

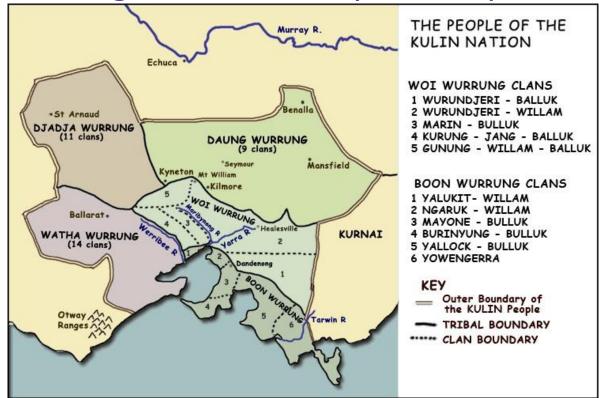
Tuesdays with Nexus: **Demystifying Medicinal Cannabis**

Kah-Seong Loke, Consultant Psychiatrist, Nexus Dual Diagnosis Consultation Service

Tuesday 7/2/2023 - 9.30 am



We respectfully acknowledge the Traditional custodians of the land on which we meet today, the Wurundjeri people of the Kulin Nation, and we pay respect to all Aboriginal Community Elders, past and present.

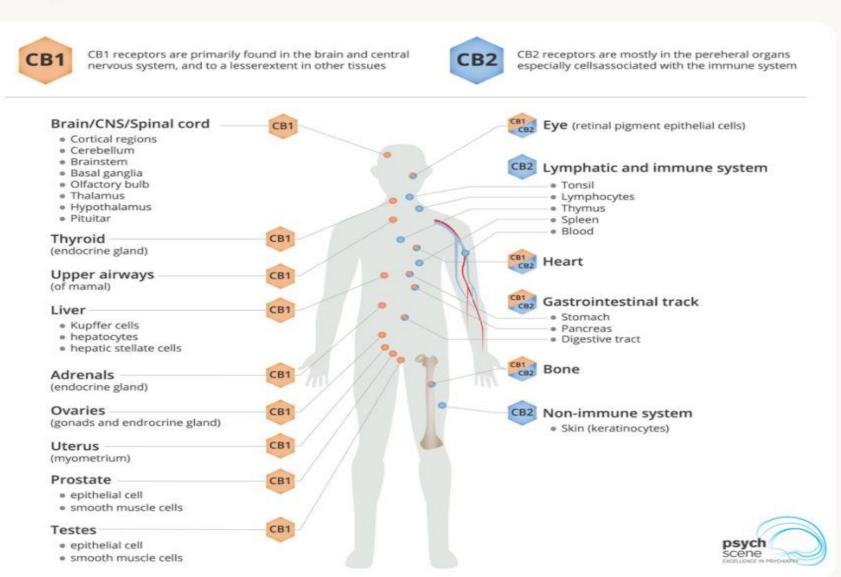




Endocannabinoid System

CANNABINOID RECEPTOR

The cannabinoid receptors are G protein-coupled receptors that are activated by endocannabinoids or exogenous agonists such as tetrahydrocannabinol. CBD does not directly fit CB1 or CB2 rceptors but has powerful indirect effects still being studied.





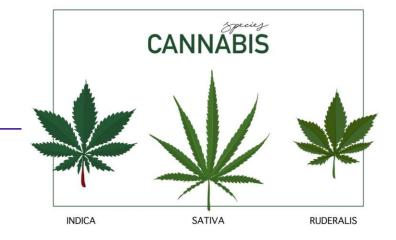
Endocannabinoids (eCB)

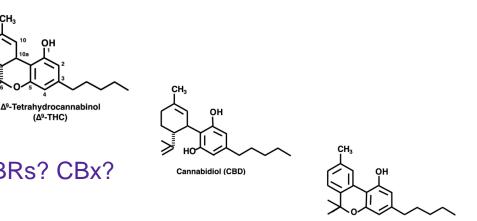
- 2-arachidonoylglycerol (2-AG)
- anandamide (AEA) [N-arachidonoylethanolamide]

Cannabis

- Derived from Indian hemp plants (Cannabis sativa, indica, ruderalis)
- 3 main psychoactive ingredients (phytocannabinoids):
 - Δ^9 -tetrahydrocannabinol (THC) [dronabinol: synthetic Δ^9 -THC]
 - cannabidiol (CBD)
 - cannabinol (CBN) [25% potency of THC]
- THC MoA agonist at CB1 receptors in CNS

 agonist at CB2 receptors in PNS
- CBD MoA allosteric modulator? indirect antagonist of CBRs? CBx?
- CNS depressant; Hallucinogenic effects in large doses
- Most commonly & frequently used illicit drug amongst Australians aged over 14*
 - 36% have used in their lifetime
 - 11.6% have used in the last 12 months
 - 37% of cannabis users using it weekly or more often





Cannabinol (CBN)

Potency of cannabis and perception of risk from cannabis use among adolescents, Europe and FIG. 27 United States, 1995–2019

Perception among adolescents of Cannabis potency (Δ9-THC content) risk/harm of smoking cannabis regularly in cannabis herb 16 80 14 70 12 Percentage 60 10 50 8 40 6 30 20 4 2 10 0 0 1995 1999 2001 2005 2005 2009 2011 2013 2013 2013 2013 2013 2013 1<mark>999</mark> 1997 1995 2001 2005 2005 2007 2009 2011 2013 2013 2015 2015 2019 2019 1997 Europe Linear trend (Europe) United states Linear Trend (United States)

Percentage

Page 6



Marijuana usually mixed with tobacco (& very occ'ly speed/ice/cocaine/heroin) in a "mull bowl" \rightarrow "mull" or "mix"



Cannabis Misuse in Mental Illness



Why do people with severe mental illness (SMI) use cannabis?

Main reasons given:

- reduce boredom
- to socialise
- to enjoy positive mood from intoxication

Nearly half of patients use cannabis:

- to get relief from dysphoria & agitation
- to sleep better

A minority use it to reduce their suspiciousness

Self-medication has been proposed as a reason (yet to be supported by research evidence)

The CBD in cannabis has anti-anxiety & anti-psychotic effects

(but street cannabis contains very small quantity of CBD & high quantity of THC)

None of the models proposed explain the interaction b/SMI & substance use disorder nor has a satisfactory evidence base & it is thought that a multiple risk factor model is needed.

Reasons For Use Scale ①

Which drug do you use the most or causes most concern for you? (Write drug name here): Manguan

Considering your current use of that substance, how often do you use that drug for the following reasons? (Tick a box for each reason)

14.1		1 Almost never/ never	2 Some of the time	3 Half of the time	4 Most of the time	5 Aimost always/ always			1 Almost never/ never	2 Some of the time	3 Half of the time	4 Most of the time	5 Almost always/ always
1	To relieve boredom				V		14	To get away from the voices	V				
2	To make it easier to sleep		1				15	Because you feel more self confident and sure	./				
3	To slow down racing thoughts		V				16	of yourself Because it helps when	V		6233		
4	To be sociable	V						you feel nervous	V				
5	To relax	See.			~		17	Because it's what most of your friends do when you get together		~			
6	To be part of a group	V	2.7				18	As a way to celebrate	~			1	
7	To get high			\checkmark	WH		19	To decrease restlessness (huma)		1.00	V		
8	To decrease (うう suspiciousness / paranola	F	V		5		20	Help me concentrate	V				
9	To forget your worries	V					21	Because your friends pressure you to do it	\checkmark				
10	Because it's fun	1					22	To be liked	V				
11	To reduce side effects of medication	V					23	So you won't feel left out	V		Sector L	103.0 5	1 97.2
12	Because it makes a social gathering more enjoyable	\checkmark			- 1		24	It helps when you feel	1		itelli indi		
13	To help you talk to others	\checkmark				1993		depressed heren:	V				-
	1					A	25	To feel more motivated	1 7		?		
5	Spencer, Castle, Michie, 200	2: based on D	MQ: Cooper	1994 (with a	iditional item	s).	26	Because it makes you feel good		V			

Synthetic cannabinoids

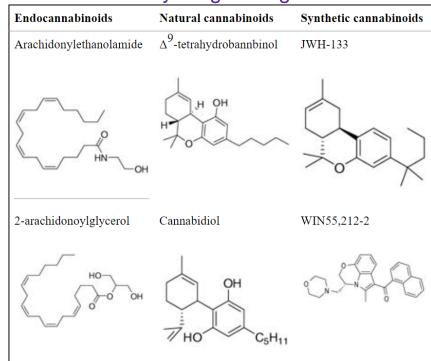


• CB-1 and CB-2 agonists

- Synthetic cannabinoid families (e.g. AM-xxx, CP-xx,xxx, HU-xx, JWH-xxx) which are classified by the creator of the substance; e.g. benzoylindole, cyclohexylphenol, naphthoylindole, phenylacetylindole
- aka Kronic, K2, Karma, Spice, Voodoo, Aroma and Dream (sold with herbal substances)
- most synthetic cannabinoid receptor agonists show **higher affinity** for CB1 (and CB2) receptors than THC (**† toxicity risk**)
- not able to be detected by most pathology labs ⇒ use in occupations where mandatory drug testing occurs







Medicinal cannabis – clinical decisions



- Varying proportions of CBD:THC
- Formulations: capsule, oil/oral liquid, flower
- Multiple suppliers
- Varying cost / value for \$







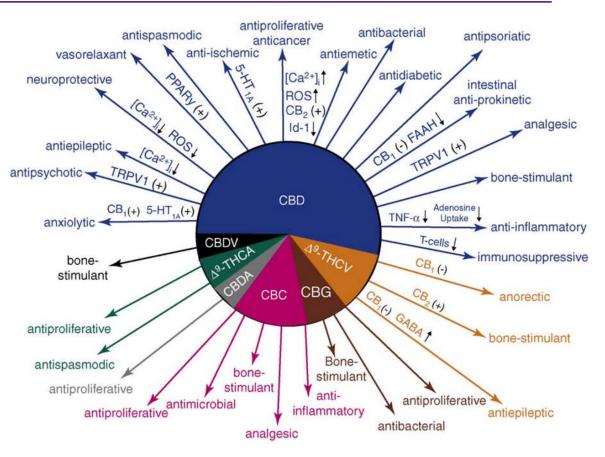


THC vs CBD



ТНС	CBD
Intoxicating	Non-intoxicating
Anti-inflammatory and reduces pain	Anti-inflammatory and reduces pain
May improve appetite	May reduce anxiety
May reduce nausea	Anticonvulsant
May help with insomnia	Regulate THC effects

https://www.xativahub.com/cannabis



Izzo AA, Borrelli F, Capasso R, Di Marzo V, Mechoulam R. Non-psychotropic plant cannabinoids: netherapeutic opportunities from an ancient herb. Trends Pharmacol Sci. 2009 Oct;30(10):515-27. doi: 10.1016/j.tips.2009.07.006. Epub 2009 Sep 2. Erratum in: Trends Pharmacol Sci. 2009 Dec;30(12):609. PMID: 19729208.

https://www.cell.com/trends/pharmacological-sciences/pdf/S0165-6147(09)00182-5.pdf

Effects of tetrahydrocannabinol (THC) and cannabidiol (CBD)



Effect	THC	CBD
Receptor/Non-Receptor Effects		
CB1 (CNS/PNS receptors)	++	±
CB2 (peripheral receptors	+	±
Vanilloid (TRPV1) receptors	-	-
Anti-inflammatory	+	+
COX-1, COX-2 inhibition	-	-
Immunomodulatory	+	+
CNS Effects		
Anticonvulsant	+	++
Muscle relaxant	++	+
Antinociceptive	++	+
Psychotropic	++	-
Anxiolytic	±	++
Antipsychotic	-	++
Neuroprotective antioxidant	+	++
Antiemetic	++	+
Sedation	+	-
Agitation (Alzheimer disease)	+	-
Tic reduction (Tourette syndrome)	+	?
Opiate withdrawal reduction	+	?

Russo E, Guy GW. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol.

Med Hypotheses. 2006;66(2):234-46.

doi: 10.1016/j.mehy.2005.08.026. Epub 2005 Oct 4. PMID: 16209908.

Effect	THC	CBD
Migraine treatment	+	+
Bipolar disease	+	?
Dystonia		+
Parkinsonian symptoms	+	2
Withdrawal symptoms to other drugs (reduction)	+	+
Motor neurone disease (ALS) (increased survival, function)	+	+
Cardiovascular Effects		
Bradycardia	-	+
Tachycardia	+	
Hypertension	+	-
Hypotension		+
Appetite/Gastrointestinal		
Appetite	+	
GI motility (slowed)	++	+
Anti-Carcinogenesis		-
Glioma (apoptosis)	+	+
Glioma cell migration		+
Ophthalmological		
Intra-ocular pressure (reduced)	++	+
Night vision	+	

CBD only	THC only	THC + CBD		
Anxiety	Anxiety	Anxiety		
ASD		ASD		
Cancer pain & Sx Mx	Cancer pain & Sx Mx	Cancer pain & Sx Mx		
Chronic pain	Chronic pain	Chronic pain		
Epilepsy				
Migraine	Migraine			
Movement disorder		Movement disorder		
Multiple Sclerosis				
		Nausea		
Neuropathic pain	Neuropathic pain	Neuropathic pain		
Palliative care	Palliative care	Palliative care		
Sarcoidosis				
Sleep disorder	Sleep disorder			
Tinnitus				
Tourette Syndrome				



TGAapproved indications [formulationdependent]

Formulations / Delivery methods & Pharmacokinetics



Inhalation	Bioavailability Onset of action Peak effect Duration of action	10-35% 5-10 min 15-30 min 2-3 hrs	Pros Rapid onset (PRN), shorter therapeutic duration. Mitigate GI upset. Cons Inhalation may have negative impact on lungs. Titration challenges. Vaporisers are expensive. Ability to medicate in public without unwanted attention is difficult. Higher risk of tolerance development.
Oromucosal	Bioavailability Onset of action Peak effect Duration of action	6-19% 15-45 min 2-4 hrs 6-8 hrs	Pros Duration good for chronic conditions. Clinically proven products available. Mitigate Gl upset. Cons Expensive. Products with low terpenes may have more absorption challenges.
Oral/Sublingual	Bioavailability Onset of action Peak effect Duration of action	6-19% 1-1.5 hrs 2-4 hrs 6-8 hrs	Pros Duration good for chronic conditions. Easier than inhalation to find therapeutic dose. Cons Possibility of GI upset.
	Bioavailability Onset of action Peak effect Duration of action	Varies Varies Varies Varies	Pros Good for localised symptoms. Cons Limited availability in Australia. Only localised effects.

https://catalyst.honahlee.com.au/article/cannabis-delivery-methods-quick-guide/

Use in Psychiatry



TGA-approved

- Anxiety
- ADHD
- ASD
- PTSD
- Sleep disorder

TGA Non-Approved

- Cannabis Use Disorder
- Depression
- Psychosis
- Bipolar Disorder

Contraindications, Adverse effects and Drug interactions

Contraindications

- Young people <25yo (potential adverse effects on developing brain) [NB: use in severe, treatment-resistant epilepsy in children]
- Pregnancy/lactation
- Cardiac history severe and unstable heart disease (angina, peripheral vascular disease, cerebrovascular disease and arrhythmias) or risk factors for heart disease

Adverse / Undesirable Effects

Increased heart rate, dizziness, impaired coordination and reaction times, drowsiness, impaired short-term memory, dry mouth, nausea, anxiety, respiratory irritation (if inhaled), increased appetite, euphoria

Drug interactions

- 1. Medicinal cannabis can interact with other medicines, particularly **other CNS depressants**, causing drowsiness and potentiating any side effects; this also applies to **alcohol**.
- 2. Pharmacokinetics:
- Metabolism: THC (2C9, 3A4), CBD (2C19, 3A4), CBN (2C9, 3A4)
- THC (& tobacco smoking): induces 1A2 (clozapine, olanzapine), inhibits 2C9, 3A4
- CBD: inhibits 1A2 (CLZ, OLZ), 2D6 (antidepressants, antipsychotics), 3A4 (AED), UDP-glucuronosyltransferases UGT1A9 and 2B7, (?) P glycoprotein (P-gp)

References:

Medicinal Cannabis—Potential Drug Interactions

Specific examples: [not an exhaustive list]

- Anti-depressants (fluoxetine, fluvoxamine)
- Anti-coagulants (warfarin, apixaban, rivaroxaban)
- · Antiretroviral drugs used in the treatment of HIV/AIDS
- Stomach acid inhibitors (omeprazole)
- Certain antibiotic and antifungal medications (ketoconazole, itraconazole, ritonavir, clarithromycin; rifampicin)
- Some heart medications (amiodarone, diltiazem, verapamil)
- Some anti-epileptic medications (carbamazepine, phenytoin, clobazam)
- St John's Wort
- Cannabinoid Metabolites as Inhibitors of Major Hepatic CYP450 Enzymes, with Implications for Cannabis-Drug Interactions
- Sativex Product Information (PI); Spectrum Cannabis Softgels Consumer Medicine Information (CMI)

Medicinal Cannabis		THC/unit	CBD/unit	Amount/Volume	Total THC content	Total CBD content	Cost	THC cost/mg	CBD cost/mg	Cost/mg	
Brand	Product	(mg)	•	-				\$ \$/m			
Spectrum gel (CBD/THC)	Spectrum Cannabis Yellow Softgels 20mg	<1				600		70	0.12		
Spectrum gel (CBD/THC)	Spectrum Cannabis Blue Softgels 2.5mg	2.5	3.75			225		70 0.4			
Spectrum gel (THC/CBD)	Spectrum Cannabis Red Softgels 2.5mg	2.5	<1	60	150		(55 O.	5		Nexu
Spectrum gel (THC/CBD)	Spectrum Cannabis Red Softgels 10mg	10	<1	30	300		-	75 0.2	5		Dural Diagnostic Consultation Son
		(mg/mL)	(mg/mL)	(mL)	(mg)	(mg)		\$ \$/m	g		Dual Diagnosis Consultation Serv
Spectrum liquid (CBD/THC)	Spectrum Therapeutics Cannabis Oil Yellow Oral Liquid	<1		40		800		95	0.12	2	
Spectrum liquid (CBD/THC)	Spectrum Therapeutics Cannabis Oil Blue Oral Liquid	10	15	40	400	600) 11	LO 0.2	8 0.18	3	
Spectrum liquid (THC/CBD)	Spectrum Therapeutics Cannabis Oil Red Oral Liquid	26.3	<1	40	1052		11	LO 0.1	0		
Spectrum liquid (CBD/THC)	Spectrum Therapeutics Cannabis Oil White Oral Liquid	0	100	50		5000	29	95	0.06	5	
		(mg)	(mg)	(wafers)	(mg)	(mg)		\$ \$/m	g \$/mg	S	
X Syrinx Pty Ltd (CBD) wfr	iX Biopharma Xativa sublingual wafers 12.5mg S4	0						39	0.12		
X Syrinx Pty Ltd (CBD) wfr	iX Biopharma Xativa sublingual wafers 25mg S4	0	25	60	0	1500) 14	16	0.10	0.097	
Cannatrek (CBD) oil	C25 Sunstone 25mg CBD capsules S8	0	25	60	0	1500) 15	50	0.1	L 0.1	
Cannatrek (CBD) oil	C115 Sunstone CBD oil (115mg/mL) S8	0	115	30 mL	. 0	3450	24	15	0.07	0.07	
Cannatrek (CBD/THC) oil	C20 (20:1mg/mL) CBD oil S8 (new - C25 - 25:1)	<1	20	25mL	. <25	500) 10)5 4.	2 0.21	L 0.2	
Cannatrek (CBD/THC) oil	C100 Amber (100:4 mg/mL) CBD oil S8	<4	100	30mL	. 120	3000	25	55 2.12	5 0.085	0.08	
Cannatrek (CBD/THC) oil	C200 Amber (200:8 mg/mL) CBD oil	<8	200	30mL	. 240	6000	42	25 1.7	7 0.07	0.069	
Cannatrek (CBD/THC) oil	C20T5 Ruby (20:5 mg/mL) CBD oil S8	5	20	30mL	. 150	600) 9	90 0.	6 0.15	0.12	
Cannatrek (CBD/THC) oil	C12T12 Ruby (12.5:12.5 mg/mL) balanced CBD oil S8	12.5	12.5	30mL	. 375	375	5	0.2	4 0.24	0.12	
Cannatrek (THC) oil	T20 Indica oil (THC 20mg/mL) S8	20	0	25	500		\$10)5 0.2	1	0.21	
Cannatrek (THC) oil	T25 Ruby oil (THC 25mg/mL) S8	25	0	30	750		9	90 0.1	2	0.12	
								\$			
Beacon	Girl Scout cookies (10g)						15	50			
Cannatrek flowers (THC)	T15 Flower (Sativa Avadia) - 60% Sativa:40% Indica - S8	15%	0	10gm	1500	0) 17	70 0.1	1	0.11	
lower (THC)	T18 Flower (Uplift Lemnos)- 60% Sativa:40% Indica - S8	18%	0	10gm	1800	0	17	70 0.0	9	0.09	
lower (THC)	T19 Flower (Beersheba) - 70% Sativa:30% Indica - S8	19%	0	10gm	n 1700	0) 15	50 0.0	9	0.09	
Flower (THC)	T17 Flower (Jerusalem) - 50% Sativa:50% Indica - S8	17%	0	10gm	n 1700	0	15	50 0.0	9	0.09	
Flower (THC)	T18 Flower (Jasmine) - 5% Sativa: 95% Indica - S8	18%	0	10gm	1800	0) 15	50 0.0	9	0.09	
Flower (THC)	T20 Flower (Relax Daylesford)- 30%Sativa:70%Indica-S8	20%	0	10gm	2000	0	17	70 0.0	8	0.08	
Medical Vapouriser devices	3 approved TGA devices (150+\$, 500\$, 800\$)										
Dry Herb Vaporisers											



For nurse and medical practitioners seeking to prescribe a medicinal cannabis product not included in the Australian Register of Therapeutic Goods (ARTG), Therapeutic Goods Administration (TGA) approval is required.

- TGA's Special Access Scheme
- Authorised Prescriber ('established history of use'; must report the number of patients treated every 6 months; "Treatment of refractory anxiety [and/or chronic pain] in adult patients")

New SAS submission							
		Lookup records					
Prescriber details	The TGA regulates therapeutic goods as either Medicines , Biologicals or Medical Devices . These definitions may differ from those used in the clinical setting. For example, the TGA regulates blood products as medicines and not biologicals. It is recommended that you search all three therapeutic good types <i>before</i> utilising the free text function. If you use the free text function and categorise your product incorrectly, you will be asked to withdraw the application/notification and create a new submission.	category Q					
Product	Therapeutic Good Type * Medicine	✓ Name ♠					
selection	Medicine Biological Medical Device	Category 1-CBD medicinal cannabis product (CBD≥98%)					
		Category 2-CBD dominant medicinal cannabis product (CBD≥60% and less than 98%)					
Product details	Medicine Please use the search below to make your product selection (including active ingredient, dosage form	Category 3-Balanced medicinal cannabis product (CBD less than 60% and ≥40%)					
	and indication).	Category 4-THC dominant medicinal cannabis product (THC 60-98%)					
Patient details	Active ingredient(s) *	Category 5-THC medicinal cannabis product (THC greater than 98%)					
	The active ingredient(s) I need could not be found through the search tool						
Summary	Patient has chronic generalised anxiety which has not resp treatment including prescription medications and psychology	Ociciti Galicel Handre Handre					
	4-weekly monitoring; 2-year permit	Page 18					

Victorian Department of Health – Medicines and Poisons Regulation (MPR)



- Any doctor or nurse practitioner in Victoria can prescribe medicinal cannabis for any patient with any condition, if they believe it is clinically appropriate to do so.
- **Commonwealth** and/or state approvals may be required
- From 28 February 2022, prescribers no longer require a Schedule 8 treatment permit from the Victorian Department of Health when prescribing a Schedule 8 medicinal cannabis product to non-drug dependent patients
- For drug-dependent patients, an application for a treatment permit can be made Application for a permit to treat a patient with Schedule 8 drugs form [specify pt is drug-dependent]
- Prescribers are still required to check SafeScript each time before prescribing any Schedule 8 medicinal cannabis products to any patient."

Medicinal cannabis

Prescribing medicinal cannabis

https://www.health.vic.gov.au/drugs-and-poisons/medicinal-cannabis

Informed Consent



Informed consent should include an adequate knowledge of:

- the condition and its consequences
- treatment options
- the likelihood of recovery
- the long-term prognosis
- Patients should be specifically informed:
 - of the possible benefits of treatment and any known risks and side effects
 - that unknown risks and late side effects are possible
 - of any alternative treatments using approved products which are available
- Driving:
 - Medicinal cannabis [THC>>CBD] can impair a patient's ability to drive and/or operate machinery due to the risk of experiencing drowsiness [and other neurocognitive effects].
 - "Patients treated with medicinal cannabis should not drive or operate machinery."
 - THC can be detected in saliva for many hours after administration and in urine many days after the last dose.
 - Patients may be charged with drug-driving if THC is detected in their saliva or urine.

Case vignettes



55yo woman with COPD who continues to smoke cannabis (and tobacco) for anxiety and insomnia. Problems accessing cannabis with 5km lockdown restriction

- Trialled THC/CBD 2.5/3.75mg capsule
- Started stronger formulations of THC/CBD THC 10 mg/CBD <1 mg cap.; THC <1 mg/CBD 20 mg cap.

30yo woman living alone referred for anxiety symptoms. Smoking cannabis 1-2g/d supplied by b/friend 'for free'. Commenced THC/CBD 2.5/3.75mg capsule. Partner increasingly hostile; places ice pipe on coffee table.

Substance use coercion – perpetrators of intimate partner violence undermine and control their partners through substance use related tactics and actively keep them from meeting treatment and recovery goals.



60yo woman with BPD, Alcohol use disorder, cannabis use disorder

- Wanted to reduce cannabis 1g/d (28g/month)
- Trialled THC/CBD 10/15 mg/mL; oral liquid (oil)
- Cost reduced from \$300/month -> \$220/month

37yo woman – cannabis (\$400/wk with partner) for anxiety and insomnia

- Commenced THC/CBD 2.5/3.75mg capsule
- -> \$270 /week (~ 2/3) [lower, less intoxicating dose]

Case vignette



45yo woman, employed, high functioning. Mood and psychotic symtpoms (paranoia)

- CBD wafers, Adherence Tx, ↓THC (self, but ↓)
- Progress ↑adherence / ↓THC / ↓psychosis

Synthetic Δ-9-Tetrahydrocannabinol (Dronabinol) Can Improve the Symptoms of Schizophrenia

Schwarcz, Glenn MD^{*†‡}; Karajgi, Basawaraj MD^{*}; McCarthy, Richard MD, PhD^{§∥}

Author Information⊗

4 of 6 treatment-refractory patients with severe chronic schizophrenia but who had a self-reported history of improving with marijuana abuse improved with dronabinol. This improvement seems to have been a reduction of core psychotic symptoms in 3 of the 4 responders and not just nonspecific calming.

Take home messages



- Can be effective for anxiety disorders
- Can be useful for harm reduction in current cannabis users [anecdotal evidence]:
 - Financial harm
 - COPD
 - Family/IPV violence
 - Reduced psychotic symptoms (CBD formulations only)
 - BUT ? duration of therapy, tapering/cessation process

? harm reduction/substitution for other substances, e.g. stimulants and (illicit) opioids Risk of losing licence for drug driving (CBD-only formulations; rinse mouth if THC-containing preparations, especially oils)

- TGA permit process: Psychiatrist? GP with letter from psychiatrist?
- Consider addressing tobacco/nicotine

Further reading



General

https://www.reddit.com/r/MedicalCannabisAus/comments/jwbbjd/new_to_medical_cannabis_here_are_the_best/ https://www.reddit.com/r/MedicalCannabisAus/wiki/index https://cannareviewsau.co/ https://cannareviewsau.co/products_[registration required]

Prescribers

https://www.medihuanna.com/ https://catalyst.honahlee.com.au/app

Patients

https://cannareviewsau.co/cannabis-clinic-price-comparison https://honahlee.com.au/



We recognise and value the knowledge and wisdom of people with lived/living experience, their supporters and the practitioners who work with them. We celebrate their strengths and acknowledge the important contribution that they make to the development and delivery of health and community services.







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