Cannabis and multiple sclerosis

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ABSTRACT
Patients with multiple sclerosis have long turned to complementary therapies to manage symptoms that licensed products can only partially control. Around half of patients with multiple sclerosis admit to previous or current cannabis use for medicinal purposes and would endorse legalisation. Despite many governments worldwide relaxing regulations around medicinal cannabis, there remain many unanswered questions as to how clinicians should prescribe or recommend products, and access to pharmaceutical-grade products remains highly restricted. Here we address what adult neurologists need to know about cannabis and its use in multiple sclerosis.

INTRODUCTION
With many countries worldwide relaxing their regulations regarding cannabis-based products for medicinal use, neurology clinicians and nurses have become increasingly familiar with patients asking questions about cannabis. This became particularly evident in the UK during 2018 due to the heightened media focus. These media reports are often confusing for both patients and clinicians alike, and it is becoming increasingly important for neurologists to understand the legal regulations in their country as well as the licensing and evidence base for cannabis products in different situations.

A recent survey of people with multiple sclerosis found that 47% of respondents have considered using cannabis to treat their symptoms, 26% have used cannabis for their symptoms, 20% have spoken with their physician about using cannabis, and 16% are currently using cannabis. Patients with multiple sclerosis admit using cannabinoids for several different indications, including spasticity, pain, relaxation, sleep, anxiety and tremor, consuming various cannabinoid compounds via several different routes with little understanding of the supportive efficacy data. The variability of cannabinoids prescribed, bought over the counter or bought illegally, also makes it difficult for patients and clinicians to understand the impact and potential side effects of the drug. This review attempts to address these issues in relation to the use of cannabis for patients with multiple sclerosis.

Cannabinoids
Cannabis is a flowering plant indigenous to Central Asia that is cultivated worldwide both legally and illegally for fibres (hemp) and seed production, as well as for drugs produced from dried flower buds (marijuana), resin (hashish) and oils. The plant contains over 483 identifiable chemical compounds; over 80 cannabinoids have been isolated from the plant, the most abundant being cannabidiol (CBD) and Δ9-tetrahydrocannabinol (THC). Plants can be cultivated to contain different levels of CBD and THC, with high levels of THC favoured in the illegal market for the psychoactive properties. CBD has lower psychoactive properties but can cause a stimulant effect and lower the anxiety that is often experienced as a consequence of the THC component.

Synthetic cannabis
There are two commercial synthetic cannabinoid products available medicinally: dronabinol and nabilone, both of which are synthetic THC. Nabilone (trade name Cesamet) is approved by the UK Medicines and Healthcare products Regulatory Agency (MHRA) and the US Food and Drug Administration (FDA) for use in chemotherapy-induced nausea and vomiting. Dronabinol (trade names Marinol and Syndros) has FDA approval for use in HIV/AIDS-associated anorexia and cancer-related nausea and vomiting, and is available on prescription in the USA, Germany, Australia and South Africa. It has also shown potential benefit in sleep apnoea and further trials are under way. Other non-medicinal synthetic cannabinoids are synthesised to mimic the
Table 1 Drug penalties in the UK according to the Misuse of Drugs Act 1971 (https://www.gov.uk/penalties-drug-possession-dealing)

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Possession</th>
<th>Supply and production</th>
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<tbody>
<tr>
<td>A</td>
<td>Crack cocaine, cocaine, ecstasy (MDMA), heroin, LSD, magic mushrooms, methadone, methamphetamine (crystal meth).</td>
<td>Up to 7 years in prison, an unlimited fine or both.</td>
<td>Up to life in prison, an unlimited fine or both.</td>
</tr>
<tr>
<td>B</td>
<td>Amphetamines, barbiturates, cannabis, codeine, ketamine, methylenedioxymethamphetamine (Ritalin), synthetic cannabinoids, synthetic cathinones (e.g., mephedrone, methoxetamine).</td>
<td>Up to 5 years in prison, an unlimited fine or both.</td>
<td>Up to 14 years in prison, an unlimited fine or both.</td>
</tr>
<tr>
<td>C</td>
<td>Anabolic steroids, benzodiazepines (alprazolam), gamma-hydroxybutyrate, gamma-butyrolactone, benzylpiperazines (BZP), khat.</td>
<td>Up to 2 years in prison, an unlimited fine or both (except anabolic steroids—it is not an offence to possess them for personal use).</td>
<td>Up to 14 years in prison, an unlimited fine or both.</td>
</tr>
</tbody>
</table>

Temporary class drugs
Some methylphenidate substances (ethylphenidate, 3,4-dichloromethylphenidate, methylnaphthidate [HDMP-28], isopropylphenidate [IPP or IPPD], 4-methylmethylphenidate, ethylphenidate, propylphenidate) and their simple derivatives.
None, but police can take away a suspected temporary class drug. Up to 14 years in prison, an unlimited fine or both.

LSD, lysergic acid diethylamide; MDMA, 3,4-methylenedioxymethamphetamine.

Effect of THC and are sold as designer drugs under names such as ‘Spice, K2 and Synthetic Marijuana’. There are significant health risks associated with these drugs, and they remain under class B restriction in the UK (table 1).

Route of administration
Cannabis can be administered in various ways but predominantly is inhaled (drawing smoke into the lungs) or vaped (drawing vapour into the mouth with or without inhaling). In this way the cannabinoids are rapidly absorbed into the bloodstream reaching peak plasma THC concentrations within minutes, similar to those achieved with intravenous use; this can be maintained for up to 3–5 hours. When ingested orally, THC is metabolised in the liver to 11-hydroxy-THC, a potent psychoactive metabolite. Due to the delayed peak effect of THC in orally ingested cannabis, self-titration according to symptom is more difficult; also oral cannabinoids have an unpredictable absorption and elimination, and plasma concentrations are often maintained for longer (8–20 hours), which can cause erratic psychotropic effects.

Cannabis and the law
Cannabis is classified as a class B drug in the UK under the Misuse of Drugs Act 1971 (table 1), and in the USA is federally prohibited as a schedule I category drug (table 2), which is considered to be the most dangerous category. The US federal government gives no distinction between medicinal and recreational cannabis, and doctors cannot prescribe cannabis, although they are able to recommend its use under the First Amendment. Despite this, as of September 2017, 29 states and the District of Columbia have legalised the use of cannabis for medical purposes.

Within the UK, law differentiates between THC-containing and CBD-containing products, with those containing <0.2% THC legal for distribution and available as artisanal products on the high street and internet (figure 1). However, artisanal CBD products are often not pharmaceutical-grade, and independent testing can reveal different levels of CBD and THC.

Table 2 Controlled Substances Act of 1970 from the US Drug Enforcement Administration (https://www.dea.gov/control substances-act)

<table>
<thead>
<tr>
<th>Controlled substance schedules</th>
<th>Definition</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schedule I</td>
<td>No currently accepted medical use and a high potential for abuse.</td>
<td>Heroin, LSD, cannabis and MDMA (ecstasy).</td>
</tr>
<tr>
<td>Schedule II</td>
<td>A high potential for abuse which may lead to severe psychological or physical dependence.</td>
<td>Methadone, oxycodone, fentanyl, morphine, opium, codeine, amphetamine, methamphetamine and methylenedioxymethamphetamine.</td>
</tr>
<tr>
<td>Schedule III</td>
<td>A potential for abuse that is less than substances in schedules I or II, and abuse may lead to moderate or low physical dependence or high psychological dependence.</td>
<td>Products containing not more than 90 mg of codeine per dosage unit, ketamine and anabolic steroids.</td>
</tr>
<tr>
<td>Schedule IV</td>
<td>Low potential for abuse.</td>
<td>Benzodiazepines and nabiximols (Sativex).</td>
</tr>
<tr>
<td>Schedule V</td>
<td>Low potential for abuse.</td>
<td>Cough preparations containing not more than 200 mg of codeine.</td>
</tr>
</tbody>
</table>

LSD, lysergic acid diethylamide; MDMA, 3,4-methylenedioxymethamphetamine.
Artisanal cannabidiol (CBD) is readily available online, in high street shops as well as in your local café in a number of different forms, targeted and advertised to make it part of everyday life.

than stated on the label. In addition, other cannabinoids, pesticides and substances have been found in these products, and it is therefore not advisable for medical practitioners to recommend their use. As of 2016, the MHRA has classified any CBD-containing product used for medicinal purposes as a medicine and therefore requiring a product licence (marketing authorisation).

On 26 July 2018 the UK government rescheduled cannabis-derived medicinal products so that they could be prescribed by senior clinicians. Subsequently the MHRA defined these to be strictly relating to Sativex (nabiximols; an oromucosal spray consisting of the compounds THC and CBD, derived from the cannabis leaf and flower) for the treatment of spasticity due to multiple sclerosis. Epidiolex (a purified CBD oral solution derived from the cannabis plant) was deemed to be exempt from scheduling regulations as it is a predominantly CBD-containing product. Nabilone, a synthetic cannabinoid, used for nausea and vomiting caused by chemotherapeutic agents, also has marketing authorisation in the UK. Other cannabis-derived products are still class B drugs and cannot be prescribed. A Home Office licence is needed for research using any raw cannabis. UK guidelines for prescribing cannabis-based products vary between England, Scotland and Wales, and to date only Sativex has been reviewed by these bodies (Table 3). The UK National Institute for Health and Care Excellence is currently undertaking a wider review of cannabis-based products due for publication in October 2019.

Cannabinoids and the nervous system

Both plant and synthetic cannabinoids have multiple modes of action. The molecules are highly hydrophobic and rapidly enter the CNS, acting at various receptors throughout the brain and the spinal cord. The cannabinoid receptors, cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2), are transmembrane G protein-coupled receptors (GPCRs) present throughout the central and peripheral nervous system and immune system. The CB1 receptors occur abundantly in the CNS located in areas of pain signalling control; however, they are also found in the cerebellum and hippocampus, and in the peripheral nerves, dorsal root ganglia and neuromuscular junction. Activation of the CB1 receptor decreases neurotransmitter release, affecting nociceptive pathways, psychoactivity, memory processing and motor control; the site of

Table 3 | UK guidelines on use of cannabis-based products

<table>
<thead>
<tr>
<th>Group</th>
<th>Date</th>
<th>Appraisal summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Wales Medicines Strategy Group</td>
<td>August 2014</td>
<td>Delta-9-tetrahydrocannabinol/cannabidiol (Sativex) is recommended as an option for use within NHS Wales as treatment for symptom improvement in adult patients with moderate to severe spasticity due to multiple sclerosis who have not responded adequately to other antispasticity medication and who demonstrate clinically significant improvement in spasticity-related symptoms during an initial trial of therapy.</td>
</tr>
<tr>
<td>NICE</td>
<td>October 2014</td>
<td>Do not offer Sativex to treat spasticity in people with multiple sclerosis because it is not a cost-effective treatment.</td>
</tr>
<tr>
<td>Scottish Medicines Consortium</td>
<td>April 2011</td>
<td>In the absence of a submission from the holder of the marketing authorisation, cannabinoid oromucosal spray (Sativex) is not recommended for use within NHS Scotland.</td>
</tr>
</tbody>
</table>

NHS, National Health Service; NICE, National Institute for Health and Care Excellence.
activation explains the symptomatic benefits and side effects that patients experience.

CB2 receptors, and to a lesser degree CB1 receptors, occur in immune cells such as macrophages, polymorphonuclear neutrophils and lymphocytes, explaining some of the anti-inflammatory properties of cannabinoids. The CB2 receptors also occur in tissues such as bone and liver, peripheral nerves, keratinocytes, as well as in brain microglia. They act predominantly in slowing chronic inflammation and in suppressing chronic pain, but their full mechanism of action is unclear. As well as acting on the CB1 and CB2 receptors, cannabinoids have an effect on other GPCRs, including the opioid and serotonin receptors, and have a modulating effect on nucleus receptors and ion channels.

The various components of the cannabis plant have different targets within the body. THC is a partial agonist at the CB1 and less so at the CB2 receptors, leading to its potential therapeutic properties including analgesia, muscle relaxation, anti-inflammatory and antioxidant effects. The high binding affinity of THC with CB1 receptors is largely responsible for the psychoactive properties including change of mood and consciousness. More recently, THC has been shown to reduce the functional connectivity between the anterior cingulate cortex and the sensorimotor cortex in patients treated with chronic neuropathic pain, the degree of connectivity reduction predictive of the response to THC.

CBD has little binding affinity for the CB1 and CB2 receptors but can antagonise these receptors in the presence of THC, reducing the potency of THC and balancing the psychoactive effect. The main effects of CBD are at the non-cannabinoid receptors, including GPCRs and ion channels, where it shows regulation of pain perception and anti-inflammatory effects through receptor modulation. The exact mechanisms of action of CBD remain unclear.

Anti-inflammatory and neuroprotective effects of cannabis

Putative anti-inflammatory mechanisms suggest the cannabinoids may suppress disease activity in multiple sclerosis. This has been supported by animal models where CBD-rich compounds have shown beneficial effects in experimental allergic encephalomyelitis, decreasing inflammatory infiltrate including microglia, macrophages and cytokines into lesions, thereby preventing demyelination. In some models this has shown to be as clinically effective as first-line disease-modifying treatment.

Cannabinoids may also have neuroprotective effects. Experimental rat models have shown CBD can increase brain-derived neurotrophic factor expression, protect against oxidative protein damage, increase mitochondrial activity and reverse markers of oxidative stress. Cannabinoids also increase remyelination in murine models.

Despite these promising experimental data, in human studies, cannabinoids have not shown to prevent disease progression or atrophy. The Cannabinoid Use in Progressive Inflammatory brain Disease (CUPID) investigator group examined oral dronabinol (Δ9-THC) in patients with secondary progressive disease, showing no significant effect on either disability or brain atrophy outcome measures. This study unfortunately, and possible prematurely, closed a chapter in the prospects for cannabis as a neuroprotective agent in multiple sclerosis. The investigators chose an oral man-made product consisting of Δ9-THC, open to first pass liver metabolism and devoid of other components of cannabis including CBD, possibly leading to reduced anti-inflammatory and neuroprotective effects. Perhaps further studies should be considered, targeting a younger age group with less established disability and atrophy.

Cannabis and pain

Many patients perceive cannabis to be the panacea for pain; however, clinical trials have shown a small-to-moderate effect only, with a high degree of heterogeneity. This can be explained in part by the variability in cannabis product used in different trials, along with the difficulty in assessment of pain in humans. However, it is encouraging that animal models show good benefit from cannabinoids in various types of pain, including acute, chronic neuropathic and chronic inflammatory pain.

The most recent Cochrane review for cannabis-based products for chronic neuropathic pain evaluated 16 studies with about 1750 participants. This included trials of medicinal, plant-derived and synthetic cannabinoids with outcome measures of 30% and 50% reduction in pain measured on patient-reported outcome scales. As often found in studies of cannabis, the quality of the evidence was deemed poor with high risk of bias and small sample size; however, the number needed to benefit for 30% and 50% reduction in pain compared with placebo, respectively, was 11 (95% CI 7 to 33) and 20 (95% CI 11 to 100). A higher number of patients withdrew from the cannabinoid treatment group due to adverse effects (number needed to harm 25 (95% CI 16 to 50)), suggesting that the potential benefits of cannabis for chronic neuropathic pain are likely outweighed by the potential harm. However, the adverse events were all short term, with long-term risks not evaluated.

Cannabis and spasticity

Spasticity often leads to considerable disability in patients with multiple sclerosis. Cannabinoids acting at the presynaptic CB1 receptors probably act in part by reducing excessive glutamate release, thereby regulating glutamatergic excitability during spasticity.
Initial studies of Δ9-THC extract did not show benefit for spasticity on objective measures, possibly relating to the use of the Ashworth score, which is a crude assessment of biological impairment rather than disability. However, a combination of Δ9-THC and CBD, namely nabiximols (Sativex), showed >20% improvement in spasticity measures after 4 weeks in over half of patients treated. This has led to approval of use of nabiximols in multiple sclerosis for management of severe spasticity, uncontrolled on at least two other agents, in several countries including Wales, but not England or Scotland. It is not clear as to why some patients and not others respond to nabiximols. Within the clinical trial, the disease characteristics including age, sex, disease duration, spasticity duration and disability were similar in the two subgroups; however, the authors speculate that the non-responders intrinsically lacked the capacity to respond to any agent rather than it being nabiximol-specific effect.

Cannabis and other symptoms
CBD probably has several other positive effects, including improving symptoms of anxiety and sleep disturbance; one retrospective case series showed 79% of patients had improved anxiety scores and 66% of patients had improved sleep scores at 1 month of treatment. Although the Cannabinoids in Multiple Sclerosis (CAMs) study showed no improvement in spasticity on objective measures, patients did report improved spasms and sleep, although no improvement in bladder dysfunction or tremor. However, other studies of patients with multiple sclerosis have indicated a positive effect on tremor and bladder frequency, although again these have been small studies with insufficient level of evidence to be conclusive. For product licensing, there need to be formal randomised placebo-controlled studies of a pharmaceutical-grade product.

Can it cause harm?
The most common side effects of cannabis relate to the THC component, and include dizziness, somnolence and nausea. The degree to which they occur depends on the specific product, but in general these side effects are self-limiting and often tolerable. More concerning are the reports of potentially significant side effects, including psychosis, schizophrenia and heart disease, with some studies suggesting inhaled cannabis affects cognition and brain volume. Again, the extent of these side effects depends on the product and the concomitant use of tobacco.

Patients often worry about their driving ability, which can be affected by cognitive side effects of medications as well as by symptoms such as weakness and spasticity. A recent review of nabiximols showed no detrimental effect on driving; indeed some patients report improved driving ability, possibly due to reduced spasticity and spasms. Patients should be counselled that using cannabinoids may affect their ability to drive and they should monitor any cognitive symptoms.

CONCLUSION
The medical use of cannabis remains controversial, and outside of the use of pharmaceutical-grade products, for licensed indications, cannabinoids should not be recommended. In multiple sclerosis, this restricts the use of cannabis to nabiximols for spasticity. However, as treating physicians, we are often compelled to advise patients outside of licensed practice based on limited evidence. Here we should be cautious in our advice, with the knowledge that non-pharmaceutical-grade products can vary considerably in their constituents and therefore in their potential benefit and side effects. Patients’ response to pharmaceutical cannabis such as nabiximols, in observed clinical practice, often does not mirror their anecdotal response to inhaled cannabis; although many patients report benefit from inhaled cannabis, the potential for harm, particularly in relation to the inhaled concomitant tobacco, has to be carefully explained. Despite this we cannot ignore the many patients with multiple sclerosis who find overwhelming benefit from cannabinoids. As a medical community, it is now important that we invest academic resources into exploring further the use of medicinal cannabis for a number of indications.

Key Points
► Cannabis may improve quality of life in some patients with multiple sclerosis.
► Patients’ perception of the benefit of cannabis is often vastly different from their clinicians.
► There are many cannabis products available and for medicinal purposes; we should refer only to specific pharmaceutical-grade products where there are research data available.
► Patients should be cautioned on the potential detrimental effects of recreational and artisanal cannabis.
► We desperately need conclusive research to understand how different formulæs of cannabis could benefit the symptoms of multiple sclerosis.

Contributors Both authors contributed to the design, writing and review of this manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests GI has accepted payments and honorariums for speaking, travel and advisory boards from Merck, Genzyme and Biogen. ORP has accepted payments and honorariums for speaking, travel and advisory boards from Merck, Genzyme, Roche, Biogen, Novartis and Teva.

Patient consent for publication Not required.

Provenance and peer review Commissioned. Externally peer reviewed by Neil Scolding, Bristol, UK.
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