

# The therapeutic potential of cannabis

David Baker, Gareth Pryce, Gavin Giovannoni, and Alan J Thompson

Research of the cannabinoid system has many similarities with that of the opioid system. In both instances, studies into drug-producing plants led to the discovery of an endogenous control system with a central role in neurobiology. Few compounds have had as much positive press from patients as those of the cannabinoid system. While these claims are investigated in disorders such as multiple sclerosis spasticity and pain, basic research is discovering interesting members of this family of compounds that have previously unknown qualities, the most notable of which is the capacity for neuroprotection. Large randomised clinical trials of the better known compounds are in progress. Even if the results of these studies are not as positive as many expect them to be, that we are only just beginning to appreciate the huge therapeutic potential of this family of compounds is clear.

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Cannabis has been used recreationally for millennia and is the third most commonly used drug after tobacco and alcohol; there are an estimated 3 million frequent users in the UK alone.<sup>1</sup> There has been a steady stream of medical claims throughout history that cannabis eases limb-muscle spasms, migraine, and pain.<sup>2</sup> Although there is evidence of medical use in Europe from the 13th century, it became more popularised in the early 19th century when cannabis was noted to have anticonvulsive, analgesic, antianxiety, and antiemetic properties. Cannabis became widely used for the treatment of cramps, asthma, and dysmenorrhoea, for which it was prescribed to Queen Victoria. However, the availability of alternative treatments and, importantly, sociopolitical pressure led to a decline in the medical use of cannabis by the beginning of the 20th century.<sup>2</sup>

Although cannabis was effectively banned in the USA in 1937, cannabis was in the British pharmacopoeia and was in occasional use until the Misuse of Drugs Act (1971) declared that it was of no medical benefit and its use was outlawed. Despite its illegality, people have continued to obtain cannabis on the black market for self-medication. This patient-led self-investigation has fuelled claims of various benefits in many disorders.<sup>3,4</sup> In response to such claims, patient pressure, and some small-scale clinical studies,<sup>5</sup> the UK parliament<sup>1</sup> felt there was sufficient evidence of benefit in some disorders, such as multiple sclerosis and pain, to warrant further investigation in large controlled trials. The current legal position in the UK is that possession and supply of cannabis is illegal. The proposed reclassification of cannabis as a schedule C drug is not an endorsement of safety but a recognition that it does not carry the same risks as other schedule B drugs, such as

amphetamine and barbiturates. Should trials show an acceptable benefit, the UK Government is likely to rethink legalisation, but only for medical use.

## Biology of cannabis

The acute effects of cannabis use are well recognised;<sup>1,6</sup> it induces a psychoactive, mildly euphoric, relaxing intoxication or “high”, which leads to slight changes in psychomotor and cognitive function.<sup>1,6</sup> In some limited cases, cannabis can also induce unpleasant effects including anxiety, panic, and paranoia, and very rarely it may lead to acute psychosis involving delusions and hallucinations.<sup>1,6</sup> Frequent users may develop an amotivational syndrome.<sup>1,6</sup> Cannabis also induces an increase in heart rate, a lowering of blood pressure due to vasodilatation (which causes the classic “red eye”), appetite stimulation (known as “the munchies”), dry mouth, and dizziness.<sup>1,6</sup> These may be thought of as adverse effects but all are due to a basic biology, which is now beginning to be understood.

The cannabis plant (*Cannabis sativa*) contains many compounds, but  $\Delta^9$  tetrahydrocannabinol (THC) is the main psychoactive ingredient. THC breaks down to produce cannabidiol and was identified—along with cannabidiol (the main non-psychoactive component)—in the 1940s.<sup>2,7</sup> However, THC was not isolated, synthesised, and stereochemically defined until the 1960s (figure 1).<sup>2</sup> THC is concentrated in the flowering head of the female plant and selective growing in the past 5–10 years has substantially increased THC content from 1–3% THC in the “flower-power” era to 6–13% and above. Thus, current users of cannabis may have very different experiences to those of the past. Cannabis may contain over 60 “classical” cannabinoid (tricyclic dibenzopyran) compounds and some, such as cannabidiol, may modulate the response to THC.<sup>2,7,8</sup> How these different compounds act has only started to become clear in the past decade.

## The cannabinoid system

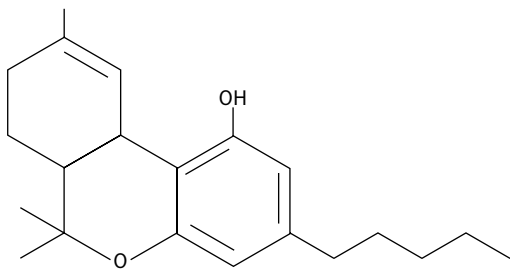
### Cannabinoid receptors

Cannabinoids are typically highly lipophilic and were originally thought simply to diffuse through cell membranes. However, in 1990 the first cannabinoid receptor—CB<sub>1</sub>—was identified; this finding revolutionised the study of cannabinoid biology.<sup>9,10</sup> A structurally diverse range of

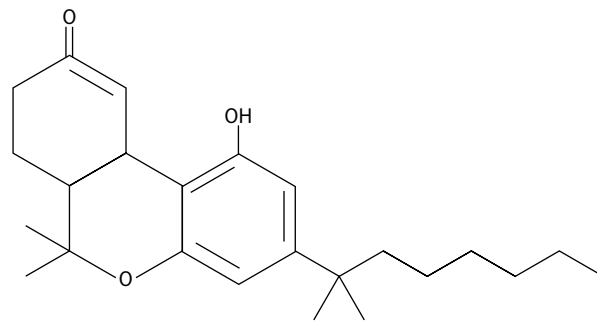
DB, GP, GG, and AJT are at the Institute of Neurology, University College London, Queen Square, London WC1N 3BG.

**Correspondence:** Prof Alan J Thompson, Institute of Neurology, Queen Square, London WC1N 3BG, UK.  
Tel +44 (0) 207 837 3611 ext 4152; fax +44 (0) 207 813 6505;  
email a.thompson@ion.ucl.ac.uk

## Cannabinoids currently licensed for clinical use

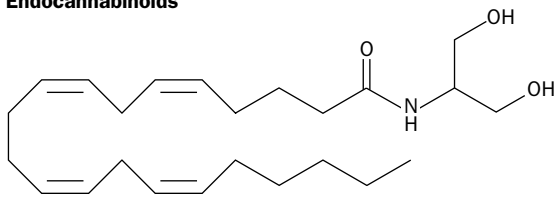


THC

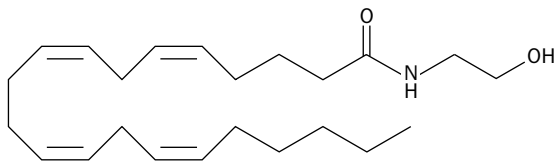


Nabilone

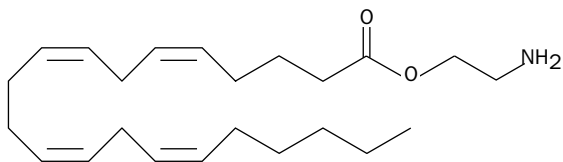
## Endocannabinoids



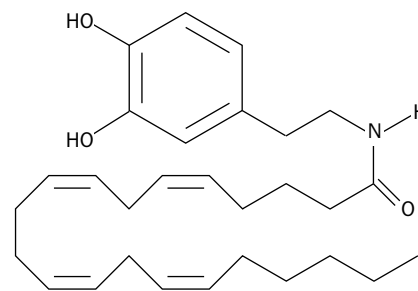
2-archidonoylglycerol



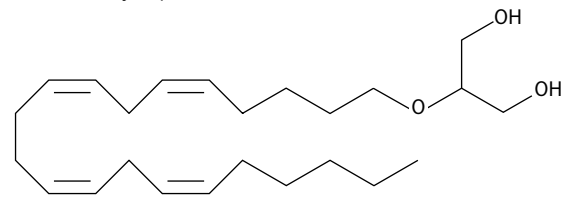
2-archidonoylglycerol



Virodhamine



N-archidonoyldopamine



Noladin ether

Figure 1. Structures of endocannabinoids and cannabinoids currently licensed for clinical use.

cannabinoid-receptor binding compounds (known now as cannabinoids) that have been essential to the elucidation of the biology of the cannabinoid system have been generated, including potent agonists and antagonists.<sup>10</sup> In the CNS, CB<sub>1</sub> is by far the most abundant G-protein coupled receptor with seven transmembrane-spanning segments, and it is also expressed on peripheral neurons and other cell types.<sup>10</sup> CB<sub>1</sub> is negatively coupled to adenylate cyclase and is either negatively or positively associated with selective ion channels.<sup>9,10</sup> CB<sub>1</sub> is expressed strongly in the basal ganglia, cerebellum, and hippocampus (figure 2), which accounts for the well-known effects of cannabis on motor coordination and short-term-memory processing.<sup>10</sup> Likewise, CB<sub>1</sub> is expressed at high concentrations in the dorsal primary afferent spinal-cord regions, which are important in pain pathways, whereas it is expressed at low concentrations in the brainstem,<sup>10</sup> which controls many autonomic functions. This may account for the lack of cannabis induced acute fatalities.<sup>1</sup> Therefore, the many effects that cannabis can have are due to the presence of CB<sub>1</sub> in

regions that control diverse neurological functions. The responsiveness of the receptor is dynamic and CB<sub>1</sub> seems to exist in a partly precoupled state that produces different degrees of stimulation in different brain regions.<sup>10</sup>

A second receptor—CB<sub>2</sub>—seems to be expressed primarily by leucocytes and, in contrast to CB<sub>1</sub>, is not linked to ion channels.<sup>10,11</sup> CB<sub>2</sub> has no known neurological activity but it may function in haemopoietic development. Selective agonists, antagonists, and mice lacking both CB<sub>1</sub> and CB<sub>2</sub> have helped elucidate cannabinoid biology.<sup>10,12,13</sup> There is increasing evidence of additional “unknown” receptors that have cannabinomimetic and therapeutic effects independent of CB<sub>1</sub> and CB<sub>2</sub>.<sup>10,14,15</sup> These receptors are more likely to be functionally rather than structurally related, as there is currently no evidence for additional cannabinoid receptors in the human genome. Furthermore, cannabinoids may also influence other receptor systems through other messenger pathways or through allosteric effects due to membrane insertion of cannabinoids.<sup>16</sup> Mice that lack CB<sub>1</sub> receptors seem

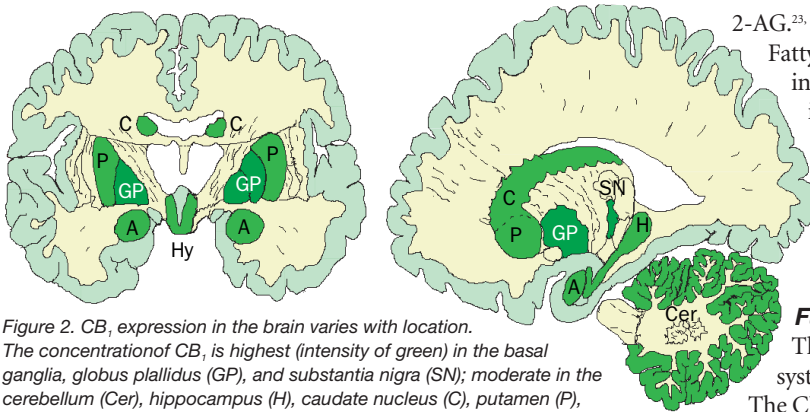


Figure 2. CB<sub>1</sub> expression in the brain varies with location. The concentration of CB<sub>1</sub> is highest (intensity of green) in the basal ganglia, globus pallidus (GP), and substantia nigra (SN); moderate in the cerebellum (Cer), hippocampus (H), caudate nucleus (C), putamen (P), hypothalamus (Hy), and amygdala (Am); low in the cortex; and very low (yellow) in white matter.

remarkably normal, despite some minor behavioural deficits,<sup>10,12</sup> which suggests that there is a compensatory mechanism. However, when normal homeostasis is lost, as happens in disease, control of the cannabinoid system may be particularly important.

**Endocannabinoids**

Several endogenous fatty-acid ligands known, as endocannabinoids, have been found. The first to be discovered—in 1992—was anandamide (arachidonylethanolamide) followed by 2-arachidonoylglycerol (2-AG; figure 1).<sup>10,17,18</sup> In the past 2 years, noladin ether, virodhamine (O-Arachidonylethanolamine), N-arachidonoyldopamine (NADA), and docosatetraenylethanolamide (DEA) have been found in the CNS. These compounds have cannabinoid receptor binding activity, but their exact physiological roles are unknown.<sup>19,20</sup>

Of the endocannabinoids, anandamide and 2-AG are the most studied.<sup>21</sup> Both are produced “on demand” from membrane associated precursors by distinct biochemical pathways involving phospholipases D and C. The endocannabinoids then bind and stimulate the CB receptors. Anandamide and NADA can also weakly stimulate vanilloid receptors (VR1), which are heat-gated, non-selective ion channels associated with hyperalgesia and account for some non-CB mediated effects of anandamide on vascular beds.<sup>10,22</sup> Consistent with a homeostatic role of cannabinoids, there is also a degradation system (figure 3) that involves reuptake into the cell by putative diffusion-facilitated endocannabinoid selective transporters and hydrolysis by fatty-acid-amide hydrolase for anandamide and 2-AG or a monoacylglycerol lipase for

2-AG.<sup>23, 24</sup> Noladin ether is degraded by acylation.<sup>20</sup> Fatty-acid-amide hydrolase is expressed strongly in the liver, is postsynaptic to CB<sub>1</sub>, and is involved in degradation of oleamide, an endogenous sleep-inducing compound related to endocannabinoids.<sup>23</sup> This degrades anandamide to arachidonic acid and ethanolamide, which do not have CB<sub>1</sub> binding activity.<sup>23</sup>

**Function of the cannabinoid system**

The main function of the endocannabinoid system is to regulate synaptic neurotransmission. The CB<sub>1</sub> endocannabinoid system regulates synaptic neurotransmission of excitatory and inhibitory circuits.<sup>10,25</sup> In response to depolarisation and Ca<sup>2+</sup> fluxes and in some instances postsynaptic group I metabotropic-glutamate-receptor activation, endocannabinoids are released that inhibit further neurotransmitter via stimulation of presynaptic CB<sub>1</sub> receptors (figure 4).<sup>25</sup>

As a regulator of neurotransmission,<sup>10,25</sup> the cannabinoid system seems to influence many different functions. There is experimental evidence that cannabinoids affect the activity of most neurotransmitters (table). What actually happens after stimulation depends on the location of the receptor within the excitatory or inhibitory neural circuit being stimulated. The sometimes paradoxical findings that cannabis suppresses or induces certain phenotypical signs (eg, convulsions, tremor)<sup>1</sup>

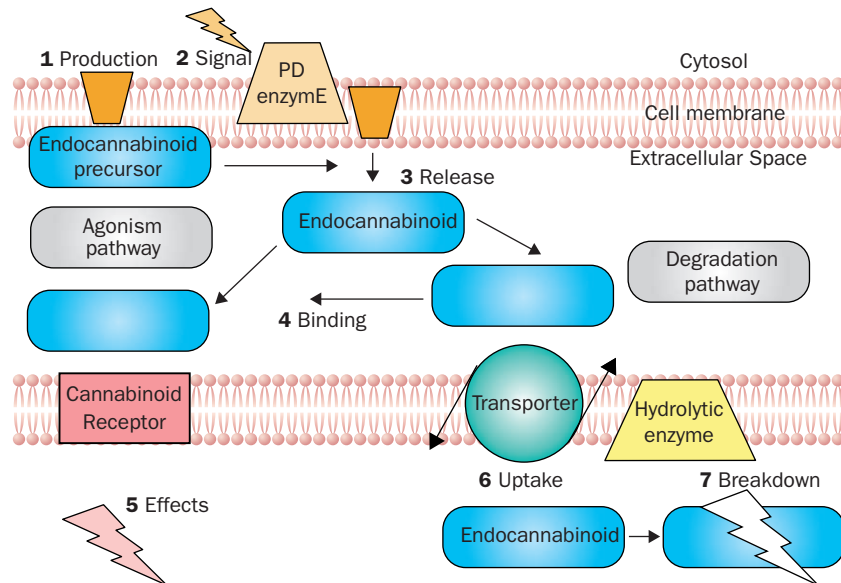


Figure 3. Endocannabinoid agonism—degradation pathway. Endocannabinoids are formed within neurons and other cell types via multiple biosynthetic pathways (1). Rather than being stored as active molecules these are produced “on demand” from membranous fatty-acid precursors via the activity of phosphodiesterase (PDE) enzymes such as phospholipase D (anandamide) and phospholipase C (2-AG). This process occurs (2) after cellular stimulation by signals such as neuronal depolarisation (Ca<sup>2+</sup> influx) to cause the extracellular release of active endocannabinoids (3). After release, the endocannabinoid can either bind cannabinoid receptors (agonism pathway) or be degraded. After receptor binding (4) the receptor signals the second messenger systems (eg, reducing adenylate cyclase and for CB<sub>1</sub>, inhibiting Ca<sup>2+</sup> channels or stimulating inwardly rectifying K<sup>+</sup> channels) that signal the cannabinimetic activities (5). There is also a degradation pathway expressed on either receptor bearing or other cells. The endocannabinoids are degraded through reuptake by a diffusion facilitated transport molecule (6) and then hydrolytically cleaved by enzymes (7) such as fatty-acid-amide hydrolase to break down the endocannabinoids to molecules such as arachidonic acid and ethanolamine.

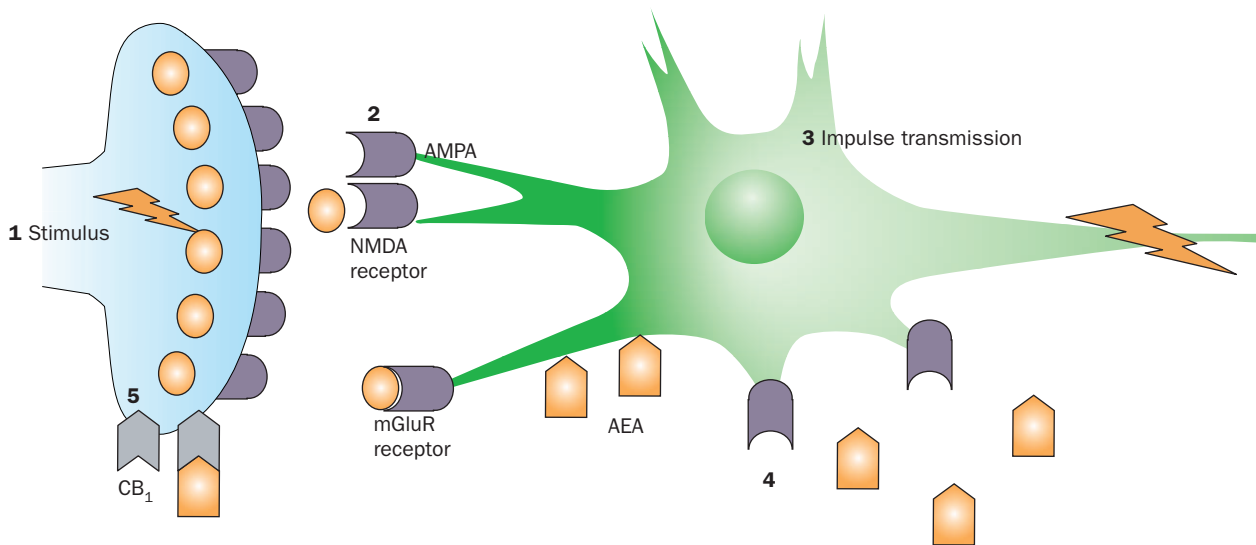


Figure 4. Endocannabinoids regulate synaptic neurotransmission. Action potentials are transmitted along the axon to the terminal end feet (1). Presynaptic stores of neurotransmitters are released into the synaptic cleft and stimulate complementary postsynaptic receptors (2). The action potential is then transmitted along neural pathways (3). As a consequence of postsynaptic depolarisation or neurotransmitter receptor signalling, endocannabinoids are released postsynaptically (4) and diffuse across the synapse to bind to presynaptic CB<sub>1</sub> receptors (5). These inhibit further neurotransmitter release.

is probably because these signs are controlled by different neuronal circuits. Many neurological diseases occur due to inappropriate neuronal signals leading to too much excitation, too little inhibition, or vice versa. Dopamine activity may be inhibited by cannabinoids in motor-control centres.<sup>26</sup> Nabilone has been shown to inhibit levodopa-induced dyskinesia in Parkinson's disease.<sup>27</sup> However, in different brain regions dopamine production can be associated with reward, addiction, and psychosis. Several studies have indicated that many people with schizophrenia use cannabis.<sup>28</sup> One explanation is that they may be attempting to self-medicate excessive dopamine. Recent evidence suggests cannabinoids enhance dopamine release in reward centres and that teenagers and young adults who smoke cannabis have a slightly higher than normal risk of developing psychosis.<sup>28,29</sup> CB<sub>1</sub> is developmentally regulated, particularly during neural development and may be important in neuronal plasticity during fetal, postnatal, and adolescent life.<sup>30</sup> Exogenous interference in the natural brain-modelling process may have risks to behavioural development during these times. Chronic

cannabis smoking can also lead to cognitive impairment in some individuals.<sup>1</sup> Cannabinoids adversely affect short-term memory processing and could be disadvantageous to cognitive ability.<sup>1,10</sup> However, sometimes patients with disorders such as post-traumatic fear responses also have to "remember to forget" and here stimulation of the cannabinoid system may be useful to extinguish certain aversive memories.<sup>31</sup> Thus, cannabis may have positive and negative outcomes, and therefore its clinical use must balance these effects against the nature of the disorder.

#### Preclinical data: rationale for clinical application

The clinical potential of the cannabinoids is large; some people suggest that cannabis could be the "aspirin of the 21st century". However, much of the evidence for the use of cannabinoids is anecdotal and is too broad in scope to review in detail here.<sup>13</sup> The lack of appropriate animal models with the complexity of the human brain hampers the study of the behavioural effects of these compounds. Therefore, most experimental studies have concentrated on measurable physiological effects, and, as a result, the understanding of the underlying biology is improving. Most claims made by patients suggest that cannabis may be useful in symptom management<sup>1,3,4</sup> and there is now experimental support for the clinical investigation of cannabis in the control of pain and spasticity in multiple sclerosis (MS). We will concentrate on these areas in order to highlight potential therapeutic uses.

#### Pain and spasticity

Cannabinoids inhibit pain in virtually every experimental pain paradigm either via CB<sub>1</sub> or by a CB<sub>2</sub>-like activity in supra-spinal, spinal, or peripheral regions, dependent on the type of nociceptive pathway being studied.<sup>32,33</sup> This finding is consistent with high concentrations of CB<sub>1</sub> receptors on primary afferent nociceptors, particularly in the dorsal spinal

#### Neurotransmitter functions under cannabinoid control

Neurotransmitter	Associated disorder
<b>Excitatory amino acids</b>	
Glutamate	Epilepsy, nerve-cell death in stroke
<b>Inhibitory amino acids</b>	
GABA	Spinal cord motor disorders, epilepsy, anxiety
Glycine	Startle syndromes
<b>Monoamines</b>	
Noradrenaline	Autonomic homeostasis, hormones, depression
Serotonin	Depression, anxiety, migraine
Dopamine	Parkinson's disease, schizophrenia, vomiting, pituitary hormones, drug addiction
Acetylcholine	Neuromuscular disorders, autonomic homeostasis, dementia, parkinsonism, epilepsy, sleep-wake cycle
Neuropeptides	Pain, movement, neural development, anxiety



cord,<sup>10</sup> whereas peripheral CB<sub>2</sub>-like receptors have been implicated in the control of “inflammatory” pain.<sup>10,34</sup>

One of the main claims for cannabis is the alleviation of painful spasms and spasticity.<sup>4</sup> This effect is currently difficult to assess objectively, owing to a lack of sensitive and reliable outcome measures. In an experimental model of MS, there is evidence of tonic control of spasticity and tremor by cannabinoids.<sup>35,36</sup> Although cannabis may contain additional therapeutic compounds to THC, the main antispastic activity seems to be mediated through CB<sub>1</sub> and comparable efficacy may be obtained with single pharmacological reagents. Despite early promise, there is no useful evidence to support an antispastic role for CB<sub>2</sub>.<sup>35</sup> Non-cannabis-derived cannabinoids can inhibit spasticity by an unknown CB<sub>1</sub>-independent mechanism.<sup>15</sup>

Although CB<sub>1</sub> agonism can inhibit spasticity, the important experimental observation was that CB<sub>1</sub> receptor antagonists made spasticity transiently worse,<sup>35,36</sup> which suggests inhibition of a tonically active, endogenous control mechanism. Indeed, inhibition of the degradation pathways of endocannabinoids by targeting of the endocannabinoid transporter or fatty-acid-amide hydrolase degradation of the endocannabinoids led to a significant antispastic effect similar to strong CB<sub>1</sub> agonists.<sup>36</sup> Importantly, such compounds do not bind directly to CB<sub>1</sub> and thus have little inherent psychoactivity.<sup>36</sup> In addition, there seems to be local upregulation of endocannabinoids in and around lesions.<sup>36</sup> Therefore, degradation inhibitors may offer some site selectivity not afforded by cannabinoid receptor agonists (figure 5). Similar dysregulation of the cannabinoid system is found in experimental pain<sup>37</sup> and experimental models of Huntington's and Parkinson's diseases. Manipulation of the endocannabinoid system may be possible in a range of neurological disorders<sup>38,39</sup> including stroke.<sup>40</sup>

### Bladder dysfunction

Bladder hyper-reflexia, a common problem in neurological disorders such as MS, has been treated by local administration of VR1 agonists.<sup>41</sup> This symptom can also be inhibited experimentally by cannabinoids, which lack the irritancy of VR1 agonists.<sup>42</sup> Recent work has suggested that VR1-stimulated effects initiate cannabinoid-receptor mediated tone and are part of a downstream effector pathway of capsaicin-induced control of bladder hyper-reflexia.<sup>43</sup> As we understand more about how cannabinoid receptors interact, a combination of agents might be used to limit the cannabinoid dose and thus limit the adverse effects. However, these studies highlight one fundamental problem with cannabis as a drug: the main target for most therapeutic activities is CB<sub>1</sub> and this is the same receptor that causes the adverse effects. Dissociation of the adverse effects from the therapeutic effects of cannabis may never be possible despite frequent claims to the contrary.

### Clinical studies

According to the UK House of Lords report (1998) that assessed all available evidence,<sup>1</sup> the best-supported indications for cannabis are spasticity in MS and pain. Large multicentre trials of dose-titrated oral cannabis and THC (Marinol) were subsequently initiated for MS spasticity (n=660)<sup>44</sup> and acute,

postoperative pain (n=400). Recruitment to the study of MS is now complete and results are expected in June, 2003. Substudies that measure the effect of these agents on cognitive and bladder function in MS are also underway. The studies of cognitive function are particularly important given the known effects of cannabis.<sup>45</sup> Large phase III trials of sublingual cannabis (high THC, high cannabidiol, or THC and cannabidiol in a one to one ratio) are in progress in MS and other disorders including pain, sleep disturbance, and cancer-associated pain.<sup>46</sup> Studies of THC hemisuccinate given as a suppository<sup>47</sup> and the effects of cannabis smoking in MS and HIV are ongoing. Therefore, concerns about route of delivery<sup>6</sup> are being addressed and in the near future we should know if there is any efficacy in MS. Comprehensive safety data will also be available.

As a prelude to the publication of these phase III studies, there have been several recent trials of cannabis or cannabinoids for the treatment of pain and MS spasticity that warn against being overoptimistic. A qualitative systematic review of nine small randomised trials of THC in 222 patients with acute cancer and chronic pain has cast doubt on its efficacy.<sup>48</sup> Where comparisons were made in acute pain studies, the level of pain reduction was similar to that for analgesics already in use and most trials reported adverse cannabimimetic effects. Although other analgesics may be able to manage acute pain, there is a need to manage chronic neuropathic pain that is unresponsive to standard analgesics; cannabinoid use for chronic pain is supported by several clinical studies.<sup>1,3,4,32</sup> Oral nabilone was investigated in people with chronic pain (n=60),<sup>49</sup> in this study six of 16 patients with MS reported some analgesic effect. However, many experienced adverse events and opted to discontinue the drug, despite having obtained a benefit.<sup>49</sup> A phase III trial (n=96) of dose-titrated oral nabilone is currently underway in patients with neuropathic pain. A phase II trial (n=34) recently found that sublingual cannabis had a significant analgesic effect in chronic pain in 28 patients with both THC-rich and, interestingly, cannabidiol-rich cannabinoids.<sup>50</sup>

Clinical evidence for the benefits of cannabis in spasticity is limited to a few case reports and some small-scale studies (n=43).<sup>5</sup> A recent, blinded, phase I/II study (n=16) of oral cannabis (THC and plant extract) did not show benefits for spasticity in MS and both preparations actually worsened the patients' “global” impression.<sup>51</sup> A larger, dose-titrated phase II study (n=57), has suggested an effect on spasms, although objective measures did not reach significance and patients were also given in-patient rehabilitation during the study.<sup>52</sup> Although published data are not yet available, preliminary reports of phase II studies of a sublingual spray of THC containing cannabis extracts have suggested benefit in bladder hyper-reflexia (n=19)<sup>53</sup> and MS symptoms (n=20).<sup>54</sup> A recent double-blind, phase III study of “self-titrated” sublingual cannabis extract have also reported benefit in neuropathic pain in MS (n=66) and brachial plexus injury (n=48), spasticity in MS (n=160), chronic refractory pain and sleep disturbances in MS, and other neurological disorders (n=70).<sup>55</sup> However, these data have not yet been published and require rigorous peer-review before benefit can be confirmed.

### The future of cannabinoid therapeutics

#### New neurological indications: neuroprotection

Although the current clinical use of cannabinoids focuses on symptom management, the biology of the cannabinoid system suggests that there may be other benefits in the treatment of neurological disease, notably the slowing of progression in neurodegenerative disorders. Selective loss of CB<sub>1</sub> receptors in the striatum is associated with the onset of signs in Huntington's disease before significant axonal loss, both in human beings and in animal models,<sup>56</sup> which suggests that some cannabinoid regulation is lost before significant pathology develops. However, activation of the remaining receptors through stimulation by endocannabinoids can limit experimental Huntington's disease.<sup>57</sup> Neurodegeneration is the main cause of morbidity in several diseases such as Huntington's, Parkinson's, Alzheimer's, and motor-neuron diseases and stroke. Neurodegenerative processes may be the fundamental reason for progressive disease in MS, despite it being thought of as an inflammatory disorder.<sup>58</sup> Although the pathways leading to neuron death will be different in these disorders, some similarities are likely, such as glutamate-induced excitotoxicity and damage from reactive oxygen species and toxic ion imbalances, which may make damaged or demyelinated axons particularly vulnerable. CB<sub>1</sub> can regulate potentially neurodegenerative effects including the inhibition of excessive glutamate production and calcium ion influx via several ion channels and reactive oxygen species.<sup>10,59,60</sup> There is increasing experimental evidence of a neuroprotective effect of cannabinoids in experimental models including ischaemia<sup>61</sup> and head trauma.<sup>62</sup> However, in contrast to the acute glutamate-induced injury in the penumbra during ischaemia, in chronic diseases the damage is probably a low grade insult that may be amenable to intervention with

neuroprotective agents. There is experimental evidence of activity in inflammatory-mediated neurodegeneration, including experimental MS models.<sup>63</sup> Although clinical neuroprotection is an exciting prospect, clinical data is lacking and will take time to assess. However, there is recent evidence to support the inhibition of abnormal glutamate hyperactivity. This is thought to cause tics associated with Tourette's syndrome and epilepsy. Although there are no reliable data on the use of cannabis in epilepsy,<sup>64</sup> a small-scale study has shown that oral THC can inhibit tics in Tourette's syndrome.<sup>65</sup> Although THC mediates many of these effects experimentally, other cannabinoids may contribute to the neuroprotective effect, such as the antioxidant properties of cannabidiol.<sup>59,60,66</sup> A synthetic, non-CB binding cannabinoid (dexanabinol, HU211) is an NMDA-receptor antagonist and phase II trials have recently shown some efficacy in the treatment of head trauma.<sup>67</sup> The CNS is plastic and can accommodate significant nerve loss before the development of symptoms. Agents that slow this process may have a great effect on the rate of disability in chronic neurodegenerative disease.

#### Clinical cannabinoid pharmacology

Results of clinical trials of oral, sublingual, and even smoked cannabis will be known soon and there will be a definitive answer as to whether cannabis, in the forms studied, has any therapeutic potential. Researchers, clinicians, and government officials will then have the knowledge to decide on the next step forward. Although the immediate future may lie in plant-based medicines, once we understand the biology of the disorders better the future for therapy must surely be in pharmaceuticals, either as single agents or in combinations that target complementary cascades. There are already indications that cannabinoids can be used in synergistic

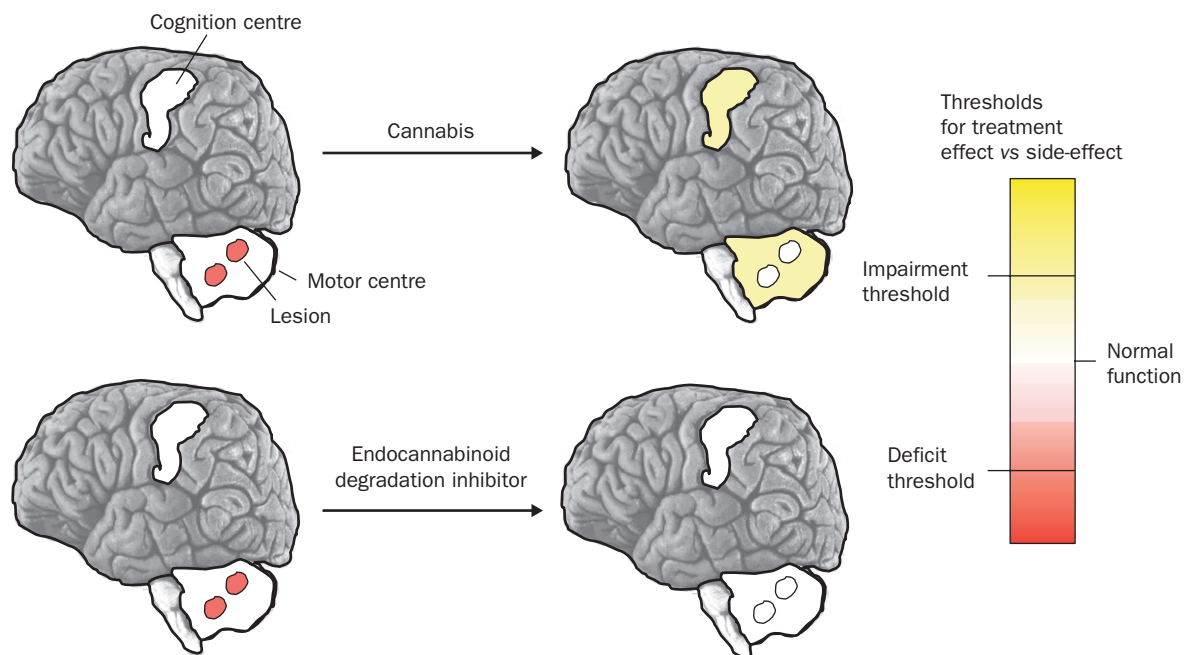


Figure 5. Endocannabinoids are upregulated in lesions in the motor centres in MS compared with unaffected areas.<sup>36</sup> Top: dosing with cannabis can cause impairment in brain regions in which THC is psychoactive as it stimulates all CB<sub>1</sub> receptors. Bottom: by inhibiting endocannabinoid degradation, the concentration is raised (eg, four fold higher than baseline). Selective increase of endocannabinoids in the lesion enables symptom management.

combination with opioids and benzodiazepines in pain relief.<sup>32</sup> Through combination, doses can be reduced with the advantage of reducing side-effects. The current clinical trials, initiated in response to patient pressure, have relied on available drugs, which had to be given orally. Although oral efficacy of nabilone and dronabinol for their clinical indications must be recognised, oral administration is probably the least satisfactory route for cannabis owing to sequestration of cannabinoids into fat from which there is slow and variable release into plasma.<sup>6</sup> In addition, significant first-pass metabolism in the liver, which degrades THC, contributes to the variability of circulating concentrations of orally administered cannabinoids,<sup>6,7,47,68,69</sup> which makes dose titration more difficult and therefore increases the potential for adverse psychoactive effects. Smoking has been the route of choice for many cannabis users because it delivers a more rapid “hit” and allows more accurate dose-titration. Smoking may also change the chemical composition such that THC carboxylic acids are readily converted to THC by heating or baking.<sup>69</sup> However, this route is not a viable option because of the potential for long-term side-effects from smoke inhalation. Delivery methods need to be developed for currently available and future compounds to allow better control of side-effects. One approach has been the development of a sublingual spray.<sup>53–55</sup> However, formulations and inhalers for delivery into the lungs, skin patches, or even the development of oral prodrugs that become active once in the blood are possible alternatives. “Smart” inhalers are being developed that allow controlled doses that can only be dispensed by the appropriate device to limit illegal use,<sup>55</sup> but the best form of prohibition is to develop more effective alternatives.

The pharmaceutical approach of making specific potent agonists has generated some compounds that have entered preliminary clinical studies (eg, nabilone and levonantradol).<sup>70</sup> Likewise, CB<sub>1</sub> antagonists (Rimonabant)<sup>71</sup> are also currently being assessed in the prevention of obesity. In addition, there are already hundreds of experimental agonists that could be used in future therapeutic trials. The variability in toleration of cannabinoids and the slight distinction between effect and side-effect,<sup>6,7,69</sup> however, suggest that there could be a real possibility for overdose with strong agonists. Excessive stimulation of the receptor leads to receptor tolerisation and is a particular problem of strong agonism.<sup>6,72</sup> Therefore, the development of clinically acceptable weak agonists may be preferable for chronic use of cannabinoid-based drugs to prevent receptor desensitisation and also increase the therapeutic window. THC is only a partial CB<sub>1</sub> agonist,<sup>10,13</sup> whereas endocannabinoids are weak agonists and these agents naturally stimulate receptors without much potential for inducing psychoactive effects.<sup>10,13</sup> These are new targets for cannabinoid therapy.<sup>36,73</sup>

Endocannabinoid release could be stimulated either directly or indirectly through the stimulation of complementary systems (eg, metabotropic type I glutamate receptors).<sup>25</sup> Importantly, these can also be stimulated through inhibition of endocannabinoid degradation (figure 3). In the case of depression, serotonin reuptake inhibitors may be preferable to direct serotonin-receptor stimulation, which might also be the case with the cannabinoids. During

### Search strategy and selection criteria

Data for this review were identified by searches of Pubmed, Current Contents and from relevant books, meeting reports and the authors' extensive files. The terms “cannabinoids” and the names of researchers involved in cannabinoid research were looked up at least weekly 2002–03. Only papers published in English were reviewed. Recent articles and reviews of a large amount of primary data were preferentially selected.

disease there are changes in endocannabinoid concentrations at the site of pathology.<sup>36,38,40</sup> Therefore, targeting of endocannabinoid degradation through inhibition of the reuptake mechanism or enzymes that cause degradation could locally target sites of damage while limiting effects in uninvolved cognitive areas (figure 5). Cannabis has no mechanism to selectively target CB<sub>1</sub> in the brain and its use will invariably be linked with unwanted biological activity. Therefore, the value of cannabis will depend on whether patients can titrate their dose before adverse effects become intolerable, the acceptability of which will depend on the patient's character and the disorder in question.

Although many adverse effects originate in the brain, CB<sub>1</sub> is expressed on nerves outside the CNS (eg, nerve terminals, dorsal root ganglia, vasculature).<sup>10</sup> Selective peripheral receptor agonism may therefore limit psychoactivity while producing benefits for disorders such as pain,<sup>33</sup> asthma (bronchodilation),<sup>74</sup> and glaucoma (neuroprotection and reduction of pressure)<sup>75</sup> by either local application (eg, eye drops for glaucoma) or by developing CNS-excluded agonists.

Several experimental agents have been made that are effective in experimental spasticity<sup>35,36</sup> and pain<sup>32,34,37</sup> as full receptor agonists that do not have psychoactive effects. Ajulemic acid,<sup>76,77</sup> a cannabinoid compound that does not directly stimulate CB<sub>1</sub> receptors significantly, has undergone safety studies in human beings. It inhibits anandamide reuptake and is antispastic, at least experimentally.<sup>73</sup>

### Conclusion

As we learn more about the pharmacological activities of compounds in cannabis and their biological targets outside the cannabinoid system, varieties of cannabis might be tailored to different diseases or used in combination with known drugs. Whatever the future holds, there are many challenges to be overcome before we view cannabinoids as routine medicine in neurological disorders.<sup>78</sup>

### Authors' contributions

DB and AJT planned and wrote the review, GG helped with editing and GP provided some of the figures.

### Conflict of interest

Costs for the experimental work on CT3 were provided to David Baker by Atlantic Technology Ventures Inc. Gavin Giovannoni has been a consultant to Atlantic Technology Ventures Inc. Alan Thompson is one of the principal investigators of the UK Cannabis trial in MS Spasticity (CAMS) funded by the Medical Research Council.

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