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CLINICAL PERSPECTIVES

Cannabis: are there any benefits?

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Abstract

Cannabis has been used as a medicine for millennia. Prohibition in the mid-20th century precluded early scientific investigation. 'Cannabis' describes three separate forms – herbal cannabis, 'hemp' products, pharmaceutical-grade regulated cannabinoid-based medical products (CBMP). In Australia, CBMP became available for prescription in November 2016. Herbal cannabis with Δ9-tetrahydrocannabinol (THC), which is illegal, and cannabidiol (CBD) in herbal extracts, are both unregulated and unreliable sources of cannabinoids. The endocannabinoid system (ECS), delineated in the late 1990s, has increased the understanding and interest in research for appropriate clinical indications. The ubiquitous ECS has homeostatic and anti-inflammatory effects and comprises cannabinoid receptors, endocannabinoids and degrading enzymes. Phytocannabinoids are partial agonists of the ECS. In pre-clinical studies, THC and CBD produce beneficial effects in chronic pain, anxiety, sleep and inflammation. Systematic reviews often conflate herbal cannabis and CBMP, confusing the evidence. Currently large randomised controlled trials are unlikely to be achieved. Other methodologies with quality endpoints are required. Rich, valuable high-quality real-world evidence for the safe and effective use of CBMP provides an opportunity to examine benefits and potential harms. Evidence demonstrates benefit of CBMP in multiple sclerosis, chronic neuropathic pain, chemotherapy induced nausea and vomiting, resistant paediatric epilepsy, anxiety and insomnia. CBMP are well tolerated with few serious adverse events. Additional clinical benefits are promising in many other resistant chronic conditions. Pharmaceutical grade prescribed CBMP has proven clinical benefits and provides another clinical option in the physician's pharmacopeia.

History of cannabinoid-based medicine products

Medical use of cannabis has been practiced for millennia and pre-dates recorded human history.[1,2] Until the mid-20th century medicinal cannabis, in tinctures, oils and flower, was prescribed and included in the pharmacopeia of most countries.[3,4] In the 1890s, cannabis was prescribed to Queen Victoria for period pain (most likely due to endometriosis).[5] However, despite its widespread support at that time from august medical associations and physicians,[4] taxation and United States of America prohibition in the 1930s effectively banned its use and legal scientific research[6] until very recently. Pharmaceutical grade cannabinoids have not been available until early this century.

In Australia, there is confusion in the press, the public and the medical profession about the term 'medicinal cannabis'. This confusion leads to misapprehension and misunderstanding of the benefits and harms of medicinal cannabis. For ease of nomenclature, we will refer to three types of 'medicinal cannabis' – the herbal cannabis plant or flower, imported or local 'hemp' products and Good Manufacturing Practice (GMP) cannabinoid-based medicine products (CBMP). First, in Australia the harvested 'herbal cannabis' is derived from the plant or flower. It is an unregulated, largely illegal botanical of unknown quality with high batch-to-batch variability and unknowable concentrations of many hundreds of active and inactive cannabinoids, flavonoids and terpenes. This product is generally smoked or ingested, most often for the euphoric intoxicating effects as a recreational product.

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Second, the 'hemp' products imported online and sold in specialty nutraceutical shops are of limited value as there is little regulation, veracity of concentration or stability of products. In the United Kingdom where cannabidiol (CBD) products are available over the counter and by importation, a recent nationwide review[7] found that 40% contained no cannabinoids at all, 20% contained Δ9-tetrahydrocannabinol (THC), which is illegal in the United Kingdom, and 20% contained inactive carboxylated cannabinoids. The report concluded that 'there's no guarantee these [CBD products] are of good quality or provide any health benefits'.

Third, CBMP, extracted to pharmaceutical-grade GMP. In Australia, these products are regulated by the Office of Drug Control and the Therapeutic Goods Administration (TGA). Access for prescription by medical practitioners is via the authorised prescriber or special access schemes. These CBMP are subject to strict pharmaceutical-grade regulation of extraction, dosing, formulation, concentration and stability. In Australia, this extraction and isolation process is confined to the two major phytocannabinoids, cannabinoids that occur naturally in the cannabis plant, Δ9-THC and CBD with the products containing less than 1% of the other cannabinoids. Most CBMP prescribed in Australia contain a combination of THC and CBD in differing concentrations in oil, alcohol-based sprays, capsules, tablets or wafers. The combinations of products range from purified CBD only, CBD rich products with low concentrations of THC, to balanced THC and CBD one-to-one ratio and TCH rich with high THC and low CBD products or THC only products. This high-level regulation in Australia provides an unprecedented opportunity for research compared to other jurisdictions where unregulated cannabinoids of unknown dosing and absorption are used widely as prescribed and self-medicated 'cannabis'. This allows Australian clinicians to examine and research the effectiveness and relative safety of CBMP in appropriate chronic conditions in those who have exhausted conventional therapies.

Pharmacology of CBMP

The molecule THC was first described in the 1960s[8] with CBD described in 1968.[9] They are 21-carbon lipid-soluble aromatic terpenoids that are partial agonists for the human endocannabinoid system (ECS). The human ECS was first described in the 1990s and has been found to be ubiquitous in human body systems and also found in all studied invertebrates and vertebrates.[10]

The ECS includes three components[11] (Fig. 1):

1 *Receptors*: CB1 (found principally in the central nervous system) CB2 (primarily expressed in immune cells) and Transient receptor potential vanilloid 1(TRPV1)[13]
2 *Endocannabinoids*: anandamide (AEA), and 2-arachidonoylglycerol (2-AG), and
3 *Degrading enzymes*: fatty acid amide hydrolase (FAAH), and monoacylglycerol lipase (MAGL)

The ECS is involved in homeostatic functions in the brain, skin, digestive tract, liver, cardiovascular system, genitourinary function and even bone.[14] The ECS also interacts with mu opioid receptors of opioid signaling.[15,16]

The pharmacokinetics of THC and CBD and the effects observed depend on the formulation and route of administration. However, oral ingestion limits consistent absorption of both molecules due to their lipophilic nature, which may lead to poor solubility. Additionally, some excipients may inhibit intestinal metabolism and medium chain triglycerides may enhance bioavailability.[17] The peak serum concentration for oral oil-based medication occurs approximately 1.5 h after ingestion in a standardised oil-based oral cannabinoid formulation and is at low untherapeutic levels after 5–6 h but may remain detectable. Both THC and CBD are hepatically metabolised, the potential exists for drug interactions via inhibition or induction of cytochrome p450 enzymes or transporters.[18] The metabolism of THC is predominantly hepatic, via cytochrome P450 (CYP 450) isozymes CYP2C9, CYP2C19 and CYP3A4. CBD is also hepatically metabolised, primarily by isozymes CYP2C19 and CYP3A4 and additionally, CYP1A1, CYP1A2, CYP2C9 and CYP2D6.[19] Such pharmacokinetic interactions may occur and care should be taken when prescribing with other hepatically metabolised medications. Vulnerable populations, such as older patients, may be at increased risk of adverse effects.[19] There continue to be limited studies of pharmacokinetic and pharmacodynamic properties for CBMP. This highlights the need to initiate prescribing of CBMP using a □start low and go slow approach. All patients commenced on CBMP require careful monitoring and observation, particularly the elderly and those with polypharmacy to achieve optimal effects and avoid adverse events.[19]

The evidence for CBMP

The evidence for the effectiveness of CBMP in specific indications is hampered by a lack of high-quality appropriately powered randomized controlled trials (RCT) and by the publication of many systematic reviews which conflate trials with differing types of medicinal cannabis such as CBMP with recreational products. Public and

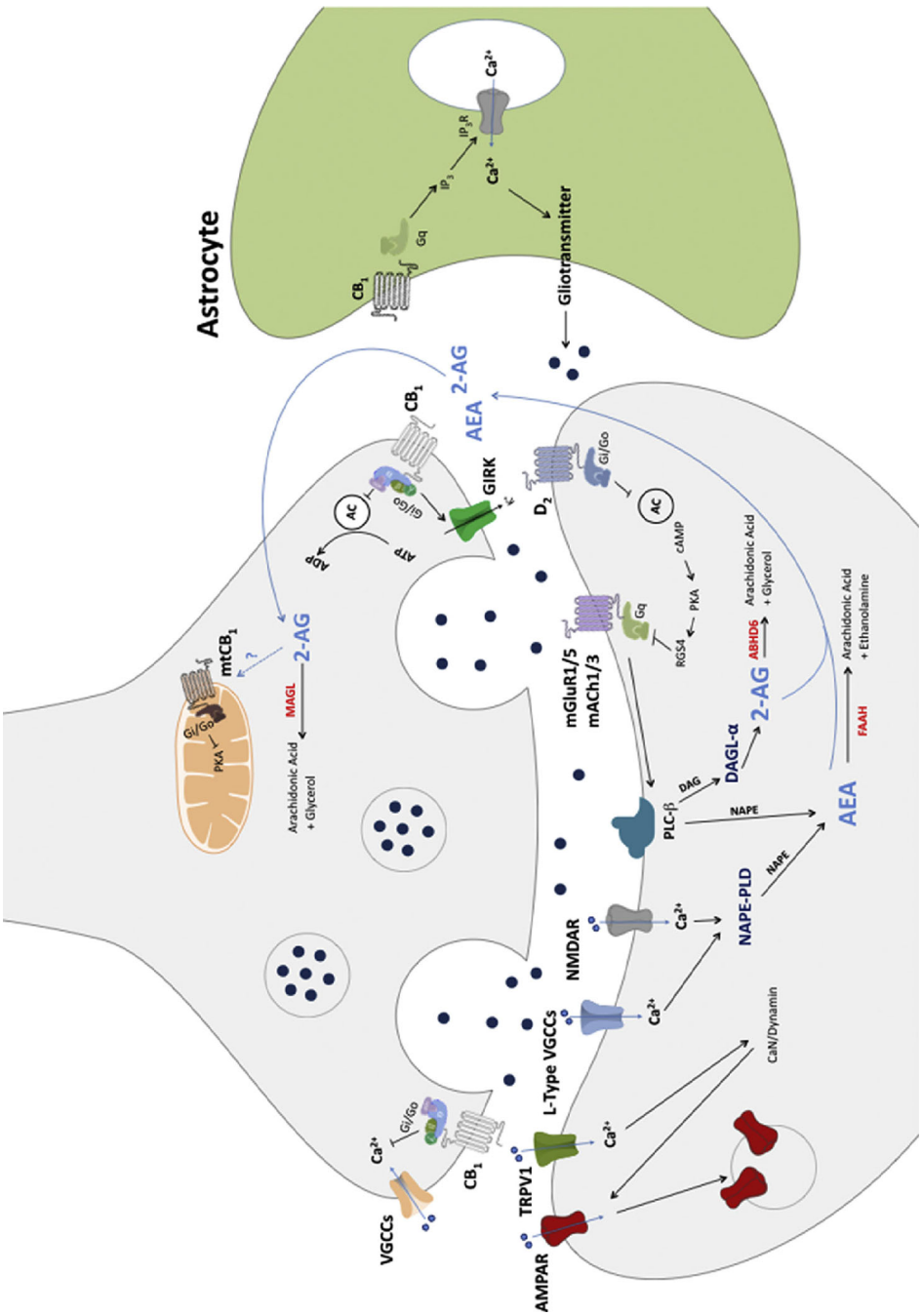

Figure 1 The endocannabinoid system. (Reproduced from Araque *et al.*,[12] with permission.)

political pressure for access to medicinal cannabis has propelled access to these products in Australia by sometimes favourable and largely uncritical internet and media views of the benefits and safety of cannabis. This has enabled cannabinoids to bypass the usual research and regulatory processes required with pharmaceutical registration before widespread clinical use. A large systematic review[20] of over 10 000 such conflated studies, made over 100 recommendations which largely influenced the Australian TGA to be 'moderately confident' to support prescription for specific approved conditions. The review found evidence for the use of medicinal cannabis in: spasticity and neuropathic pain in multiple sclerosis,[21] chronic noncancer pain,[22,23] chemotherapy-induced nausea and vomiting[22,24] and medication resistant epilepsy.[25] However, other systematic reviews have been inconclusive and often contradictory.

In Australia, the prescriptions for CBMP since November 2016 have been accelerating such that over 3000 special access approvals are given each month by the TGA, not including a similar number of authorised prescriber prescriptions. More than 10 000 individuals in Australia are currently thought to be taking regular CBMP. Surveys of patients with chronic non-cancer pain before legalised CBMP was available found that 15–20% of those with chronic non-cancer pain have tried imported or illegal cannabis[26] and 35% of patients have asked their GP about cannabinoid therapy.[27]

The issues that inhibit the conventional research and development of a pharmaceutical approach involving large high-quality RCT include: the licensing and copyright for the components of an extracted botanical oil, the very recent and small research budgets of producers and the complexity of investigating the large number and concentration of different cannabinoids, securing research funding for recently illegal medicines under the narcotics Act, navigating the varied jurisdictional cannabis regulatory requirements and obtaining ethics approval.[28]

Given these barriers for RCT, we need feasible, ethical and more sophisticated research models to help better analyse the efficacy and safety of CBMP. Real-world data (RWD) is a mechanism for breaching the evidentiary gap between controlled research and clinical practice. RWD is a study design that was used for instance for the discovery that Vitamin C deficiency caused scurvy or for neostigmine and myasthenia gravis and is most effective when there is a predictable and substantial outcome. Newly available large data sets and e-health records have afforded even stronger causal inferences to be drawn using statistical modelling such as propensity and interventional matching mitigating many confounding factors. However, randomisation is the key to drawing causal inferences and such statistical methods can provide counterfactual analysis to improve evidence that outcomes are directly attributable to the intervention.[29] Further the addition of patient-initiated data such as with health device wearables or on-line data capture can further expand the comprehensive patient data to non-clinical environments and beyond clinical contacts. It is important that real-world evidence (RWE) is used to complement rather than replace RCT evidence on CBMP but it provides another evidentiary mechanism.

Data sets drawn from standard administrative and clinical eHealth records have limitations as often the data can be unstructured, incomplete or inconsistent. The development of robust data systems with auditing and compliance mechanisms to ensure rigorous and comprehensive data capture produces high-quality RWD and subsequently worthwhile RWE. Health care technology companies that create RWE for medical science, health payers, and regulatory agencies can provide, via these mechanisms, standardised, comprehensive and consistent data platforms for such analysis. RWD contributes to the generation of evidence complementing the existing knowledge for the use of CBMP. More importantly for CBMP, now prescribed to more than 10 000 Australians, it provides guidelines on safety and tolerability. Such analysis can guide product development, commercialisation and payment innovation into new products or formulations. Therapeutic access to 'unapproved' TGA products requires quality real-world analysis to provide post-prescription surveillance and pharmacovigilance systems not only to address safety and tolerability but to gauge off-label use or unexpected adverse events in specific populations or conditions. Systematised data platforms analyse data from the real world to produce transparent, rapid and scientifically validated answers on costs, safety and clinical outcomes. This can inform the most critical decisions in relation to novel therapeutics such as CBMP – that is what works best, for whom and when.

Safety, side-effects and potential harms

Systematic reviews of the use of cannabis including unregulated herbal cannabis, synthetic cannabinoids and CBMP report serious adverse psychiatric effects such as psychosis, anxiety, mania and severe dysphoric reactions. Minor dose-related adverse effects have been reported with CBMP include somnolence/drowsiness, dizziness, dry mouth and nausea. Comparing cannabis to placebo reported both neurocognitive and non-cognitive adverse effects. However, many systematic reviews include unregulated recreational use with unknown dosage and concentrations.[30] The association between psychosis,

'psychosis-prone individuals' and high concentration of THC is related to heavy recreational usage.[31] Although there is no published literature on recreational THC dose, it is believed that an ounce (30 g) of 'herbal cannabis' per month in regular users contains between 10% and 20% THC, equivalent to 100–200 mg a day of THC.[32] In relation to efficacy a large Canadian 'systematic review of systematic reviews'[30] found that the number needed to treat (NNT) for CBMP was a wide range, between 3 and 20, for specific conditions and that the number needed to harm (NNH) was 5–8, but again this was largely on the basis of inhaled herbal cannabis and unregulated ingestibles. Further large-scale trials of CBMP will need to be completed to provide more certainty about the direct efficacy (NNT) and safety (NNH) in specific populations and conditions.

The literature regarding adverse events in relation to medicinal use of CBMP is mainly with the oro-mucosal spray nabixomols, a regulated registered balanced CBMP of 2.7 mg delta-9-THC and 2.5 mg CBD per spray for spasm and neuropathic pain in multiple sclerosis. Nabixomols have been found to be well tolerated in the elderly, in many varied conditions.[33] Side-effects have been mild or moderate, largely reversible and dose dependent.[34] Overdose of cannabis can lead to hallucinations, hyperemesis and ataxia; however, there is no known lethal dose of THC and no patient has ever been known to have died directly from intake of THC. A 1972 study gave up to 9000 mg/kg of THC to dogs and monkeys without any lethal effects.[35] There have been increasing case reports of cardiovascular deaths with high THC inhaled recreational cannabis use and the newer synthetic THC substitutes[36] and care and careful monitoring should be undertaken in prescribing CBMP for those at risk of cardiovascular disease.[37] However, the long-term effects of regular low-dose CBMP are not available and will require ongoing pharmacovigilance.

The future

There is growing evidence that demonstrates benefit of CBMP in multiple sclerosis, chronic neuropathic pain, chemotherapy induced nausea and vomiting, resistant paediatric epilepsy, anxiety and insomnia. CBMP are welltolerated with few serious adverse events. Additional clinical benefits are promising in many other resistant chronic conditions. Research utilising systematised and quality RWE is required to determine efficacy and safety in many chronic conditions and more needs to be done to determine the inter-individual pharmacokinetic variability as well as drug–drug and drug–disease interactions of the two major molecules, THC and CBD as well as the 100s of other cannabinoids. Care needs to be taken in insouciant use and prescription by medical practitioners and public pressure and hype in the lay literature for a multitude of clinical conditions need to be examined rigorously. Pharmaceutical grade prescribed CBMP has proven clinical benefits for specific indications and provides another clinical option in the physician's pharmacopeia.

Clinical case study

(This is a real-life case and consent and permission were provided by the patient. The name and some identifying historical details were altered to protect privacy. Medication, clinical outcomes and CBMP prescription are unchanged)

Ray describes a typical presentation to a specialised cannabinoid-based medicine (CBMP) clinic for chronic non-cancer pain (CNCP) having exhausted conventional therapy with concomitant post-traumatic stress disorder (PTSD), insomnia and vasculopathy. Ray is a 77-year-old, armed forces commander veteran with longstanding chronic neck, arm and back pain after deliberately leaping from a helicopter on a mission in Vietnam in 1968. His chronic pain from the injuries and numerous fractures has been worsening requiring multiple surgeries over the past 10 years, including: cervical (C5/6) fusion, lumbar (L4/5) laminectomy and pending(C6-T2) laminectomy. He has a longstanding vasculopathy requiring a carotid artery stent, and aorto–femoral–popliteal bypass but has a stable cardiovascular system currently. He has been diagnosed with war service PTSD and his sleep is severely disturbed by flashbacks and nightmares. Ray has been under numerous pain specialists and has had various numbers of nerve root sleeve injections and cryorhizotomies. His pain is inadequately controlled with opiates, pregabalin or antidepressants and he is taking benzodiazepines for his marked insomnia. Ray had exhausted all conventional medical and surgical therapy for his CNCP and was despondent and dejected by the prospect of living out his life as his pain increasingly worsened.

Case study outcomes

Ray was prescribed a balanced CBMP oil in September 2019 and he is currently taking 0.7 mL nocte (equivalent to 7 mg THC/7 mg CBD daily) 6 months later and had a remarkable transformation. He no longer experiences any neuropathic pain such that the burning in his legs and (L) arm pain has ceased. Ray was able to stop his opiates and other analgesics including tapentadol, amitriptyline and pregabalin over the last few months. He

Table 1 Results from validated standard questionnaires

		September 2019	March 2020
Pain	Severity	5	0
(BPI)	Interference	6.57	0.57
(VAS)	Analogue scale	9	0.5
Insomnia	Severity	23	4
Mental	Depression	4	0
(DASS-21)	Anxiety	0	0
	Stress	8	0
Function	Physical	55	70
(SF-36)	Emotional	56	92
	General health	35	70

BPI, Brief Pain Inventory; DASS-21, Depression, Anxiety and Stress Scale; SF-36, Rand SF-36 Health Survey; VAS, Visual Analogue Scale.

has had no side-effects and his insomnia has improved enormously. In particular, his dreaming has become less negative and the quality of his sleep has improved. His validated standardised questionnaires show a marked improvement (Table 1). He finds his demeanor has improved with more time for his family and his wife comments that his well-being has improved.

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Disclosure

Emerald Clinics is a health technology and clinical care initiative that co-creates with patients, RWE for novel therapeutic and technological interventions, to help determine – what works best, for whom and when. The clinics comprehensively assess patients for approved clinical conditions in whom conventional therapy has been exhausted and seeks TGA approval for access to CBMP which is prescribed via the special access scheme and then are monitored closely using standardised clinical assessments and questionnaires. Emerald Clinics is independent of all CBMP licenced producers. Dr A. W. Vickery holds stock in Emerald Clinics. Dr P. M. Finch holds stock in Emerald Clinics, Auscann Pty Ltd and Little Green Pharma.

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