Cannabinoids - Science & Society

The evolving story of 'medical' cannabis – seeing through the haze

Tony O'Brien

Clinical Professor of Palliative Medicine, College of Medicine & Health, University College Cork

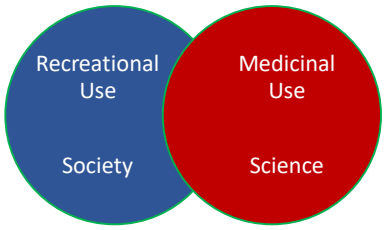
Consultant Physician in Palliative Medicine, Marymount University Hospital & Hospice / Cork University Hospital

Oxford Advanced Pain & Symptom Management Series

Nottingham June 26 2019

Disclaimer

I know nothing…… but, I learn!



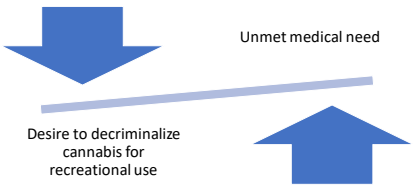
Decriminalisation

Effects of cannabis on human behaviour including cognition, motivation and psychosis – a review

Current efforts to normalize cannabis use are being driven largely by a combination of grassroots activism, pharmacological ingenuity and private profiteering

Volkow ND, Swanson JM, Evans AE et al. JAMA Psychiatry March 2016, Vol 73; No. 3. 292-297

Moves to decriminalise cannabis use



Blurring of lines between 'medical' use and 'recreational' use

What is a medicine?

Before a medicinal product may be placed on the market in Ireland, an application must be made to the HPRA for an authorization or to the European Medicines Agency

1. A medicinal product must be of adequate quality
2. The risks should be acceptable and reasonable
3. A demonstrable therapeutic benefit

HPRA Guideto Definition of a Human Medicine 28 March 2017

Authorization as a medicinal product basic requirements

Health Products Regulatory Authority

Medicines are required to have a marketing authorization which provides reassurance that a rigorous scientific assessment of the products quality, safety and effectiveness has been carried out

Based on this, the benefit / risk profile of the product is both known and considered positive

HPRA Opening statement to the Joint Committee on Health

Regulation – whose job?

Congress established the regulatory authority's (FDA) premarketing approval process to channel claims about safety and efficacy into an expert agency, where the claims can be evaluated rigorously and independently on the basis of submitted evidence

This process creates an incentive for companies to undertake scientific research

This gateway function remains a key way of ensuring that health care is based on robust science, so that patients are protected and wasteful spending is minimized

Robertson C, Kesselheim AS. N Engl J Med 2016; 375:2313-2315

Cannabis use in Ireland

Cannabis is the most widely used illegal drug in Ireland

Cannabis is classified under Schedule 1 of the Misuse of Drugs Act in Ireland
- ✓ This is not the case in the UK based on the advice of Prof Dame Sally Davies, Chief Medical Advisor

Cannabis is not an authorized medicine and has not gone through the normal regulatory procedures (Sole exception of Sativex)

The Minister may grant a license under the Misuse of Drugs Act for cannabis use for medical purposes in individual cases on receipt of an application from a medical consultant

Lennon E. Evidence to the Oireachtas Health Committee

Billy Caldwell

Dravet syndrome - a rare form of childhood epilepsy

Sought treatment in US / Canada – very successful

Returned to UK & declared cannabis oil at Heathrow

Drugs confiscated - admitted to St Thomas' in status

Home Secretary granted special licence

Billy Caldwell

Chief Medical Officer reviewed schedule 1 status of medical cannabis

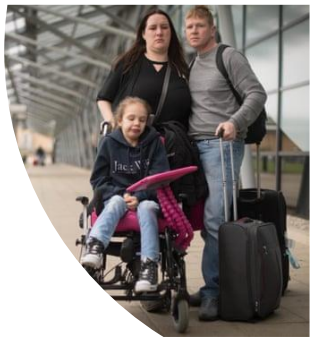
She noted that cannabis is clearly a medicine

November 1 2018 cannabis products were moved to schedule 2 of the Misuse of Drugs Act

Prescription initiation limited to 'specialists'

There are no specified medical indications for cannabis use in the UK– specialist opinion

Teagan Appleby



Imported 3 month supply of THC and CBD oil from the Hague

Lennox-Gastaut Syndrome

Drugs seized on return to the UK but since returned

The therapeutic and medicinal benefits of cannabis based products – a review of recent evidence

There is now however, conclusive evidence of the therapeutic benefit of cannabis based medicinal products for certain medical conditions and reasonable evidence of therapeutic benefit in several other medical conditions

This review does not consider the use of these products for non-medicinal or recreational purposes, or where those wishing to provide cannabis based medicinal products are not registered medical practitioners

I therefore recommend that the whole class of cannabis based medicinal products be moved out of Schedule 1.

Professor Dame Sally Davies
Chief Medical Officer for England and Chief Medical Advisor to the UK Government June 2018

Cannabis for medical use – A Scientific Review
HPRA Report January 31 2017

Such evidence as exists is confusing and frequently conflicting

There is an absence of good scientific data demonstrating the efficacy of cannabis products

The safety of cannabis as a medical treatment is not well understood, particularly in long-term use

Most cannabis products available under international access schemes do not meet pharmaceutical requirements

With due regard to the above, they (cannabis products) do not meet the minimum requirements required for authorization as medicinal products (medicines)

Significant gap between the public perception of effectiveness and safety, and the regulatory requirement for scientific data which is mandatory to determine the role of cannabis as a medicine

HPRA Cannabis for medical use –a scientific review. January 31 2017

Understanding the evidence for medical cannabis and cannabis-based medicines for the treatment of chronic non-cancer pain

References	Define cannabinoid?	Define pain types	RCT & observational evidence	IMMPACT guidelines	*n* studies (participants)	Conclusion
Whiting et al.	Yes	No	RCT only	No	28 (22454)	Moderate
National Academies of Science report	No	No	RCT only	No	Review of reviews Whiting + 3NP	Substantial evidence
Aviriam et al.	No	Yes	RCT only	No	43 (2437)	Might be effective in NP pain
Nugent et al.	No	Yes	Both	No	27 (3281)	Limited in NP Insufficient other
Mucke et al.	Yes	Yes (NP)	RCT only	Yes	16 (1750)	Harms > benefit
Stockings et al.	Yes	Yes	Both	Yes	104 (9958)	Unlikely benefit

Campbell G, Stockings E, Nielsen S. Understanding the evidence for medical cannabis and cannabis-based medicines for the treatment of chronic non-cancer pain. European Archives of Psychiatry and Clinical Neuroscience (2019) 269:135-144

Understanding the evidence for medical cannabis and cannabis-based medicines for the treatment of chronic non-cancer pain

References	Define cannabinoid?	Define pain types	RCT & observational evidence	IMMPACT guidelines	*n* studies (participants)	Conclusion
Whiting et al.	Yes	No				
						Limited in NP Insufficient other
		Yes (NP)	RCT only	Yes	16 (1750)	Harms > benefit
Stockings et al.	Yes	Yes	Both	Yes	104 (9958)	Unlikely benefit

Campbell G, Stockings E, Nielsen S. Understanding the evidence for medical cannabis and cannabis-based medicines for the treatment of chronic non-cancer pain. European Archives of Psychiatry and Clinical Neuroscience (2019) 269:135-144

It is concerning that there have been some broad recommendations for the use of medical cannabinoids in CNCP based on studies of specific conditions, particularly neuropathic pain

Many of the reviews of chronic non-cancer pain included studies for cancer pain in the analysis

Limitations of current evidence in CNCP

- ✓ Many of the typical pain populations are excluded (complex physical / mental comorbidities, substance use disorders
- ✓ Most RCTs were of limited duration – median of 8 weeks typically
- ✓ High risk of bias due to small sample sizes
- ✓ Paucity of high-quality evidence on which evidence-based decisions can reasonably be made
- ✓ Possible publication bias
  - ✓ Authors more likely to publish studies with positive findings
  - ✓ Mucke et al. reported they found 3 industry sponsored studies with negative results that had not been fully published
- ✓ Most studies added cannabinoid to established multi-drug regimens – need placebo controlled studies
- ✓ Unidimensional assessments only

Campbell G, Stockings E, Nielsen S. Understanding the evidence for medical cannabis and cannabis-based medicines for the treatment of chronic non-cancer pain. European Archives of Psychiatry and Clinical Neuroscience (2019) 269:135-144

Cannabis and the endocannabinoid system

The endocannabinoid system is an ancient, evolutionary conserved and ubiquitous lipid signaling system found in all vertebrates and which appears to have important regulatory functions throughout the human body

Described in the late 1980s / early 1990s

The leaves and flowering tops of *Cannabis* plants contain at least 700 distinct compounds distributed among 18 different chemical classes and contain more than 110 different phytocannabinoids

Health Canada – Cannabis - Information for health care professionals. February 2013

Cannabis and the endocannabinoid system

The system consists of cannabinoid 1 and cannabinoid 2 receptors (CB_1 and CB_2)

CB_1 receptors – expressed mainly by central and peripheral neurons -
Concentrated in brain regions related to executive function, cognition, mood, pain perception and movement. Also found in the heart, intestines and bladder

CB_2 receptors – expressed mainly by immune cells – involved in immune regulation -
spleen, tonsils, thymus gland, bone, skin and blood (monocytes, macrophages, B-cells and T-cells)

Recommended Reading: Palliative Care Formulary PCF 6

Twycross R, Wilcock A, Howard P. Palliative Care Formulary PCF 6, 229-234. palliativedrugs.com 2017
Health Canada – Cannabis - Information for health care professionals. February 2013
Clinical Guidelines on Cannabis for Medical Use. Department of Health 2018

Cannabis and the endocannabinoid system

The principal cannabinoids are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD)

THC is responsible for the psychoactive actions of cannabis through its actions at the CB_1 receptor, an inhibitory receptor

CBD lacks detectable psychoactivity and pre-clinical studies suggest that it has anti-inflammatory, analgesic, anti-emetic, anti-psychotic, anti-ischaemic, anxiolytic and anti-convulsant properties. No effect on CB_1 receptors

CBD does not fall under the Misuse of Drugs legislation (1977 to 2016) in Ireland
CBD is sold as a nutritional supplement or health food –
Note: It is not permissible to make medicinal claims about food

Health Canada – Cannabis - Information for health care professionals. February 2013
Clinical Guidelines on Cannabis for Medical Use. Department of Health 2018
Nolan L. HPRA – Opening statement to Joint Committee on Health
MHRA (2016) MHRA statement on products containing Cannabidiol (CBD) Available from www.gov.uk

Medicinal Cannabis

Product	Authorised in	Schedule	Contents	Dosing
Nabiximols (Sativex) *Spasticity in MS*	Ireland	2	2.7 mg delta THC, 2.5 mg CBD per 100 microlitre oro-mucosal spray. 1:1 (2.7%THC / 2.5% CBD)	Increase by one spray / day. MDD is 12 sprays per day
Nabilone (Cesamet) *Nausea / vomiting*	UK, USA, Austria, Mexico	2	1 mg Nabilone per capsule Synthetic THC	1 - 2 mg BD; MDD 6mg
Dronabinol (Marinol) *Appetite stimulation Nausea/vomiting*	USA, Germany	1	2.5mg, 5mg, 10mg soft gelatin capsule. Synthetic THC	Depends on indication. MDD 20mg
Investigational Medicinal Product				
Epidiolex *Intractable seizures*	N/A Clinical Trials	N/A	10% CBD (>98% purity) 100 mg/ml oral solution	Trials use at 5 – 25 mg / kg / day

Cannabinoids claimed therapeutic indications

Palliative care	Acute pain	Osteoarthritis	Parkinson's disease	Opioid withdrawal	Liver disease
Nausea / Vomiting	Chronic pain	Rheumatoid disease	Dementia	Psychosis	Metabolic syndrome
Aids Anorexia / cachexia	Cancer pain	Osteoporosis	Anxiety	Schizophrenia	Diabetes Mellitus
Anorexia Nervosa	Neuropathic pain	Fibromyalgia	Depression	Glaucoma	Obesity
Multiple sclerosis	Non-cancer pain	Dystonia	Sleep disorders	Inflammatory skin diseases	Pancreatic disorders
ALS / MND	Headache	Tics	Post traumatic stress disorder	Irritable bowel syndrome	Anti-neoplastic
Epilepsy	Migraine	Huntington's	Alcohol withdrawal	Inflammatory bowel disease	Tourette's syndrome

Health Canada 2013

Cannabinoids claimed therapeutic indications

Available evidence is confused and often conflicting

In general, reported benefits are largely anecdotal with perhaps the exception of CBD use in Dravet Syndrome and Lennox-Gastaut syndrome

Generally less well tolerated when compared to more conventional medications

Concern that increased use will result in emergence of more unusual adverse effects

Cost is a consideration

Barnes report

Commissioned by the All Party Parliamentary Group for Drug Policy Reform (APPG)
The global war on drugs has failed and the APPG is committed to working for drug policy reform

The authors received a small unspecified grant from APPG to undertake the work

The authors declare no commercial interest in cannabis or cannabis products

The work was carried out in a personal capacity by the authors and the views expressed are those of the authors alone

The paper was not published in any scientific journal and was not therefore subject to peer review

Cannabis: the evidence for medical use. Barnes MP & Barnes JC, May 2016

Prof Mike Barnes, University of Newcastle
Involved with GW Pharma in early 2000s
CMO Sol Global Investments
CMO European Cannabis Holdings
Theros Pharma Ltd – acquired by the Wayland Group for an initial GBP£3.8 million and an additional GBP£24 million if milestones reached

U.K's first medicinal cannabis clinic opens in Manchester

Since November 2018, specialist doctors in the UK may prescribe medicinal cannabis

Private clinic in Manchester and multiple other sites

Fees:
- GBP£200 for initial consultation
- GBP£100 for GP referral letter
- GBP£600 - £700 per month for medicinal cannabis

Clinical Director is Prof Michael Barnes: *'Patients suffering from chronic pain and other serious neurological or psychiatric conditions have been crying out for this life-changing treatment. This is a lifeline for those who have found other treatments ineffective'*

The Independent Sunday March 10 2019

Barnes report

Pain – Conclusion: good evidence for efficacy of cannabis for pain relief

This is a difficult literature to summarize as a number of formulations have been used and a number of different pain types studied

Epilepsy – Conclusion: There is only limited evidence at the moment

Robust trials are lacking but further results are awaited

Cannabis for medical use – A Scientific Review

HPRA Expert Working Group

Proposed medical conditions

1. Spasticity associated with multiple sclerosis resistant to all standard therapies and interventions
2. Intractable nausea / vomiting associated with chemotherapy, despite the use of standard anti-emetic regimens
3. Severe, refractory (treatment-resistant) epilepsy that has failed to respond to standard anticonvulsant medications

Cannabis for medical use – A Scientific Review

HPRA Expert Working Group

Proposed medical conditions

Patients accessing cannabis under this 5 year assessment programme should be:

Under the supervision of a medical consultant

Have had an inadequate response to currently available standard therapies
i.e. Cannabis is not regarded as a first line therapy for any condition

Full information such as demographic data, specific medical indication, details on the specific form of cannabis used, effects – positive and negative etc. will be collected in a standardized format and stored in a central register

The data will be the subject of on-going review and analysis

Trial of Cannabidiol for Drug-Resistant Seizures in Dravet syndrome

Double-Blind, Placebo-Controlled study of 120 children and young adults with Dravet Syndrome and drug resistant seizures

Cannabidiol oral solution of 20 mg / kg per day or matching placebo in addition to standard antiepileptic treatment

Primary outcome: change in convulsive seizure frequency over 14 week treatment period v 4 week baseline period

Median frequency of convulsive seizures per month from baseline:
- CBD: 12.4 to 5.9
- Placebo: 14.9 to 14.1

Percentage of patients with at least a 50% reduction in convulsive seizure frequency:
- CBD: 43%
- Placebo: 27%

A/Es: Diarrhoea, Vomiting, Fatigue, Pyrexia, Somnolence and abnormal liver function tests

Devinsky O, Patel AD, Cross H, Laux L, Marsh E, Miller I, Nabbout R, Scheffer IE, Thiele EA, Wright S. N Engl J Med 376; 21:2011-2020. May 25, 2017

Effect of Cannabidiol on Drop Seizures in the Lennox-Gastaut Syndrome

Double-Blind, Placebo-Controlled study of 225 patients at 30 clinical centres; age range 2 – 55 years

Cannabidiol oral solution either 20 mg / kg or 10mg / kg or matching placebo in two divided doses for 14 weeks

Cannabidiol was added to established anti-convulsant regimen

Primary outcome: Percentage change from baseline in the frequency of drop seizures during treatment period

Median % reduction from baseline:
- 76 patients - CBD 20mg: 41.9% (p=0.005 for CBD 20mg v placebo)
- 73 patients - CBD 10 mg: 37.2% (p=0.002 for CBD 10mg v placebo)
- 76 patients - Placebo: 17.2%

A/Es: Somnolence, decreased appetite, diarrhoea, elevated aminotransferase; 7 patients withdrew (6 x 20mg & 1 x 10mg)

Devinsky O, Patel AD, Cross H, Villanueva V, Wirrell EC, Privitera M, Greenwood SM, Roberts C, Checketts D, VanLandingham KE, Zuberi SM. N Engl J Med 378;20. May 17 2018

The Opportunity of CBD – Reforming the Law

Annual US sales of CBD in excess of US$200 million

FDA has ruled that CBD cannot be legally sold in either supplements or foods

Many manufacturers are choosing to defy this ruling

The only FDA approved indication for CBD is in the treatment of intractable seizures in Dravet syndrome and Lennox-Gastaut syndrome

No large, high-quality clinical trials in other conditions

FDA has raised concerns regarding the long-term safety of CBD
- ✓ Somnelence
- ✓ Anorexia
- ✓ Diarrhoea
- ✓ Increased liver enzymes

Cohen PA, Sharfstein J. The Opportunity of CBD – Reforming the Law. N Engl J Med June 12 2019. DOI:10.1056/NEJMp1906409

Cannabis for medical use – A Scientific Review
HPRA Expert Working Group

Irish Pain Society Response

Welcomed the report – 'well-researched, well-written and important contribution to the debate on medical cannabis'

Controversially, the HPRA recommended against the use of cannabis in chronic pain

The majority of clinical studies, meta-analyses and systematic reviews cited in the HPRA report conclude that cannabis or individual cannabinoids afford moderate to substantial benefit to patients with chronic pain

The Irish Pain Society recommends that:

- Medical cannabis could be prescribed initially by a pain specialist/ consultant only
- Do as much as possible to make new treatments such as cannabinoids with proven efficacy and fewer adverse effects available to patients

Prof David Finn, UCG
President of the Irish Pain Society, February 2017

Access to medical marijuana and opioid overdose deaths

US states that allow access to medical marijuana do not, on average, see fewer deaths from opioid poisoning than the rest of the country, research published in the *Proceedings of the National Academy of Sciences* has shown

A 2014 study published in *JAMA Internal Medicine* made headlines around the world when it found that opioid mortality from 1999 to 2010 was lower in US states that allowed medical marijuana than elsewhere in the country

MJ 2019; 365 doi: https://doi.org/10.1136/bmj.l4188 (Published 12 June 2019)Cite this as: *BMJ* 2019;365:l4188

The cannabinoid system and pain
Neuropharmacology
*Stephen G Woodhams, Victoria Chapman, **David P Finn**, Andrea G Hohmann*

Chronic pain states are highly prevalent yet poorly controlled by currently available analgesics

The endocannabinoid system is a major endogenous pain system running in parallel to the opioid system

The initial promise of augmenting EC signaling via specific enzyme inhibitors has been diminished by recent clinical failures

Within the field of endocannabinoid research, significant fundamental questions remain unanswered

Whilst much has been achieved in the past few decades, more work is necessary to characterise both efficacy and safety profiles of existing EC directed therapeutic strategies

Woodhams SG et al. The cannabinoid system and pain. Neuropharmacology (2017) http://dx.doi.org/10.1016/j.neuropharm.2017.06.1015

Efficacy and safety

Safety of cannabis as a medical treatment is not well characterized

Insufficient information on its safety during long-term use

Quality of evidence is poor

All researchers cite the need for formal, placebo-controlled studies

Conflicting interpretations of the published literature

Major limitation is lack of clarity or standardization of formulation used, especially THC / CBD ratio

Clinical Guidelines on Cannabis for Medical Use. Department of Health 2018

Cannabis: Potential drug interactions

THC potentiators	
CYP2C9 inhibitors: Amiodarone, cimetidine, cotrimoxazole, metronidazole, fluoxetine, fluconazole, voriconazole	*CYP3A4 inhibitors:* Ketoconazole, clarithromycin, erythromycin, cyclosporine, verapamil, itraconazole, voriconazole
THC inhibitors	
CYP2C9 inducers: Barbiturates, carbamazepine, phenytoin	*CYP3A4 inducers:* Carbamazepine, dexamethasone, phenobarbital, rifampicin
CBD potentiators	
CYP2C19 inhibitors: Clopidrogel, fluoxetine	*CYP3A4 inhibitors:* See above
CBD inhibitors	
CYP2C19 inducers: Barbiturates, phenytoin, rifampicin	*CYP3A4 inducers:* See above

Howard I. Journal of Palliative Medicine – Case discussions. 14 May 2019 / https://doi.org/10.1089/jpm.2018.0531

New Zealand passes laws to make medical marijuana widely available

Legislation comes ahead of a referendum on recreational marijuana use in next two years

@EleanorAingeRoy

New Zealand's government has passed a law that will make medical marijuana widely available for thousands of patients over time, after years of campaigning by chronically ill New Zealanders who say the drug is the only thing that eases their pain.
The legislation will also allow terminally ill patients to begin smoking illegal pot immediately without facing the possibility of prosecution

The Guardian. December 11 2018

Faculty of Pain Medicine
Australian and New Zealand College of Anaesthetists

''False hope'' driving claims medicinal cannabis is ''magic pill'' for chronic pain relief

Prescribing medicinal cannabis for patients with chronic non-cancer pain is not going to revolutionize their treatment and should not be supported until there is substantial proof of its effectiveness

Professor Milton Cohen
Medicinal cannabis for chronic non-cancer pain: promise or pothole?
Australian and New Zealand College of Anaesthetists (ANZCA) annual scientific meeting Brisbane. May 13, 2017

Faculty of Pain Medicine
Australian and New Zealand College of Anaesthetists

Using human suffering to push for cannabis is 'irresponsible'

The political push for cannabis to be legalized for pain relief because "people are suffering now" is morally and socially irresponsible because it ignores medical findings that the drug is a poor pain reliever and can be harmful

There is little evidence to support the use of marijuana for pain apart from personal testimonials - that is not science

Facebook and Twitter are not science

The medical evidence from trials that have been done suggests that marijuana does not work well at treating the kinds of pain we regularly encounter, including cancer pain. It comes off second best to existing drugs

Marijuana would also fall at the first hurdle in terms of its safety profile

Cannabis and cannabinoids for treatment of chronic noncancer pain: a systematic review and meta-analysis of controlled observational studies

1. **NNTB – to achieve a 30% reduction in pain for ONE patient was 24 (95% CI 15-61)**
2. NNTH – for ONE patient to experience any AE compared with placebo was 6 (95% CI 5-8)
3. Previous studies in neuropathic pain: (Lancet Neurology 2015;14:162-73)
   - Opioids: NNTB was 4.3 (95% CI 3.4-5.8)
   - Pregabalin: NNTB was 7.7 (95% CI 6.5-9.4)
   - TCADS: NNTB was 3.6 (95% CI 3.0 – 4.4)
4. Cochrane review: NNTH with opioids – for one patient to experience any AE compared with placebo was 5 (95% CI 4-9). (Cochrane Database Syst Rev 2017; 10:CD012509)

Stockings E, Campbell G, Hall WD, Nielsen S, Zagic D, Rahman R, Murnion B, Farrell M, Weier M, Degenhardt L
PAIN October 2018 Vol. 159; Issue 10:1932-1954

Adverse Health Effects of Marijuana Use

Effects of Short-Term Use

Impaired short-term memory, making it difficult to learn and to retain information

Impaired motor coordination, interfering with driving skills and increasing risk of injury

In high doses, paranoia and psychosis

Volkow ND, Baler RD, Compton WM, Weiss SRB. Adverse Health Effects of Marijuana Use NEJM 2014 ;370:2210-2227

Adverse Health Effects of Marijuana Use

Effects of Long-Term or Heavy Use

- Addiction – 9% of users overall; 17% of those who start in adolescence and 25 – 50% of daily users
- Altered brain development
- Poor educational outcomes, with increased risk of dropping out of school
- Cognitive impairment with lower IQ among those who were frequent users during adolescence
- Diminished life satisfaction and achievement
- Symptoms of chronic bronchitis
- Increased risk of chronic psychosis (including schizophrenia) in persons with a predisposition to such disorders

Volkow ND, Baler RD, Compton WM, Weiss SRB. Adverse Health Effects of Marijuana Use NEJM 2014 ;370:2210-2227

Cannabis use and mental health

Although causality has not been conclusively demonstrated, heavy cannabis use is associated with increased risk of:

- Mental disorders
- Psychosis
- Addiction
- Depression
- Suicidality
- Cognitive impairment
- Amotivation

Acute THC administration causes increased dopamine release and neuronal activity, long term use is associated with blunting of the dopamine system

Bloomfield MAP, Ashok, AH, Volkow NV, Howes OD Nature Vol 359, 17 November 2016

Effects of cannabis on human behaviour including cognition, motivation and psychosis – a review

Cannabis use and schizophrenia

Longitudinal investigations show a consistent association between adolescent cannabis use and schizophrenia

Cannabis use is considered a preventable risk factor for psychosis

The link between cannabis and schizophrenia could stem from:

- Direct causality
- Gene-environment interactions
- Shared aetiology

There is a strong mechanistic link between cannabis use and schizophrenia

Volkow ND, Swanson JM, Evans AE et al. JAMA Psychiatry March 2016, Vol 73, No. 3. 292-297

Cannabis use and psychotic disorder

does cannabis use influence rates of psychotic disorder

Many countries have decriminalized cannabis use

- Will this result in an increase in cannabis use and consequent harm?

Cross-sectional and prospective epidemiological studies <u>support</u> a causal link between cannabis use and psychotic disorder

Meta-analysis shows a dose-response association with the highest odds of psychotic disorder in those with the heaviest cannabis use

Previous studies have demonstrated the harmful effects on mental health of daily use of cannabis

Di Forti M, Freeman TP, Tripoli G, Gayer-Anderson C, Quigley H, Rodriguez V, et al.
The Contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicenter case-control study. Lancet Psychiatry March 19 2019. 1 – 9.

Cannabis use and psychotic disorder

does cannabis use influence rates of psychotic disorder?

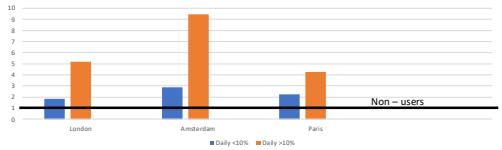
- Transnational case-control study (11 sites, Europe and Brazil)
- 901 patients with first episode psychosis v 1237 population controls from same sites
- Two categories of THC potency: THC<10% and THC >10%
- Daily cannabis use associated with increased odds of psychotic disorder v non-users
- The strongest independent predictor of whether an individual would have a psychotic disorder or not were:
  - Daily use of cannabis
  - Use of high-potency cannabis
- Compared with never users, users of high potency cannabis on a daily basis had:
  - Four times greater odds of psychosis (whole sample)
  - London: 5-fold increase risk; Amsterdam: 9-fold increased risk

Di Forti M, Freeman TP, Tripoli G, Gayer-Anderson C, Quigley H, Rodriguez V, et al.
The Contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicenter case-control study. Lancet Psychiatry March 19 2019. 1 – 9.

Cannabis use and psychotic disorder

does cannabis use influence rates of psychotic disorder?

Adjusted Odds Ratio of psychotic disorder for daily users in London, Amsterdam and Paris



Di Forti M, Freeman TP, Tripoli G, Gayer-Anderson C, Quigley H, Rodriguez V, et al.
The Contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. Lancet Psychiatry March 19 2019. 1 – 9.

Cannabis and psychosis: triangulating the evidence

- ✓Could cannabis cause / predispose individuals to develop psychosis?
- ✓Perhaps individuals with pre-clinical or undiagnosed psychosis are more likely to use cannabis
- ✓There certainly is a genetic predisposition
- ✓Need to identify individuals who have this genetic susceptibility – education / intervention

Gage SH. Cannabis and psychosis: triangulating the evidence. Lancet Psychiatry March 19 2019.

The Irish Times

Monday June 24 2019

Number of young adults admitted to psychiatric hospitals with cannabis related psychiatric disorder has risen by 130% in 8 years

Cannabis causes one in five new cases of psychosis

General population survey found that 22% of young adults users had features of cannabis dependence

Between 2007 and 2015, number of young adults presenting with cannabis addiction increased by 300%

The proportion of the general population who see regular cannabis use as posing 'little or no risk' has doubled

Cannabis Risk Alliance

Effects of cannabis on human behaviour including cognition, motivation and psychosis – a review

Vulnerable populations such as children, adolescents, the elderly or individuals with other disorders may experience novel toxic effects (as well as the potential benefits)

If we stay the current course, we are likely to uncover effects that were rare in the past only because the use was not as widespread as that of legal drugs

Volkow ND, Swanson JM, Evans AE et al. JAMA Psychiatry March 2016, Vol 73, No. 3. 292-297

Cannabis Hyperemesis Syndrome in Palliative Care: A Case Study and Narrative Review

31 year old male with ALS/MND

Three characteristic features:
✓ Chronis cannabis use
✓ Severe cyclical nausea and emesis
✓ Frequent hot bathing – symptom relief with hot showers / baths

Cases of acute renal failure and death related to cannabis hyperemesis syndrome are described

Survey of 155 chronic cannabis users attending emergency department:
✓ 32% reported features of Cannabis Hyperemesis Syndrome

Howard I. Journal of Palliative Medicine – Case discussions. 14 May 2019 / https://doi.org/10.1089/jpm.2018.0531

Use of Medicinal Cannabis Products in Queensland

While there are anecdotal reports of the therapeutic value of medicinal cannabis, the evidence to support the safety and efficacy of these products is limited

While animal data shows therapeutic potential and some human research has suggested some therapeutic potential, there is insufficient evidence by contemporary standards, such as randomized controlled trials, for most indications

The document should not be construed as an endorsement about the use of medicinal cannabis in individual patients

Clinical Guidance for the use of medicinal cannabis products in Queensland. March 2017

Use of Medicinal Cannabis Products in Queensland

Cannabis products are NOT considered first-line therapy for any indication

Cannabis products have NOT undergone the rigorous testing required to ensure safety and efficacy

Research suggests that there MAY be some therapeutic benefit from various cannabinoids

Medical practitioners are enabled to access medicinal cannabis products BEFORE they have reached the standard required for a pharmaceutical product

Clinical Guidance for the use of medicinal cannabis products in Queensland. March 2017

Recommendations on cannabis-based products for medicinal use

Chemotherapy induced nausea and vomiting –

1. Effective but high side effect profile
2. More efficacious agents available
3. High discontinuation rates
4. Relatively old data
5. Adverse effects – psychological, neurological, gastrointestinal. Psychosis is particular concern

Royal College of Physicians, Royal College of Radiologists, Faculty of Pain Medicine, Royal College of Anaesthetists October 2018

Recommendations on cannabis-based products for medicinal use

Pain –

1. Limited evidence available on which to formulate guidelines
2. Studies show mixed results / uncertain clinical significance
3. Use in treatment of pain in palliative care patients is unclear and not recommended in routine clinical practice

Royal College of Physicians, Royal College of Radiologists, Faculty of Pain Medicine, Royal College of Anaesthetists October 2018

Recommendations on cannabis-based products for medicinal use

Chronic neuropathic pain

1. Lack of good evidence that any cannabis–derived product works for any chronic neuropathic pain (Cochrane review, March 2018)
2. Benefits might be outweighed by harms
3. It appears unlikely that cannabinoids are highly effective medicines for chronic non-cancer pain. (Editorial, *Pain* 2018; 159:1932-54)
4. Recommend against use of cannabinoids in neuropathic pain mainly because of negative results, diversion and long-term mental health risks particularly in susceptible individuals

Recommendations on cannabis-based products for medicinal use

Conclusions:

Medicinal use of cannabinoids needs to be carefully considered and researched in a comprehensive fashion, as would be the case for any new medicinal product

Anecdotal positive reporting is not a mechanism to protect public safety

We recommend that a database is established for the analysis of data from all areas. Such a database needs to be independent, compulsory, fully funded and under the auspices of a suitable organization (e.g. NICE) to assess value of treatments

Medicinal Cannabis use in chronic non-cancer pain

1. Changed Regulatory Environment
2. Political imperatives and societal demands
3. Principle – *All substances intended for therapeutic purposes be fully characterized chemically, pharmacologically and toxicologically to the extent that are are eligible for registration by the competent regulatory authority*

Medicinal Cannabis use in chronic non-cancer pain

4. The sociopsychobiomedical framework that informs assessment and management of people with chronic pain requires active engagement of patients with multimodal management programmes, and recognizes the adverse effects associated with polypharmacy in general and with cannabinoids in particular

5. Concern about the adverse effect profile especially in young people

6. Currently, scientific evidence for the efficacy of cannabinoids is insufficient to justify endorsement of their clinical use

7. Clinical trials should be conducted on a coordinated national basis

Cannabis and chronic pain management

Public interest in use of cannabis for medical purposes has been accelerated by advocacy and by the legalization of marijuana for recreational and medical use

15 systematic reviews identified

The reviews cover the same limited evidence

Of the 37 countries in the European Pain Federation, none has produced a national guideline on the use of cannabis-based medicines for chronic pain

Cancer Pain
Key Point

Nabiximols oro-mucosal spray can be considered as part of an add-on individual therapeutic trial for cancer pain without sufficient relief from opioids or other established analgesics

Four studies, 1130 patients, duration of 2 – 9 weeks

All studies failed to meet the primary end-point –
Statistically significant superiority over placebo in pain relief of 30% or greater or mean pain intensity reduction with *p-values* >0.05 to <0.10

Chronic neuropathic pain
Key Point

Cannabis based medicines can be considered as third-line therapy for chronic neuropathic pain

A systematic overview concluded that there were inconsistent findings on the efficacy of cannabinoids in chronic neuropathic pain

The authors concluded that there was no high quality evidence that any cannabis based medicine was of value in treating people with chronic neuropathic pain

Psychiatric disorders occurred in 17% of participants using cannabis based medicines and in 5% using placebo

Nervous system adverse events occurred in 61% of participants using cannabis based medicines and in 29% using placebo.

The potential benefits of cannabis based medicines might be out-weighed by their potential harms (Mucke, 2018)

European Pain Federation (EFIC) position paper on appropriate use of cannabis-based medicines and medical cannabis for chronic pain management. Eur J Pain 2018;22:1547-1564

Chronic Pain Management
Summary and conclusions

Evidence is insufficient

Further studies are in the design phase or have commenced

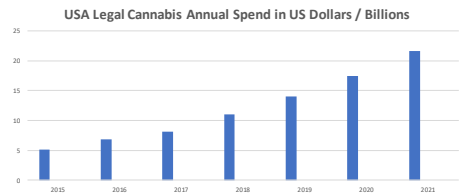
The expansion in the number of countries that have authorized medical cannabis for chronic pain will afford the opportunity for larger scale empirical studies

We expect the quality and quantity of evidence and clinical experience to improve within the next three years

We will update the position paper in 2021

European Pain Federation (EFIC) position paper on appropriate use of cannabis-based medicines and medical cannabis for chronic pain management. Eur J Pain 2018;22:1547-1564

The state of legal marijuana markets
Actual and predicted



State of Legal Marijuana Markets 5th edition. www.arcviewmarketresearch.com