CLINICAL UPDATE

Medical cannabis: What practitioners need to know

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The South African (SA) Constitutional Court recently decriminalised the private cultivation, possession and use of cannabis by adults. Cannabis contains varying amounts of the cannabinoids delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), depending on various cultivation factors. No commercial plant-derived cannabis products are currently registered by the SA Health Products Regulatory Authority (SAHPRA) for medical use. Such products are therefore unregulated, but are freely available in SA, and may be of inadequate quality and unverified composition, and not guaranteed to be safe or effective. SAHPRA has to date approved only one synthetic medical cannabis product, dronabinol. Evidence supporting benefit from medical cannabis exists for two drug-resistant childhood forms of epilepsy, Dravet syndrome and Lennox-Gastaut syndrome. Adjuvant therapy with medical cannabis can reduce seizure frequency for Lennox-Gastaut syndrome and Dravet syndrome by 18.8% and 22.8%, respectively, and may be beneficial for other rare forms of epilepsy. There is moderate evidence for chemotherapy-induced nausea and vomiting with the synthetic cannabinoids. Multiple sclerosis-associated spasticity showed a small clinical improvement in self-reported spasticity when a purified form of THC/CBD was added to existing therapy. Currently, low-level or no convincing evidence exists for the use of medical cannabis for chronic pain, sleep and weight disorders, and neuropsychiatric disorders. Cannabis is associated with a greater risk of adverse effects than active and placebo controls, and may be involved in clinically significant drug-drug interactions. The evolving regulatory and legal landscape on the use of medical cannabis will guide prescription and recreational use in the coming years.

On 18 September 2018, the South African (SA) Constitutional Court decriminalised the private cultivation, possession and use of cannabis by private by adults.[2] Section 22A(9)(a)(i) of the Medicines and Related Substances Act (Act 101 of 1965) was deemed to be constitutionally invalid and the wording needed to be revised by Parliament. In February 2019, the SA Health Products Regulatory Authority (SAHPRA) issued a communication that the Constitutional Court judgment should not be interpreted that persons are allowed to prepare cannabis-containing products in a private place and sell such products to the public.[10] Provisions of section 14(1) of the Medicines and Related Substances Act prohibit the selling of unregistered cannabis-containing medicines and products that are currently available in SA. In May 2019, this Act was subsequently amended by the Minister of Health to exclude from the schedule of medicines cannabidiol (CBD)-containing preparations with a maximum daily dose ≤20 mg CBD, or raw cannabis materials that do not contain >0.0075% CBD and 0.001% delta-9-tetrahydrocannabinol (THC).[5] Such preparations should, however, have acceptable low risk and health claims. For patients and healthcare practitioners, this is in conflict with several outlets and individuals selling cannabis-containing products (including oils) for medical use, with much higher concentrations of CBD and other cannabinoids, and with sensational health claims. Few healthcare practitioners are equipped with knowledge of the evidence, indications and legislation to support the safe use of medical cannabis.[16] In this overview, we summarise the indications for the clinical administration of medical cannabis, how practitioners may access medical cannabis and the current published evidence base. We emphasise that unregulated and unregistered cannabis products sold as medical cannabis may be of inadequate quality and unverified composition, and are not guaranteed to be safe or effective.

Cannabinoids and medical cannabis

The pharmacologically active ligands in medical cannabis are the cannabinoids. Over the past years, almost 200 cannabinoids have been identified, and the type of cannabinoids differs depending on whether they are endogenous (endocannabinoids), plant derived (phytocannabinoids) or synthetic.[15,17] The endocannabinoid system consists of endogenous lipid-based neurotransmitters that bind to cannabinoid receptors expressed widely throughout the body. The endocannabinoid system purportedly has two types of receptors, CB1 and CB2.[14] CB1 receptors are abundant in the brain and central nervous system, but are also found in various other tissues.[30] CB1 receptors are thought to regulate functions such as memory, nausea and vomiting, nociception, sleep and appetite.[30] CB2 receptors are mostly found in immune cells and the cardiovascular, gastrointestinal...
and reproductive systems, where it is considered to regulate various functions. The CB₁ and CB₂ receptors can be stimulated by endocannabinoids, phytocannabinoids or synthetic cannabinoids. An important consideration is that the affinity and potency of the different cannabinoids for CB₁ and CB₂ receptors differ such that efficacy and safety of one cannabinoid cannot be applied to another.

Phytocannabinoids are isolated from the Cannabis sativa and Cannabis indica plants. THC and CBD are the most widely researched phytocannabinoids. The psychoactive effects of cannabinoids have been attributed to THC, a major compound of the C. sativa plant, while CBD is thought to inhibit these effects. THC functions as an agonist with high affinity for both CB₁ and CB₂ receptors. CBD has low affinity for CB₁ and CB₂, and displays antagonism and inverse agonism at these receptors. This implies that the ratio of THC and CBD in phytocannabinoids would affect the ultimate clinical effect. The strain of cannabis and the cultivation environment, such as soil type, irrigation, harvesting and processing, all affect the quality and composition of phytocannabinoids. Different parts of the cannabis plant also have differing concentrations of phytocannabinoids, with THC generally being most abundant in the flowers and leaves, and CBD in the leaves and stems.

Cannabis products are therefore prone to variability, which underpins the strict enforcement of the Medicines and Related Substances Act by SAHPRA. Accordingly, unregistered and unregistered cannabis products sold as medical cannabis may be of inadequate quality and unverified composition, and are not guaranteed to be safe or effective.

Medical cannabis refers to medical products that contain purified phytocannabinoids or synthetically derived cannabinoids that have been approved by regulatory authorities for medical use. Regulatory authorities evaluate medical cannabis products for acceptable product variability, and only effective, safe and good-quality products complying with good manufacturing practices (GMP) are marketed. To date, the US Food and Drug Administration (FDA) has approved three drugs that contain cannabinoids: a plant-derived CBD solution, and two synthetic cannabinoids structurally related to THC, nabilone and dronabinol. A purified form of THC and CBD in a 1:1 ratio, known as nabiximols, has been approved by Health Canada and several other countries. Approved medical cannabis products on the market are oral formulations administered either as capsules, oral solutions or oromucosal sprays. These standardised preparations aim to provide accurate dosing and improve safety.

Numerous products that contain raw or herbal cannabis, also referred to as non-medical products, have not received approval from the FDA or other regulatory authorities, such as the European Medicines Agency (EMA). Many of these unregulated products that are readily available on the market claim to contain only CBD, but some contain both CBD and THC that differ in their CBD:THC ratios. They also tend to contain higher amounts of psychoactive THC and lower amounts of CBD than regulated products. A study evaluating the accuracy of labelling of unregulated cannabis-containing products in various states in the USA, showed discrepancies between the labelling and actual CBD and THC content. Unregulated cannabis products are freely available on the open market and unknowing patients and carers can access these formulations, which are sold with unfounded claims regarding efficacy and safety.

There are >480 constituents in cannabis plants, which can lead to significant variation in unregulated cannabis products. Therefore, the quality, efficacy and safety of these unregulated products are questionable. Importantly, regulatory oversight is essential for ongoing safety monitoring of medicines. In 2008, the anti-obesity drug rimonabant, a synthetic CB₁ antagonist and inverse agonist, was withdrawn from the European market after approval in 2006, owing to serious central nervous system side-effects. SAHPRA has to date approved only one medical cannabis product, dronabinol, for marketing in SA, although section 21 approval has been granted for some cannabis-containing products registered in other countries to meet local clinical needs. Section 21 of the Medicines Act allows controlled patient access to medical cannabis registered by other regulatory authorities to which SAHPRA aligns. For patients to access these medicines that are not registered in SA, a medical practitioner needs to apply to SAHPRA to allow specific named patient access.

Evidence for the use of medical cannabis
Clinical evidence of the indications for the use of medical cannabis is currently supported by a limited evidence base, but the field is evolving. Medical cannabis has been shown to be effective for certain conditions, but the benefit for most investigated indications is limited, in many cases by poor-quality studies, risk of bias and clinically non-significant findings. The synthetic cannabinoids were mostly assessed, as standardisation of phytocannabinoids cannot be ensured, and the bioavailability of inhaled cannabis cannot be guaranteed. Evidence supporting benefit from the use of medical cannabis exists for two drug-resistant childhood forms of epilepsy, Dravet syndrome and Lennox-Gastaut syndrome. Three randomised controlled trials (RCTs) assessed the effect of a pharmaceutical plant-derived CBD solution (Epidiolex), and found that when added as adjuvant therapy at the maximum recommended dose, it led to a significant reduction in the median frequency of monthly seizures when compared with placebo for Lennox-Gastaut syndrome (~18.8%; 95% confidence interval (CI) –31.8 - –4.4; p=0.009), and for Dravet syndrome (~22.8%; 95% CI –41.1 - –5.4; p=0.01). Based on these findings, the FDA approved the plant-derived CBD for Dravet and Lennox-Gastaut syndromes, and approval by the EMA followed thereafter. Long-term therapy with CBD in these epilepsy syndromes has also found sustained response and acceptable tolerability. Data for other types of epilepsy are more limited, but there does appear to be benefit for children and adults who have epilepsy that is refractory to appropriately dosed antiseizure medications. An open-label drug trial established modest evidence for the long-term safety and efficacy of CBD administration in patients with medically refractory epilepsy associated with cyclin-dependent kinase-like 5 (CDKL5) mutations, as well as Aicardi syndrome, 15q11-q13 duplication (dup15q), also known as the Prader-Willi/Angelman critical region (PWACR), and myoclonic-atactic (Doose) syndromes. However, even with this apparent tolerability, clinicians must be aware of potential drug-drug interactions between the commonly used antiseizure medications and CBD. As an example, clobazam plasma concentrations are increased when administered with CBD, this potentiation of activity has been noted as an independent factor in the apparent improved response of epilepsy to CBD. Studies in patients not using clobazam and other interacting medications will be important in the future.

For other conditions, there is moderate evidence for the management of chemotherapy-induced nausea and vomiting (CINV) and multiple sclerosis (MS)-associated spasticity. The synthetic cannabinoids dronabinol and nabilone showed the best efficacy in reducing CINV, but the risk of bias and lack of consistency of findings in trials limit their recommendation. Nevertheless, dronabinol...
and nabilone have both received FDA approval for refractory CINV.\[23,24\] Nabiximols showed a small, but significant, clinical improvement in self-reported MS-associated spasticity when added to existing therapy.\[13,47\] Evidence for an overall beneficial effect of dronabinol for MS-associated spasticity, however, was not found.\[48\]

Currently, low-level or no convincing evidence exists for chronic pain, sleep and weight, or neuropsychiatric disorders. Chronic pain studies evaluated a wide spectrum of differing pain conditions, outcome measures and cannabinoids, with most studies having a high or unclear risk of bias.\[14,49,50\] Some studies showed significant findings, but were not consistent across trials.\[14,49\] Furthermore, improvement in pain scores were generally not clinically significant (e.g. a weighted mean difference in pain improvement of 0.46 points on an 11-point numeric rating scale (0 - 10)).\[34\] A trend towards benefit for neuropathic pain, however, was suggested.\[34\]

A meta-analysis\[49\] pooling 9 RCTs estimated that the number needed to treat to benefit for at least a 30% reduction in pain for any chronic pain condition was 24 (95% CI 15 - 61). This implies that 24 patients need to be treated for 1 patient to have a 30% reduction in pain. The number needed to harm for any adverse effect was 6 (95% CI 5 - 8).

Studies assessing cannabis for sleep, weight gain and neuropsychiatric disorders (depression, anxiety and psychosis) did not show meaningful benefit. These trials had significant limitations of low quality, high risk of bias, small sample sizes and/or non-significant clinical implications.\[14\]

### Harm-benefit ratio

Before prescribing any medicine, the harm-benefit ratio should be evaluated. Cannabis is associated with a greater risk of adverse effects (AEs) than active and placebo controls, including serious AEs and withdrawal from studies due to AEs.\[14,49,50\] The risk of AEs are independent of the type of cannabinoid used. Common AEs included gastrointestinal disorders, dizziness, cognitive and neuropsychiatric disorders and nausea.\[14,49,50\] Medical cannabinoids (phyto and synthetic) have the potential to alter concomitantly administered drug plasma concentrations via drug-drug interactions.\[51\]

Conversely, cannabinoid concentrations may in turn be altered by the effect of other drugs. This is primarily mediated through inhibition or induction of the cytochrome P450 (CYP450) enzymes, but may also involve inhibition or induction of conjugation reactions.\[51\]

While these interactions pose a potential risk, there is a paucity of data to guide clinical decision-making.

A likely hindrance for access to registered medical cannabis is cost. As an example, the CBD solution marketed as Epidiolex and nabilone have both received FDA approval for refractory CINV.\[23,24\] Nabiximols showed a small, but significant, clinical improvement in self-reported MS-associated spasticity when added to existing therapy.\[13,47\] Evidence for an overall beneficial effect of dronabinol for MS-associated spasticity, however, was not found.\[48\]

Current...
Conflicts of interest.

Author contributions.

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Cannabis is associated with a greater risk of adverse effects than medications for the management of CINV and MS-associated spasticity. Unfortunately, the cost of medical cannabis may be prohibitive for these patient groups. The regulatory and legal landscape on the use of medical cannabis is evolving, and will guide prescription and recreational use in the coming years. Until then, healthcare practitioners should be aware of their role in responsible prescription and provision of advice to patients.

Key points

• Few healthcare practitioners are adequately equipped with knowledge of the evidence, indications and legislation to support the safe use of medical cannabis.

• Grown cannabis contains varying amounts of THC and CBD, depending on various cultivation factors.

• Unregulated and unregistered cannabis products may be of inadequate quality and unverified composition, and are not guaranteed to be safe or effective.

• Convincing evidence exists for the use of registered medical cannabis for Dravet and Lennox–Gastaut syndromes. Moderate evidence exists for the management of CINV and MS-associated spasticity. Currently, low-level or no convincing evidence exists for chronic pain, sleep and weight disorders, and neuropsychiatric disorders.

• Cannabis is associated with a greater risk of adverse effects than active and placebo controls, including serious adverse effects.

• The evolving regulatory and legal landscape on the use of medical cannabis will guide prescription and recreational use in the coming years.

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