

CANNABIS

How it affects our health

ROYAL
SOCIETY
TE APĀRANGI

WHAT IS CANNABIS?

Cannabis grows as separate male and female plants and produces a large number of bioactive compounds. The best known are THC (Tetrahydrocannabinol) that produces a 'high' when taken and CBD (cannabidiol) that doesn't but has other effects on the body.





The use of cannabis-based medicines to treat a variety of conditions, and the use of cannabis as a recreational drug, is currently of interest to both the general public and the medical community. This paper summarises the current research evidence on the health impacts of cannabis and cannabinoids to assist these communities in considering the opportunities and risks associated with cannabis use.

He tuhinga whakarāpopoto

SUMMARY

- There is evidence that cannabis-based medicines have some therapeutic effects in specific clinical situations such as chronic pain, chemotherapy induced nausea, muscle spasms due to multiple sclerosis, and certain types of epilepsy.
- There is evidence that recreational cannabis use is associated with negative health outcomes including mental illness (particularly in youth), drug use disorders, respiratory illness, impaired cognition, increased road accidents and lower birthweight in babies born to women exposed to cannabis.
- The wide range of research methodologies in the literature makes it difficult to come to definitive conclusions in many cases.
- There is a particular research gap in understanding the health effects of both recreational cannabis use and cannabis-based medications on specific population groups.
- The lack of evidence-based information on both the potential therapeutic effects and harms of cannabis and cannabinoids poses a public health risk.



INTRODUCTION

New Zealand, like many jurisdictions, has begun reviewing its laws on cannabis-based medicines and recreational cannabis use.

For medicinal use, New Zealand introduced an exception to the law in late 2018, which facilitates use of cannabis by those requiring palliative care. Of the two primary substances found in the cannabis plant with potential therapeutic value, medicines comprised predominantly of cannabidiol (CBD), which is not associated with euphoria, can now be prescribed for use under the Medicines Act 1981 so long as the psychoactive compound, tetrahydrocannabinol (THC), comprises no more than 2%. The medicine Sativex[®], a cannabis-based oral spray that contains both CBD and THC, can also be prescribed for multiple sclerosis sufferers who meet certain criteria, without approval from the Ministry of Health.

For recreational use, cannabis is currently a class B drug (processed cannabis) or class C drug (unprocessed cannabis) in New Zealand, indicating that it has been deemed to pose a high or moderate risk of harm to individuals, or to society, by its misuse.¹

To report on the health risks and potential benefits of medicinal and recreational cannabis, this paper draws upon a 2017 report published by the US National Academies of Sciences, Engineering and Medicine: *The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research*², as well as additional literature.

History of cannabis

Archaeological evidence points to a long association between humans and the cannabis plant.³ Its cultivation and use spread across Asia and gradually west towards Africa, Europe and the Americas.

The first written record of medicinal use of the cannabis plant comes from China, around 6,000 years ago.⁴ As Europeans expanded their exploration from Asia into Africa, interest in cannabis made its way to Europe, where medicinal use of the plant is recorded in the 19th century as a treatment for tetanus and for mental disorders. It appeared in both the British and US lists of medicines of that time, with descriptions of how to prepare the dried flowers for medicinal use. However, concerns about the plant's social use, variability in composition and short shelf life led to it being removed from the British medicine list in 1932, and the US medicine list in 1942, as its use was being replaced by opiates and new drugs with more reliable effects.²

Cannabis is currently regulated under international drug control interventions, notably the three United Nations conventions, to which New Zealand is a signatory: the 1961 Single Convention on Narcotic drugs, the 1971 Convention on Psychotropic Substances and the 1988 Convention against Illicit Trafficking of Psychotropic Substances.⁵

HOW LONG
HAVE HUMANS
USED CANNABIS
AS A MEDICINE?



Written records show cannabis was used for medicinal purposes in China as far back as 6,000 years ago.

The cannabis plant, active ingredients and the body's receptors

THE CANNABIS PLANT AND PHYTOCANNABINOIDS

The cannabis plant is a member of the Cannabaceae family, of which the other best-known member is hops, used to flavour beer. Plant products, as well as the dried plant itself, are known by many names, including marijuana, hashish, weed, pot, dabs and hash.

Cannabis grows as separate male and female plants. It produces a large number of biologically active compounds known as phytocannabinoids. To date, over 100 of these have been isolated. The two best known are THC, found in the highest concentrations on small outgrowths around the unfertilised female flower head, and CBD, which lacks the intoxicating properties of THC.^{2, 6} Through rigorous study, both THC and CBD have been identified as potential medicinal compounds for specific conditions. It is possible that other similar compounds in the cannabis plant may have other, yet to be discovered, therapeutic effects.²

Different varieties of cannabis have been bred to give differing ratios of THC to CBD, with average concentrations of THC having increased in recent decades due to intended recreational use for its psychoactive effects.⁷ The chemical composition of raw plant material varies considerably depending on growing conditions, local climate and soil types, pesticide use, harvest time, post-harvest preparation and storage conditions.⁸

THE ENDOCANNABINOID SYSTEM

The human body produces its own internal cannabinoids (endocannabinoids) that act on cannabinoid receptors in the body. These are the same receptors that are activated by THC, the primary chemical component in most cannabis plants. This endocannabinoid system is widely found in many species,⁹ and was first discovered in the 1980s, initially in rats.¹ At present, two types of cannabinoid receptors have been identified in the human body: Type-1 cannabinoid receptors (CB1) are found in high concentrations in brain areas responsible for appetite regulation, memory, fear extinction, motor responses and posture. They are also found in non-neural tissues, including the gastro-intestinal system. Type-2 receptors (CB2) are mainly associated with the body's immune system, although they can also be found in many other tissues.¹¹

THC mimics endocannabinoids by binding and partially activating the CB1 cannabinoid receptors in the brain and body, affecting various physiological and cognitive processes and leading to the characteristic 'high'. In contrast, CBD does not interact strongly with the body's cannabinoid receptors and its primary mechanism of action is still unknown. In animal and cellular studies, it appears to have antioxidant and anti-inflammatory properties, which may explain its potential neuroprotective action observed in preclinical models.¹² There is some evidence that these CBD characteristics can be exploited in the treatment and relief of a variety of neurological disorders including epilepsy and seizures,^{13, 14} psychosis,¹⁵ anxiety,¹⁶ movement disorders such as Huntington's disease^{17, 18} and multiple sclerosis,¹⁹ however clinical research has yet to provide rigorous evidence in support of these uses.

WHY DOES CANNABIS AFFECT US?



Compounds in cannabis, like THC, affect us because they interact with our own cannabinoid system. We have cannabinoid receptors in our brain and gut, in particular, and we produce cannabinoids to regulate appetite, form memories, calm fear, affect our movement and posture and regulate our immune system.



WHAT CANNABIS
-BASED MEDICINES
ARE AVAILABLE
IN NEW ZEALAND?







Medical cannabis preparations with low levels of the psychoactive compound, THC, can be prescribed for palliative care and the oral spray Sativex® can be prescribed for those with multiple sclerosis. Changes are underway, however, to allow doctors to prescribe medicinal cannabis more widely.



Medicinal cannabis

Pharmaceutical companies have already developed a number of cannabis-based medicines and pure preparations, either from phytocannabinoids found in cannabis or from synthetically prepared compounds similar to those found in the plant. Approved uses vary by jurisdictions. Only Sativex® is currently registered as an approved medicine in New Zealand, and only for the treatment of muscle spasms in multiple sclerosis; it is not currently funded, so must be purchased by patients after receiving a prescription from their specialist neurologist. The predominant medicinal products with approved uses in some other jurisdictions are summarised in Table 1, below.^{2,20}

Medicinal cannabis product	Registration details	Product description	Approved uses
 <p>NABIXIMOLS</p>	'Sativex' by GW pharmaceuticals, UK	A cannabis-derived spray administered under the tongue with THC and CBD at approximately 1:1 ratio	Used for chronic nerve pain and muscle spasms in multiple sclerosis (multiple countries, and approved by Medsafe in New Zealand only for the management of muscle spasms in multiple sclerosis); and for advanced cancer pain (Canada)
 <p>CBD</p>	'Epidiolex' by GW pharmaceuticals, UK, and 'CBD Max', produced by Tilray, Canada	Concentrated CBD in oil from cannabis extract	Used for specific severe epileptic conditions in childhood (Dravet syndrome and Lennox-Gastaut syndrome) in the US and UK
 <p>NABILONE AND DRONABINOL</p>	'Cesamet' by Meda pharmaceuticals, and 'Marinol' by Solvay pharmaceuticals US	Oral capsules containing an analogue to THC, and a synthetic THC, respectively	Used for stimulation of appetite in AIDS-related anorexia and weight loss; and for severe nausea and vomiting associated with cancer chemotherapy (US)
 <p>THC AND CBD PHARMACEUTICAL GRADE PLANT PREPARATIONS</p>	'Bedrocan', The Netherlands, and 'Tilray', Canada	Whole, dried pharmaceutical-grade cannabis products including female flowers and cannabis oil	Products meet Good Manufacturing Practice (GMP) standards and are supplied to some jurisdictions that have approved medicinal use of cannabis in certain circumstances, including New Zealand



WHAT MEDICAL CONDITIONS CAN CANNABIS TREAT?



The evidence for cannabis-based medicine is not well established as it hasn't been widely tested in clinical trials. There is evidence that cannabis-based medicines may have some effect as an additional treatment option for controlling chronic pain in adults, reducing nausea and vomiting from chemotherapy, easing pain from muscle spasms in people with multiple sclerosis and treating two rare forms of severe epilepsy in children.



Ngā Āhuatanga Haumanu

THERAPEUTIC EFFECTS

A number of clinical trials have sought to ascertain the effectiveness of cannabis-based medicines for a range of clinical conditions. However, the quality and level of evidence is often low and not compared directly against prescription medicines representing the current standard of care.²

Evidence from the literature points to some therapeutic effects of certain cannabis-based medicines for pain relief, seizure control, as anti-nausea and vomiting treatment for chemotherapy patients, and for the relief of some symptoms of multiple sclerosis. The evidence summarised here is based on that which the US National Academies of Sciences, Engineering and Medicine 2017 report considers to have a conclusive, substantial or moderate evidence base according to their definitions of these categories.²

Muscle spasms due to multiple sclerosis or spinal cord injury

Multiple sclerosis patients report reduced muscle spasm symptoms with oral cannabinoid treatment. However, there is only limited evidence for objectively measured effects,^{2, 21, 29} and Sativex® use for this condition was not recommended for funding in New Zealand by the Pharmacology and Therapeutics Advisory Committee in 2015, although it is registered for use in New Zealand for patients who meet certain criteria.³⁰

Chronic pain

There is evidence that cannabinoids may be effective for chronic pain in adults, with reported benefits but also adverse side effects.^{21, 22} Of the various types of chronic pain, nerve and cancer pain have been the most widely studied to date, with studies generally showing marginal improvement in comparison with a placebo.^{21, 23, 24} In a clinical setting, pharmaceutical grade cannabis-based medicines and cannabinoids will be more consistent in terms of cannabinoid composition, compared with the non-pharmaceutical cannabis forms used by the general population. However, although pain might not, or only marginally, improve, other effects of cannabis and cannabinoids might still result in a patient feeling better.²⁵

Chemotherapy-induced nausea and vomiting

There is evidence that cannabinoids can relieve the nausea and vomiting side effects of chemotherapy.^{21, 26} Nabilone and dronabinol have been licensed in the US for over 30 years for this purpose, and other cannabinoids have also been shown to be effective, with dronabinol found to be equivalent to one other modern nausea and vomiting suppressant.²⁷ The mechanisms of chemotherapy-induced nausea and vomiting vary enormously between patients, and cannabinoid use is re-emerging as a potential treatment option in addition to current regimens.²⁸



Epilepsy

Randomised controlled trials have found the use of highly concentrated CBD to be a safe and effective add-on treatment for two forms of child-onset severe epilepsy, although the mechanism of action is still unclear.³¹ In 2018, the US Food and Drug Administration approved Epidiolex for the treatment of seizures associated with two forms of epilepsy, Lennox-Gastaut syndrome and Dravet syndrome, in patients two years of age and older.

Other therapeutic effects

There is evidence that cannabinoids, primarily nabiximols, are effective at improving sleep in the short term for people with obstructive sleep apnoea syndrome, fibromyalgia, chronic pain and multiple sclerosis.^{2,21} However, no clinical trials have evaluated the effects of cannabinoids in patients with chronic insomnia that is caused by other conditions.

There is evidence of a statistical association between cannabis smoking and improved airway dynamics with short-term use, but not with long-term use (see *Evidence of health risks*, page 10).³²

There is currently insufficient evidence to reach definite conclusions on potential therapeutic effects of cannabinoids for other conditions.²


He aha ngā momo pānga o te hauora ki te pāpori?

EVIDENCE OF HEALTH RISKS

Cannabis is the most widely used illicit drug globally.³³ Recreational use of cannabis, particularly smoked plant material within the general population, is a public health concern, and there is evidence for harm caused by its use in non-therapeutic situations, both physically and mentally.^{34, 35}

METHOD OF CANNABIS INTAKE

Medical cannabis preparations are usually delivered as a spray, oil or capsule. However, the most popular recreational consumption of cannabis is smoking. This means that the active substances affect the body within seconds to minutes of inhalation. Vaporising, where the plant is heated to a temperature below which toxic compounds are created through combustion, is an alternative form of inhalation^{2, 36} and, again, provides for rapid uptake. However, the use of additives, solvents and flavourings in some products can produce harmful chemicals when vaporised, and the heating element of e-cigarettes can release harmful heavy metals.^{37, 38} In comparison, cannabis food products designed for recreational use take much longer to affect the body – from 30 minutes up to several hours. Edible forms have been implicated in the consumption of excessively high doses,³⁹ and edibles have also contributed to a number of cases of accidental ingestion of cannabis by children.⁴⁰

A close-up photograph of a person's hands rolling a cannabis joint. The person is using a metal grinder to grind the cannabis buds into a fine powder, which is then being placed into a white rolling paper. The person is wearing a silver ring on their finger. The background is blurred, showing more of the grinder and the person's hands.

WHAT RISKS ARE ASSOCIATED WITH THE WAY PEOPLE TAKE CANNABIS?



The safest form is pharmaceutical products such as sprays, oils or capsules. **Smoking** cannabis exposes users to toxic compounds created at high temperatures and it can lead to a chronic cough and phlegm production. Vaporising at lower temperatures (such as **vaping**) also exposes a user to toxic compounds from additives, solvents and flavouring. **Edible** forms can lead to excessively high doses and accidental ingestion. **Synthetic** cannabis poses the greatest risk because the active chemicals are much stronger than natural cannabis and can have longer lasting and more dangerous effects on the body.

HOW DOES RECREATIONAL CANNABIS AFFECT PHYSICAL HEALTH?



Smoking cannabis regularly can cause a chronic cough and phlegm production. It can affect brain development and short term memory, particularly in young people, making learning more difficult.

It can also lead to drug use disorders. Maternal cannabis exposure can lead to lower birthweights and negatively affect a baby's brain and nerve development. Cannabis use can also lead to increased road accidents.



Physical effects

RESPIRATORY SYMPTOMS

Smoking cannabis on a regular basis is associated with chronic cough and phlegm production.³² There is evidence of a statistical association between long-term cannabis smoking, worsening respiratory symptoms, and more frequent bronchitis episodes for chronic sufferers.⁴¹⁻⁴³

IMPAIRED COGNITION

Adolescence is often a time when people begin to experiment with drugs, including the recreational consumption of cannabis.^{44, 45} The brain is undergoing significant development in both structure and function during these adolescent years and it is possible that recreational use of cannabis at this time may have a lasting impact on cognitive performance.⁴⁶ Studies on learning, memory and attention conclude that there is evidence of an association between acute cannabis use and impairment in all three. Potential recovery after prolonged abstinence from cannabis use remains under-researched.⁴⁷ Brain scans indicate that in some cases, while there was no difference in terms of performance on memory tasks, cannabis users may use different parts of their brain to achieve equivalent performance to non-cannabis users on these tasks.⁴⁸ These findings highlight the need for further research on how cannabis may impact the regions of the brain that drive cognition and the processing of memory.^{49, 50}

MATERNAL CANNABIS USE AND CHILD OUTCOMES

Maternal cannabis use is associated with lower birthweight babies.^{2, 51} The findings for birthweight are consistent with the by-products produced by smoking cannabis and cigarette smoking, rather than cannabis itself. For example, carbon monoxide, which is associated with a reduced capacity of the blood to carry oxygen, may be up to five-fold higher after smoking cannabis than smoking cigarettes.⁵²

THC can cross the placenta⁵³ and is also secreted in breast milk, where it can accumulate to high concentrations.⁵⁴ Cannabinoids produced in the body play roles in a broad array of critical neurodevelopmental processes⁴⁶ from early neural stem cell development⁵⁵ to connectivity and synaptic function in the adolescent brain.⁵⁶ Although results have been variable, depending on factors such as timing of exposure and age of offspring at assessment, prenatal exposure may interfere with normal brain maturation.⁵⁷

OVERDOSE INJURIES

There is evidence of a statistical association between cannabis use and increased risk of overdose injuries, including respiratory distress, for children.⁵⁸⁻⁶⁰ There are no reports in the literature in which cannabis use was determined to be the cause of overdose death in the adult population. However, there are increasing cases of mortality linked to synthetic cannabinoids.^{61, 62}



Mental health effects

Some associations between cannabis use and adverse mental health effects have been described and are detailed below. While these are generally rare, they remain an area of concern for vulnerable populations.

SCHIZOPHRENIA AND PSYCHOSIS

There is evidence of an association between cannabis use and the development of schizophrenia and symptoms of psychoses, with the highest risk among the most frequent users.⁶³⁻⁶⁵ However, there is also evidence of an association between a history of cannabis use and better cognitive performance among individuals with psychotic disorders such as schizophrenia.⁶⁶⁻⁶⁸

BIPOLAR DISORDER

There is evidence of an association between regular cannabis use and increased symptoms of both mania and hypomania, among people diagnosed with bipolar disorder.⁶⁹

DEPRESSION AND SUICIDAL BEHAVIOUR

The endocannabinoid system is known to play a role in mood regulation.² There is evidence of an association between cannabis use, particularly heavy cannabis use, and an increased risk of depressive disorder,⁶⁹ particularly in youth.⁷⁰ However, the relationship is complex and the association may not necessarily be causative. There is evidence of an association between cannabis use and increased incidence of suicidal thoughts and suicide attempts, with a higher incidence among heavy users, particularly for women.^{71,72}

ANXIETY

The relationship between cannabis and anxiety disorders shows mixed results. There is evidence of an association between cannabis use and an increased incidence of social anxiety disorder.⁷³

PROBLEM CANNABIS USE

Cannabis use disorder (CUD) has been termed an official psychiatric disorder.⁷⁴ Progress has been made in standardising terminology. However, patterns of use that precede abuse and dependence are still unclear.⁷⁵

More frequent cannabis use is associated with progressing towards problem use.^{76,77} Risk factors for developing problem cannabis use include: initiating cannabis use at an earlier age;⁷⁸ being male;^{79,80} previous exposure to drugs, including tobacco and alcohol;⁸¹ reactions to cannabis when first used;⁸² and major depressive disorders.⁸³

There is also evidence that risk factors for developing problem cannabis use during adolescence include: frequency of cannabis use;⁸⁴ oppositional behaviours;⁸⁵ a younger age of first alcohol and nicotine use;⁸⁶ parental substance use;^{80,86} poor school performance;⁸⁷ and childhood sexual abuse.⁸⁰

HOW DOES RECREATIONAL CANNABIS AFFECT MENTAL HEALTH?



Cannabis may have an adverse effect on mental health but more research is needed to confirm this. It may increase the risks of schizophrenia and psychosis, bipolar disorder, depression and anxiety. Also, people can develop problem cannabis use and may become addicted.



Other public health impacts

INCREASED ROAD ACCIDENTS

Driving while under the influence of cannabis is shown to increase the risk of motor vehicle crashes.^{2,88} However, a missing piece of information is the dose of cannabis at which driving becomes unsafe, further complicated by varied responses to cannabis in the population, which has a known genetic component.⁸⁹ Some simulator studies found that motor skills become increasingly impaired at higher doses⁹⁰ but it is unclear whether this can be extrapolated to real-life situations. One confounding factor is that cannabis use is often associated with the same population group that already has a high crash risk: youth, males and those using drugs and/or alcohol.²

GATEWAY TO OTHER DRUG DEPENDENCIES

There is evidence of an association between cannabis use and the use of, or dependence on, other substances including alcohol,⁹¹ tobacco⁹² and other illicit drugs.⁹³ This is particularly the case in younger people. Recent research indicates that cannabis use is likely to increase the risk of dependence on other substances² and vice versa.

NON-MEDICINAL SYNTHETIC CANNABINOIDS

Many synthetic cannabinoids have been researched and developed by scientists in order to investigate the consequences of cannabinoid receptor activation.^{94,95} Some of these have become targets for illicit use because they induce psychoactive effects mimicking THC. Furthermore, the chemical nature of the synthetic compounds is often different from THC such that these have avoided legal restriction in many jurisdictions.⁹⁶

Synthetic cannabinoid products are a blend of various types of plant material, typically herbs and spices, sprayed with one of these synthetic cannabinoids and sometimes other non-cannabinoid psychoactive drugs. More than 140 different synthetic cannabinoids have been identified in herbal mixtures consumed as recreational drugs since 2009.² The synthetic cannabinoids used in 'herbal mixtures' are chemically variable, appeal especially to young cannabis and multi-drug users because they are relatively inexpensive, are easily available through the internet, and difficult to identify with standard drug screening techniques.



IS IT SAFE TO DRIVE AFTER USING CANNABIS?

Driving under the influence of cannabis increases the risk of having a crash. The amount of cannabis at which driving becomes unsafe is unknown and impairment from cannabis is difficult to measure.

In contrast to THC, which only partially activates the cannabinoid receptors, many of the synthetic cannabinoids activate these receptors strongly and could have long-lasting effects. Novel synthetic cannabinoids have typically received little characterisation and have completely unknown toxicity profiles in humans. The contents of products claiming to be equivalent can vary considerably over time, as producers seek to avoid detection by authorities.⁹⁷ All of these factors lead to higher potential for toxicity.⁹⁸

Synthetic cannabinoids can cause a range of symptoms, including psychosis, mania and suicidal ideations,⁹⁹ as well as agitation, irritability, seizures and memory loss.¹⁰⁰ Synthetic cannabinoids can also raise blood pressure and cause a reduced blood supply to the heart (myocardial ischemia) and have been associated with heart attacks and seizures.^{97,101} Regular synthetic cannabis users may experience severe withdrawal and symptoms of dependence.¹⁰² Pharmacological properties predict that synthetic cannabinoids pose a high risk for addiction and dependence.⁹⁷

Since 2013 the New Zealand Psychoactive Substances Act has prohibited substances that are intended to produce psychoactive effects unless safety has been established. However, illicit markets continue to pose a considerable public health concern. Approximately 45 deaths in New Zealand were linked to synthetic cannabinoid use in 2017, with ambulance services reporting multiple life-threatening cases related to synthetic cannabinoids per day.¹⁰³



WHAT IS SYNTHETIC CANNABIS?



Synthetic cannabis is non-cannabis plant material sprayed with chemicals that mimic the effect of cannabis but often has a stronger effect on the body so is more risky to take. Approximately 45 deaths in New Zealand were linked to synthetic cannabis use in 2017 and ambulance services report multiple life-threatening cases related to synthetic cannabis use every day. Its use would remain illegal regardless of the outcome of the recreational cannabis referendum.

KNOWLEDGE GAPS

There is a growing body of research into cannabis and its medicinal effects. However, urgent research is needed in those sectors of the population perceived to be at most risk, including those under 18, pregnant and breastfeeding women, people over 50 years of age and heavy cannabis users.² High priority should also be given to areas where current research shows the promise of cannabis and cannabinoids as therapies for specific conditions.

There is a need to:

- characterise the health effects of cannabis, cannabis derived products and cannabinoids on unstudied and under-studied health areas, such as symptoms of post-traumatic stress disorder, and childhood and adult cancers
- ensure long-term data collection strategies are in place, prior to further changes in legislation in New Zealand, to enable robust assessment of benefit and harm at both population and individual level
- increase international collaboration in cannabis-related research using standardised outcome measures to facilitate meaningful future meta-analyses
- investigate the response and interactions of cannabis in the body, modes of delivery, the dose–response relationships of cannabis and THC or other cannabinoids, and the impact these cannabinoids may have on the metabolism of other prescribed medications
- conduct well-controlled trials to establish the potential harmful or beneficial health effects of using different forms of cannabis, such as inhaled (smoked or vaporised), whole cannabis plant and oral cannabis, including cannabis-related overdose and poisoning.



WHAT MORE DO WE NEED TO KNOW ABOUT THE EFFECTS OF CANNABIS?

The lack of quality information on the effects of both medicinal and recreational cannabis poses a public health risk because we don't know enough about how safe or effective it is. Urgent research is needed on population groups thought to be at most risk: those under 18, pregnant and breastfeeding women, people over 50 years and heavy cannabis users.





Ngā mātanga pūtaiao

OUR EXPERTS

This paper was authored by Royal Society Te Apārangi, drawing on the evidence in the US National Academies of Sciences, Engineering and Medicine report: *The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research*,² and other recent research.

The Society would like to thank the following experts and organisations for their valuable input in contributing to and commenting on the paper:

Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists; Professor Richard Beasley FRSNZ; Associate Professor Joe Boden; Dr Irene Braithwaite; Professor Michelle Glass; Dr Natasha Lillia Grimsey; Associate Professor Giles Newton-Howes; Professor Lynette Sadleir; New Zealand Psychological Society; and Dr Alex Semprini.

Dr Ziva Cooper provided independent international review of this paper.

FOR FURTHER INFORMATION

Please contact info@royalsociety.org.nz
or visit our website www.royalsociety.org.nz

REFERENCES

1. New Zealand Government, *Misuse of Drugs Act 1975*, P.C. Office, Editor. 1975: Wellington, New Zealand.
2. National Academies of Sciences, Engineering and Medicine, *The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research*. 2017: National Academies Press.
3. Russo, E.B., *History of cannabis and its preparations in saga, science, and sobriquet*. Chemistry & biodiversity, 2007. 4(8): p. 1614-1648.
4. Barnes, M.P. and J.C. Barnes, *Cannabis: The evidence for medical use*. 2016: All Party Parliamentary Group for Drug Policy Reform.
5. United Nations Office on Drugs and Crime. *International Drug Control Conventions*. 2019 [8 March 2019]; Available from: <https://www.unodc.org/unodc/en/commissions/CND/conventions.html>.
6. Pertwee, R.G., *Pharmacology of cannabinoid CB1 and CB2 receptors*. Pharmacology & therapeutics, 1997. 74(2): p. 129-180.
7. ElSohly, M.A., et al., Changes in cannabis potency over the last 2 decades (1995–2014): Analysis of current data in the United States. Biological psychiatry, 2016. 79(7): p. 613-619.
8. Potter, D.J., *A review of the cultivation and processing of cannabis (Cannabis sativa L.) for production of prescription medicines in the UK*. Drug testing and analysis, 2014. 6(1-2): p. 31-38.
9. Oltrabella, F., et al., *Role of the endocannabinoid system in vertebrates: Emphasis on the zebrafish model*. Development, growth & differentiation, 2017. 59(4): p. 194-210.
10. Devane, W.A., et al., *Determination and characterization of a cannabinoid receptor in rat brain*. Molecular pharmacology, 1988. 34(5): p. 605-613.
11. Mackie, K., *Cannabinoid receptors as therapeutic targets*. Annual Review of Pharmacology and Toxicology, 2006. 46: p. 101-122.
12. Scuderi, C., et al., *Cannabidiol in medicine: A review of its therapeutic potential in CNS disorders*. Phytotherapy research: An international journal devoted to pharmacological and toxicological evaluation of natural product derivatives, 2009. 23(5): p. 597-602.
13. Hofmann, M.E. and C.J. Frazier, *Marijuana, endocannabinoids, and epilepsy: Potential and challenges for improved therapeutic intervention*. Experimental neurology, 2013. 244: p. 43-50.
14. Jones, N.A., et al., *Cannabidiol displays antiepileptiform and antiseizure properties in vitro and in vivo*. Journal of pharmacology and experimental therapeutics, 2010. 332(2): p. 569-577.
15. Leweke, F.M., et al., *Therapeutic potential of cannabinoids in psychosis*. Biological psychiatry, 2016. 79(7): p. 604-612.
16. Bergamaschi, M.M., et al., *Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naive social phobia patients*. Neuropsychopharmacology, 2011. 36(6): p. 1219.
17. Lago, E.D. and J. Fernandez-Ruiz, *Cannabinoids and neuroprotection in motor-related disorders*. CNS & neurological disorders-drug targets (formerly Current drug targets-CNS & neurological disorders), 2007. 6(6): p. 377-387.
18. Iuvone, T., et al., *Cannabidiol: A promising drug for neurodegenerative disorders?* CNS neuroscience & therapeutics, 2009. 15(1): p. 65-75.
19. Lakhan, S.E. and M. Rowland, *Whole plant cannabis extracts in the treatment of spasticity in multiple sclerosis: A systematic review*. BMC neurology, 2009. 9(1): p. 59.
20. Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine, *Statement on "Medicinal Cannabis" with particular reference to its use in the management of pain in patients with chronic non-cancer pain*. 2019. <http://fpm.anzca.edu.au/documents/pm10-2018.pdf>
21. Whiting, P.F., et al., *Cannabinoids for medical use: A systematic review and meta-analysis*. Jama, 2015. 313(24): p. 2456-2473.
22. Campbell, G., et al., *Effect of cannabis use in people with chronic non-cancer pain prescribed opioids: Findings from a 4-year prospective cohort study*. The Lancet public health, 2018. 3(7): p. e341-e350.
23. Stockings, E., et al., *Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: A systematic review and meta-analysis of controlled and observational studies*. Pain, 2018. 159(10): p. 1932-1954.
24. Allan, G.M., et al., *Simplified guideline for prescribing medical cannabinoids in primary care*. Canadian family physician, 2018. 64(2): p. 111-120.
25. Steele, G., T. Arneson, and D. Zylla, *A comprehensive review of cannabis in patients with cancer: Availability in the USA, general efficacy, and safety*. Current oncology reports, 2019. 21(1): p. 10.
26. Smith, L.A., et al., *Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy*. Cochrane database of systematic reviews, 2015(11).
27. Meiri, E., et al., *Efficacy of dronabinol alone and in combination with ondansetron versus ondansetron alone for delayed chemotherapy-induced nausea and vomiting*. Current medical research and opinion, 2007. 23(3): p. 533-543.
28. Pergolizzi, J.V., et al., *Concise review of the management of iatrogenic emesis using cannabinoids: Emphasis on nabilone for chemotherapy-induced nausea and vomiting*. Cancer chemotherapy and pharmacology, 2017. 79(3): p. 467-477.
29. Koppel, B.S., et al., *Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders: Report of the Guideline Development Subcommittee of the American Academy of Neurology*. Neurology, 2014. 82(17): p. 1556-1563.



30. Ministry of Health, *Summary of approvals required to prescribe cannabis-based products*. 2017, Ministry of Health: Wellington, New Zealand.
31. Ali, S., I.E. Scheffer, and L.G. Sadleir, *Efficacy of cannabinoids in paediatric epilepsy*. *Developmental medicine & child neurology*, 2019. 61(1): p. 13-18.
32. Tetrault, J.M., et al., *Effects of marijuana smoking on pulmonary function and respiratory complications: A systematic review*. *Archives of internal medicine*, 2007. 167(3): p. 221-228.
33. United Nations Office on Drugs and Crime, *World Drug Report 2018*. 2018, United Nations: Vienna, Austria.
34. Windle, S.B., et al., *Potential harms from legalization of recreational cannabis use in Canada*. *Canadian journal of public health*, 2019. 110(2): p. 222-226.
35. Memedovich, K.A., et al., *The adverse health effects and harms related to marijuana use: An overview review*. *CMAJ open*, 2018. 6(3): p. E339.
36. Eisenberg, E., M. Ogintz, and S. Almog, *The pharmacokinetics, efficacy, safety, and ease of use of a novel portable metered-dose cannabis inhaler in patients with chronic neuropathic pain: A phase 1a study*. *Journal of pain & palliative care pharmacotherapy*, 2014. 28(3): p. 216-225.
37. Meehan-Atrash, J., W. Luo, and R.M. Strongin, *Toxicant formation in dabbing: The terpene story*. *ACS omega*, 2017. 2(9): p. 6112-6117.
38. Gaur, S. and R. Agnihotri, *Health effects of trace metals in electronic cigarette aerosols—A systematic review*. *Biological trace element research*, 2019. 188(2): p. 295-315.
39. MacCoun, R.J. and M.M. Mello, *Half-baked—The retail promotion of marijuana edibles*. *New England journal of medicine*, 2015. 372(11): p. 989-991.
40. Wang, G.S., et al., *Association of unintentional pediatric exposures with decriminalization of marijuana in the United States*. *Annals of emergency medicine*, 2014. 63(6): p. 684-689.
41. Hancox, R.J., et al., *Effects of quitting cannabis on respiratory symptoms*. *European respiratory journal*, 2015. 46(1): p. 80-87.
42. Tashkin, D.P., et al., *Respiratory symptoms and lung function in habitual heavy smokers of marijuana alone, smokers of marijuana and tobacco, smokers of tobacco alone, and nonsmokers*. *American review of respiratory disease*, 1987. 135(1): p. 209-216.
43. Aldington, S., et al., *Effects of cannabis on pulmonary structure, function and symptoms*. *Thorax*, 2007. 62(12): p. 1058-1063.
44. Johnston, L.D., et al., *Monitoring the future national survey results on drug use, 1975–2017: Overview, key findings on adolescent drug use*. 2018. The University of Michigan Institute for Social Research. <http://hdl.handle.net/2027.42/150623>
45. Fergusson, D. and J. Boden, *Cannabis use in adolescence*. Improving the Transition, reducing social and psychological morbidity during adolescence (pp. 257-271). Auckland, NZ: Office of the Prime Minister's Science Advisory Committee
46. Brumback, T., et al., *Effects of marijuana use on brain structure and function: Neuroimaging findings from a neurodevelopmental perspective, in International review of neurobiology*. 2016. 129.: p. 33-65.
47. Broyd, S.J., et al., *Acute and chronic effects of cannabinoids on human cognition—A systematic review*. *Biological psychiatry*, 2016. 79(7): p. 557-567.
48. Batalla, A., et al., *Structural and functional imaging studies in chronic cannabis users: A systematic review of adolescent and adult findings*. *PLoS one*, 2013. 8(2): p. e55821.
49. Meier, M.H., et al., *Persistent cannabis users show neuropsychological decline from childhood to midlife*. *Proceedings of the National Academy of Sciences*, 2012. 109(40): p. E2657-E2664.
50. Jackson, N.J., et al., *Impact of adolescent marijuana use on intelligence: Results from two longitudinal twin studies*. *Proceedings of the National Academy of Sciences*, 2016. 113(5): p. E500-E508.
51. Gunn, J., et al., *Prenatal exposure to cannabis and maternal and child health outcomes: A systematic review and meta-analysis*. *BMJ open*, 2016. 6(4): p. e009986.
52. Wu, T.-C., et al., *Pulmonary hazards of smoking marijuana as compared with tobacco*. *New England journal of medicine*, 1988. 318(6): p. 347-351.
53. Bailey, J., et al., *Fetal disposition of Δ9-tetrahydrocannabinol (THC) during late pregnancy in the rhesus monkey*. *Toxicology and applied pharmacology*, 1987. 90(2): p. 315-321.
54. Garry, A., et al., *Cannabis and breastfeeding*. *Journal of toxicology*, 2009(299): p.596149.
55. Keimpema, E., K. Mackie, and T. Harkany, *Molecular model of cannabis sensitivity in developing neuronal circuits*. *Trends in pharmacological sciences*, 2011. 32(9): p. 551-561.
56. Lubman, D.I., A. Cheetham, and M. Yücel, *Cannabis and adolescent brain development*. *Pharmacology & therapeutics*, 2015. 148: p. 1-16.
57. Wu, C.-S., C.P. Jew, and H.-C. Lu, *Lasting impacts of prenatal cannabis exposure and the role of endogenous cannabinoids in the developing brain*. *Future neurology*, 2011. 6(4): p. 459-480.
58. Wang, G.S., et al., *Unintentional pediatric exposures to marijuana in Colorado, 2009–2015*. *JAMA pediatrics*, 2016. 170(9): p. e160971-e160971.
59. Le Garrec, S., S. Dauger, and P. Sachs, *Cannabis poisoning in children*. *Intensive care medicine*, 2014. 40(9): p. 1394-1395.
60. Wang, G.S., G. Roosevelt, and K. Heard, *Pediatric marijuana exposures in a medical marijuana state*. *Jama Pediatrics*, 2013. 167(7): p. 630-633.

61. Dart, R.C., et al., *Poisoning in the United States: 2012 emergency medicine report of the National Poison Data System*. Annals of emergency medicine, 2015. 65(4): p. 416-422.
62. New Zealand Police, *Joint statement from the Chief Coroner's office and Police on the significant number of synthetic cannabis related deaths in Auckland, 2017*, New Zealand Police.
63. Marconi, A., et al., *Meta-analysis of the association between the level of cannabis use and risk of psychosis*. Schizophrenia bulletin, 2016. 42(5): p. 1262-1269.
64. Moore, T.H., et al., *Cannabis use and risk of psychotic or affective mental health outcomes: A systematic review*. The lancet, 2007. 370(9584): p. 319-328.
65. Di Forti, M., et al., *The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): A multicentre case-control study*. The lancet psychiatry, 2019. 6(5): p. 427-436.
66. Yücel, M., et al., *The impact of cannabis use on cognitive functioning in patients with schizophrenia: A meta-analysis of existing findings and new data in a first-episode sample*. Schizophrenia bulletin, 2010. 38(2): p. 316-330.
67. Rabin, R.A., K.K. Zakzanis, and T.P. George, *The effects of cannabis use on neurocognition in schizophrenia: A meta-analysis*. Schizophrenia research, 2011. 128(1-3): p. 111-116.
68. Donoghue, K. and G.A. Doody, *Effect of illegal substance use on cognitive function in individuals with a psychotic disorder, a review and meta-analysis*. Neuropsychology, 2012. 26(6): p. 785.
69. Lev-Ran, S., et al., *Bipolar disorder and co-occurring cannabis use disorders: Characteristics, co-morbidities and clinical correlates*. Psychiatry research, 2013. 209(3): p. 459-465.
70. Leadbeater, B.J., M.E. Ames, and A.N. Linden-Carmichael, *Age-varying effects of cannabis use frequency and disorder on symptoms of psychosis, depression and anxiety in adolescents and adults*. Addiction, 2019. 114(2): p. 278-293.
71. Borges, G., C.L. Bagge, and R. Orozco, *A literature review and meta-analyses of cannabis use and suicidality*. Journal of affective disorders, 2016. 195: p. 63-74.
72. Shalit, N., et al., *The association between cannabis use and suicidality among men and women: A population-based longitudinal study*. Journal of affective disorders, 2016. 205: p. 216-224.
73. Kedzior, K.K. and L.T. Laeber, *A positive association between anxiety disorders and cannabis use or cannabis use disorders in the general population: A meta-analysis of 31 studies*. BMC psychiatry, 2014. 14(1): p. 136.
74. World Health Organization, *The ICD-10 classification of mental and behavioural disorders: Clinical descriptions and diagnostic guidelines*. 2015, Geneva: World Health Organization.
75. Casajuana, C., et al., *Definitions of risky and problematic cannabis use: A systematic review*. Substance use & misuse, 2016. 51(13): p. 1760-1770.
76. Blanco, C., et al., *Cannabis use and risk of psychiatric disorders: Prospective evidence from a US national longitudinal study*. JAMA psychiatry, 2016. 73(4): p. 388-395.
77. Coughle, J.R., et al., *Probability and correlates of dependence among regular users of alcohol, nicotine, cannabis, and cocaine: Concurrent and prospective analyses of the National Epidemiologic Survey on Alcohol and Related Conditions*. The Journal of clinical psychiatry, 2016. 77(4): p. e444-50.
78. Silins, E., et al., *Young adult sequelae of adolescent cannabis use: An integrative analysis*. The lancet psychiatry, 2014. 1(4): p. 286-293.
79. Haberstick, B.C., et al., *Prevalence and correlates of alcohol and cannabis use disorders in the United States: Results from the national longitudinal study of adolescent health*. Drug and alcohol dependence, 2014. 136: p. 158-161.
80. Boden, J.M., D.M. Fergusson, and L. John Horwood, *Illicit drug use and dependence in a New Zealand birth cohort*. Australian and New Zealand journal of psychiatry, 2006. 40(2): p. 156-163.
81. Chen, C.-Y., M.S. O'Brien, and J.C. Anthony, *Who becomes cannabis dependent soon after onset of use? Epidemiological evidence from the United States: 2000-2001*. Drug and alcohol dependence, 2005. 79(1): p. 11-22.
82. Fergusson, D.M., et al., *Early reactions to cannabis predict later dependence*. Archives of general psychiatry, 2003. 60(10): p. 1033-1039.
83. Pacek, L.R., S.S. Martins, and R.M. Crum, *The bidirectional relationships between alcohol, cannabis, co-occurring alcohol and cannabis use disorders with major depressive disorder: Results from a national sample*. Journal of affective disorders, 2013. 148(2-3): p. 188-195.
84. Swift, W., et al., *Are adolescents who moderate their cannabis use at lower risk of later regular and dependent cannabis use? Addiction*, 2009. 104(5): p. 806-814.
85. Pingault, J.-B., et al., *Childhood trajectories of inattention, hyperactivity and oppositional behaviors and prediction of substance abuse/dependence: A 15-year longitudinal population-based study*. Molecular psychiatry, 2013. 18(7): p. 806.
86. Behrendt, S., et al., *The relevance of age at first alcohol and nicotine use for initiation of cannabis use and progression to cannabis use disorders*. Drug and alcohol dependence, 2012. 123(1-3): p. 48-56.
87. Hayatbakhsh, M.R., et al., *Multiple risk factor model predicting cannabis use and use disorders: A longitudinal study*. The American journal of drug and alcohol abuse, 2009. 35(6): p. 399-407.



88. Røgeberg, O. and R. Elvik, *The effects of cannabis intoxication on motor vehicle collision revisited and revised*. *Addiction*, 2016. 111(8): p. 1348-1359.
89. Hryhorowicz, S., et al., Pharmacogenetics of cannabinoids. *European journal of drug metabolism and pharmacokinetics*, 2018. 43(1): p. 1-12.
90. Sewell, R.A., J. Poling, and M. Sofuoglu, *The effect of cannabis compared with alcohol on driving*. *American journal on addictions*, 2009. 18(3): p. 185-193.
91. Buu, A., et al., *Gender differences in the developmental risk of onset of alcohol, nicotine, and marijuana use and the effects of nicotine and marijuana use on alcohol outcomes*. *Journal of studies on alcohol and drugs*, 2014. 75(5): p. 850-858.
92. Timberlake, D.S., et al., *Progression from marijuana use to daily smoking and nicotine dependence in a national sample of US adolescents*. *Drug and alcohol dependence*, 2007. 88(2-3): p. 272-281.
93. Fergusson, D.M., J.M. Boden, and L.J. Horwood, *The developmental antecedents of illicit drug use: Evidence from a 25-year longitudinal study*. *Drug and alcohol dependence*, 2008. 96(1-2): p. 165-177.
94. Iversen, L.L., *The science of marijuana*. 2001, Oxford, UK: Oxford University Press.
95. Pertwee, R.G., *Targeting the endocannabinoid system with cannabinoid receptor agonists: Pharmacological strategies and therapeutic possibilities*. *Philosophical transactions of the Royal Society B: Biological sciences*, 2012. 367(1607): p. 3353-3363.
96. Wells, D.L. and C.A. Ott, *The "new" marijuana*. *Annals of pharmacotherapy*, 2011. 45(3): p. 414-417.
97. Ford, B.M., et al., *Synthetic pot: Not your grandfather's marijuana*. *Trends in pharmacological sciences*, 2017. 38(3): p. 257-276.
98. Hermanns-Clausen, M., et al., *Adverse effects after the use of JWH – 210 – A case series from the EU Spice II plus project*. *Drug testing and analysis*, 2016. 8(10): p. 1030-1038.
99. Weinstein, A.M., et al., *Synthetic cathinone and cannabinoid designer drugs pose a major risk for public health*. *Frontiers in psychiatry*, 2017. 8: p. 156.
100. Yeruva, R.R., et al., *Synthetic cannabinoids— "Spice" can induce a psychosis: A brief review*. *Innovations in clinical neuroscience*, 2019. 16(1-2): p. 31.
101. Cohen, K. and A.M. Weinstein, *Synthetic and non-synthetic cannabinoid drugs and their adverse effects: A review from public health prospective*. *Frontiers in public health*, 2018. 6: p. 162.
102. Tait, R.J., et al., *A systematic review of adverse events arising from the use of synthetic cannabinoids and their associated treatment*. *Clinical toxicology*, 2016. 54(1): p. 1-13.
103. Wilkins, C. and M. Rychert, *Responding to a new wave of high potency synthetic cannabinoids*. *The New Zealand medical journal*, 2018. 131(1481): p. 6-9.



Royal Society Te Apārangi

11 Turnbull Street, Thorndon, Wellington 6011
PO Box 598, Wellington 6140, New Zealand

Phone +64 4 472 7421


Email info@royalsociety.org.nz

Whakapā mai | Connect with us

 **RoyalSocietyNZ**

 **@royalsocietynz**

 **royalsociety.org.nz**

 **royalsocietynz**

Print ISBN: 978-1-877317-45-3

Digital ISBN: 978-1-877317-46-0

Except for figures and the Society logo,
expert advice papers are licensed under a
Creative Commons 3.0 New Zealand License.

Please contact info@royalsociety.org.nz
or visit the Society's webpage
royalsociety.org.nz/CannabisHealthImpacts
for further information.

Published December 2019

