

# Clinical research

## *Cannabinoids in health and disease*

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**C***annabis sativa L.* preparations, such as marijuana, hashish, and dagga, have been used in medicine for millenia.<sup>1</sup> Investigations into the chemistry of *Cannabis* began in the mid-19th century, following a major trend in chemical research at the time, which centered on the quest for active natural products. Numerous alkaloids were isolated in pure form from various plants, and many of them were fully or partially characterized. Morphine, cocaine, strychnine, and many others were purified and used in medicine. However, most of the terpenoids—a major class of secondary plant metabolites, to which the plant cannabinoids also belong—were not isolated until the end of the century or even much later, and in many cases their purity was doubtful.

*Cannabis sativa L. preparations have been used in medicine for millenia. However, concern over the dangers of abuse led to the banning of the medicinal use of marijuana in most countries in the 1930s. Only recently, marijuana and individual natural and synthetic cannabinoid receptor agonists and antagonists, as well as chemically related compounds, whose mechanism of action is still obscure, have come back to being considered of therapeutic value. However, their use is highly restricted. Despite the mild addiction to cannabis and the possible enhancement of addiction to other substances of abuse, when combined with cannabis, the therapeutic value of cannabinoids is too high to be put aside. Numerous diseases, such as anorexia, emesis, pain, inflammation, multiple sclerosis, neurodegenerative disorders (Parkinson's disease, Huntington's disease, Tourette's syndrome, Alzheimer's disease), epilepsy, glaucoma, osteoporosis, schizophrenia, cardiovascular disorders, cancer, obesity, and metabolic syndrome-related disorders, to name just a few, are being treated or have the potential to be treated by cannabinoid agonists/antagonists/cannabinoid-related compounds. In view of the very low toxicity and the generally benign side effects of this group of compounds, neglecting or denying their clinical potential is unacceptable—instead, we need to work on the development of more selective cannabinoid receptor agonists/antagonists and related compounds, as well as on novel drugs of this family with better selectivity, distribution patterns, and pharmacokinetics, and—in cases where it is impossible to separate the desired clinical action and the psychoactivity—just to monitor these side effects carefully.*

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## Selected abbreviations and acronyms

<b>ALS</b>	<i>amyotrophic lateral sclerosis</i>
<b>CBD</b>	<i>cannabidiol</i>
<b>DA</b>	<i>dopamine</i>
<b>HD</b>	<i>Huntington's disease</i>
<b>IOP</b>	<i>intraocular pressure</i>
<b>MS</b>	<i>multiple sclerosis</i>
<b>PD</b>	<i>Parkinson's disease</i>
<b>PTSD</b>	<i>post-traumatic stress disorder</i>
<b>THC</b>	<i>tetrahydrocannabinol</i>

In 1840, Schlessinger was apparently the first investigator to obtain an active extract from the leaves and flowers of hemp.<sup>2</sup> A few years later, Decourtive described the preparation of an ethanol extract that on evaporation of the solvent gave a dark resin, which he named “cannabin.”<sup>3</sup> For a detailed history of early *Cannabis* research see ref 4. The chemical research on the plant cannabinoids and their derivatives over nearly two centuries is described in ref 5. It was, however, not until 1964 that  $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC), the major psychoactive component of *Cannabis*, was isolated in pure form and its structure was elucidated.<sup>6</sup> Shortly thereafter it was synthesized and became widely available. These chemical advances led to an avalanche of publications on  $\Delta^9$ -THC, as well as on cannabidiol (CBD), a nonpsychoactive plant cannabinoid.<sup>7</sup> However, concern about the dangers of abuse led to the banning of marijuana and its constituents for medicinal use in United States and many other countries in the 1930s and 1940s. It took decades until cannabinoids came to be considered again as compounds of therapeutic value, and even now their uses are highly restricted. Here we present an overview of the addictive and side effects of cannabinoids vs their therapeutic potential.

## Addiction to cannabis, and the influence of cannabis on addiction to other substances

Marijuana may produce mild dependence in humans.<sup>8-12</sup> This was shown to depend on the personality type of the addicts,<sup>13</sup> and can be successfully reversed by abstinence or treated by cognitive-behavioral therapy,<sup>14</sup> without the occurrence of major withdrawal symptoms. Cannabinoids act on brain reward processes and reward-related behaviors by a mechanism similar to that found with other addictive drugs. In animal models they enhance electrical brain-stimulation reward in the core meso-accumbens

reward circuitry of the brain and neural firing of a core dopamine (DA) component and thus elevate DA tone in the reward-relevant meso-accumbens DA circuit. In some animal models they produce conditioned place preference (CPP) and self-administration.<sup>15,16</sup> Other studies, however, find THC to be a poor reinforcer, with no or little self-administration.<sup>17</sup>

The abuse of other substances is influenced by the cannabinoids. The cannabinoid system is involved in alcohol-consumption behavior. Cannabinoid CB1 receptor agonists have been found to specifically stimulate alcohol intake and its motivational properties in rats.<sup>18</sup> The high ethanol preference of young mice is reduced by the cannabinoid receptor 1 (CB1) antagonist SR141716A (rimonabant) to levels observed in their CB1 knockout littermates.<sup>19</sup> Dopamine release induced by ethanol in brain was reduced by SR141716A,<sup>20</sup> which can explain in part the antiaddictive effect of the drug. Cocaine is another substance of abuse in whose acquisition and consolidation cannabinoids may be involved. High prevalence of alcohol dependence and cannabis dependence can be found in patients with cocaine dependence.<sup>21</sup> Marijuana smoking increases plasma cocaine levels and subjective reports of euphoria in male volunteers.<sup>22,23</sup> Furthermore, a recent genetic study found an association between an n triplet repeat polymorphism in the CB1 encoding *CNRI* gene with cocaine addiction in the African-Caribbean population.<sup>24</sup> In another study it was found that withdrawal from repeated access or exposure to cocaine and then a reinstatement of cocaine-seeking behavior or a sensitized locomotor response to a single cocaine challenge, respectively, was potentially reduced by pretreatment with rimonabant.<sup>25</sup> Similarly, acute administration of rimonabant blocked expression of nicotine-induced conditioned place preference.<sup>26</sup> Rimonabant also reduces nicotine self-administration, and may be effective not only as an aid for smoking cessation, but also in the maintenance of abstinence.<sup>27</sup> As the endocannabinoid system plays a role in nicotine addiction,<sup>28</sup> the potential of cannabinoid antagonists to treat it is self-evident.<sup>29-31</sup> Opiate and CB1 receptors are coexpressed in the nucleus accumbens and dorsal striatum, and the interaction between the two systems is well known.<sup>32</sup> The reinforcing properties of morphine and the severity of the withdrawal syndrome are strongly reduced in CB1-knockout mice<sup>33</sup>; this observation opens an opportunity to treat opiate addiction with rimonabant, as noted with alcohol, cocaine, and nicotine addiction.<sup>34,35</sup>

## Negative effects of cannabis other than addiction

There are some negative effects of cannabis use other than addiction, most of them related to alterations of attentional and cognitive functions or other neuropsychological and behavioral effects. Most of them are noted as a result of early-onset cannabis use (during adolescence).<sup>36</sup> Electrophysiological measures have revealed long-term deficits in attention among cannabis users.<sup>37</sup> In another study, impairment both in cognitive function and mood following cannabis use was noted.<sup>38</sup> However, in another study, cannabis users and controls performed equally well in a working memory task and a selective attention task. Furthermore, cannabis users did not differ from controls in terms of overall patterns of brain activity in the regions involved in these cognitive functions.<sup>39</sup> Prenatal exposure to cannabis is associated with only minor impaired cognitive and attentional effects.<sup>40-42</sup> Cannabis use in adolescence increases the risk of schizophrenia-like psychoses.<sup>43</sup> Cognitive dysfunction associated with long-term or heavy cannabis use is similar in many respects to the cognitive endophenotypes that have been proposed as vulnerability markers of schizophrenia.<sup>44</sup> Also, evidence exists that cannabis use may trigger acute schizophrenic psychosis.<sup>45,46</sup> Cannabis was found to produce a broad range of transient symptoms, behaviors, and cognitive deficits in healthy individuals that resemble some aspects of endogenous psychoses.<sup>46</sup> Amotivational syndrome is a chronic psychiatric disorder characterized by a variety of changes in personality, emotions, and cognitive functions such as lack of activity, inward-turning, apathy, incoherence, blunted affect, inability to concentrate, and memory disturbance. The syndrome was first described in the 1960s among patients with a history of longtime cannabis use.<sup>47</sup> A useful animal model for this disorder was found in rat, where the cannabis-caused catalepsy-like immobilization is related to a decrease in catecholaminergic and serotonergic neurons in the nucleus accumbens and amygdaloid nucleus, and thus can serve as a model for amotivational syndrome.<sup>48</sup> In another study, heavy cannabis use was found to cause an amotivational syndrome in adolescents.<sup>49</sup> The treatment of cannabis use disorders has recently been reviewed.<sup>12</sup> However, the occurrence of amotivational syndrome as a result of cannabis exposure remains controversial.<sup>50</sup> The data from other studies do not support the hypothesis that marijuana impairs motivation.<sup>51,52</sup> Although most of the cannabis-related negative effects relate to its

neuropsychologic and behavioral effects, other negative reactions to cannabis are sometimes found. For example, cannabis can cause acute pancreatitis, although the exact mechanism remains unknown.<sup>53</sup>

## Therapeutic uses of cannabinoids

### Obesity, anorexia, emesis

Cannabis has been known for centuries to increase appetite and food consumption.<sup>54</sup> More recently this propensity of the drug was substantiated when the CB1 receptor was shown to have a role in central appetite control, peripheral metabolism, and body weight regulation.<sup>55</sup> Genetic variants at CB1 coding gene *CNR1* are associated with obesity-related phenotypes in men.<sup>56</sup> In animals, CB1 receptor antagonism decreases motivation for palatable foods. Rimonabant administration caused suppression of the intake of a chocolate-flavored beverage over a 21-day treatment period, without any apparent development of tolerance.<sup>57</sup> CB1 receptors were found to be preferentially involved in the reinforcing effects of sweet, as compared to a pure fat, reinforcer.<sup>58</sup> Rimonabant selectively reduces sweet rather than regular food intake in primates,<sup>59</sup> which suggests that rimonabant is more active on the hedonic rather than nutritive properties of diets.

Rimonabant leads to significant weight loss in obese human subjects. Treatment with rimonabant was also associated with beneficial effects on different metabolic parameters and cardiovascular risk factors linked with overweight.<sup>60,61</sup> In clinical trials rimonabant was found to cause a significant mean weight loss, reduction in waist circumference, increase in HDL cholesterol, reduction in triglycerides, and increase in plasma adiponectin levels.<sup>62</sup> Patients who were switched from the rimonabant treatment to placebo after a 1-year treatment regained weight, while those who continued to receive rimonabant maintained their weight loss and favorable changes in cardiometabolic risk factors.<sup>63,64</sup> Rimonabant was shown to be safe and effective in treating the combined cardiovascular risk factors of smoking and obesity.<sup>65</sup> It also diminishes insulin resistance, and reduces the prevalence of metabolic syndrome. Many of the metabolic effects, including adiponectin increase, occur beyond weight loss, suggesting a direct peripheral effect of rimonabant.<sup>66</sup> Therapy with rimonabant is also associated with favorable changes in serum lipids and an improvement in

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glycemic control in type 2 diabetes.<sup>67</sup> The activity of rimonabant in the management of obesity has been described in recent reviews.<sup>31,68</sup> It has been approved for the treatment of obesity in the European Union, and is sold under the trade name Acomplia. Surprisingly, the US Food and Drug Administration has declined to approve rimonabant, primarily due to its slight potential to enhance anxiety and suicidal thoughts. The atmosphere of consternation and possible legal action due to side effects may have led to this decision.

The other side of the same coin is anorexia. While in obese populations weight loss is the main goal, in other populations, such as patients with cancer or AIDS, it is an immense problem. Dronabinol (synthetic THC, known as Marinol and approved for the treatment of nausea and vomiting in cancer and AIDS patients) is associated with consistent improvement in appetite.<sup>69</sup> It was found to be safe and effective for anorexia associated with weight loss in patients with AIDS, and is associated with increased appetite, improvement in mood, and decreased nausea. In clinical trials, weight was stable in dronabinol patients, while placebo recipients lost weight.<sup>70,71</sup> Dronabinol was found to be safe and effective for treatment of HIV wasting syndrome,<sup>72</sup> as well as in patients with Alzheimer's disease<sup>73</sup> and with advanced cancer.<sup>73,74</sup> The possible mechanisms of these actions have been reviewed.<sup>75</sup> Cannabinoids have a positive effect in controlling chemotherapy-related sickness.<sup>76</sup> They are more effective antiemetics than the dopamine receptor antagonists such as chlorpromazine-type drugs.<sup>77</sup> Direct comparisons with serotonin (5-HT)<sub>3</sub> antagonists, which are widely used as antiemetics, have not been reported. However, while these antagonists are not effective in delayed vomiting, THC is known to reduce this side effect of chemotherapy.

## Pain

Cannabis has been used for millennia as a pain-relieving substance. Evidence suggests that cannabinoids may prove useful in pain modulation by inhibiting neuronal transmission in pain pathways. Considering the pronounced antinociceptive effects produced by cannabinoids, they were proposed to be a promising therapeutic approach for the clinical management of trigeminal neuralgia.<sup>78</sup> THC, CBD, and CBD-dimethyl heptyl (DMH) were found to block the release of serotonin from platelets induced by plasma obtained from the patients during migraine attack.<sup>79</sup> However, in other reports

cannabinoids are much less successful in pain-relieving. In a clinical trial THC did not have any significant effect on ongoing and paroxysmal pain, allodynia, quality of life, anxiety/depression scores and functional impact of pain. These results do not support an overall benefit of THC in pain and quality of life in patients with refractory neuropathic pain.<sup>80</sup> Similarly, in an additional clinical trial, no evidence was found<sup>81</sup> of analgesic effect of orally administered THC in postoperative pain in humans. Other studies show much better results of pain relief. When THC was given to a patient with familial Mediterranean fever, with chronic relapsing pain and gastrointestinal inflammation, a highly significant reduction in pain was noted.<sup>82</sup> Mild improvement was noted with cannabis-based medicines for treatment of chronic pain associated with brachial plexus root avulsion.<sup>83</sup> In neuropathic pain patients, median spontaneous pain intensity was significantly lower on THC treatment than on placebo treatment, and median pain relief score (numerical rating scale) was higher.<sup>84</sup> It was also effective in treating central pain.<sup>85</sup> The administration of single oral doses of THC to patients with cancer pain demonstrated a mild analgesic effect.<sup>86,87</sup> Patients who suffer from pain also tend to self-medicate with marijuana. In an anonymous cross-sectional survey, 72 (35%) of chronic non-cancer pain patients reported having used cannabis for relieving pain.<sup>88</sup> Cannabis-treated AIDS patients reported improved appetite, muscle pain, nausea, anxiety, nerve pain, depression, and paresthesia.<sup>89</sup> Not only THC, but also other cannabinoids can potentially affect different types of pain. Nabilone is a synthetic cannabinoid approved for treatment of severe nausea and vomiting associated with cancer chemotherapy.<sup>90</sup> In Canada, the United States, and the United Kingdom, nabilone is marketed as Cesamet. A significant decrease in disabling spasticity-related pain of patients with chronic upper motor neuron syndrome (UMNS) was found with nabilone.<sup>91</sup> Another cannabinoid, ajulemic acid (AJA), was effective in reducing chronic neuropathic pain,<sup>92</sup> although cannabinoid side effects (tiredness, dry mouth, limited power of concentration, dizziness, sweating) were noted. Cannabimimetic effects with ajulemic acid in rodents have also been recorded.<sup>93</sup>

The combination of THC with the nonpsychotropic cannabis constituent CBD has a higher activity than THC alone.<sup>94</sup> The CBD/THC buccal spray (Sativex) was found to be effective in treating neuropathic pain in multiple sclerosis (MS).<sup>95</sup> Chronic neuropathic pain can also

be treated with cannabis extracts containing THC, or CBD, or with Sativex.<sup>96,97</sup> The latter also was effective in reducing sleep disturbances in these patients and was mostly well tolerated.<sup>97</sup> Sativex is the first cannabis-based medicine to undergo conventional clinical development and be approved as a prescription drug. It is efficacious and well tolerated in the treatment of symptoms of multiple sclerosis, notably spasticity and neuropathic pain.<sup>98</sup> Sativex has been approved for use in neuropathic pain due to multiple sclerosis in Canada [for reviews on Sativex and on pain see refs 94, 99, and 100].

### **Multiple sclerosis, neuroprotection, inflammation**

Inflammation, autoimmune response, demyelination, and axonal damage are thought to participate in the pathogenesis of MS. Increasing evidence supports the idea of a beneficial effect of cannabinoid compounds for the treatment of this disease. In clinical trials, it has been shown that cannabis derivatives are active on the pain related to MS,<sup>84,85,95,97,98</sup> However, this is not the only positive effect of cannabinoids in this disease. In rat experimental autoimmune encephalomyelitis (EAE), a laboratory model of MS, THC, given once after disease onset, significantly reduced maximal EAE score. Reduction in the inflammatory response in the brain and spinal cord was also noted in animals treated with dexamabinol (HU-211 a non-psychoactive synthetic cannabinoid).<sup>101</sup> In another trial in rats, all animals treated with placebo developed severe clinical EAE and more than 98% died, while THC-treated animals had either no clinical signs or mild signs, with delayed onset with survival greater than 95%.<sup>102</sup> WIN-55,212-2, another synthetic cannabinoid, also was found to ameliorate the clinical signs of EAE and to diminish cell infiltration of the spinal cord, partially through CB2.<sup>103</sup> Using a chronic model of MS in mice, it was shown that clinical signs and axonal damage in the spinal cord were reduced by the synthetic cannabinoid HU210.<sup>104</sup> To more fully understand the involvement of the endocannabinoid system in MS, the status of cannabinoid CB1 and CB2 receptors and fatty acid amide hydrolase (FAAH) enzyme in brain tissue samples obtained from MS patients was investigated. Selective glial expression of cannabinoid CB1 and CB2 receptors and FAAH enzyme was found to be induced in MS.<sup>105</sup> In mice with chronic relapsing experimental allergic encephalomyelitis (CREAE), a chronic model of MS that reproduces many of the pathological hallmarks of the human disease, a moderate decrease in

the density of CB1 receptors in the caudate-putamen, globus pallidus, and cerebellum was found. These observations may explain the efficacy of cannabinoid agonists in improving motor symptoms (spasticity, tremor, ataxia) typical of MS in both humans and animal models.<sup>106</sup> Spasticity is a common neurologic condition in patients with MS, stroke, cerebral palsy, or an injured spinal cord. Marijuana was suggested as treatment of muscle spasticity as early as the 1980s.<sup>107</sup> In an experiment in mice, control of spasticity in a MS model was found to be mediated by CB1, but not by CB2, cannabinoid receptors.<sup>108</sup> In clinical trials, patients treated with THC had significant improvement in ratings of spasticity compared to placebo.<sup>109</sup> In one case report nabilone improved muscle spasms, nocturia, and general well-being.<sup>110</sup> In another case report, the chronic motor handicaps of an MS patient acutely improved while he smoked a marijuana cigarette.<sup>111</sup> THC significantly reduced spasticity by clinical measurement. Responses varied, but benefit was seen in patients with tonic spasms.<sup>112</sup> At a progressive stage of illness, oral and rectal THC reduced the spasticity, rigidity, and pain, resulting in improved active and passive mobility.<sup>113</sup> However, in other clinical trials, cannabinoids appeared to reduce tremor but were ineffective in spasticity.<sup>114,115</sup> Moreover, in one trial marijuana smoking further impaired posture and balance in patients with spastic MS.<sup>116</sup> The inconsistent effects noted might be due to dose-dependency. Improved motor coordination was seen when patients with MS, seriously disabled with tremor and ataxia, were given oral THC.<sup>117</sup> In another study, cannabis extract did not produce a functionally significant improvement in MS-associated tremor.<sup>118</sup> Suppression of acquired pendular nystagmus (involuntary movement of the eyes) was seen in a patient with MS after smoking cannabis resin, but not after taking nabilone tablets or orally administered capsules containing cannabis oil.<sup>119</sup> There are also findings suggestive of a clinical effect of cannabis on urge incontinence episodes in patients with MS.<sup>120</sup> In the treatment of MS, as well as in pain reduction described earlier, there is a preferential effect of a THC+CBD combination (Sativex).<sup>121</sup> A mixture of 2.5 mg THC and 0.9 mg cannabidiol (CBD) lowered spasm frequency and increased mobility, with tolerable side effects, in MS patients with persistent spasticity not responding to other drugs.<sup>122</sup> Oromucosal sprays of Sativex significantly reduced spasticity scores in comparison with placebo.<sup>123</sup> Long-term use of Sativex maintains its effect in those patients who perceive initial benefit.<sup>124</sup> Zajicek et al origi-

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nally reported that cannabinoids did not have a beneficial effect on spasticity; however, there was an objective improvement in mobility and some patients reported an improvement in pain.<sup>125</sup> Later the same group also found positive effects on muscle spasticity with prolonged treatment.<sup>126</sup> The subject has been thoroughly reviewed.<sup>99,127-130</sup> MS is not the only disease state where the neuroprotective potential of cannabinoids can be seen. In animal experiments, 2 weeks after the application of 6-hydroxydopamine, a significant depletion of dopamine contents and a reduction in tyrosine hydroxylase activity in the lesioned striatum were noted, and were accompanied by a reduction in tyrosine hydroxylase-messenger ribonucleic acid (mRNA) levels in the substantia nigra. Daily administration of THC over 2 weeks produced a significant irreversible waning in the magnitude of these changes, which may be relevant in the treatment of Parkinson's disease (see below).<sup>131</sup> The cannabinoids have a neuroprotective activity not only in vitro but also in vivo: HU-210, a potent synthetic analog of THC, increases survival of mouse cerebellar granule cells exposed to 6-hydroxydopamine.<sup>131</sup> In a model of experimental stroke, rimonabant reduced infarct volume by approximately 40%. Rimonabant exerted neuroprotection independently of its cannabinoid receptor-blocking effect.<sup>132</sup> In clinical trials, dexanabinol-treated patients achieved significantly better intracranial pressure/cerebral perfusion pressure control without jeopardizing blood pressure. A trend toward faster and better neurologic outcome was also observed.<sup>133</sup> However, in further experiments, dexanabinol was not found to be efficacious in the treatment of traumatic brain injury.<sup>134</sup> A wide range of cannabinoids has been shown to help in pathologies affecting the central nervous system (CNS) and other diseases that are accompanied by chronic inflammation.<sup>130,135,136</sup> In a rodent model of chronic brain inflammation produced by the infusion of lipopolysaccharide into the fourth ventricle of young rats, the cannabinoid agonist WIN-55212-2 reduced the number of LPS-activated microglia.<sup>137</sup> Direct suppression of CNS autoimmune inflammation was seen by activation of CB1 receptors on neurons and CB2 receptors on autoreactive T cells.<sup>138</sup> Atherosclerosis is a chronic inflammatory disease, and is the primary cause of heart disease and stroke in Western countries. Oral treatment with a low dose of THC inhibits atherosclerosis progression in an apolipoprotein E knockout mouse model, through pleiotropic immunomodulatory effects on lymphoid and myeloid cells. Thus, THC may be

a valuable target for treating atherosclerosis.<sup>139</sup> N-palmitoyl-ethanolamine is an endogenous endocannabinoid-like compound. Its concentrations are significantly increased in three different inflammatory and neuropathic conditions. The enhanced levels may possibly be related to a protective local anti-inflammatory and analgesic action.<sup>140</sup> CBD has been shown to exert potent anti-inflammatory and antioxidant effects. High-glucose-induced mitochondrial superoxide generation, NF-kappaB activation, nitrotyrosine formation, iNOS and adhesion molecules ICAM-1 and VCAM-1 expression, monocyte-endothelial adhesion, transendothelial migration of monocytes, and disruption of endothelial barrier function in human coronary artery endothelial cells (HCAECs) were attenuated by CBD pretreatment.<sup>141</sup>

In experiments with obese vs lean rats, rimonabant was found to be a potent inhibitor of sensory hypersensitivity associated with CFA-induced arthritis in obese rats, in which the inflammatory reaction is more severe than in lean rats. It may thus have therapeutic potential in obesity-associated inflammatory diseases.<sup>142</sup>

## **Parkinson's disease, Huntington's disease, Tourette's syndrome, Alzheimer's disease, epilepsy**

*Parkinson's disease (PD)* is a chronic, progressive neurodegenerative disorder. The main pathological feature of PD is the degeneration of dopamine (DA)-containing neurons of the substantia nigra, which leads to severe DAergic denervation of the striatum. The irreversible loss of the DA-mediated control of striatal function leads to the typical motor symptoms observed in PD, ie, bradykinesia, tremor, and rigidity. It has been proposed that cannabinoids may have some beneficial effects in the treatment of PD.<sup>129</sup> In animal experiments cannabinoids provide neuroprotection against 6-hydroxydopamine toxicity in vivo and in vitro.<sup>131</sup>

The majority of PD patients undergoing levodopa therapy develop disabling motor complications (dyskinesias) within 10 years of treatment. Recent studies in animal models and in the clinic suggest that CB1 receptor antagonists could prove useful in the treatment of both parkinsonian symptoms and levodopa-induced dyskinesia, whereas CB1 receptor agonists could have value in reducing levodopa-induced dyskinesia.<sup>143</sup> In the reserpine-treated rat model of PD, the dopamine D2 receptor agonist quinpirole caused a significant alleviation of the akinesia. This effect was significantly reduced by coinjec-

tion with the cannabinoid receptor agonist WIN 55,212-2. The simultaneous administration of the CB1 antagonist rimonabant with quinpirole and WIN 55,212-2 blocked the effect of WIN 55,212-2 on quinpirole-induced alleviation of akinesia.<sup>144</sup> In animal experiments, chronic levodopa produced increasingly severe orolingual involuntary movements which were attenuated by WIN 55,212-2. This effect was also reversed by rimonabant.<sup>145</sup> In other studies, rimonabant was found to possess some beneficial effects on motor inhibition typical of PD, at least in some doses. The injection of 0.1 mg/kg of rimonabant partially attenuated the hypokinesia shown by PD animals with no effects in control rats, whereas higher doses (0.5-1.0 mg/kg) were not effective.<sup>146</sup> A nigrostriatal lesion by MPTP is associated with an increase in CB1 receptors in the basal ganglia in humans and nonhuman primates; this increase could be reversed by chronic levodopa therapy, which suggests that CB1 receptor blockade might be useful as an adjuvant for the treatment of parkinsonian motor symptoms.<sup>147</sup> High endogenous cannabinoid levels are found in the cerebrospinal fluid of untreated PD patients.<sup>148</sup> Administration of inhibitors of endocannabinoid degradation reduced parkinsonian motor deficits in vivo.<sup>149</sup> Thus, both agonists and antagonists of CB receptors seem to help in some parkinsonian symptoms. In clinical trials, the cannabinoid receptor agonist nabilone significantly reduced levodopa-induced dyskinesia in PD.<sup>150</sup> THC improved motor control in a patient with musician's dystonia.<sup>151</sup> In contrast to these findings, some studies find no effect of cannabinoids on PD: orally administered cannabis extract resulted in no objective or subjective improvement in either dyskinesias or parkinsonism,<sup>152</sup> no significant reduction in dystonia following treatment with nabilone,<sup>153</sup> and rimonabant could not improve parkinsonian motor disability.<sup>154</sup> However, an anonymous questionnaire sent to all patients attending the Prague Movement Disorder Centre revealed that 25% of the respondents had taken cannabis and 45.9% of these described some form of benefit.<sup>155</sup> Thus cannabinoids seem to be able to treat at least some symptoms of neurological diseases.<sup>156-158</sup>

*Huntington's disease (HD) or Huntington's chorea* ("chorea" meaning "dance" in Greek) is a disorder characterized by a distinctive choretic movement, progressive motor disturbances, dementia, and other cognitive deficits. Neuropathologically, HD is characterized by a degeneration of medium spiny striato-efferent  $\gamma$ -aminobutyric acid (GABA)ergic neurons and by an atrophy of the caudate nucleus. Advanced grades of HD showed an almost total

loss of CB1 receptors and a further depletion of D1 receptors in the caudate nucleus, putamen, and globus pallidus internus, and an increase in GABA<sub>A</sub> receptor binding in the globus pallidus internus.<sup>159,160</sup> Loss of cannabinoid receptors is also seen in the substantia nigra in HD.<sup>161</sup> These findings suggest a possible therapeutic role of cannabinoid agonists in HD. Indeed, arvanil, a hybrid endocannabinoid and vanilloid compound, behaves as an antihyperkinetic agent in a rat model of HD generated by bilateral intrastriatal application of 3-nitropropionic acid (3-NP).<sup>162</sup> The reduction in the increased ambulation exhibited by 3NP-lesioned rats in the open-field test caused by AM404 (anandamide's transport inhibitor, which also binds to vanilloid receptor 1) was reversed when the animals had been pretreated with capsazepine (VR1 antagonist), but not with SR141716A, thus suggesting a major role of VR1 receptors in the antihyperkinetic effects of AM404. However, both capsaicin (VR1 agonist) and CP55,940 (an CB1 agonist) had antihyperkinetic activity.<sup>163</sup> Quinolinic acid (QA) is an excitotoxin which, when injected into the rat striatum, reproduces many features of HD by stimulating glutamate outflow. Perfusion with WIN 55,212-2 significantly and dose-dependently prevented the increase in extracellular glutamate induced by QA. Thus, the stimulation of CB1 receptors might lead to neuroprotective effects against excitotoxic striatal toxicity.<sup>164</sup> In a clinical trial CBD was neither symptomatically effective nor toxic in neuroleptic-free HD patients.<sup>165</sup>

*Tourette syndrome (TS)* is a complex inherited disorder of unknown etiology, characterized by multiple motor and vocal tics. Anecdotal reports have suggested that the use of cannabis might improve tics and behavioral problems in patients with TS. Indeed, THC reduced tics in TS patients,<sup>166</sup> without causing acute and/or long-term cognitive deficits.<sup>167</sup> In another clinical trial, where tic severity was assessed using a self-rating scale and examiner ratings, patients also rated the severity of associated behavioral disorders. There was a significant improvement of motor tics, vocal tics and obsessive-compulsive behavior after treatment with THC. There was a significant correlation between tic improvement and maximum 11-OH-THC plasma concentration, suggesting a possible role of this THC metabolite on the positive effect of THC.<sup>168</sup> In another, longer clinical trial, THC was also found to be effective and safe in the treatment of tics.<sup>169</sup> In view of the positive effect of CB1 agonists in the treatment of TS, CB1 gene mutations were investigated. However, TS was not found to be caused by mutations in the *CNRI* gene.<sup>170</sup>

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*Amyotrophic lateral sclerosis (ALS)* is a fatal neurodegenerative disorder characterized by a selective loss of motor neurons in the spinal cord, brain stem, and motor cortex. Many effects of marijuana may be applicable to the management of ALS. These include analgesia, muscle relaxation, bronchodilation, saliva reduction, appetite stimulation, and sleep induction. In addition, its strong antioxidative and neuroprotective effects may prolong neuronal cell survival.<sup>171</sup> Indeed, treatment of postsymptomatic, 90-day-old SOD1G93A mice (a model of ALS) with WIN 55,212-2, significantly delayed disease progression. Furthermore, genetic ablation of the FAAH enzyme, which results in raised levels of the endocannabinoid anandamide, prevented the appearance of disease signs in these mice. Surprisingly, elevation of cannabinoid levels with either WIN 55,212-2 or FAAH ablation had no effect on life span. Ablation of the CB1 receptor, in contrast, had no effect on disease onset in these mice, but significantly extended life span. Together these results show that cannabinoids have significant neuroprotective effects in this model of ALS, and suggest that these beneficial effects may be mediated by non-CB1 receptor mechanisms.<sup>172</sup> THC was also found to delay the progression of disease.<sup>173,174</sup> Treatment with AM1241, a CB2-selective agonist, was effective at slowing signs of disease progression, when administered after onset of signs in an ALS mouse model. Administration at the onset of tremors delayed motor impairment in treated mice when compared with vehicle controls<sup>175</sup>; moreover, AM-1241 prolonged survival in these mice.<sup>176</sup> In a survey among ALS patients, cannabis was reported to be moderately effective in reducing symptoms of appetite loss, depression, pain, spasticity, and drooling.<sup>177</sup> Cannabinoids were also proposed to have a role in the treatment of *Alzheimer's disease (AD)*. THC competitively inhibits acetylcholinesterase (AChE) and prevents AChE-induced amyloid beta-peptide (A $\beta$ ) aggregation, the key pathological marker of AD.<sup>178</sup> THC treatment also decreased severity of disturbed behavior, and this effect persisted during the placebo period in patients who had received THC.<sup>179</sup> Compared with baseline, THC led to a reduction in nocturnal motor activity. These findings were corroborated by improvements in the Neuropsychiatric Inventory total score, as well as in subscores for agitation, aberrant motor, and nighttime behaviors; no side effects were observed.<sup>180</sup> Studies on *cannabinoid anticonvulsant activity* began in 1975, when CBD, and four CBD derivatives, (CBD-alde-

hyde-diacetate, 6-oxo-CBD-diacetate, 6-hydroxy-CBD-triacetate and 9-hydroxy-CBD-triacetate) were shown to protect against maximal electroshock convulsions in mice, to potentiate pentobarbital sleeping-time and to reduce spontaneous motor activity.<sup>181</sup> Later additional CBD analogs were shown to be active.<sup>182-184</sup> CBD was found to be an effective anticonvulsant with specificity more comparable to drugs clinically effective in major, but not in minor seizures. Furthermore, it appears that CBD enhances the anticonvulsant effects of drugs in major seizures and reduces their effects in minor seizures.<sup>185,186</sup> Hence, CBD was suggested as a drug for the treatment of children with pharmacoresistant epilepsy.<sup>187</sup> The application of the CB1 receptor antagonists SR141716A or AM251 to "epileptic" neurons caused the development of continuous epileptiform activity, resembling electrographic status epilepticus. The induction of status epilepticus-like activity by CB1 receptor antagonists was reversible and could be overcome by maximal concentrations of CB1 agonists.<sup>188</sup> Arachidonyl-2'-chloroethylamide (ACEA), a highly selective cannabinoid CB1 receptor agonist, enhances the anticonvulsant action of valproate in a mouse maximal electroshock-induced seizure model.<sup>189</sup> There are currently insufficient data to determine whether occasional or chronic marijuana use influences seizure frequency.<sup>190</sup> In one case report, marijuana smoking was proposed to induce seizures.<sup>191</sup> In another study, patients suffering from secondary generalized epilepsy with temporal focus treated with CBD remained almost free of convulsive crises throughout the experiment; other patients demonstrated partial improvement in their clinical condition.<sup>192</sup>

## **Bipolar disorder, schizophrenia, post-traumatic stress disorder (PTSD), depression, anxiety, insomnia**

Cannabis use is common in patients with *bipolar disorder*, and anecdotal reports suggest that some patients use marijuana to alleviate symptoms of both mania and depression.<sup>193</sup> In a case report, one female patient found that cannabis curbed her manic rages; others described the use of cannabis as a supplement to lithium (allowing reduced consumption) or for relief of lithium's side effects.<sup>194</sup>

The effect of cannabinoids on *schizophrenia* is controversial. Neuropsychological results in THC-intoxicated normal volunteers exhibit strong similarities with data acquired from patients suffering from productive schiz-

ophrenic psychoses, as regards disturbances in internal regulation of perceptual processes.<sup>195</sup> In a recent study, it was found that anandamide levels are enhanced in first-episode schizophrenic patients, and that THC downregulates anandamide signaling.<sup>196</sup> This observation possibly means that THC lowers endogenous production of anandamide, which may actually be a defense mechanism—presumably comparable to the known observation that administration of corticosteroids blocks corticosteroid synthesis. Data from experimental-psychological tests show that personality changes generated by schizophrenia progression are comparable to psychopathological phenomenon due to cannabis intoxication.<sup>197</sup> In another study, psychosis, which develops or recurs in the context of cannabis use, did not have a characteristic psychopathology or mode of onset.<sup>198</sup> First-episode schizophrenic patients with long-term cannabis consumption were significantly younger at disease onset, mostly male, and suffered more often from paranoid schizophrenia (with a better prognosis) than those without cannabis consumption.<sup>199</sup> However, a trend towards more insight and of fewer abusive or accusatory hallucinations was seen amongst cannabis users. This argues against a distinct schizophrenia-like psychosis caused by cannabis.<sup>200</sup> Less avolition and fewer apathy symptoms were detected in patients with schizophrenia and cannabis abuse than in those with no abuse.<sup>201</sup> In another clinical trial, the role of CB1 receptors in schizophrenia was studied by administration of CB1 antagonist to patients. The group receiving the CB1 antagonist did not differ from the group receiving placebo on any outcome measure.<sup>202</sup> CBD causes antipsychotic effects.<sup>203</sup> It was found to be a safe and well-tolerated alternative treatment for schizophrenia.<sup>204</sup> (See, however, also ref 205).

*Post-traumatic stress disorder (PTSD)* is a term for severe psychological consequences of exposure to, or confrontation with, stressful, highly traumatic events. Cannabinoids are believed to help in such cases. AM404-treated animals showed decreased shock-induced reinstatement of fear.<sup>206</sup> In conditioned fear and Morris water maze experiments, FAAH (-/-) mice and mice treated with the FAAH inhibitor OL-135 did not display any memory impairment or motor disruption, but did exhibit a significant increase in the rate of extinction. SR141716 blocked the effects of OL-135, suggesting that endogenous anandamide plays a facilitator role in extinction through a CB1 receptor mechanism of action. In contrast, THC failed to affect extinction rates, suggesting that

FAAH is a more effective target facilitating extinction than a direct-acting CB1 receptor agonist.<sup>207</sup> Acutely, the absence of CB1 receptors reduces the neuroendocrine response and does not affect the behavioral response to moderate stress. However, upon repeated stress or acute severe stress, CB1 receptor deficiency causes persistent behavioral inhibition. Repeated bell stress seemed to cause a cumulative fear in CB1 receptor knockout mice.<sup>208</sup> In self-reports of substance use among help-seeking veterans, PTSD diagnosis was significantly associated with marijuana use.<sup>209</sup> These observations suggest that the endocannabinoid system can be modulated to enhance emotional learning, and that endocannabinoid modulators may be therapeutically useful as adjuncts for exposure-based psychotherapies, such as those used to treat PTSD and other anxiety disorders. CB1 receptor gene polymorphism is known to modify transcription of the gene. In patients with Parkinson's disease, the presence of two long alleles, with more than 16 repeated AAT trinucleotides in the CNR1 gene, was associated with a reduced prevalence of depression.<sup>210</sup>

CBD, and some derivatives, were found to cause a selective anxiolytic effect in the elevated plus-maze, within a limited range of doses.<sup>211,212</sup> A single dose of nabilone produced only mild improvement in anxiety<sup>213</sup>; in a repeated-dose treatment a dramatic improvement in anxiety was noted in the nabilone group.<sup>214</sup>

The effects of marijuana on human sleep patterns were noticed long ago.<sup>215-217</sup> Reduced eye movement density was seen, with some tolerance developing to this effect.<sup>218,219</sup> THC is sedative, while CBD has alerting properties as it increased awake activity and counteracted the residual sedative activity of THC.<sup>220</sup>

### **Asthma, cardiovascular disorders, glaucoma**

*Asthma* is a chronic disease of the respiratory system in which the airway occasionally constricts, becomes inflamed, and is lined with excessive amounts of mucus. In animal experiments, after methacholine-induced or exercise-induced bronchospasm, marijuana caused a prompt improvement of the bronchospasm and associated hyperinflation.<sup>221</sup> In humans, habitual smoking of marijuana may cause mild, but significant, functional lung impairment<sup>222</sup>; However, a mild and inconstant bronchodilatory action was found for THC.<sup>223</sup> In other clinical trials, smoking marijuana or ingesting THC were found to increase airway conduction.<sup>224,225</sup> Other plant cannabinoids did not provide

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effective bronchodilation. The daily use of THC was not associated with clinical tolerance.<sup>226</sup> THC administered in metered volumes by inhalation from an aerosol device to patients judged to be in a steady state, increased peak expiratory flow rate (PEFR) and forced expiratory volume in 1 second (FEV1) and produced bronchodilatation.<sup>227</sup> In another study, salbutamol and THC significantly improved ventilatory function. Maximal bronchodilatation was achieved more rapidly with salbutamol, but at 1 hour both drugs were equally effective. No cardiovascular or mood disturbance was detected, and plasma total cannabinoids at 15 minutes were not detected by radioimmunoassay. The mode of action of THC differed from that of sympathomimetic drugs.<sup>228</sup>

In another study, THC induced sympathetic stimulation and parasympathetic inhibition of *cardiovascular control pathways*. The peak heart rate rise after THC was attenuated by atropine and by propranolol, and nearly abolished by atropine-propranolol pretreatment.<sup>229</sup> Acute THC significantly increased heart rate, shortened pre-ejection period (PEP) and prolonged left ventricular ejection time (LVETc) without any change in afterload; it enhanced cardiac performance. Partial inhibition of this effect was achieved with prior  $\beta$ -adrenergic blockade.<sup>230</sup> In contrast, following the smoking of one to three marijuana cigarettes, the heart rate rose, cardiac output rose, stroke volume, ejection fraction, PEP and LVET did not change; thus, in long-term heavy users of cannabis, marijuana has no significant effect on myocardial contractility independent of its effect on heart rate.<sup>231</sup> Cardiovascular effects of acute THC administration included increased sympathetic and reduced parasympathetic tone; supine tachycardia and increased blood pressure with upright hypotension were observed. With repetitive dosing supine bradycardia and decreased blood pressure with tolerance to orthostatic hypotension were observed.<sup>232,233</sup> Rimonabant attenuated the hypotensive effect of smoked marijuana in male smokers, suggesting a role for the CB1 receptor in cannabinoid hypotensive action.<sup>234</sup>

A number of studies suggest that there is a correlative, but not necessarily causal, relationship between *glaucoma* and systemic hypertension. Ocular hypertension (OHT) refers to any situation in which intraocular pressure is higher than normal, and is the most important risk factor for glaucoma. THC, CBN, and nabilone were active in lowering intraocular pressure (IOP) in rabbits, while CBD was inactive.<sup>235</sup> Certain derivatives of THC were more active in lowering IOP than the parent cannabinoid<sup>236</sup>; some topi-

cally used soft analogs that have no systemic effects were also active in IOP reduction.<sup>237</sup> The effect on IOP of 2-AG was biphasic (ie, an initial increase in IOP followed by a reduction). In contrast, noladin ether decreased IOP immediately after topical administration, and no initial IOP increase was observed. AM251 blocked the effect on IOP of noladin ether, but did not affect the action of 2-AG.<sup>238</sup> Topical administration of anandamide and arachidonyl propionitrileamide decreased IOP; rimonabant antagonized the IOP reduction, suggesting that cannabinoids lower IOP through CB1 receptors.<sup>239,240</sup> Significantly, higher levels of CB1 mRNA levels were found in the ciliary body than in the iris, retina, and choroid. CB2 mRNA was undetectable. This expression pattern supports a specific role for the CB1 receptor in controlling IOP.<sup>241</sup> When delivered topically to cat eyes with osmotic minipumps, whole marijuana extract, THC and other plant cannabinoids reduced IOP, while cannabichromene was inactive. Ocular toxicity was seen after THC treatment, consisting of conjunctival erythema and chemosis as well as corneal opacification. Although these changes also occurred with marijuana extract, their intensity was much reduced. In contrast, no ocular toxicity was apparent during administration of plant cannabinoids other than THC.<sup>242-244</sup> Marijuana smoking was shown to reduce IOP as early as 1971; the effect was later confirmed.<sup>245-248</sup> The peak effect of THC on the central nervous system coincided well with the reduction in intraocular pressure induced by the drug; However, hypotonia outlasted euphoria. The results indicate that THC may have value as a hypotonizing ocular drug.<sup>249</sup> The functional responses after THC inhalation in sitting normotensive and hypertensive patients included invariable increases in heart rate followed by substantial decreases in systolic pressure, diastolic pressure, and intraocular pressure. The intensity and duration of the arterial and ocular pressure responses to THC were greater in hypertensives than in normotensive patients; the changes in ocular pressure paralleled the changes in blood pressure in glaucoma patients.<sup>250</sup> A single sublingual dose of THC, but not cannabidiol, reduced the IOP temporarily and was well tolerated by most patients.<sup>251</sup>

## Cancer

The antiproliferative action of cannabinoids on cancer cells was first noticed in the 1970s. Since then cannabinoids were found to act on various cancer cell lines, through various mechanisms.<sup>252,253</sup> Cannabinoids were

also found to be suppressors of angiogenesis and tumor invasion.<sup>254</sup> Our knowledge on the anticancer activity of cannabinoids is rapidly expanding; hence only results of recent research on this topic are presented here. The cannabinoid agonists HU-210 and JWH-133 promoted glial differentiation in a CB receptor-dependent manner. Moreover, cannabinoid challenge decreased the efficiency of glioma stem-like cells to initiate glioma formation in vivo.<sup>255</sup> The nonpsychoactive cannabidiol triggered caspase activation and oxidative stress in human glioma cells.<sup>256</sup> Human melanomas express CB1 and CB2 cannabinoid receptors. Activation of these receptors decreased growth, proliferation, angiogenesis, and metastasis, and increased apoptosis, of melanomas in mice.<sup>257</sup> THC, through activation of CB2 cannabinoid receptors, reduced human breast cancer cell proliferation by blocking the progression of the cell cycle and by inducing apoptosis. THC arrested cells in G2→M via downregulation of Cdc2.<sup>258</sup> Cannabinoids induced apoptosis of pancreatic tumor cells via stress protein p8 and endoplasmic reticulum stress-related genes. These effects were prevented by blockade of the CB2 cannabinoid receptor or by pharmacologic inhibition of ceramide synthesis de novo.<sup>259</sup> THC-induced apoptosis in Jurkat leukemia T cells was found to be regulated by translocation of Bad to mitochondria.<sup>260</sup> Exposure of leukemia cells to CBD led to CB2-mediated reduction in cell viability and induction in apoptosis (although CBD is considered not to bind to either CB1 or CB2 receptors). It is noteworthy that CBD exposure led to an increase in reactive oxygen species (ROS) production as well as an increase in the expression of the NAD(P)H oxidases Nox4 and p22(phox).<sup>261</sup> Cannabinoid-induced apoptosis of human prostate cancer cells LNCaP proceeded through sustained activation of ERK1/2 leading to G1 cell cycle arrest.<sup>262</sup> Rimonabant inhibited human breast cancer cell proliferation through a lipid raft-mediated mechanism.<sup>263</sup> In a pilot phase I trial, nine patients with recurrent glioblastoma multiforme, that had previously failed standard therapy (surgery and radiotherapy) and

had clear evidence of tumour progression, were administered THC intratumorally. THC inhibited tumor-cell proliferation in vitro, decreased tumor-cell Ki67 immunostaining and prolonged the survival time of two of the patients.<sup>264</sup>

## Conclusion

Many drugs used today can cause addiction and are misused and abused, for example opiates,<sup>265</sup> cocaine,<sup>266</sup> benzodiazepines,<sup>267</sup> barbiturates,<sup>268</sup> cholinergic agonists,<sup>269</sup> ketamine,<sup>270,271</sup> dopaminergic agonists,<sup>272</sup> amphetamines,<sup>273</sup> and others. Nevertheless they are still an important part of our pharmacopeia. Marijuana was used for centuries as a medicinal plant, but during the last century, because of its abuse and addictive potential it was taken out of clinical practice. Now, we believe that its constituents and related compounds should be brought back to clinical use. The reasons are: (i) the therapeutic potential of CB1 agonists is huge, as described in this review; (ii) for local action, topical CB1 agonists, or agonists that do not penetrate the blood-brain barrier, can be used; (iii) cannabinoids acting specifically on CB2 receptors, which cause no psychoactivity, may be used on peripheral targets (such as osteoporosis,<sup>274,275</sup> which is only one of many examples); (iv) there are additional, new cannabinoid targets distinct from the CB1/CB2 receptors<sup>276-278</sup> which do not cause psychoactivity; (v) there are cannabinoids, such as CBD, which do not cause psychoactivity, but have various therapeutic effects.

The endocannabinoid system is a very complex one and regulates numerous processes, in parallel with other well-known systems, such as the adrenergic, cholinergic, and dopaminergic systems. Neglecting the potential clinical uses of such a system is, in our view, unacceptable; instead we need to work on more selective agonists/antagonists, more selective distribution patterns, and in cases where it is impossible to separate between the desired clinical action and the psychoactivity, to monitor these side effects carefully. □

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## **Cannabinoides en la salud y en la enfermedad**

Las preparaciones de *Cannabis sativa* L. se han empleado en medicina desde hace milenios. Sin embargo, la preocupación acerca de los peligros del abuso condujo a la prohibición de la utilización médica de la marihuana en la mayoría de los países en la década de 1930. Sólo recientemente, los agonistas y antagonistas naturales y sintéticos de los receptores de marihuana, como también compuestos químicamente relacionados, cuyo mecanismo de acción todavía es confuso, han vuelto a reconsiderar el valor terapéutico. Pero su empleo está estrictamente limitado. A pesar de la adicción leve a cannabis y el posible incremento de la adicción a otras sustancias de abuso, cuando se combinan con cannabis, el valor terapéutico de los cannabinoides es muy alto como para no tomarlo en cuenta. Numerosas enfermedades como la anorexia, la emesis, el dolor, la inflamación, la esclerosis múltiple, trastornos neurodegenerativos (Enfermedad de Parkinson, Enfermedad de Huntington, Síndrome de Tourette, Enfermedad de Alzheimer), epilepsia, glaucoma, osteoporosis, esquizofrenia, trastornos cardiovasculares, cáncer, obesidad, y trastornos relacionados con el síndrome metabólico, por nombrar sólo algunas, están siendo tratadas o tienen el potencial de tratarse por agonistas o antagonistas de los cannabinoides o compuestos relacionados con ellos. Dada la muy baja toxicidad y los efectos secundarios generalmente benignos de este grupo de compuestos, desatender o negar su potencial clínico es inaceptable; hay que trabajar en el desarrollo de agonistas y antagonistas, y compuestos relacionados que sean más selectivos para el receptor de cannabinoides, como también de nuevos fármacos de esta familia con mejor selectividad, patrones de distribución y fármaco-cinética, y -en casos donde sea imposible separar la acción clínica deseada y la psicoactividad- igual monitorear estos efectos secundarios cuidadosamente.

## **Cannabinoides: efectos chez le sujet sain et utilisation en thérapeutique**

Depuis des millénaires, des préparations à base de *Cannabis sativa* L ont été utilisées en médecine. Dans les années 1930 cependant, des inquiétudes concernant le danger lié à l'abus de cette substance ont conduit à l'interdiction de l'utilisation médicale de la marijuana dans la plupart des pays. Ce n'est que depuis peu que la marijuana et les agonistes et antagonistes des récepteurs cannabinoïdes synthétiques et naturels, ainsi que les composés chimiquement apparentés dont le mécanisme d'action est encore obscur, sont à nouveau considérés comme ayant un intérêt thérapeutique. Leur usage est cependant très limité. Malgré la dépendance modérée au cannabis et la possible stimulation de la dépendance à d'autres drogues lorsqu'elles sont associées au cannabis, la valeur thérapeutique des cannabinoïdes est trop élevée pour être négligée. De nombreuses pathologies, telles que l'anorexie, les vomissements, la douleur, l'inflammation, la sclérose en plaques, les troubles neurodégénératifs (maladie de Parkinson, chorée de Huntington, syndrome de Gilles de la Tourette, maladie d'Alzheimer), l'épilepsie, le glaucome, l'ostéoporose, la schizophrénie, les troubles cardiovasculaires, le cancer, l'obésité et les troubles liés au syndrome métabolique, pour n'en nommer que quelques-unes, sont traitées ou pourraient être traitées par des agonistes/antagonistes des cannabinoïdes, ou substances apparentées. Au regard de la très faible toxicité et des effets secondaires généralement bénins de cette classe de produits, il serait inacceptable de négliger ou de nier leur potentiel clinique. Il faut au contraire travailler au développement de récepteurs agonistes/antagonistes des cannabinoïdes et de composés apparentés sélectifs, ainsi qu'à de nouveaux médicaments de cette famille plus sélectifs, avec un mode de distribution et une pharmacocinétique meilleurs. Et lorsqu'il est impossible de séparer l'action clinique désirée et les effets psychoactifs, il est simplement nécessaire de surveiller attentivement les effets indésirables.

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