遠大於上癮、對身體可能造成危害的隱憂，正是目前所有辯論的核心。

因為大麻既具有許多疾病的療效潛力，卻也會造成上癮、吸食後行為改變等問題。放大優點或缺點，是藥或是毒，就成為支持大麻合法與否的關鍵。

「從醫療角度看，現在藥物合成、分離技術這麼多，我們需要的是大麻中的 CBD，那就直接把這個有效成分分離出來，做成藥品，再按照一般藥品上市的先決條件，證明它藥理上有效、安全，沒問題就上市，這議題（醫用大麻合法）其實就沒什麼好爭議的！」高雄醫學大學藥學系教授李志恆說。

醫療用大麻，就是放大其優點，萃取大麻中的 CBD 做成藥品、發揮療效。可惜目前公眾的討論從提案連署，到政黨推動醫用大麻合法，社會討論似乎都不夠對焦、大眾也沒有明確接收到相關資訊。

不過如今政府跨越了第一步，讓罕病患者多了一線希望；3 年下來，能夠成功使用 CBD 藥品的病患也愈來愈多，讓大麻這株「是藥也是毒」的天然植物，能發揮醫療潛力，成為患者的另一線生機。

## Attachment 5 Legalizing Medical marijuana? Ministry of Health and Welfare answered

附件五 開放醫療用大麻？ 衛福部回答了

<https://news.tvbs.com.tw/life/1320504>

近日有人在公共政策網路參與平臺「提點子」提案「開放醫療用大麻」，對此，今(7)天衛生福利部表示，大麻素製劑因所含成分不同有不同管理規定，其中針對第二級管制藥品四氫大麻酚(THC)主要用於小兒頑固型癲癇罕病患者，國內已核准由區域醫院以上之教學醫院、精神科教學醫院提出申請。衛福部表示，醫療使用上，大麻素製劑因所含成分不同，有不同管理規定，如僅以大麻二酚(CBD)為成分者，不屬於管制藥品，另依產品之處方、成分、含量、用法用量、作用、效能說明等中英文詳細資料，符合藥事法第6條規定者則以藥品列管。衛福部提到，目前國內未核准任何含大麻二酚(CBD)成分之藥品，若民眾經醫師診斷評估後開立此類藥品處方，可依「藥物樣品贈品管理辦法」申請供個人自用大麻二酚(CBD)藥品專案進口。衛福部指出，如大麻二酚(CBD)成分之藥品內含四氫大麻酚(THC)成分或以大麻成熟莖及種子所製成之製品，THC含量超過10ug/g(10ppm)者則屬於第二級管制藥品，依專家就現有臨床文獻所提專業評估意見，僅 Dravet syndrome 跟 Lennox-Gastaut syndromes 小兒頑固型癲癇罕病患者有使用此類大麻素製劑之需求，建議經醫師診斷評估後得依「管制藥品管理條例」及「特定藥物專案核准製造及輸入辦法」，由區域醫院以上之教學醫院、精神科教學醫院提出申請。衛福部進一步表示，一般稱「大麻」係指大麻植物，與大麻素、大麻素製劑不同。大麻植物包含多種大麻素，如四氫大麻酚(THC)、及大麻二酚(CBD)等；而以大麻素為原料藥經加工調製，製成一定劑型及劑量的藥品，則為大麻素製劑。大麻及四氫大麻酚(THC)屬於第二級毒品及管制藥品；大麻二酚(CBD)不屬於

毒品及管制藥品，考量具有多種藥理活性及可能的醫療用途，我國以一般藥品列管。最後，衛福部提醒，依據美國國家藥物濫用研究所(Nation Institute on Drug Abuse, NIDA)公開資料顯示，使用大麻對身體及心理會產生不良影響，例如對肺部有刺激性，導致咳嗽及痰液增加，增加肺部感染風險；造成心跳加快，增加心臟病發作的機會；孕婦及兒童使用大麻，可能影響胎兒或兒童大腦發育；長期使用大麻也可能導致反覆性嚴重噁心、嘔吐和脫水症狀。心理方面的影響除了產生幻覺、妄想及使得精神分裂症患者的症狀加重以外，還有成癮問題，不可不慎。食藥署也呼籲民眾，目前國內尚未有經查驗登記合格上市的大麻素製劑，若民眾有相關疾病問題，應儘速就醫，由醫師診斷評估是否須開立此類藥品處方，切勿自行購買使用，以免危害自身健康，花錢又傷身。

## Attachment 6 Cannabis Addiction and the Brain: a Review J Neuroimmune Pharmacol. 2018; 13(4): 438–452.

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INVITED REVIEW



### Cannabis Addiction and the Brain: a Review

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#### Abstract

Cannabis is the most commonly used substance of abuse in the United States after alcohol and tobacco. With a recent increase in the rates of cannabis use disorder (CUD) and a decrease in the perceived risk of cannabis use, it is imperative to assess the addictive potential of cannabis. Here we evaluate cannabis use through the neurobiological model of addiction proposed by Koob and Volkow. The model proposes that repeated substance abuse drives neurobiological changes in the brain that can be separated into three distinct stages, each of which perpetuates the cycle of addiction. Here we review previous research on the acute and long-term effects of cannabis use on the brain and behavior, and find that the three-stage framework of addiction applies to CUD in a manner similar to other drugs of abuse, albeit with some slight differences. These findings highlight the urgent need to conduct research that elucidates specific neurobiological changes associated with CUD in humans.

**Keywords** Substance use disorders · Dopamine · Marijuana · THC

#### Introduction

Cannabis is the most commonly used substance of abuse in the United States after alcohol and tobacco (Carliner et al. 2017). In the US, cannabis use increased from 4% to 9.5% between 2001 and 2002 and 2012–2013 and the prevalence of Cannabis Use Disorder (CUD) increased from 1.5% to 2.9% in the same time (Hasin et al. 2015). Despite these increases in cannabis use and CUD, attitudes towards cannabis use have softened: adult and adolescent perceptions of cannabis use risk have decreased since 2001 (Hasin et al. 2015; Carliner et al. 2017). These shifting attitudes have intergenerational consequences as offspring of parents who are early-onset cannabis users and who meet criteria for CUD are more likely to become early-onset cannabis users themselves (Henry and Augustyn 2017). With increases in cannabis use and decreases in perceived risk, it is necessary to reevaluate the addictive potential of cannabis (Carliner et al. 2017; Hasin 2018).

In this review, we explore the nature of cannabis addiction through a prominent model of drug addiction (Koob and Volkow 2016). We first explain the model, which proposes a dysregulation of motivational circuits in three stages of addiction: binge/intoxication, withdrawal/negative affect, and pre-occupation/anticipation. Second, we summarize empirical evidence for preclinical and human studies on the acute and long-term effects of cannabis use on the brain and behavior (similar to those of other drugs of abuse). Third, we review potential therapeutic agents for CUD that may provide further evidence for dysregulation in motivational circuits in CUD. After reviewing the acute and chronic effects of cannabis use on the brain and behavior and treatment options for cannabis abusers, we discuss whether there is empirical evidence that the three stages of addiction apply to CUD (Fig. 1 provides an overview of the current literature supporting this model).

#### Theoretical Model of Addiction

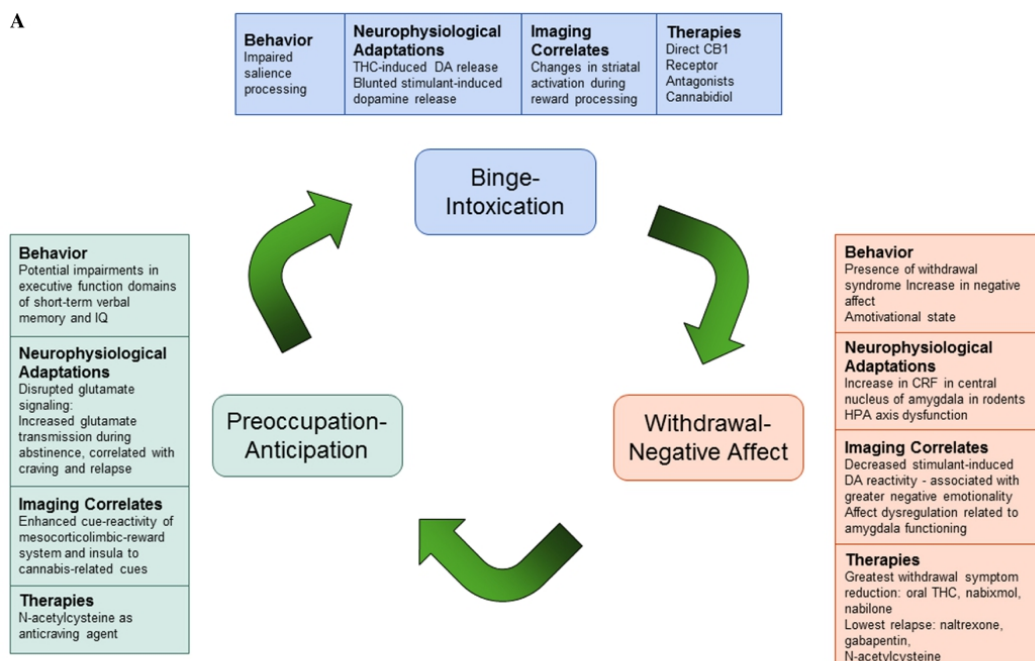
Koob and Volkow (2016) define drug addiction as a “chronically relapsing disorder” marked by compulsive drug seeking and intake, loss of control in limiting intake, and the emergence of a negative emotional state when access to a drug is prevented. This model proposes three stages of addiction with disturbances in three major neurocircuits: the binge/intoxication stage driven by changes in the basal ganglia; the

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**Fig. 1 a.** Model of neurocircuitry and correlating disruptions in brain function and neurophysiology that contribute to behaviors underlying drug addiction. **b.** Summary of the changes in neurocircuitry associated with each stage

withdrawal/negative affect stage driven by changes in the extended amygdala; and the preoccupation/anticipation driven by changes in the prefrontal cortex (PFC). Within these domains, Koob and Volkow (2016) describe neuroadaptations in 18 subsystems including the ascending mesocorticolimbic dopamine system, corticotropin-releasing factor (CRF) in the central nucleus of the amygdala, and corticostriatal glutamate projections.

The binge-intoxication stage of addiction is characterized by an excessive impulsivity and compulsivity to use drugs despite negative consequences associated with such use. This stage involves hyperactivation of the mesocorticolimbic dopaminergic reward pathway of the brain associated with the positive reinforcement of the rewarding effects of drugs. A hallmark of the binge/intoxication stage is an impairment in incentive salience, whereby drug-associated cues and contexts associated with the initial exposure to a drug are attributed exaggeratedly high rewarding properties and become conditioned to elicit dopamine (DA) release. This incentive salience dysfunction appears to drive DA signaling to maintain motivation to take the drug upon exposure to conditioned-cues and even when its pharmacological effects lessen, secondary to the development of tolerance (Koob and Volkow 2016).

The withdrawal/negative affect stage is then triggered by opponent-process responses following binge episodes. These

opponent-process responses are marked by within-systems and between-systems neurobiological changes that drive the loss of motivation towards non-drug rewards and impaired emotion regulation seen in this stage. Within-systems neuroadaptations include changes in the function of brain reward systems including decreased dopaminergic signaling in the nucleus accumbens (NAcc) and dorsal striatum that result in an elevation of reward thresholds for non-drug reinforcers, which contributes to amotivation. Between-systems neuroadaptations include dysfunction of neurochemical systems that are not primarily involved in the rewarding effects of drugs of abuse; this includes changes in brain systems involved in stress responses such as increased CRF release in the amygdala and HPA-axis dysfunction. The changes resulting from opponent-processes responses drive characteristic symptoms of a withdrawal symptom such as increased anxiety-like responses, chronic irritability, malaise, and dysphoria during acute and protracted abstinence from a drug of abuse (Koob and Volkow 2016).

The preoccupation/anticipation stage is implicated in the reinstatement of substance use following abstinence. Executive control over craving and impulsivity is key in maintaining abstinence and is mediated by the PFC. The preoccupation/anticipation stage is marked by dysregulation of signaling between the PFC and areas of the brain that



<b>B</b>			
<b>STAGE</b>	<b>CHANGES</b>	<b>SUMMARY</b>	<b>REFERENCES</b>
<b>Binge-intoxication</b>	Behavior	THC-induced DA release disrupts incentive salience attribution	(Koob and Mason 2016; Bhattacharyya et al. 2012; Wijayendran et al. 2016)
	Neurophysiological Adaptations	Acute THC leads to striatal DA release in animals and humans	(Bloomfield et al. 2016; Bossong et al. 2015)
		Chronic THC downregulates CB1Rs and blunts striatal DA release in animals and humans	(Van De Giessen et al. 2017; Volkow et al. 2014; Scherma et al. 2016; Colizzi et al. 2016)
	Imaging Correlates	Heightened, THC-induced ventral striatal activation to losses in MID task driven by chronic, relapsing cannabis users.	(Yip et al. 2014)
		Chronic cannabis use associated with blunted DA response to reward anticipation in the NAcc in MID task	(Martz et al. 2016)
		It has been established that hyper-sensitivity to the rewarding properties of drugs contribute to positive reinforcement, which is driven by disrupted incentive salience processing	(Filbey et al. 2013)
	Therapies	Therapies with greatest reduction in binge-intoxication antagonize CB1Rs and include: rimonabant, which blocks the intoxicating and tachycardic effects of smoked cannabis	(Crippa et al. 2012, Danovitch and Gorelick 2012)
Partial agonists, which block the reinforcing effects of other drugs of abuse, have the potential to reduce the effects of cannabis intoxication		(Koob and Mason 2016)	
Strains with higher CBD to THC ratios reduce the appetitive effects of cannabis compared to strains with lower CBD to THC ratios, suggesting CBD as a potential treatment for acute cannabis intoxication		(Morgan et al. 2010)	
<b>Withdrawal-negative affect</b>	Behavior	Presence of withdrawal syndrome marked by: irritability, anxiety decreased appetite, restlessness, and sleep disturbances	(Karila et al. 2014; Katz et al. 2014; Davis et al. 2016)
		Increase in negative affect after prolonged cannabis use in adults and adolescents	(Dorard et al. 2008; Katz et al. 2014; Volkow et al. 2014c; Heitzeg et al. 2015; Davis et al. 2016)
		Presence of an amotivational state after prolonged cannabis exposure in rhesus monkeys and humans	(Volkow et al. 2014a, 2016; Becker et al. 2014; Panlilio et al. 2015; Heitzeg et al. 2015)
	Neurophysiological Adaptations	In rodents, cannabis withdrawal is associated with an increase in CRF in central nucleus of the amygdala	(Rodriguez de Fonseca et al. 1997; Caberlotto et al. 2004; Curran et al. 2016)
		In human studies, cannabis withdrawal seems to be related to HPA axis dysfunction	(Somaini et al. 2012; Cuttler et al. 2017)
	Imaging Correlates	Chronic cannabis use is associated with decreased stimulant-induced DA reactivity that is associated with greater negative emotionality	(Volkow et al. 2014c)
		Chronic cannabis use and cannabis withdrawal are associated with affect dysregulation related to amygdala functioning	(Filbey et al. 2013; Pujol et al. 2014; Heitzeg et al. 2015; Spechler et al. 2015; Zimmermann et al. 2017)
Therapies	Therapies with the greatest reduction of withdrawal symptoms target CB1R and include: oral THC, nabiximol, nabilone all of which have a lower abuse potential than smoked cannabis	(Balter et al. 2014; Allsop et al. 2015; Tsang and Giudice 2016; Brezing and Levin 2018)	
	Therapies that have shown the greatest reduction of withdrawal symptoms and the lowest rates of relapse include naltrexone (a mu opioid receptor antagonist), gabapentin (a GABA-a receptor agonist), and N-acetylcysteine	(Brezing and Levin 2018)	
<b>Preoccupation-anticipation</b>	Behavior	Preclinical and clinical models demonstrate impaired executive function in domains of memory and IQ result from acute and chronic cannabis use. Age-specific effects may be present.	(Koob and Volkow 2016; Renard et al. 2016; Broyd et al. 2016; Becker et al. 2014; Volkow et al. 2014a; Caballero and Tseng 2012)
		No significant long-term effects of adolescent cannabis use on executive function was found in several longitudinal co-twin cohort studies. Social and environmental factors may explain poor executive function among cannabis users	(Meier et al. 2017; Jackson et al. 2016)
	Neurophysiological Adaptations	Animal studies demonstrate increased glutamate transmission during drug self-administration while animals receiving glutamate receptor antagonists show reduced relapse rates.	(Caprioli et al. 2017)
	Imaging Correlates	Increased BOLD response to cannabis cues compared to naturally hedonic cues in mesocorticolimbic regions among cannabis users.	(Filbey et al. 2016).
		Positive correlations between cue-induced self-rated craving for cannabis and BOLD responses within the mesocorticolimbic system and the insula.	(Filbey et al. 2016; Norberg et al. 2016)
	Therapies	N-acetylcysteine is a proposed anticraving agent as it acts on the cysteine-glutamate antiporter to reduce glutamate neurotransmission that is upregulated during withdrawal. Preliminary clinical studies have demonstrated reduced craving and relapse rates in cannabis users.	(Asevedo et al. 2014; Samuni et al. 2013)

Fig. 1 (continued)

control decision making, self-regulation, inhibitory control and working memory and might involve disrupted GABAergic and glutamatergic activity (Koob and Volkow 2016). Behaviorally, this translates into excessive salience attribution to drug-paired cues, decreases in responsiveness to non-drug cues and reinforcers, and decreases in the ability to inhibit maladaptive behavior (Koob and Volkow 2016).

## Evidence

### Acute Effects and Insight into Reinforcing/Addictive Properties of Cannabis

All drugs of abuse increase DA release — a key neurobiological process that generates their reinforcing effects (Koob and Volkow 2016). Here we evaluate the acute changes in DA circuitry associated with cannabis intake in preclinical and clinical studies that provide basis for the reinforcing effects of cannabis. While the two main constituents of cannabis are delta9-tetrahydrocannabinol (THC) and cannabidiol (CBD), THC seems to be responsible for cannabis' addictive potential due to its psychoactive properties and associated effects on brain dopaminergic function. Acute THC administration elicits striatal DA release in animals (Ng Cheong Ton et al. 1988) and humans (Stokes et al. 2010; Bossong et al. 2015; Bloomfield et al. 2016). However, another study found no evidence for THC-induced DA release (Barkus et al. 2011); this may be because THC induces quantitatively less DA release than psychostimulants such as methylphenidate or amphetamine (Volkow et al. 1999a). Nonetheless, these findings suggest that THC increases DA release similar to other drugs of abuse.

Several animal models of cannabis exposure have been established in rodents and non-human primates (Panlilio et al. 2015). In studies with rodents, neurophysiological methods such as intracranial microinjection, microdialysis, and single-unit electrophysiological recording techniques are used to study the acute effects of THC and other cannabinoids in the brain directly (Oleson and Cheer 2012; Panlilio et al. 2015). Behavioral methods include the use of place conditioning, drug discrimination, intracranial self-stimulation, or intravenous self-administration to study the reinforcing effects of cannabinoids *in vivo* (for further details see: Maldonado and Rodriguez de Fonseca 2002; Tanda and Goldberg 2003; Maldonado et al. 2011; Panlilio et al. 2015; Zanda and Fattore 2018). Robust intravenous self-administration paradigms in animals have been difficult to establish. That is, in rodents THC is unable to sustain intravenous self-administration (Lefever et al. 2014), whereas squirrel monkeys have found to self-administer THC; suggesting differences in species. However, other behavioral methodologies, such as drug discrimination and conditioned place preference

paradigms, reveal the rewarding effect of THC and other cannabinoids (Maldonado and Rodriguez de Fonseca 2002; Tanda and Goldberg 2003; Maldonado et al. 2011; Oleson and Cheer 2012; Panlilio et al. 2015).

In rodents, THC-induced DA release is associated with increased intracranial self-stimulation in key reward pathways of the brain (Katsidoni et al. 2013). Likewise, low doses of a cannabinoid-1 receptor (CB1R) agonist in the PFC increased spontaneous firing and bursting rates of ventral tegmental area (VTA) DA neurons, which was associated with potentiated salience of fear memories in rats (Draycott et al. 2014). THC elicits striatal DA release by activating CB1R, which are colocalized with DA receptors in the striatum and substantia nigra, regions implicated in salience processing (Wijayendran et al. 2016). This suggests that the endocannabinoid system (eCS) is involved in regulating DA release during salience attribution (Bloomfield et al. 2016), and that acute THC dysregulates the dopaminergic and endocannabinoid systems which then leads to impairments in salience processing (Wijayendran et al. 2016). These pre-clinical findings may provide a biological basis for human studies which show impaired salience processing after THC administration. In one study, THC-potent cannabis was found to increase attentional bias towards cannabis-related stimuli in cannabis users during a computer-based dot-probe behavioral task (Morgan et al. 2010). In a separate fMRI task, healthy participants performed a visual oddball paradigm; THC administration resulted in making non-salient stimuli appear more salient (Bhattacharyya et al. 2012). Together, these pre-clinical and clinical findings reveal that THC administration has reinforcing properties that alter salience processing via increased dopaminergic signaling like other drugs of abuse (Morgan et al. 2010; Bhattacharyya et al. 2012; Draycott et al. 2014; Wijayendran et al. 2016; Bloomfield et al. 2016).

### Long-Term Effects of Cannabis: Behavior and Cognition

Chronic cannabis use is associated with an increased risk of developing substance use disorders (SUD); about 9% of those who use cannabis present with characteristic symptoms of dependence according to DSM-IV criteria (Volkow et al. 2014a). Diagnoses of cannabis abuse and dependence in the DSM-IV did not include withdrawal due to uncertainty of its diagnostic features (Katz et al. 2014). In the DSM-5, however, cannabis abuse and dependence fall under a diagnosis of CUD which now includes withdrawal from cannabis. Withdrawal was added as a diagnostic criteria for CUD as it is often accompanied by increased functional impairment of normal daily activities similar to those seen in other SUD (Karila et al. 2014; Katz et al. 2014; Davis et al. 2016). Symptoms of cannabis withdrawal

also seem to appear in a similar time course and manner as withdrawal from other substances (Karila et al. 2014).

A clinical diagnosis of cannabis withdrawal includes irritability, anger or aggression, nervousness or anxiety, sleep difficulty, decreased appetite or weight loss, restlessness, depressed mood, and physical symptoms causing significant discomfort such as shakiness or tremors, sweating, fever, chills, and headaches (Karila et al. 2014; Katz et al. 2014). Typically, symptoms of cannabis withdrawal occur 1 to 2 days after cessation of heavy use and can last between 7 and 14 days (Davis et al. 2016). The most common symptoms observed during cannabis withdrawal include irritability, anxiety, decreased appetite, restlessness, and sleep disturbances (Oleson and Cheer 2012; Panlilio et al. 2015; Curran et al. 2016; Gates et al. 2016). Sleep disturbances seem to be characterized by trouble falling asleep, decrease in total sleep time, and the presence of nightmares and strange dreams (Gates et al. 2016). The severity of withdrawal symptoms was associated with greater negative impact on normal, daily activities (Davis et al. 2016) suggesting that the effects of cannabis withdrawal seem to parallel withdrawal in other drugs of abuse.

Koob and Volkow (2016) posit that the withdrawal stage of addiction is marked by an increase in negative affect which also seems to be the case for cannabis addiction (Volkow et al. 2014c). In addition to acute withdrawal-related emotional disturbances such as irritability and anxiety (Katz et al. 2014; Davis et al. 2016), prolonged cannabis use is associated with long-term affect dysregulation. In a longitudinal study of adolescents, cannabis users consistently reported greater negative emotionality than healthy controls between the ages of 13 and 23; moreover, as healthy controls showed a decrease in negative emotionality with age, negative emotionality remained elevated for cannabis users during over the same time (Heitzeg et al. 2015). Another study of adolescents found that half of a group of adolescents undergoing treatment for cannabis withdrawal had at least one comorbid diagnosis of anxiety or depression; additionally, for these adolescents greater cannabis use was associated with increased depressive and anxiety-like symptoms (Dorard et al. 2008).

These changes in the affective state after prolonged cannabis use may also influence motivation. In both rhesus monkeys and humans, withdrawal from cannabis seems to involve the presence of an amotivational state (Karila et al. 2014; Panlilio et al. 2015; Volkow et al. 2014a, b, c, 2016). The amotivational state has been previously described as a “reduced motivation and capacity for usual activities required for everyday life, a loss of energy and drive to work and personality deterioration” (Karila et al. 2014). The origin of this amotivational state is still unknown and may be related to changes in executive function (Karila et al. 2014) and to reduced dopamine signaling after chronic cannabis use (Bloomfield et al. 2014; Volkow et al. 2014c). In rhesus monkeys, chronic cannabis smoke exposure was associated with

lower motivation scores in a place conditioning paradigm, although these effects disappeared two to three months after cessation of the cannabis treatment (Paule et al. 1992). In one study of neurocognition, chronic cannabis users demonstrated impairments in verbal memory, spatial working memory, spatial planning, and motivated decision-making compared to healthy controls (Becker et al. 2014). These findings suggest that the amotivational state during withdrawal may be related to cognitive dysfunction and to reduced dopamine signaling after chronic cannabis use.

Cognitive dysfunction, specifically impairments in executive domains, after chronic cannabis use is a key feature of the neurobiological model of addiction (Koob and Volkow 2016). Deficits in executive function after chronic cannabis use have been shown in both preclinical and clinical studies. In one preclinical study, chronically administering a synthetic cannabinoid agonist to adolescent rats impaired short-term working memory in adulthood (Renard et al. 2016). Specifically, this chronic cannabinoid exposure altered PFC structure and impaired cortical synaptic plasticity from reduced long-term potentiation (LTP) in the hippocampus-PFC circuit. These findings support the theory that adolescent cannabis use causes lasting deficits in memory. However, they are likely age-specific effects as preclinical and clinical studies have demonstrated a lack of long-lasting cognitive impairments from adult chronic cannabis use (Renard et al. 2016).

Many clinical studies have investigated the long-term effects of chronic cannabis use on markers of executive function such as IQ, verbal learning, and memory. The results are varied and equivocal, as longitudinal studies with controlled confounds are difficult to establish. Volkow et al. (2014a, b, c) report that cannabis use during adolescence and young adulthood is associated with impaired functional connectivity in the brain and corresponding declines in IQ. A 2016 systematic review of 105 papers assessing the acute and chronic effects of cannabis on human cognition found that memory has been the most consistently impaired cognitive measure (both after acute and chronic cannabis use), with the strongest effects in the verbal domain (Broyd et al. 2016). The evidence for impairments in other domains of executive function such as reasoning, problem solving, and planning was less conclusive, as numerous studies found no significant differences in case-control comparisons. However, studies examining heavy users as well as early-onset users reported impaired executive function, especially when the sample was predominantly older participants (Becker et al. 2014; Broyd et al. 2016). This may suggest a conditional effect, unique to adolescent and heavy cannabis users while moderate and adult users are less vulnerable to the harmful effects of cannabis on cognition.

Despite earlier findings of impaired executive functioning in adolescent- and early-onset users, it is important to note that several recent studies found no significant long-term effects of adolescent cannabis use on executive function. Meier



et al. (2018) report a longitudinal co-twin control study that showed no significant association between adolescent cannabis use and neuropsychological decline, and instead suggest social and environmental factors as explanations for poor executive function among cannabis users. This study was particularly insightful because of a large sample size ( $n = 1989$ ) and IQ assessments prior to the onset of cannabis use (IQ obtained at age 5, 12, and 18). It demonstrated that adolescents who used cannabis had a lower childhood IQ and a lower IQ at 18 than non-users, but that there was no decline in IQ from pre- to post-cannabis use (Meier et al. 2018). These results are in line with another co-twin longitudinal study that investigated two large cohorts of twins and found no significant difference in IQ change over time between twins discordant for cannabis use (Jackson et al. 2016). However, lower baseline IQ was associated with adolescent cannabis use suggesting that social and environmental factors influence an adolescent's subsequent cannabis use (Jackson et al. 2016). Together, these studies suggest that lower IQ may be a risk factor for cannabis abuse rather than the use of cannabis resulting in neuropsychological decline. However findings on the effects of cannabis exposure during adolescents are controversial and require investigation with prospective designs that take advantage of brain imaging technologies. The ABCD study, a prospective study that aims to follow 10,000 children as they transition into adulthood with a detailed phenotypic characterization including periodic brain imaging, would help clarify what effects cannabis consumption might have on brain development, neurocognitive function and mental illness (Volkow et al. 2017b).

#### Long-Term Effects of Cannabis: Neurophysiological Changes

The chronic relapsing nature of addiction seems to involve underlying neurophysiological changes in reward, stress, and executive function circuits (Koob and Volkow 2016). Here we summarize findings about the effects of chronic cannabis use on these circuits.

Chronic cannabis abuse is modeled in animals with repeated treatments of cannabis (through smoke exposure) or THC and other cannabinoids (typically intravenous injections). Neurophysiological changes after these different methods of chronic cannabis treatment are then typically measured through electrophysiological recordings and microdialysis (Maldonado and Rodriguez de Fonseca 2002; Tanda and Goldberg 2003; Maldonado et al. 2011; Oleson and Cheer 2012; Panlilio et al. 2015).

In rats, early-life exposure to THC blunts dopaminergic response to naturally rewarding stimuli that elicit DA release later in life (Bloomfield et al. 2016). Likewise in rats, adolescent exposure to THC resulted in increased self-administration of and blunted striatal DA response to CB1R agonists in

adulthood (Scherma et al. 2016). Changes in reward-related circuitry after chronic cannabis use may be related to changes in the eCS after prolonged cannabis use. The eCS has been implicated in reward-processing and reward-seeking behavior given that CB1 receptors are densely expressed in areas associated with reward processing and conditioning including the amygdala, cingulate cortex, PFC, ventral pallidum, caudate putamen, NAcc, VTA, and lateral hypothalamus (Parsons and Hurd 2015; Volkow et al. 2017a). In animals, activation of CB1 receptors seems to influence the hedonic effects of natural rewards after THC administration, suggesting that cannabis can affect reward sensitivity via activation of CB1 receptors (Parsons and Hurd 2015).

Chronic THC exposure has further been shown to downregulate CB1Rs, providing a neurobiological basis for the development of tolerance and desensitization to the rewarding effects of THC (Colizzi et al. 2016). In rodents, chronic administration of THC or CB1R agonists leads to tolerance in most responses as well as a decrease in CB1R availability in many brain areas (Maldonado and Rodriguez de Fonseca 2002; Tanda and Goldberg 2003; Maldonado et al. 2011). In cannabis users, withdrawal symptoms have also been associated with reductions in CB1R availability as assessed by [ $^{11}$ C]OMAR PET imaging (Curran et al. 2016; D'Souza et al. 2016). Hirvonen et al. (2012) found that cannabis use downregulates CB1R in cortical regions, potentially altering the brain's reward system. However, they also found that after 4 weeks of abstinence, CB1R density returned to normal in cannabis users in all regions except the hippocampus. This suggests that some neurobiological changes of chronic cannabis use are reversible (Hirvonen et al. 2012).

Chronic cannabis use and administration is also associated with neurophysiological changes in stress responsivity. In rodents, the neurophysiological changes associated with cannabis withdrawal are modeled through precipitated withdrawal through the use of rimonabant (a selective CB1R blocker) after repeated cannabinoid treatment (Maldonado et al. 2011; Oleson and Cheer 2012; Panlilio et al. 2015). Cannabinoid withdrawal in rodents is associated with an increase in the stress peptide CRF in the central nucleus of the amygdala (Rodriguez de Fonseca et al. 1997; Maldonado et al. 2011; Panlilio et al. 2015; Curran et al. 2016), which suggests the presence of between-systems changes in brain stress systems, as described by the Koob and Volkow model (2016). In addition, the eCS seems to be involved in regulating the stress response through its action on the amygdala and HPA axis (Dow-Edwards and Silva 2017; Volkow et al. 2017a). The eCS modulates interactions between the PFC, amygdala, and hippocampus which are all involved in emotional memory, anxiety-related behaviors, and drug cue-induced craving in SUD (Jasinska et al. 2014). Additionally, endocannabinoids seem to be required for feedback to normal stress responses: glucocorticoids increase the endogenous cannabinoids

anandamide (AEA) and 2-acylglycerol (2-AG) in the paraventricular nucleus while CB1R antagonists increase HPA axis output. In rodents, exogenous cannabinoids seem to create a dysregulation of stress responsivity and anxiety-related behaviors (Dow-Edwards and Silva 2017).

Moreover, chronic cannabis abuse is associated with the dysregulation of stress responsivity in humans (Curran et al. 2016). Studies in cannabis users show that chronic cannabis use is related to both blunted and hyperactive stress responses (Somaini et al. 2012; Cuttler et al. 2017). Cuttler et al. (2017) found that healthy controls had an increase in cortisol levels under a stress-provoking condition compared to baseline but did not find the same increase in active cannabis users. In another study, both active and abstinent cannabis users had persistent hyperactivity of the HPA axis (measured by blood cortisol and ACTH levels) compared to healthy controls (Somaini et al. 2012). This pattern of HPA axis dysregulation is also seen in alcohol users: chronic alcohol use seems to attenuate the cortisol response to acute psychological stimulation of the HPA axis, but is related to elevated cortisol levels during alcohol intoxication and abstinence in dependent users (Stephens and Wand 2012).

In addition to its role in HPA axis dysfunction and reward processing, the hyperactivation of the eCS may also play a role in the executive dysfunction sometimes observed in cannabis use. The eCS is highly active in adolescent brain development, particularly in the PFC, a region that exercises executive function (Dow-Edwards and Silva 2017). Exogenous cannabinoids hyperactivate CB1 receptors which are expressed in pyramidal neurons and GABAergic interneurons, indicative of the regulatory role of the eCS in GABA and glutamate neurotransmission (Caballero and Tseng 2012; Volkow et al. 2017a). Activation of presynaptic CB1 receptors inhibits glutamate transmission onto GABAergic cells in the PFC, reducing the function of inhibitory prefrontal circuits. Therefore, hyperactivation by exogenous cannabinoids during development could disrupt the maturation of GABAergic interneurons in the PFC and desynchronize PFC circuits (Caballero and Tseng 2012). Thus, adolescent cannabis use may affect brain development and result in enduring alterations in the GABA/glutamate balance in the PFC (Renard et al. 2016).

Neuroadaptations in glutamatergic signaling resulting from repeated cannabis use are likely also implicated in periods of cannabis abstinence and craving (Samuni et al. 2013). This theory is supported by a review of animal studies that demonstrated increased glutamate signaling during drug self-administration and relapse, offering a potential neurochemical target for treatment in preventing craving and subsequent relapse. For example, rodent and nonhuman primate models receiving periodic injections of glutamate receptor antagonists have shown a reduction in relapse rates (Caprioli et al. 2017). Nonetheless, these findings need to be corroborated in rodents

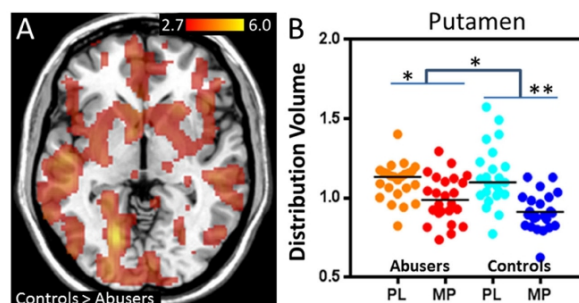
since there is conflicting evidence for whether self-administration in rodent models provides robust evidence of THC as a behavioral reinforcer (Tanda and Goldberg 2003; Maldonado et al. 2011; Panlilio et al. 2015; Melis et al. 2017).

### Long-Term Effects of Cannabis on the Brain: Neuroimaging Studies

Addiction is a recurring cycle that worsens over time and involves neuroplastic changes in the brain reward, stress, and executive function systems (Koob and Volkow 2016). Previous neuroimaging studies reveal the long-term effects of chronic cannabis use on several different brain systems including the reward, endocannabinoid, and stress systems as well as brain areas involved in emotion processing and decision making.

Similar to animal models of chronic THC exposure, chronic cannabis use has been shown to blunt DA response to DA-releasing stimulant drugs in the striatum with both [<sup>11</sup>C]-(+)-PHNO and [<sup>11</sup>C]raclopride PET imaging (Volkow et al. 2014c; Bloomfield et al. 2016; van de Giessen et al. 2017) and to decrease DA synthesis as assessed with PET imaging with [<sup>18</sup>F]DOPA (Bloomfield et al. 2014) (Fig. 2). This pattern of decreased stimulant-induced DA release is also seen with chronic use of other drugs of abuse such as alcohol, cocaine, and nicotine (Koob and Volkow 2016). However, cannabis users do not show lower baseline D2/D3 receptor availability in the striatum compared to healthy controls – a pattern seen in chronic alcohol, nicotine, cocaine, opiate and methamphetamine users (Volkow et al. 1996b, 2001, 2002, 2014b, 2017c; Wang et al. 1997; Martinez et al. 2012; Tomasi et al. 2015b; Wiers et al. 2016a, 2017; Ashok et al. 2017). Moreover, the stimulant challenge led to significantly lower self-reported ratings of feeling high (Volkow et al. 2014c), and decreased brain glucose metabolism in the striatum, thalamus, and midbrain (Wiers et al. 2016b) in cannabis users versus controls. Cannabis users had higher negative emotionality and lower positive emotionality personality scores than controls, and negative emotionality scores were inversely correlated with methylphenidate-induced dopamine increases in the ventral striatum (Volkow et al. 2014c; Wiers et al. 2016b). These findings offer an explanation for decreased dopamine reactivity in the striatum during abstinence that may contribute to negative emotionality, which is consistent with lower reward sensitivity in cannabis users during the withdrawal phase of addiction (Volkow et al. 2014c). In another study, a stimulant challenge also led to blunted brain glucose metabolism in striatal regions, which was associated with craving (Wiers et al. 2016b). Together these findings from stimulant challenges indicate functional changes in the dopaminergic reward system in chronic cannabis users.

Furthermore, fMRI studies have also revealed functional and structural changes in brain areas involved in reward



**Fig. 2** a. Statistical group differences in the effect of methylphenidate on the distribution volume between controls and marijuana abusers. Methylphenidate-induced decreases in distribution volumes were stronger in controls than in marijuana abusers ( $p < 0.005$ ). There were no regions where marijuana abusers showed greater decreases than controls.

b. Individual distribution volume values in putamen after placebo (PL) and after methylphenidate (MP) for marijuana abusers and controls.  $*p < 0.05$ ,  $**p < 0.005$ . (Figure adapted with permission from Volkow et al. 2014a, b, c)

processing after chronic cannabis use. In one study, participants in a cannabis-dependent group had greater activation in the ventral striatum in response to losses during a monetary incentive delay (MID) task compared to healthy controls (Yip et al. 2014). Compared to controls, the cannabis-dependent participants also had smaller putamen volumes, a brain region involved in habit formation. These differences seemed to be driven by participants who were unable to stay abstinent from cannabis and were comparable to findings in tobacco smokers suggesting similar changes in reward functioning in both tobacco and alcohol addiction (Yip et al. 2014). In another fMRI study with the MID task, cannabis users in withdrawal had greater activation in the ventral striatum in response to positive incentives compared to healthy controls during the MID task, similar to findings in alcohol users (Filbey et al. 2013). Persistent cannabis use also seems to be related to a blunted response to reward anticipation in the NAcc during the MID task: in this study, even after controlling for prior and current use of other drugs, greater cannabis use was related to decreased activation in the NAcc during reward anticipation at baseline, 2 year, and 4 year follow ups (Martz et al. 2016). Together, these findings suggest that chronic cannabis use produces functional alterations in areas involved in reward processing.

A recent fMRI study investigated whether cannabis use sensitizes and disrupts the mesocorticolimbic reward processes during a hedonic cue-reactivity task. A cohort of chronic cannabis users (requiring 72 h of abstinence) showed greater BOLD response for cannabis cues compared to natural reward cues (fruit) in the orbitofrontal cortex (OFC), striatum, anterior cingulate gyrus, and VTA, regions along the mesocorticolimbic-reward pathway (Filbey et al. 2016). In cannabis users, there were also significant positive correlations between cue-induced self-rated craving for cannabis and BOLD responses within the mesocorticolimbic system

and in the insula. The latter data supports the addictive model of cannabis as insula activation may serve as a biomarker to help predict relapse (Filbey et al. 2016). This brain region contributes to interoceptive awareness of negative emotional states and is differentially activated during craving (Koob and Volkow 2016). This is also consistent with prior findings that the dopaminergic reward system is reactivated during acute craving episodes (Volkow et al. 1999b, 2005; Koob and Volkow 2016). Moreover, in cannabis abusers, but not in controls, acute THC intoxication elicited activation of brain reward regions as assessed by increases in brain glucose metabolism in striatum and orbitofrontal cortex (Volkow et al. 1996a). Overall, these studies demonstrate that chronic cannabis use sensitizes the mesocorticolimbic-reward system to cannabis cues and to THC (Volkow et al. 1996a; Filbey et al. 2016). These findings suggest that chronic cannabis use affects key brain circuits involved in the reward system similar to other drugs of abuse.

In addition to changes in reward processing, chronic cannabis use also seems to affect emotion processing. Several MRI studies reveal functional and structural differences in the amygdala – a key brain structure in processing emotions – after chronic cannabis use. Compared to healthy controls, adolescents who used cannabis had lower activation in the amygdala in an emotional arousal word task during fMRI (Heitzeg et al. 2015). However, in another fMRI study, adolescent cannabis users showed greater amygdala activation to angry faces compared to controls (Spechler et al. 2015). Another study of facial emotion recognition found that during abstinence, cannabis-dependent patients performed significantly worse than controls in the identification of negative emotions suggesting a lasting impact on emotion recognition after chronic cannabis use (Bayrakçi et al. 2015). Together, these fMRI findings indicate that chronic cannabis use alters amygdala function.



The association between amygdala structure and cannabis use is relatively unclear. Some studies have found morphological and volumetric differences in the amygdala between healthy controls and cannabis users in both adolescent and adult cohorts (Gilman et al. 2014; Lorenzetti et al. 2015). On the other hand, other studies that controlled for alcohol and tobacco use found no differences in amygdala volume or shape between cannabis users and healthy controls (Weiland et al. 2015; Manza et al. 2018). A longitudinal study with cannabis users and healthy controls found no volumetric differences in gray matter at baseline or a three-year follow up (Koenders et al. 2016). Despite these inconclusive structural MRI findings, there is evidence that chronic cannabis use may contribute to emotional dysregulation through functional changes in the amygdala (Heitzeg et al. 2015; Spechler et al. 2015).

Further evidence of emotion dysregulation after chronic cannabis use is seen in fMRI functional connectivity studies with cannabis users (Pujol et al. 2014; Zimmermann et al. 2018). In one study, cannabis users showed increased resting-state functional connectivity between posterior cingulate cortex (PCC) and other regions of the default mode network (including angular gyri, medial and lateral PFC, ACC and temporal cortex), and an anticorrelation between PCC activation and insula activation. These connectivity patterns were associated with a reduction in anxiety scores suggesting an alteration of affect state that is related to changes in brain function during cannabis addiction. As the insula is involved in integrating interoceptive information for emotion, these findings suggest that cannabis may enhance visceral sensations via insula activation to modify affect state (Pujol et al. 2014). Additionally, these resting-state functional connectivity patterns lasted one month after cessation of cannabis use suggesting long-lasting changes in brain function after chronic cannabis use (although functional connectivity patterns in other networks normalized with abstinence, see Pujol et al. 2014). In another fMRI study, cannabis-dependent subjects completed task and resting state fMRI 28 days after abstinence (Zimmermann et al. 2018). During the task, in which participants were passively exposed to pictures of negative and neutral valence, negative emotional stimuli elicited larger increases in medial orbitofrontal cortex (mOFC) activity in cannabis-dependent users than in healthy controls; researchers also found greater functional connectivity between the mOFC and dorsal striatal region as well as the mOFC and amygdala compared to healthy controls during the task. Given that the mOFC is a region implicated in emotional regulation, these connectivity findings suggest the existence of persistent emotional processing alterations in cannabis-dependent users even after cessation of cannabis use (Zimmermann et al. 2018).

In addition to contributing to emotion dysregulation, cessation of chronic cannabis use is associated with the development of craving (Davis et al. 2016). Cue-reactivity is a

neurobiological metric to evaluate cue-induced craving, a strong predictor of relapse for substance use (Budney et al. 2008; Wilson and Sayette 2015). A 2016 meta-analysis of cue-reactivity in regular cannabis users reported moderate to extreme cue-reactivity despite self-reports of low craving (Norberg et al. 2016). These results may indicate that cannabis users underestimate their own excessive salience, suggesting that self-reports may not accurately reflect cannabis craving intensity. Thus, excessive salience attribution to cannabis-related cues appears to be a hallmark of cannabis addiction. These studies further demonstrate the importance of collecting objective measures of craving when studying the effects of chronic cannabis use.

Finally, one of the most consistent neuroimaging findings in addiction is that of dysregulation of frontal cortical regions involved with executive function including the dorsolateral prefrontal cortex, the ACC and the inferior frontal cortex. Imaging studies investigating brain glucose metabolism, which serves as a marker of brain function, reported decreased frontal metabolism in cannabis abusers when compared with controls (Sevy et al. 2008; Wiers et al. 2016b) and in polysubstance users who consumed cannabis (Moreno-Lopez et al. 2012).

## Treatment Options

Treatments for CUD seem to target aspects of the binge-intoxication, withdrawal-negative affect, and preoccupation-anticipation stages described by Koob and Volkow (2016).

Pharmacological treatments for the binge-intoxication stage of cannabis addiction have focused on cannabinoid receptors. One mechanism of action involves direct antagonism of CB1Rs. CB1R selective antagonists such as rimonabant have been shown to block the subjective intoxicating and tachycardic effects of smoked cannabis (Crippa et al. 2012; Danovitch and Gorelick 2012). Despite the potential acute benefits, direct antagonism with rimonabant is associated with anxiety and depression (Taylor 2009; Danovitch and Gorelick 2012). Up to 10% of patients experienced anxiety and depression following use of rimonabant (Food and Drug Administration 2007). Another downfall of this therapy is that in order to avoid precipitated withdrawal, participants are required to abstain from drug use prior to administration of antagonist medications, leading to poor compliance rates (Vandrey and Haney 2009). While partial agonists have been proposed to block the reinforcing effects of other drugs of abuse like opioids and nicotine (Koob and Mason 2016), no partial agonists have been found to reduce cannabis use.

Many different pharmacological treatments have been investigated for reduction of cannabis withdrawal symptoms, primarily through modulation of cannabinoid receptors but also through other neurotransmitter systems including

glutamate, dopamine, norepinephrine, serotonin, and GABA (Balter et al. 2014; Levin et al. 2016; Brezing and Levin 2018). In their comprehensive review of the different pharmacological treatments for CUD and cannabis withdrawal, Brezing and Levin (2018) conclude that therapies targeting specific symptoms of withdrawal (such as anxiety, irritability, sleep disturbances, and decreased appetite) should be administered in conjunction with treatments that target reduction in cannabis use and prevention of relapse. Promising candidates for treatment of CUD that prevent relapse include naltrexone, gabapentin, and N-acetylcysteine (NAC) (Mason et al. 2012; Brezing and Levin 2018). The greatest reduction in multiple withdrawal symptoms has been shown with treatment using CB1R agonists such as dronabinol (oral THC), nabixmols (a combination of THC and CBD), and nabilone (Balter et al. 2014; Brezing and Levin 2018); surprisingly, previous studies have not shown cannabidiol as a potential treatment for cannabis withdrawal despite its anxiolytic effects (Brezing and Levin 2018). With CB1R agonists as potential treatments, it is necessary to consider the abuse potential of these drugs. Dronabinol, nabilone, and nabixmols seem to have a lower abuse potential than smoked cannabis (Allsop et al. 2015; Tsang and Giudice 2016), but in one study of cannabinoid replacement therapy, dronabinol and nabixmol had higher self-reports of liking than placebo drugs (Allsop et al. 2015).

NAC is being investigated as an anticraving agent in cannabis addiction therapy due to its regulatory role in glutamate and dopamine signaling (Samuni et al. 2013). NAC helps regulate the intra- and extracellular levels of glutamate through the cysteine-glutamate antiporter. Increased extracellular glutamate levels activate inhibitory metabotropic glutamate receptors, reducing glutamate neurotransmission (Samuni et al. 2013). The upregulation of glutamate signaling during the anticipation/preoccupation phase may be counteracted with NAC treatment, reducing clinical symptoms of craving and therefore reducing relapse rates. A 2014 review article summarizes two studies that evaluated NAC therapy in CUD. In one study, the placebo cohort reported twice as many positive urine cannabinoid tests as compared to the NAC cohort (Asevedo et al. 2014). The other study did not report group differences in positive urine tests, but did find a significant reduction in self-reported cannabis craving in the treatment group (Asevedo et al. 2014). These studies reinforce the role of glutamate upregulation during cannabis abstinence on clinical outcomes such as craving and relapse.

## Discussion

After examining the acute and long-term effects of cannabis, CUD appears to conform to the general patterns of changes described in the Koob and Volkow model of addiction. Previous preclinical and clinical studies indicate that features

of the three stages of drug addiction described by Koob and Volkow are also present in cannabis addiction (Fig. 1), although these findings may not be as robust as other drugs of abuse.

As described in the Koob and Volkow model (2016), most drugs of abuse result in the hyperactivation of the mesocorticolimbic dopaminergic reward pathway in the binge-intoxication stage of addiction. This hyperactivation seems to be present in cannabis addiction but to a lower extent. Acute THC administration elicits striatal DA release in animals (Bloomfield et al. 2016) and THC challenges were shown to increase striatal DA transmission in humans (Stokes et al. 2010; Bossong et al. 2015); although other studies have found no THC-induced increases in striatal DA (Barkus et al. 2011; Urban et al. 2012). Additionally, there are no baseline differences in dopamine D2/D3 receptor availability between cannabis users and healthy controls (Volkow et al. 2014c; van de Giessen et al. 2017), a finding that does not parallel addiction to other drugs of abuse (including cocaine, alcohol, methamphetamine, nicotine, or heroin) which is associated with substantial reductions in D2R availability in the ventral striatum (Wang et al. 1997; Volkow et al. 2001, 2014c, 2017c; Martinez et al. 2012; Albrecht et al. 2013; Tomasi et al. 2015a; Wiers et al. 2016a; Ashok et al. 2017). Nonetheless, as with other drugs of abuse, chronic cannabis use still results in blunted dopamine reactivity to a stimulant challenge (Volkow et al. 2014c; van de Giessen et al. 2017).

This blunted stimulant-induced dopamine reactivity has been associated with negative emotionality (Volkow et al. 2014c) a key feature of withdrawal/negative affect stage described by Koob and Volkow (2016). With the addition of withdrawal as a symptom of CUD, it is evident that the development of cannabis addiction parallels addiction to other drugs of abuse. In addition, chronic cannabis use has been associated with affect dysregulation that may involve changes in amygdala functioning (Filbey et al. 2013; Heitzeg et al. 2015; Spechler et al. 2015). As with other drugs of abuse, cannabis seems to disrupt HPA axis function (Somaini et al. 2012; Cuttler et al. 2017), another key neuroadaptation of the withdrawal/negative affect stage described by Koob and Volkow (2016).

Chronic cannabis use is also associated with the presence of cannabis cue-induced craving after abstinence (Filbey et al. 2016; Norberg et al. 2016), a hallmark of the preoccupation/anticipation stage of the Koob and Volkow framework (2016). The presence of cannabis cue-induced craving seems to be related to the loss of executive control over excessive salience for cannabis (Norberg et al. 2016). In addition, chronic cannabis use has been linked to impaired memory and IQ, suggesting changes in executive functioning after chronic cannabis use. However, IQ deficits appear to be present before initiation of cannabis use which may suggest that lower IQ could be a risk factor for cannabis addiction (Jackson et al. 2016).



Interestingly, chronic cannabis use is associated with a downregulation of CB1R – THC’s target receptor – that is restored after 4 weeks of abstinence in humans (Hirvonen et al. 2012). This pattern of abstinence-induced changes in target receptor density is also seen after abstinence from other drugs of abuse such as heroin, stimulants, and alcohol (in humans and animals) but with some caveats: the changes found are not consistent across brain regions for every drug and abstinence periods are not congruent between studies (Wang et al. 2012; Seip-Cammack et al. 2013; Ashok et al. 2017; Volkow et al. 2017c). Future studies should examine to whether changes in target receptors after abstinence are comparable across brain regions and if they follow the same time course in CUD and other SUD.

Future studies should also investigate if there are other features of the addiction framework proposed by Koob and Volkow in cannabis addiction. Specifically, more longitudinal studies should investigate behavioral and mood changes (such as changes in IQ or the presence of a mood disorder) before and after the onset of cannabis use to determine whether variations in behavior and mood are risk factors or the result of cannabis addiction rather than a consequence. Additionally, with the increasing potency of THC in street cannabis (EISOHLY et al. 2016), it is necessary to evaluate whether long-term changes may be related to the THC content of cannabis. Future studies should also investigate the specific neurocircuitry Koob and Volkow (2016) implicate in the three stages of addiction: specifically, how cannabis use impacts glutamate signaling in the VTA (disrupted during binge/intoxication) and PFC (disrupted during preoccupation/craving) and acetylcholine signaling in the habenula (disrupted during withdrawal/negative affect).

Future research should also consider whether THC’s effects on neurons and microglia are related to addiction. Previous research indicates that chronic THC exposure in animals seems to activate microglia and produce neuroinflammation that may underlie some of the cognitive deficits associated with CUD (Melis et al. 2017); additionally, changes in neuron and glia morphology after chronic cannabis exposure may also contribute to the persistent cognitive and behavioral deficits linked to CUD (Cutando et al. 2013; Kolb et al. 2018). Therefore, future studies should investigate whether chronic THC exposure in animals and humans is linked to changes in various cell types in the brain that contribute to cannabis addiction through neuroinflammation. THC has also been shown to have immunosuppressant properties in animals (Suarez-Pinilla et al. 2014) while cannabis use has been associated with adverse cardiovascular effects in humans (Pacher et al. 2017; Goyal et al. 2017; Thomas et al. 2018); these peripheral effects could be another line of future research.

Although further research is necessary (Box 1), the findings summarized here indicate that neurobiological changes in CUD seem to parallel those in other addictions, albeit to a

lesser extent in some brain systems. This is critical in light of recent findings demonstrating an increase in cannabis use and CUD and a corresponding decrease in the perceived risk of cannabis (Carliner et al. 2017; Hasin 2018).

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#### Box 1. Questions for future research

- Do changes in CB1R density after abstinence from cannabis parallel changes in target receptors of other drugs of abuse?
  - Are behavioral and mood variations associated with cannabis use a risk factor or consequence of cannabis addiction?
  - Are long-term behavioral and neurophysiological changes related to the THC content in cannabis?
  - Is cannabis use associated with long-term changes in glutamate signaling as seen in other drugs of abuse?
  - Is cannabis use associated with disruptions in the amygdala and habenula as seen with other drugs of abuse?
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#### Compliance with Ethical Standards

**Conflicts of Interest** The authors report no biomedical financial interests or potential conflicts of interest.

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# Attachment 7 Therapeutic potential of medicinal marijuana: an educational primer for health care professionals *Drug Healthc Patient Saf.* 2018; 10: 45–66.

Drug, Healthcare and Patient Safety

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REVIEW

## Therapeutic potential of medicinal marijuana: an educational primer for health care professionals

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**Abstract:** With the proposed Canadian July 2018 legalization of marijuana through the Cannabis Act, a thorough critical analysis of the current trials on the efficacy of medicinal marijuana (MM) as a treatment option is necessary. This review is particularly important for primary care physicians whose patients may be interested in using MM as an alternative therapy. In response to increased interest in MM, Health Canada released a document in 2013 for general practitioners (GPs) as an educational tool on the efficacy of MM in treating some chronic and acute conditions. Although additional studies have filled in some of the gaps since the release of the Health Canada document, conflicting and inconclusive results continue to pose a challenge for physicians. This review aims to supplement the Health Canada document by providing physicians with a critical yet concise update on the recent advancements made regarding the efficacy of MM as a potential therapeutic option. An update to the literature of 2013 is important given the upcoming changes in legislation on the use of marijuana. Also, we briefly highlight the current recommendations provided by Canadian medical colleges on the parameters that need to be considered prior to authorizing MM use, routes of administration as well as a general overview of the endocannabinoid system as it pertains to cannabis. Lastly, we outline the appropriate medical conditions for which the authorization of MM may present as a practical alternative option in improving patient outcomes as well as individual considerations of which GPs should be mindful. The purpose of this paper is to offer physicians an educational tool that provides a necessary, evidence-based analysis of the therapeutic potential of MM and to ensure physicians are making decisions on the therapeutic use of MM in good faith.

**Keywords:** medicinal marijuana, cannabis, endocannabinoid system, Cannabis Act, multiple sclerosis, Parkinson's disease, Tourette's syndrome, gastrointestinal disorders, pregnancy, epilepsy, Access to Cannabis for Medical Purposes Regulations

### Introduction


In Canada, marijuana or cannabis (used interchangeably hereafter) has been used recreationally and medicinally for generations but was first legally available as medicinal marijuana (MM) in 2001 through the Medical Marijuana Access Regulations.<sup>1</sup> In its most recent form, the Access to Cannabis for Medical Purposes Regulations states that physicians have the responsibility of authorizing patients to access MM.<sup>2,3</sup> Health Canada and the provincial medical colleges have published guidelines for physicians to follow and approve MM for their patient's safety.<sup>4</sup> Despite these guidelines, physicians remain uncomfortable authorizing MM due to a lack of evidence-based literature and the perceived lack of education surrounding the subject.<sup>5-7</sup> Many physicians feel that a robust understanding of cannabis would increase their comfort with

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MM.<sup>6,7</sup> The basis of this knowledge is particularly relevant for a large demographic of the population presenting with chronic conditions that have reported to be self-medicating with marijuana where conventional therapies have failed in improving the overall quality of life (QOL).<sup>7</sup>

Therefore, this review aims to serve as an educational tool that provides relevant information of which physicians must be mindful when authorizing MM. The information is primarily appropriate due to the expected increase in use following the proposed legalization of marijuana for recreational purposes by July 2018 through the Cannabis Act. Here, we provide a summary of the basic science behind cannabis and the endocannabinoid system, as well as the current Canadian laws and authorization guidelines for MM. We simplify and analyze new literature that has emerged since the 2013 release of the Canadian medical marijuana guidelines, delineate therapeutic uses of cannabis and its contraindications and outline gaps present in the current literature. We ultimately hope that this succinct review provides physicians with the necessary resources required for MM-related decision-making and improves the general practitioner's level of comfort with MM and their capacity to attend to such patients.

## Methods

This literature search identified articles using PubMed, EMBASE Ovid, and the Cochrane Library to determine high-quality, multicenter randomized controlled trials, systematic reviews, meta-analyses, and practice guidelines from February 2013 to August 2017. The assessment of the therapeutic potential of MM allowed in the identification of gaps including conflicting and inconclusive results in our knowledge since the release of the 2013 Health Canada guidelines that may pose a challenge for physicians. This review aims to supplement the Health Canada document by providing physicians with a critical yet concise update on the recent advancements for the prescribed use of MM. This paper presents an overview of previously published reviews and, as such, requires no ethics approval.

## Canadian medical regulatory authorities' policies and guidelines

Although the Cannabis Act is currently on track to its projected enactment taking place in July 2018, some challenges regarding MM use that are not addressed by the 2013 Health Canada guidelines remain. Specifically, under the ACMPR,<sup>2</sup> physicians are required to sign a medical document to authorize patients to access a specific quantity of cannabis. This medical report resembles a prescription; however, unlike

all other prescribed medications, Health Canada has not reviewed data on the safety or efficacy of MM.

In light of the scarcity of data available to physicians, the medical regulatory authorities (colleges) have recently implemented policies on MM to assist physicians in making informed decisions that are most beneficial for their patients.<sup>8-16</sup> Current guidelines and policies issued to date by these colleges repeatedly state that physicians should only sign the medical document if they have the necessary clinical knowledge; furthermore, physicians are not obligated to prescribe marijuana if they do not believe it is clinically appropriate for their patients.<sup>17</sup> Collectively, the colleges agree that MM is not appropriate in a number of circumstances including for patients under the age of 25 years, have a current or past substance use disorder, have personal or family history of mental illness (psychosis), have a history of chronic lung, cardiovascular, and/or kidney disease, and who are pregnant or breastfeeding. Moreover, all colleges recommend that informed consent should be obtained from patients before authorizing MM.<sup>8-16</sup> During this process, physicians must discuss the risks and benefits of MM with their patients, including the necessary precautions that patients need to take when engaging in activities requiring mental alertness such as driving and operation of heavy machinery.

While the rules and restrictions that govern the authorization of MM may be challenging to interpret, determining the safe therapeutic dose for each patient will present a more significant challenge for physicians. Therefore, all colleges advise physicians to proceed cautiously where patients "start low and go slow" until a dose is reached that achieves symptom management while causing minimal euphoria or cognitive impairment.<sup>18-20</sup> To ensure that these expectations are met, physicians must specify the quantity of marijuana to be dispensed to the patients as well as the (-)- $\Delta^9$ -trans-(6aR,10aR)-tetrahydrocannabinol ( $\Delta^9$ -THC or THC) content (the relevance of this is discussed below) on every medical document. Furthermore, most colleges recommend that physicians follow up with their patients every 3 months to monitor for any emerging complications or risks of abuse, misuse, or diversion, even though the authorization of medical cannabis is valid for up to 1 year. To minimize risks, some medical regulatory authorities such as the Colleges of Physicians and Surgeons in Ontario, Saskatchewan, and Quebec require physicians to obtain a signed written treatment agreement from their patients before MM authorization.<sup>8,10,11</sup> This agreement must contain a statement from patients that they will not seek marijuana from another physician or any other source, will only use marijuana as prescribed, will store their

marijuana safely and securely, and will not sell or give away their marijuana. Additional province-specific details can be found in [Table S1](#).

### Brief overview of the mechanisms of action of MM

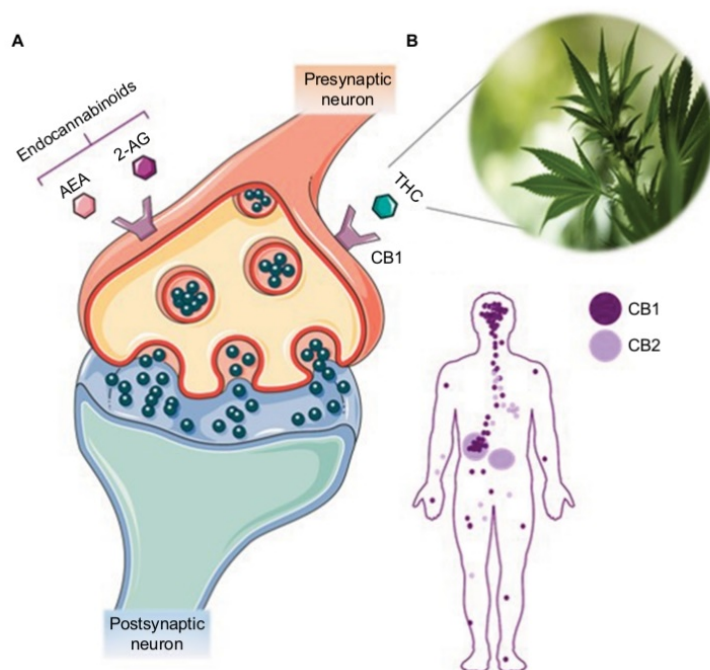
Given the pending legalization of MM for recreational purposes through the enactment of the Cannabis Act, it is important for family physicians to understand the underlying effects of cannabis. This statute is to provide legal access to marijuana and to control and regulate its production, distribution, and sale.

### The endocannabinoid system and MM

The endocannabinoid system is a naturally occurring communication network that plays a role in many physiological processes.<sup>21</sup> Currently, this system has been found to be implicated in gastrointestinal (GI) function,<sup>22</sup> appetite and metabolism,<sup>23–25</sup> pain,<sup>26,27</sup> memory,<sup>28</sup> movement,<sup>29</sup> immunity,<sup>30</sup> and inflammation.<sup>31</sup> The endocannabinoid system comprises

two G-protein-coupled receptors (GPCRs): cannabinoid receptors 1 (CB1) and 2 (CB2).<sup>32,33</sup> CB1 possesses psychoactive potential and is expressed in the central nervous system (CNS), Gastrointestinal (GI) system, adipocytes, liver tissue, and skeletal muscle.<sup>32,34,35</sup> In contrast, CB2 receptors are more restricted in their distribution and are primarily found on immune cells located in the tonsils, thymus, spleen, and bone marrow,<sup>32,34,35</sup> as well as in the enteric nervous system within the GI tract.<sup>36</sup> Activation of these receptors is dependent on endogenous endocannabinoids anandamide (AEA) and 2-arachidonoylglycerol (2-AG).<sup>37,38</sup>

Due to its abundance in the body, particularly in the nervous system, CB1 and its subsequent psychoactive effects have been extensively studied. As illustrated in Figure 1, cannabinoid binding regulates presynaptic Ca<sup>++</sup> levels generally leading to a reduced release of neurotransmitters. This mechanism plays an essential role in maintaining homeostasis, thereby implicating this system in several physiological and pathological conditions that have been previously reported in detail.<sup>39</sup>



**Figure 1** The endocannabinoid system and CB1/CB2 distribution. **(A)** The mechanism of action of the endocannabinoid system is depicted, with human endocannabinoids AEA or 2-AG binding to CB1 to initiate a signaling cascade through the release of neurotransmitters. THC is also able to bind to CB1, exerting its effects on the central nervous system and peripheral system. **(B)** Distribution of CB1 and CB2 in the body. CB1 is concentrated in the central and peripheral nervous systems. CB2 is more abundant in the immune system and, to a lesser degree, in the nervous system.

**Abbreviations:** CB1/CB2, cannabinoid receptor 1/cannabinoid receptor 2; AEA, anandamide; 2-AG, 2-arachidonoylglycerol; THC, (-)- $\Delta^2$ -trans-(6aR,10aR)-tetrahydrocannabinol.



The medicinal properties of cannabis can be attributed primarily to phytocannabinoids  $\Delta^9$ -THC or THC and cannabidiol (CBD).<sup>40-42</sup> THC and CBD are the most biologically active phytocannabinoids and are capable of mimicking human endocannabinoids AEA and 2-AG, respectively.<sup>40-42</sup>  $\Delta^9$ -THC has been shown to bind to CB1 in the nervous system,<sup>21</sup> and the effects of THC on the CNS and peripheral body are outlined in Figure 2 and Table 1, respectively.

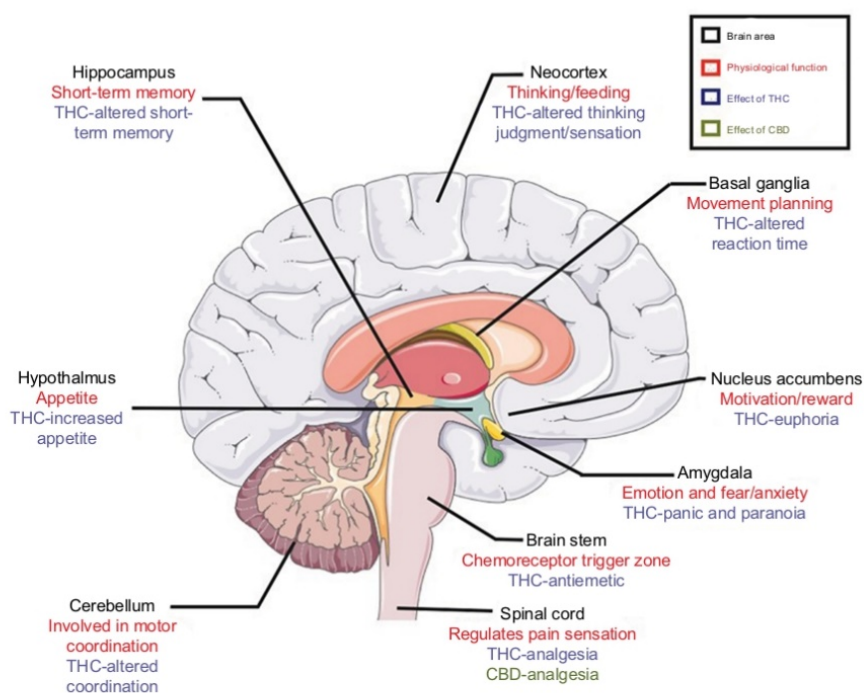
In contrast, non-psychoactive CBD has high binding affinity to the CB2 receptor and exerts its effects on the immune system, resulting in its application for the treatment and management of neuropathic pain.<sup>43</sup> However, conflicting reports suggest that CBD indirectly mediates its effects by interacting with CB1 and CB2, the mechanism(s) of which is not well understood.<sup>44</sup> Given this inconclusive information, it is omitted from Table 1.

The potency of the mediating effects of THC on the endocannabinoid system depends on several factors that need to be considered before prescribing its use for treatment. In the unprocessed form,  $\Delta^9$ -THC and CBD concentrations depend on the species, strain, cultivation, and storage of the plant.<sup>45,46</sup>

Of the three species of cannabis identified (*Cannabis sativa*, *C. sativa*, *C. indica*, and *C. ruderalis*), *C. sativa* contains higher THC than CBD levels while the *C. indica* is richer in CBD compared to THC.<sup>47</sup> CBD attenuating the psychotropic actions of  $\Delta^9$ -THC on the body is thought to be due to affecting  $\Delta^9$ -THC metabolism and inhibiting the formation of 11-OH-THC, its more psychoactive metabolite.<sup>47-49</sup> To summarize, a higher THC:CBD ratio is associated with more prominent psychoactive symptoms, whereas lower THC:CBD ratio suppresses psychoactive symptoms and has more sedative and relaxing effects.<sup>50</sup> Due to the varying effects of MM, pharmacokinetics is another critical aspect that physicians need to consider before authorizing the use of MM.

### Pharmacokinetics of MM

In addition to understanding the effects of phytocannabinoids on the endocannabinoid system, physicians should be mindful of the chemical composition and available routes of administration if considering the authorization of MM. Phytocannabinoids are lipophilic and require heat for










**Figure 2** The effects of cannabis on the central nervous system. Brain areas in the central nervous system (in black) and their physiological functions (in red) are listed alongside potential effects of THC and CBD (in blue and green), respectively.

**Abbreviations:** THC, (-)- $\Delta^9$ -trans-(6aR,10aR)-tetrahydrocannabinol; CBD, cannabidiol.

activation, as accomplished through both the inhalation routes of administration.<sup>51-53</sup> The course of administration also determines the absorption and metabolism of phytocannabinoids.

The currently available routes of administration of cannabinoids are discussed as follows, with the most common forms summarized in detail in Table 2.

**Table 1** Specific effects of THC in the peripheral system

	THC indication	THC effects	Adverse effects
Eyes 	Glaucoma	↓IOP, ↑lubrication of conjunctiva, vasodilation	Dryness of eyes, redness of eyes
Mouth 		↓Saliva production	Dryness of mouth
Lung 		Ventilation, bronchodilation	Low dose: stimulates cough High dose: depresses cough
Heart 		Acute dosage: tachycardia Chronic use: bradycardia	Palpitations, ↑cardiac demand
GIT 	Nausea, vomiting, anorexia	Antiemetic, ↑appetite	
Reproductive system 		↓Sperm count and motility, suppression of ovulation	Infertility, menstrual changes
Cancer 	Role in cancer and chemotherapy	Antitumor activity	

**Abbreviations:** THC, (-)- $\Delta^9$ -trans-(6aR,10aR)-tetrahydrocannabinol; GIT, gastrointestinal tract.

**Table 2** Mode of administration of  $\Delta^9$ -THC

	Mode of administration				
	Inhalation	Orumucosal	Oral		
	<b>Cannabis</b>	<b>Nabiximols</b>	<b>Cannabis</b>	<b>Dronabinol</b>	<b>Nabilone</b>
Approved	✓	✓	✓	✓	✓
Available	✓	✓	✓	X	✓
Constitution and source	<i>Cannabis sativa</i>	THC + CBD; botanical extract from <i>Cannabis sativa</i>	<i>Cannabis sativa</i>	Synthetic $\Delta^9$ -THC	Synthetic $\Delta^9$ -THC analog
Onset of action	5 min	15%–40%	4–6 hours	30–60 min	60–90 min
Bioavailability	2%–56% 25%–27%	35%	10%–20% 4%–22%	6%–15%	20%
Duration of action	2–4 h	2–4 h	Longer than smoking	4–6 h	8–12 h
Approved indications		Symptomatic relief of spasticity in adults with MS		Aids-related anorexia associated with weight loss; severe nausea and vomiting associated with cancer chemotherapy	Severe nausea and vomiting associated with cancer chemotherapy

**Notes:** The composition, pharmacokinetics, approval, and availability in Canada for the different modes of administration of THC. The double-headed arrow corresponds to the onset of action and the duration of action.

**Abbreviations:** THC, (-)- $\Delta^9$ -trans-(6aR,10aR)-tetrahydrocannabinol; MS, multiple sclerosis.

**Inhalation: smoking or vaporization**

Inhalation is the most commonly used route of administration with the quickest onset of action<sup>54</sup> and shortest duration,<sup>55</sup> giving patients the capacity to titrate their dose through adaptive smoking behavior. Of the two inhalation options, vaporization is more discreet and has fewer toxic by-products,<sup>56,57</sup> while inhalation is an appropriate option for patients requiring rapid relief for a shorter duration.

**Oral**

Oral cannabinoid administration offers a longer duration and a slower onset of action compared to inhalation, making titration challenging for patients attempting to achieve desired effects. Cannabinoids administered through the oral route can be taken as pills, such as nabilone (Cesamet®) and dronabinol (Marinol®) (which is no longer available in Canada), or mixed in with foods such as butter, oils, or teas. Administration of oral cannabis can be presented as a potential option for individuals in need of relief of symptoms such as chronic pain, arthritis, movement disorders, and select psychiatric disorders. At this time, there is no robust evidence to support cannabis as a treatment for any psychiatric disorders. The cannabis trials for acute anxiety, schizophrenia, and posttraumatic stress disorder (PTSD) are rather still preliminary, and cannabis is not standard of care treatment for any mental illness at this time.

**Oromucosal**

Oromucosal cannabinoid administration offers a balance between speed of onset and duration of action when compared to inhalation and oral routes. Nabiximol is currently the only oromucosal product approved for prescription, containing a combination of  $\Delta^9$ -THC and CBD in spray form allowing simple self-titration. Oromucosal cannabinoid administration is recommended for the symptomatic relief of spasticity in adults with multiple sclerosis (MS) but may also be a good option for patients in need of rapid relief for longer durations, such as in neuropathic pain.

**Rectal**

The rectal route of cannabinoid administration, though uncommon, has been shown to be efficacious in patients presenting with chemotherapy-related nausea and emesis.<sup>58</sup>  $\Delta^9$ -THC-hemisuccinate, a prodrug, is delivered as opposed to  $\Delta^9$ -THC because it is quickly absorbed, having a higher bioavailability than oral administration. Although rectal products are currently unavailable in Canada, they may be of future interest for patients unable to tolerate oral medications, for

the pediatric population, for palliative use, and for patients unable to take oral medication or via inhalation.

**Topical**

Topical cannabinoid administration has been considered as a treatment for glaucoma.<sup>59</sup> However, due to its high lipophilicity, transport of  $\Delta^9$ -THC across aqueous layers in the body is a rate-limiting step<sup>55</sup> but can be overcome through the use of  $\Delta^9$ -THC prodrugs resulting in improved penetration into the anterior eye, reducing intraocular pressure.<sup>59</sup>

**Metabolism, excretion, and long-term detection of THC**

The metabolism and excretion of cannabinoids are highly regulated and affect many other metabolic processes that need to be considered if advising the medicinal use of cannabis. In brief, cannabinoids are mainly metabolized in liver by the cytochrome P450 (CYP 450) enzymes.<sup>60</sup> Once absorbed, ~97% of  $\Delta^9$ -THC and its metabolites bind to plasma proteins<sup>61-63</sup> and are incorporated into fatty tissue and highly perfused organs, such as heart, brain, lungs, and liver,<sup>55</sup> with the majority of  $\Delta^9$ -THC accumulating in cardiac and fat tissues.<sup>64</sup> Cannabinoids and their metabolites that are not absorbed are excreted in feces (65%) and, to a lesser extent, in urine (20%).<sup>55</sup> Given the complex processes involved in the metabolism and excretion of THC in addition to the prolonged detection of THC, it is essential to consider the underlying drug interactions and subsequent effects on patients presenting with additional chronic conditions.

**Therapeutic options applicable for the authorization of MM use**

As previously discussed, many physicians feel uncomfortable with authorizing MM use due to a lack of educational resources available. Although Health Canada released "Information for Healthcare Professionals, Cannabis (Marihuana, Marijuana) and the Cannabinoids" in February 2013 to educate health care professionals on cannabis, physicians continue to be apprehensive about recommending cannabis as a treatment option for patients who present with chronic conditions. A detailed summary of the Health Canada document can be found in [Table S2](#). Updated evidence-based recommendations and short critical analyses on MM use for various chronic conditions are discussed below.

**Multiple sclerosis**

MS is a chronic inflammatory, demyelinating autoimmune disease of the CNS.<sup>65</sup> Current therapies decrease additional



MS attacks and delay progression but are unsuccessful in improving patient QOL.<sup>66</sup> Patients with MS often seek psychoactive drugs to cope with their disabilities, with numerous studies showing increased rates of recreational and MM use in patients experiencing spasticity.<sup>67-69</sup> In light of this, it is critical for primary care physicians to make educated assessments when deciding whether to authorize MM as a therapeutic option.

Recent studies on the use of MM in MS suggest that cannabinoid use is associated with improvements in spasticity, but they fail to show statistical significance.<sup>70-80</sup> Nevertheless, clinical significance was observed where patients reported a subjective sense of a reduction in spasticity-related symptoms. Many observational open-labeled studies reported promising data on the role of cannabinoids in the treatment of MS in clinical practice.<sup>75-80</sup> Overall, cannabinoids appear to be a well-tolerated add-on treatment associated with a more significant average improvement on the Ashworth Scale (is a measure of spasticity, as indicated by the amount of resistance encountered during passive stretching of soft-tissue, and the Modified Ashworth Scale (MAS) has an additional scoring category) or spasticity compared to placebo, although not statistically significant. However, there are conflicting studies that failed to demonstrate statistical significance in the efficacy of MM on the progression of MS after use for 36 months (95% CI, 2.0-0.2).<sup>71,72</sup> Similarly, a study investigating the time to treatment failure and maintenance efficacy, an oromucosal spray which has an equal (1:1) ratio of THC:CBD (Sativex®), as an add-on treatment in the management of central neuropathic pain revealed conflicting results in the long-term efficacy maintenance of this treatment option.<sup>70</sup> The primary endpoint of time to treatment failure was statistically significant ( $P=0.04$ ) in favor of THC:CBD spray, where 57% of the placebo group failed treatment, compared to only 24% of the THC:CBD group.

There is a scientific rationale for the role of MM in MS based on the understanding of the endocannabinoid system as well as improvements in subjective assessments of spasticity and other related symptoms. However, there is residual uncertainty about whether the effects of cannabinoids are real. These results may not be detected by "objective" outcome measures like the Ashworth scale, or if the perceived consequences are owing to the general psychoactive effect of THC on the CNS. Furthermore, although there were some promising findings in the Health Canada document, the fact remains that adverse effects of cannabis on cognition in people with MS does occur, as changes in cognitive function affects 40%-60% of patients with MS.<sup>81</sup> Therefore, changes

in cognitive function should be appropriately monitored in individuals who begin a cannabis regimen. In addition, new clinical trials should explore other objective modalities such as the stretch reflex test which has demonstrated a statistically significant reduction in stretch reflex amplitude as well as statistically significant reductions in numeric rating scale (NRS) and MAS scores in assessing the improvement of MS-related spasticity.<sup>74</sup>

Although there are indications that MM is effective in reducing patient-reported symptoms such as spasticity and pain, studies also show that cannabinoids have no proven overall effect on the progression of MS.<sup>71,72</sup> Additional research on the long-term outcomes of MM in MS patients is required.

### Epilepsy

As with MS patients who do not see an improvement in QOL following treatment, approximately one third of epileptic patients fail to respond to currently available antiepileptic drugs fully. Patients with treatment-resistant epilepsy have a higher prevalence of comorbidities,<sup>82,83</sup> psychosocial and cognitive problems,<sup>84</sup> negative public attitudes,<sup>82,83</sup> decreased QOL and increased risk of mortality.<sup>85-87</sup> According to the 2013 Health Canada document on cannabinoids, the action of cannabinoid THC was too broad for therapeutic purposes, and there was insufficient evidence on CBD<sup>4</sup> to recommend MM as a potential treatment option for patients with epilepsy.

We identified five new trials published since 2013 investigating the therapeutic potential of CBD in the treatment of drug-resistant epilepsy in children or young adults failing to respond to conventional anticonvulsive medications.<sup>88-92</sup> In addition to being administered CBD, these participants also continued their anticonvulsant drug regimen, most commonly clobazam (marketed under the brand names Frisium, Urbanol, Onfi, and Tapclob) and valproates, for the duration of the trials. Partial and atonic seizures had the most significant reduction in frequency followed by tonic and tonic-clonic seizures. CBD has shown some promise as a potential medical alternative in the treatment of drug-resistant epilepsy with minimal side effects. Based on the high-quality multicentered randomized controlled trials (RCTs) enrolling hundreds of patients to date,<sup>90,92,93</sup> there is evidence that CBD is effective on Lennox Gastaut, Dravet syndrome, and other types of childhood treatment-resistant epilepsy. In one study, a wide range of CBD is administered (from 0.5 to 50 mg/kg/day) with no correlation to the amount administered and adverse events.<sup>90</sup> Also, the mechanism(s) behind CBD therapy in the treatment of drug-resistant epilepsy is not well understood; thus,

elucidating the pathway(s) of action is required to develop a more targeted treatment. Since CBD most potently inhibited the catalytic activity of human CYP3A4 and CYP3A5,<sup>94,95</sup> co-administered anticonvulsant medication needs to be monitored and adjusted on a regular basis.

### Movement disorders

Given the location of cannabis receptors in the CNS, the scientific rationale for the use of MM to alleviate the symptoms associated with movement disorders is perhaps not surprising. Although several disorders could be considered, the therapeutic value of MM has only been investigated in Parkinson's disease (PD) and Tourette's syndrome (TS).<sup>96</sup>

#### Parkinson's Disease

PD is the second most common neurological illness in Canada following Alzheimer's disease<sup>97</sup> and is characterized by the loss of nigrostriatal dopamine neurons leading to a tetrad of tremors, bradykinesia, rigidity, and postural instability.<sup>98</sup> Levodopa that replaces dopamine to improve motor symptoms is the current medication for PD, but fails to improve QOL, and is associated with many adverse effects such as dyskinesia.<sup>98</sup> Given the increasing evidence that suggests a prominent modulatory function of the endocannabinoids in the basal ganglia, the use of cannabinoids as a new therapeutic target has been recommended as a promising therapy for PD as well as for levodopa-induced dyskinesia.<sup>99</sup>

In a double-blind clinical trial,<sup>100</sup> PD patients without dementia or comorbid psychiatric conditions were assigned to one of three groups: placebo, CBD 75 mg/day, and CBD 300 mg/day. There were no statistically significant differences in motor symptoms, neuroprotective effects, or magnetic resonance spectroscopy measures between the three groups; however, the 300 mg/day CBD group had a significantly different mean total score in well-being and QOL ( $P=0.05$ ) compared to placebo, suggesting a possible effect of CBD in improving QOL in PD patients. In two open-label observational studies<sup>101,102</sup>, PD patients demonstrated statistically significant improvements in their United Parkinson's Disease Rating Scale ( $P<0.001$ ), tremor ( $P<0.001$ ), rigidity ( $P=0.004$ ), and bradykinesia ( $P<0.001$ ). They also demonstrated significant improvement in their sleep and pain scores just 30 minutes after smoking cannabis. Moreover, a case-series study that treated four PD patients suffering from "random eye movement" sleep behavior disorder (RBD) with 75–300 mg/day of CBD found that patients had a prompt and substantial reduction in the frequency of RBD-related events without side effects.<sup>103</sup>

More extensive, controlled, randomized, and blinded clinical trials are required to better assess the role of cannabinoids in the treatment of PD and levodopa-associated dyskinesia, as small sample size and variability in study design limit our ability to draw definitive conclusions. Additional research is required to determine whether subsets of individuals with various neurological and psychiatric diseases derive the same therapeutic benefits from cannabis. However, these studies collectively demonstrate that marijuana plays a role in improving QOL measures in PD, with further studies being required to elucidate the exact effects/mechanisms of action.

#### Tourette's Syndrome

TS is a common neurobehavioral disorder characterized by multiple motor and phonic tics, generally starting in childhood.<sup>104</sup> There are a substantial number of TS patients who are unsatisfied with the current treatment strategies due to either minimal efficacy or significant adverse effects.<sup>105</sup> Moreover, there is a lack of medications effective against both behavioral disorders and the tics associated with TS, resulting in many TS patients seeking alternative or complementary treatments including special diets, nutritional supplements, and drugs such as nicotine, alcohol, and *C. sativa* to alleviate their symptoms.<sup>106</sup> Therefore, it is exceedingly important for physicians to understand the efficacy of MM when advising patients on alternate treatment options.

According to Health Canada,<sup>18</sup> anecdotal and case reports have suggested an improvement in symptoms associated with TS when smoking cannabis. The Health Canada document also cites two small RCTs that assessed the effects of short duration. To our knowledge since then, there have been no recent clinical trials that study the role of MM in TS except for two case reports, both investigating the role of Sativex® in the treatment of TS. In the first study,<sup>107</sup> the patient received 10.8 mg THS and 10 mg CBD daily, in the form of two oromucosal sprays of Sativex®, twice daily. In the second case report,<sup>108</sup> the patient started on at a dose of 1 puff per day and slowly increased up to a dosage of 3×3 puffs per day. Both the studies demonstrated a significant reduction in motor and vocal tic severity and frequency following MM treatment. Moreover, the second case report showed a substantial improvement in the QOL associated with MM treatment. More extensive clinical trials studying the effects of MM on alleviating TS symptoms are required for physicians to comfortably decide whether the use of MM would be an appropriate alternative option.



### GI disorders

The endocannabinoid system is vastly integrated within the GI tract, particularly within the enteric nervous system.<sup>109</sup> A high expression of CB1 on epithelial cells, submucosal neurons, and myenteric neurons and elevated expression of CB2 on immune cells within the GI tract suggest that there is a therapeutic rationale for MM use as treatment options for patients with GI disorders.<sup>110,111</sup>

### Inflammatory bowel disease

Inflammatory bowel disease (IBD) includes Crohn's disease (CD) and Ulcerative Colitis (UC), causing inflammation of the bowel.<sup>112</sup> Significant morbidity occurs in IBD patients whose symptoms are uncontrolled by conventional therapies. Trials reported in Health Canada's document demonstrated that cannabinoids might attenuate intestinal inflammation and symptoms of IBD in animal models through the activation of cannabinoid receptors in the GI tract.<sup>4</sup> Although cannabis could be used in the treatment of refractory IBD, clinical data did not show a strong association between cannabis and symptom relief in IBD patients.

A significant portion of self-medicating IBD patients found cannabinoids helpful for symptoms such as abdominal pain,<sup>113–115</sup> poor appetite,<sup>113,114</sup> nausea,<sup>113,114</sup> diarrhea,<sup>113–115</sup> and joint pain.<sup>115</sup> It was also found that CD patients were more likely to be cannabis users compared to those with UC and IC.<sup>114</sup> RCT set out to examine the therapeutic effects of smoked cannabis,<sup>116</sup> and the effects of CBD in treatment-refractory CD,<sup>116</sup> as defined by the Crohn Disease Activity Index score.<sup>117</sup> While these reports initially demonstrated that THC was involved, the role of CBD was unclear. Furthermore, anecdotal data focused on the positive effects of cannabis use in the treatment of IBD, making it challenging to conclude the therapeutic efficacy of such compounds as treatment options. Due to the small sample sizes and the short course marked differences in the dose administered (115 mg  $\Delta^9$ -THC/negligible CBD and 10 mg CBD twice a day, respectively), there remains a lack of reliable clinical evidence to support the use of MM in the treatment of IBD. A concerning finding was the correlation between long-term cannabis use and increased rate of surgical procedures in IBD patients,<sup>115</sup> with cannabis use potentially masking disease activity leading to worsened disease outcomes. Future studies should focus on more substantial double-blinded RCTs to assess the efficiency and safety of MM treatment in IBD patients, focusing on optimal routes of administration and dosing.

### Anorexia

Anorexia is often associated with a variety of chronic illnesses such as Anorexia Nervosa (AN), HIV infection, and cancer.<sup>118</sup> Health Canada's 2013 document reported several promising findings on the use of MM as an alternative agent for patients presenting with anorexia as a result of HIV infection. Specifically, patients with HIV who were administered non-dronabinol were reported to have a statistically significant increase in caloric intake compared to placebo, particularly in patients with substantial cachexia.<sup>119</sup> Furthermore, most public anorexia trials published in the Health Canada document,<sup>4</sup> as well as one of two new trials we found published since,<sup>120</sup> have used dronabinol, a synthetic  $\Delta^9$ -THC compound that is no longer available in Canada. Theoretically, dronabinol studies may be applied to other forms of THC; however, the dosing, side effects, long- and short-term safety, and comparative efficacy against placebo or other appetite stimulants may differ among different formulations.

Since the Health Canada document, there have been only two ongoing trials using cannabinoids in anorexia, both in the context of cancer. A pilot study out of Israel is currently analyzing the use of "Cannabis Capsules" (THC extract) for cancer-related anorexia.<sup>121</sup> The second trial, a randomized double-blinded study in Mexico, is looking at the effect of nabilone as an appetite stimulant in terminal lung-cancer patients.<sup>122</sup> Both the trials may have future utility as they offer alternatives to dronabinol and new evidence in a cancer population. However, despite the potential of MM as a therapeutic option, the fact remains that there is little-to-no clinical trial evidence guiding the use of non-dronabinol cannabinoids in anorexia. For future trials, we suggest the use of available THC sources and incorporate cannabis naïve populations or use comparison against other appetite stimulants as opposed to placebo. With these tenets in mind, evidence can guide the use of cannabinoids in anorexia and potentially improve patient outcomes.

### Nausea and vomiting

According to the Health Canada document, nabilone, dronabinol, and levonantradol perform significantly better than placebo and slightly better than conventional dopamine D2-receptor antagonist anti-emetics in suppressing chemotherapy-induced nausea and vomiting (CINV).<sup>4</sup> Ondansetron and dronabinol provided same relief of CINV, but there was no additive benefit.<sup>4</sup> The  $\Delta^9$ -THC capsule had an equivalent effect to smoked cannabis. Although cannabinoids were

associated with higher incidence of adverse events such as dizziness, dysphoria, euphoria, and sedation, some participants expressed a preference for cannabinoids over other antiemetics. There is still limited information on the relative efficacy of cannabinoids over the newer antiemetics such as 5-HT<sub>3</sub> (ondansetron and granisetron) or neurokinin-1 receptor antagonists.

Two placebo-controlled trials on the effect of cannabinoids on postoperative nausea and vomiting were identified. Participants have been pretreated with 0.5 mg nabilone before surgery,<sup>123</sup> or administered 0.125 mg/kg THC intravenously at the end of surgery.<sup>124</sup> There was no significant difference in nausea and vomiting reduction between cannabinoids and placebo groups in both the trials, and clinically relevant psychotropic THC side effects such as sedation and confusion that were deemed unacceptable were reported.<sup>124</sup> Therefore, while chemotherapy patients should be aware of cannabinoids as an alternative treatment of CINV, the side effects have been deemed unacceptable in the outpatient and acute settings.

#### Pain

The endocannabinoid system is a critical endogenous pain control system<sup>27,125</sup>, as such, the targeting of this system with cannabis may provide a therapeutic advantage in the treatment of pain.<sup>125</sup> This system is present throughout several pain pathways, with cannabinoid receptor agonists demonstrating antinociceptive effects in animal models of acute, inflammatory, and neuropathic pain. The modulation of pain is thought to be due to inhibition of presynaptic neurotransmitter release and modulation of postsynaptic excitability.<sup>39,126</sup>

#### Acute pain

The Health Canada document presented mixed results in the efficacy of cannabinoids in acute, experimentally induced pain.<sup>4</sup> The variety of administration modes, such as nabiximol, smoked cannabis, and oral THC, as well as small sample sizes may explain this inconsistent result.<sup>4</sup> Since 2013, there has been one randomized, placebo-controlled, double-blind clinical trial on this subject, finding that smoked marijuana and dronabinol decreased pain sensitivity (3.56% THC, 20 mg, respectively) and increased pain tolerance (1.98% THC, 20 mg, respectively) when compared against placebo.<sup>127</sup> However, the small sample size (N=30), exclusion of naïve users, including only THC content, and use of dronabinol necessitate further research before commenting on the efficacy of cannabis in the treatment of acute pain.

#### Chronic neuropathic pain

Neuropathic pain is a complex, chronic pain state that affects over 2 million Canadians,<sup>128,129</sup> with half of the sufferers failing to achieve adequate relief.<sup>130,131</sup> In 2015, the Canadian Pain Society updated their guidelines for the management of neuropathic pain moving cannabis from the fourth- to a third-line medication.<sup>132</sup> In recognition of the growing body of evidence, the 2013 Health Canada document also indicated that the addition of cannabinoid medications to conventional therapy was a moderately active short-term treatment of neuropathic pain.<sup>4</sup> However, additional research needs to be done examining modes of administration further to inhalation, as well as the use of non-dronabinol to maintain consistency with currently available medications.

Since the publication of the document, 10 relevant studies were published about cannabinoids in neuropathic pain (see [Table S3](#) for a detailed summary of trial data).<sup>130,131,133-140</sup> These studies addressed several gaps present in the Health Canada document including examining both THC<sup>131,136-138,140</sup> and THC/CBD blends at various concentrations and routes of administration,<sup>130,135,139</sup> such as oral tablets,<sup>137,138</sup> oromucosal spray,<sup>130,135,139</sup> vaporizing,<sup>131,136</sup> and metered-dose inhaler.<sup>140</sup> Specifically, two studies examined the mode of action of cannabinoids in neuropathic pain by using functional magnetic resonance imaging (fMRI), demonstrating that THC may act on the active qualities of chronic pain by reducing sensory limbic functional connectivity between the amygdala and the primary somatosensory cortex.<sup>133,134</sup> Also, three long-term trials demonstrated long-term efficacy, safety, and tolerability.<sup>130,138,139</sup> Lastly, in the remaining eight studies, six studies were blinded, randomized-controlled trials<sup>130,131,135-138</sup> and two were open-label trials,<sup>139,140</sup> all of which had differing experimental designs. They unanimously demonstrated statistical significance in at least one or more measurements of neuropathic pain, including some responders with 30% reduction in pain, visual analog scale, and (NRS).<sup>130,131,135-140</sup> These data have strengthened the evidence for the use of cannabinoids as adjuvant therapy in chronic neuropathic pain; however, gaps remain that need to be addressed in future research, such as the use of other cannabinoids, terpenes, and additional investigations regarding modes of administration. Nonetheless, these gaps should not prevent health care professionals from using marijuana and its analogs to combat neuropathic pain.

#### Chronic non-cancer-related pain

Health Canada initially grouped chronic non-cancer pain with neuropathic pain; however, we believe that chronic



non-cancer pain best fits into its category. Four trials found that causes of pain included functional chest pain,<sup>141</sup> chronic pancreatitis-related pain,<sup>142</sup> chronic abdominal pain,<sup>143</sup> and unspecified chronic non-cancer pain.<sup>144</sup> Each trial examined a different cause of pain, and the results were inconsistent with the neuropathic pain trials regarding efficacy. This contradiction of the findings creates a need for each case to be examined individually to determine the effectiveness and is the main reason for the separation of the data from the neuropathic pain section. The results of each trial have been summarized and included in [Table S3](#).

#### Cancer-related pain

In Canada, it is estimated that in 2017 there will be over 200,000 newly diagnosed cancer patients.<sup>145</sup> Because pain is the most commonly experienced symptom by cancer patients,<sup>146</sup> Health Canada reviewed the therapeutic efficacy of dronabinol and nabiximols in the management of cancer-related pain and found them to be efficacious in providing relief, although not all results were statistically significant.<sup>4</sup> However, trials with larger sample sizes investigating alternative modes of administration of cannabinoids are required to comment on the efficacy of cannabis in cancer conclusively.

Since 2013, three studies have been published regarding cannabis use in cancer pain. An observational study demonstrated that 70% of patients who were prescribed marijuana for pain management reported subjective improvement in their pain control.<sup>5</sup> Similarly, an open-label extension study on the long-term efficacy and safety of Sativex spray reported a decrease from the mean baseline pain of 0.63 ( $P=0.014$ ) in THC/CBD spray group versus placebo.<sup>147</sup> To further confirm these results, an extension of this study demonstrated a decrease in mean Brief Pain Inventory Short Form (BPI-SF) scores for pain, severity, worst pain, and pain interference domains with the THC/CBD spray.<sup>147</sup> Unfortunately, this study had a significant dropout rate (42/43 patients), with almost half citing adverse events as the reason for leaving the study, suggesting that the harmful effects may outweigh the benefits of cannabinoid use in cancer.<sup>147</sup> Finally, a blinded RCT study examining nabilone in head and neck cancers determined that there was no difference in pain between intervention and placebo groups ( $P=0.6048$ ) and that nabilone did not alter the time required for progression of illness by 20% ( $P=0.46$ ).<sup>148</sup>

The study results, excluding the observational questionnaire, are in contrast to the trials analyzed in the Health Canada document and may be attributed to small sample

sizes and significant dropout rates. Given the quality of the evidence reviewed, it can be concluded that these studies have not significantly added to the current knowledge on treatment of pain in cancer, and thus more research will be needed to clarify this. Future blinded RCT studies on the role of cannabis in the treatment of cancer pain should include examining a variety of modes of administration in large patient populations and examining both short-term and long-term efficacy and safety profiles of cannabis products.

#### Headaches

Since the Health Canada review, many survey studies,<sup>149–152</sup> and a chart review<sup>153</sup> have studied the therapeutic efficacy of MM in the treatment of headaches, however only one controlled clinical trial was conducted.<sup>154</sup> In this trial, nabilone (0.5 mg) was used in a randomized, double-blind, crossover design against ibuprofen (400 mg) in 30 patients with a medication-overuse headache (MOH) and daily analgesic intake. Primary outcome measures included headache frequency, daily analgesic intake, pain intensity and duration, level of dependence, and pain-free days. While both the drugs resulted in statistically significant improvement in all primary outcomes, nabilone was superior to ibuprofen (greater effect size) in all parameters. In addition, subgroup analyses showed that patients who received ibuprofen in the second half of the study (crossing over from nabilone) did not demonstrate ibuprofen-associated improvements seen in the overall data. Furthermore, these patients did not experience continued improvement 2 weeks following the study endpoint, unlike patients who received nabilone following treatment with ibuprofen. This methodologically sound study makes a compelling case for the efficacy of nabilone compared to ibuprofen in the MOH population but is limited by a small sample size, patient dropout (four of 30 patients), missing controls for cannabis-experienced or naïve patients, and a lack of a psychoactive placebo (affecting patient blinding). However, given the subjective nature of pain, the psychoactive effects of cannabinoids may be considered a new part of the therapeutic profile of cannabis if they affect the perception of pain.

#### Special considerations

Although there are some promising therapeutic applications of MM in the treatment of several conditions outlined above, a thorough understanding of patient history and specific patient subpopulations presenting with other states should be considered. These contradictions are outlined in detail below.



### Mental health

According to the 2013 Health Canada report,<sup>4</sup> there was a dose–response relationship between cannabis use and the risk of psychotic disorders. Early exposure and greater use were linked to initial symptom onset, particularly in those predisposed to mental illness. Furthermore, cannabis use after the first psychotic episode or schizophrenia diagnosis was associated with weak prognostic features, such as multiple relapses and worse symptoms.

Since the Health Canada report, literature has confirmed a dose-dependent relationship between cannabis use and the risk of psychotic disorders.<sup>155–157</sup> Early exposure (ie, before the age of 15 years<sup>158,159</sup> or during adolescence<sup>160</sup>), greater use,<sup>158–160</sup> and escalation to daily use<sup>160</sup> have all been linked to an earlier initial psychotic episode relative to nonusers. Specifically, patients with a history of cannabis use experienced their first psychotic episode from 2.6<sup>161</sup> to 2.9 years earlier than nonusers.<sup>162</sup> This information is particularly relevant for individuals at a higher risk for psychiatric illness, with predictive factors for conversion to psychotic disorders including psychotic features with cannabis use,<sup>159</sup> high potency cannabis, and high frequency of use.<sup>158,163</sup> Furthermore, studies on the effects of other substances in attenuating the relationship between cannabis use and mental health outcomes seem to be insignificant.<sup>164,165</sup> In addition, these materials were not significant predictors of psychosis onset,<sup>158,159,163</sup> which could be due to the relatively low rate of other substance abuse.

### Schizophrenia

Patients with schizophrenia have been found to be ~10 times more likely to use cannabis than the general population.<sup>166,167</sup> For schizophrenia, there is early evidence that CBD may be a helpful treatment, while THC seems to worsen psychosis. Eight recent correlational studies not included in Health Canada Report investigated the effects of marijuana on schizophrenia severity, including positive and negative symptoms and level of function. However, it is noteworthy to mention that these studies are meant to provide information on patients with psychosis who use recreational cannabis and are not treatment studies. Across all reviewed studies, cannabis use had no significant effect on negative symptoms based on the Positive and Negative Syndrome Scale (PANSS).<sup>157,168–174</sup> Some studies reported an increased prevalence of positive symptoms with cannabis use (PANSS-P),<sup>157,172,173</sup> while others reported no significant effect.<sup>168–171</sup> In a meta-analysis, history of or current cannabis use had a moderate effect on positive symptoms when compared to cannabis naïve participants.<sup>174</sup>

However, due to the high heterogeneity between the included studies, we advise interpreting results with caution.

Lastly, there was no significant difference between cannabis users and nonusers in the ability to adapt to various problems-in-living, based on the Global Assessment of Functioning (GAF) scale.<sup>157,169–173</sup> It is possible that an upper limit on the safe quantity of cannabis exists after which GAF declines. During a follow-up period, a change in cannabis use, whether escalation or de-escalation, exhibited a reverse relationship with GAF.<sup>157,170,171</sup> The change indicates that the effects of cannabis were reversible and corresponded to the amount used. As an alternative, there could have been confounding variables that were not accountable. Overall, these findings imply that not all people are affected equally by cannabis and that physicians should advocate against heavy and early cannabis use.

### Treatment adherence

The majority of studies did not control for treatment adherence, which is an important confounding variable, as current cannabis users are less likely to adhere to psychiatric medical therapy than nonusers and former users by a factor of 4.8 and 4.5, respectively.<sup>175</sup> High potency (defined as a high ratio of THC:CBD), cannabis being particularly noxious, is a statistically better predictor of nonadherence than low potency or infrequent use.<sup>176</sup> Nonadherence to medical treatment is a significant risk for clinical and psychosocial remission.<sup>177</sup> Nonadherence can also partially confound the effect of cannabis use on the risk of relapse, some relapses, time until relapse, and care intensity.<sup>178</sup> Future studies need to control for a wide array of confounding variables including treatment adherence, other substance use, and baseline differences.

### Cognition

People with psychotic illness develop a more significant decline in their cognitive abilities relative to other mood disorders.<sup>179</sup> We identified seven recent articles that addressed the relationship between cannabis use and cognitive skills in psychotic illness. Only one study detected a diminished cognitive performance in social cognition with a long-term cannabis use.<sup>180</sup> However, other cognitive domains were unaffected. After controlling for confounders, such as age, the age of illness onset, socioeconomic status, premorbid IQ, the effect of cannabis on cognitive function was not significant based on The Digit Symbol Coding Test.<sup>181,182</sup> Paradoxically, some studies report that cannabis use was associated with small but statistically significant improvement in global

cognitive index,<sup>183,184</sup> attention and psychomotor speed,<sup>184</sup> verbal learning and memory,<sup>184</sup> processing speed,<sup>183</sup> executive function,<sup>183</sup> working memory,<sup>183</sup> and visual memory.<sup>183</sup> A reverse association was detected in control populations without psychiatric illness. It is possible that the disease itself exerts a stronger effect on cognitive performance than cannabis. Alternatively, a subpopulation of patients who uses marijuana could be functioning better relative to nonusers. This could explain that abstinence from cannabis resulted in statistically significant improvement in memory and learning.<sup>185,186</sup> Cannabis users could also develop compensatory mechanisms. Based on the functional imaging studies between healthy cannabis users and nonusers, despite no difference in cognitive performance, cannabis users exhibited slightly different brain activity relative to nonusers, which was described as a “compensatory” effort.<sup>187</sup> Overall, there is no convincing evidence due to cannabis use for a diminished cognitive performance in patients with psychiatric illness.

Physicians should strongly advise against daily or high potency cannabis use, early onset of use, and any use if it is associated with subthreshold psychotic features to prevent future psychiatric complications. However, evidence around cannabis use during mental illness is conflicting. Currently, there is no evidence of active adverse effects for cannabis use, except for moderate exacerbation of positive symptoms, reversible effects on global function, and some cognitive domains. Additional longitudinal research is needed to examine various levels of cannabis use on psychiatric symptoms and cognitive function with better control for confounding variables.

#### Post-Traumatic Stress Disorder

PTSD can have a variety of triggers that affect multiple populations that are encountered within primary care, such as veterans and sexual assault victims.<sup>188</sup> Despite this, there has been limited research into the management of treatment-refractory PTSD.<sup>189</sup> Within Health Canada’s document, only one pilot study on PTSD was covered, showing a positive effect of nabilone on helping with PTSD-associated nightmares.<sup>190</sup> Of the patients with treatment-refractory nightmares, 60% reported a total cessation of nightmares, 13% reported a “satisfactory reduction” of nightmares, and 28% withdrew the study due to adverse events.

Since Health Canada’s review, we identified two studies exploring the effects of cannabis on PTSD-associated nightmares. A recent open-label pilot study administering 5 mg THC in oil daily for 3 weeks showed a reduction in nightmare frequency.<sup>191</sup> The blinded placebo-controlled trial conducted

by the Canadian Forces randomized patients with PTSD to 7 weeks of placebo or nabilone in a crossover design with a 2-week washout period between regimens.<sup>192</sup> The nabilone group had significantly less frequent and intense distressing dreams compared to placebo ( $P=0.03$ ). For these studies, the cognitive effects (acute or chronic) associated with cannabinoid use should be examined carefully in patients with cognitively demanding occupations such as active military duty, as PTSD is highly prevalent in this population. Currently, there are multiple ongoing trials, including two in Canada,<sup>193,194</sup> which investigate smoked, vaporized, and ingested cannabis for use in PTSD which would help address the gaps in current knowledge and solidify the evidence for or against the use of marijuana in PTSD.

#### Cannabis and pregnancy

Cannabinoid receptors have been detected in the placenta,<sup>195</sup> and some cannabinoids, such as THC, can cross the placenta,<sup>196,197</sup> accumulating in breast milk.<sup>198</sup> Concerns are raised about potential adverse effects of cannabinoid exposure on fetal development. According to the 2013 Health Canada report, the short-term effects of cannabis on neonatal outcomes were inconsistent, with some studies reporting reduced birth weight and length,<sup>199–201</sup> as well as a non-statistically significant trends toward sudden death,<sup>202</sup> while others reported no effect.<sup>203–205</sup> Long-term effects included poor attention, visual analysis, and executive function but no IQ changes.<sup>206,207</sup> Exposure to cannabis in breast milk also transiently hindered motor development at 1 year of age.<sup>208</sup>

Smoking marijuana during pregnancy had no direct effect on maternal health, labor complications, or postnatal problems; however, increased maternal anemia was reported.<sup>209</sup> It is possible that this finding is secondary to a confounding variable or type I error. Cannabis users are more likely to be single,<sup>210,211</sup> have a low income,<sup>211</sup> or be unemployed,<sup>212</sup> which may predispose infants toward nutritional deficiency. It is possible that cannabis use during pregnancy has an equivalent effect on maternal health as on any other adult user. However, according to various reports, marijuana use during pregnancy falls between 3.1% to 29.6%,<sup>213</sup> thus sufficiently powered, and well-controlled matched cohort studies are warranted to identify adverse effects on maternal health.

Furthermore, maternal cannabis consumption was associated with a 109.42 g reduction in newborn birth weight.<sup>209</sup> However, that decline is not clinically significant and is not associated with a statistically significant increase in the risk of developing teratogenic effects, fetal deformities, fetal distress, fetal demise, or abnormal lab values among cannabis



users.<sup>209,214</sup> However, neonatal intensive care unit/intensive care unit (NICU/ICU) admissions significantly increased from 54% to 102% for newborns exposed to cannabis as compared to nonusers.<sup>209,214</sup> Torri et al<sup>213</sup> reported a significant cumulative effect on morbidity and mortality for newborns of marijuana smokers, particularly in infection-related morbidity, such as sepsis, pneumonia, or bacterial meningitis, and neurological morbidity. However, the study is not sufficient to detect individual risks as it comprises only 48 marijuana users compared to 1562 nonusers. Large-scale trials, with sufficient power, are required to identify the underlying cause of NICU/ICU admissions and cumulative morbidity.

We could not identify any recent research on the effect of cannabis use on breastfeeding or long-term outcomes since the 2013 Health Canada report. Such research is challenging due to the extended follow-up period needed and the presence of many confounding variables, such as parental cannabis use, socioeconomic status, family dynamic, and neighborhood influence. Although studies have reported no or transient effects of early cannabinoids exposure on growth,<sup>215</sup> motor,<sup>216–218</sup> and cognitive development,<sup>216–219</sup> these earlier findings have limited applications today, given that new cannabis strains are more potent than before.<sup>220</sup>

Since cannabis use during pregnancy has a noticeable effect on early childhood morbidity, physicians should strongly advise against its recreational use during pregnancy. Pregnant women refusing or incapable of stopping cannabis use should be encouraged to obtain cannabis from approved sources where the exact amount of marijuana used can be monitored. Such information could be used in future research to quantify better cannabinoids consumed and identify dose-dependent outcomes. The new study should also consider various routes of cannabis administration, whether edible, smoked, or vaporized, and control confounding variables such as maternal health and socioeconomic status.

#### Cannabis and opioids

The widespread abuse of opioids has led to a spike in opioid-related death to 8.8 per 100,000 in Canada.<sup>221</sup> The increased prescribing practices of these drugs and the introduction of highly addictive, potent synthetics such as fentanyl may be attributed to the rampant spread of this epidemic. Methadone, buprenorphine, and naltrexone are the only three US Food and Drug Administration-approved drugs for long-term treatment of opiate addiction.<sup>222</sup> Several studies have hypothesized the potential use of cannabis for the treatment of opioid addiction; however, results from studies conducted on these proposed uses have shown conflicting results. Can-

nabis smoking during a methadone taper demonstrated no evidence for cannabis smoking reducing opioid-withdrawal symptoms ( $P=0.52$ ).<sup>223</sup> Although smoked cannabis was not shown to be successful in reducing opioid withdrawal symptoms, it is yet to be seen if isolated cannabinoids such as CBD or different concentrations of cannabinoids have a role in opioid withdrawal. CBD may play a role due to its anti-anxiety effect,<sup>224</sup> curbing the extreme anxiety associated with opioid withdrawal.<sup>225</sup>

#### Additional considerations

First, it is essential to remark that a single dose of  $\Delta^9$ -THC in chronic smokers can be detected up to 13 days following intake,<sup>226</sup> while in others, 80%–90% of a total  $\Delta^9$ -THC dose will be excreted within 5 days.<sup>227</sup> Additional evidence has shown that both  $\Delta^9$ -THC and 11-OH-THC (an active  $\Delta^9$ -THC metabolite) can be detected in circulation for up to 1 month after intake, causing neurocognitive impairment in the first weeks of abstinence.<sup>228</sup>

Second, it has been shown that cannabinoids can cause increased glucose intake and lipogenesis.<sup>229</sup> Therefore, if authorizing the use of medicinal cannabis for obese diabetic patients who are receiving insulin injections, the effects of MM on blood glucose levels and the patients' response to their current treatment regimen should be examined with these underlying impacts in mind, particularly when considering a change in treatment or dose.

#### Cannabis abuse

Tolerance to THC is theorized to be due to downregulation and desensitization of CB1<sup>230,231</sup> and has been documented in heavy and therapeutic users, but not in social users.<sup>232,233</sup> Physical and psychological dependence also occurs with heavy usage.<sup>234,235</sup> However, according to National Epidemiological Survey on Alcohol and Related Conditions, the rate of transition to dependence for cannabis is 8.9%, which is small percentage relatively to 22.7% and 67.5% for alcohol and nicotine, respectively.<sup>236</sup> Moreover, the withdrawal symptoms of marijuana are milder than other drugs,<sup>231</sup> such as alcohol, cocaine, heroin, and include anger, depressed mood, irritability, anxiety, restlessness, insomnia, strange dreams, weight loss, and decreased appetite.<sup>40</sup> The delayed onset of withdrawal due to THC's relatively long half-life and relative mildness of symptoms compared to other substances contributes to apprehensions of its clinical implications.<sup>231,237</sup>

A few studies examined agonist therapy with synthetic cannabinoids to attenuate withdrawal symptoms and promote cannabis use cessation. In the placebo-controlled trial,

dronabinol suppressed cannabis withdrawal symptoms in a dose-dependent manner based on the withdrawal discomfort score ( $P < 0.05$ ).<sup>238</sup> Another study using nabiximols significantly attenuated withdrawal symptoms relative to placebo ( $P = 0.01$ ) but did not have a better effect than placebo on a complete cessation of cannabis use ( $P = 0.75$ ).<sup>239</sup> A similar study using Sativex was found to reduce withdrawal symptoms ( $P < 0.01$ ) with high fixed doses but was also unable to demonstrate long-term cessation.<sup>240</sup> The attenuation of withdrawal could be due to the tapering off effect created by supplementing cannabis with synthetic cannabinoids. However, because opioids and cannabinoids have been shown to interact synergistically with each other, if a patient is prescribed both opioid and cannabis, care providers should know that opioid may need to be reduced to avoid dependency.<sup>241</sup> Further research needs to be done on the amount and THC/CBD ratio of cannabinoids necessary to safely taper withdrawal.

Other studies investigated vilazodone,<sup>242</sup> escitalopram,<sup>243</sup> buspirone,<sup>244</sup> lithium carbonate,<sup>245</sup> and a combination of lofexidine and dronabinol,<sup>246</sup> to treat cannabis dependence, but none showed any significant results. Only gabapentin significantly reduced the amount of marijuana smoked per week based on patient self-report ( $P = 0.004$ ) and the biochemical urine analysis ( $P = 0.001$ ).<sup>247</sup> However, gabapentin also carries abuse potential.<sup>248–250</sup> The addiction potential of cannabis is a concern to clinicians and should be discussed with patients. The risk of addiction must be weighed against the benefit on a case-by-case basis. Currently, an accepted pharmacological treatment for cannabis-use disorders does not exist.

## Conclusion

In summary, the effect of cannabis has been intensely studied in several disease states, as previously discussed; however, gaps in our knowledge remain. Although recent research has advanced our understanding from the release of the 2013 Health Canada document, there is a need for additional research that addresses different modes of administration, controlling for cannabis users and cannabis naïve individuals, as well as for other contraindications. Bearing this in mind, our current knowledge on cannabis use suggests that cannabis presents as an appropriate alternative therapy option for patients who have epilepsy, movement disorders, and pain. For individuals with MS, GI disorders, anorexia, and headaches, further research is recommended to improve our understanding of the effects of MM, and caution is advised when considering the authorization of MM use. For patients

who are under the age of 25 years, pregnant, or present with a history of mental health and substance use, it is safe to err on the side of caution and avoid MM authorization. Overall, MM is an exciting field of exploration, and the diverse range of receptor expression in the human body offers many therapeutic benefits, yet additional research is required for a more robust understanding and characterization of the mechanism of action of MM to achieve maximal therapeutic efficacy.

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## Data sharing statement

The data sets supporting the conclusions of this article are included within the article and in the supplementary material.

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## Author contributions

MRS conceived the review of the article and obtained funding; YM, AV, BQ, MS, SMSF, CN, AL, and UB designed the study, carried out the searches, refined the study design, selected studies and extracted data, and conducted the thematic analyses; YM, AV, BQ, MS, and MRS led the writing of the draft manuscript as contributing first authorship. All Authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

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## **Attachment 8 Cannabis: the facts**

Cannabis: the facts <https://www.nhs.uk/live-well/healthy-body/cannabis-the-facts/>

Cannabis (also known as marijuana, weed, pot, dope or grass) is the most widely used illegal drug in the UK.

The effects of cannabis vary from person to person:

you may feel chilled out, relaxed and happy

some people get the giggles or become more talkative

hunger pangs ("the munchies") are common

colours may look more intense and music may sound better

time may feel like it's slowing down

Cannabis can have other effects too:

if you're not used to it, you may feel faint or sick

it can make you sleepy and lethargic

it can affect your memory

it makes some people feel confused, anxious or paranoid, and some

experience panic attacks and hallucinations – this is more common with stronger forms of cannabis like skunk or sinsemilla

it interferes with your ability to drive safely

If you use cannabis regularly, it can make you demotivated and uninterested in other things going on in your life, such as education or work.

Long-term use can affect your ability to learn and concentrate.

Can you get addicted to cannabis?

Research shows that 10% of regular cannabis users become dependent on it. Your risk of getting addicted is higher if you start using it in your teens or use it every day.

As with other addictive drugs, such as cocaine and heroin, you can develop a tolerance to cannabis. This means you need more to get the same effect.

If you stop using it, you may get withdrawal symptoms, such as cravings, difficulty sleeping, mood swings, irritability and restlessness.

If you smoke cannabis with tobacco, you're likely to get addicted to nicotine and risk getting tobacco-related diseases such as cancer and coronary heart disease.

If you cut down or give up, you will experience withdrawal from nicotine as well as cannabis.

See tips for stopping smoking.

### Cannabis and mental health

Regular cannabis use increases your risk of developing a psychotic illness, such as schizophrenia. A psychotic illness is one where you have hallucinations (seeing things that are not really there) and delusions (believing things that are not really true).

Your risk of developing a psychotic illness is higher if:

you start using cannabis at a young age

## Attachments

you smoke stronger types, such as skunk

you smoke it regularly

you use it for a long time

you smoke cannabis and also have other risk factors for schizophrenia, such as a family history of the illness

Cannabis also increases the risk of a relapse in people who already have schizophrenia, and it can make psychotic symptoms worse.

## Other risks of cannabis

Cannabis can be harmful to your lungs

People who smoke cannabis regularly are more likely to have bronchitis (where the lining of your lungs gets irritated and inflamed).

Like tobacco smoke, cannabis smoke contains cancer-causing chemicals, but it's not clear whether this raises your risk of cancer.

If you mix cannabis with tobacco to smoke it, you risk getting tobacco-related lung diseases, such as lung cancer and chronic obstructive pulmonary disease (COPD).

You're more likely to be injured in a road traffic accident

If you drive while under the influence of cannabis, you're more likely to be involved in an accident. This is one reason why drug driving, like drink driving, is illegal.

Cannabis may affect your fertility

Research in animals suggests that cannabis can interfere with sperm production in males and ovulation in females.

If you're pregnant, cannabis may harm your unborn baby

Research suggests that using cannabis regularly during pregnancy could affect your baby's brain development.

Regularly smoking cannabis with tobacco increases the risk of your baby being born small or premature.

Cannabis increases your risk of cardiovascular disease and stroke

If you smoke it regularly for a long time, cannabis raises your chances of developing these conditions.

Research suggests it's the cannabis smoke that increases the risk, not the active ingredients in the plant itself.

Does my age affect my risks?

Your risk of harm from cannabis, including the risk of schizophrenia, is higher if you start using it regularly in your teens.

One reason for this is that, during the teenage years, your brain is still growing and forming its connections, and cannabis interferes with this process.

Does cannabis have medicinal benefits?

Cannabis contains active ingredients called cannabinoids. Two of these – tetrahydrocannabinol (THC) and cannabidiol (CBD) – are the active ingredients of a prescription drug called Sativex. This is used to relieve the pain of muscle spasms in multiple sclerosis.



## Attachments

Another cannabinoid drug, called Nabilone, is sometimes used to relieve sickness in people having chemotherapy for cancer.

Trials are under way to test cannabis-based drugs for other conditions including cancer pain, the eye disease glaucoma, appetite loss in people with HIV or AIDS, and epilepsy in children.

We will not know whether these treatments are effective until the trials have finished.

**Article : ICESCR 13**

**Topic : CDC, please don't use parents' money to harm kids- so called "gender-equal clubs" are wolves in sheep clothing (NO Attachment)**