

# Synthetic forms of THC in clinical treatment settings

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The marijuana plant has been used for both herbal medication and as a mild intoxicant for centuries. There is anecdotal evidence of its effectiveness in treating the symptoms of several diseases, and currently laboratory and clinical studies are attempting to provide clear, scientific information on the issue. The medical use of marijuana poses several challenges. The debate is based on its therapeutic value relative to the potential harm posed by the drug. In an attempt to circumvent the smoking of marijuana, while retaining the therapeutic value of the drug, two synthetic forms of marijuana have been developed. The purpose of this article is to provide an overview of the basis for developing these medications and to examine their usefulness in a clinical setting.

## History and pharmacology

*Cannabis sativa*, or marijuana as it is more commonly known, contains literally hundreds of identified chemicals. One group of chemicals, known as the cannabinoids, is responsible for all of the drug's psychoactive effects. The main psychoactive ingredient is delta-9-tetrahydrocannabinol (THC). This compound was identified in 1964, when scientists were able to synthesize it and study its structure, pharmacology and actions in the brain<sup>2</sup>. For several years afterward, the precise mechanism by which THC exerted its effects remained unknown. It was not until 1988, with the use of emerging technology, that it was found that THC was attaching to cell membranes, suggesting that there was a specific receptor to which the compound was bound.<sup>3</sup> A short time later, the first cannabinoid receptor (CB1) was discovered and cloned in the central nervous system (CNS).<sup>4</sup> Within a few years a second cannabinoid receptor (CB2) was found in peripheral tissues.<sup>5</sup> It was shown that THC binds to these receptors with different potency, and they produce different effects in the body.

The discovery of the cannabinoid receptors prompted scientists to search for a chemical that is produced by the brain itself (endogenous) that binds to these receptors. Two such chemicals have been identified, N-arachidonyl ethanolamine (anandamide) and N-arachidonylglycerol.<sup>6</sup> Since then, both have been

synthesized and studied for their effects in the brain and other areas. Much has been discovered as to how the cannabinoids exert their effects, what effects they have, and where the receptors are located in the brain and peripheral tissues.

## Prescription THC

The medical benefits of smoking marijuana have been reported anecdotally for centuries. With the discovery of the endogenous cannabinoid system, it was possible to develop drugs that targeted the system directly, in an attempt to mimic the effects of smoking marijuana. Smoked marijuana is a crude drug delivery system that contains variable amounts of THC and also delivers harmful substances to the smoker. Marijuana smoke contains tars and other chemicals similar to that found in tobacco smoke, and is associated with an increased risk of lung disease and an increase in cellular mutations in lung tissue.<sup>7</sup> Because of this, it was of great interest to develop alternate methods of drug delivery.

At present, there are two compounds based on THC that are marketed as prescription drugs. Dronabinol (Marinol) is synthetic THC, structurally identical to the psychoactive THC found in marijuana. It has been approved for use in the United States since 1986, and is also commercially available in Canada. Nabilone (Cesamet) is an analogue of THC. It is available by prescription in Canada and the United Kingdom, however the United States has not approved this drug for prescription use. Both drugs are available in pill form.

Other forms of synthetic THC exist, such as levonantradol, a THC analogue, and HU-210, which is an analogue much more potent than the THC found in marijuana.<sup>8</sup> These drugs are not commercially available and have not been approved for prescription use.

## Effectiveness in treatment

Initial evidence for the potential efficacy of any new drug is typically obtained through research with animals in a laboratory setting. Animal studies have shown synthetic THC to be

effective in stimulating appetite, preventing nausea and vomiting, in pain management and in relieving muscle tremors associated with several disorders (multiple sclerosis, epilepsy).<sup>9</sup> The results from animal research have been the basis for beginning clinical trials in human patients.

Clinical trials with human patients are subject to a host of specialized problems that are not present in animal research. Trials involving human subjects are less tightly controlled than in the laboratory, and increases in individual variability through medical history or current conditions can influence the study outcome. Small sample sizes are also a limitation in clinical trials, where individual variability can have a more profound impact. The most effective method of clinical trial involves random assignment of patients to either a drug condition or to an inactive (placebo) or an active control condition. Neither the experimenters nor the patients know which they have received, which reduces the possibility of an individual's expectations or preconceptions influencing the results. These caveats should inform the reader to be cautious in interpreting the results of clinical trials involving human subjects and synthetic THC, as many clinical studies use small samples and inadequate control groups.

### Anti-nausea treatment

There is a large body of literature examining the anti-nauseant properties of THC. One study has attempted to consolidate the literature and clarify the effectiveness of cannabinoids for the treatment of nausea and vomiting.<sup>10</sup> The review began with 198 studies, and using standard methods found that only 30 met the criteria for completely randomized clinical trials. In these 30 clinical trials, data from 1366 patients were analyzed. The drugs studied were oral nabilone, oral dronabinol, and intramuscular levonantrodol (synthetic analogue of THC). Trials compared the cannabinoids to both placebo and active control. It was found that cannabinoids were slightly more effective than standard anti-nausea drugs and placebo for controlling nausea and vomiting associated with moderate chemotherapy treatment, but not when patients were receiving very low or very high chemotherapy.

None of the trials included in the previous study compared cannabinoids to the most effective and commonly used drugs for controlling nausea and vomiting, the serotonin

receptor blockers, ondansetron and granisetron. There is evidence that cannabinoids are not more effective than serotonin blockers for controlling nausea and vomiting associated with chemotherapy.<sup>11</sup>

### Appetite stimulation

'Wasting Syndrome' in acquired immune deficiency syndrome (AIDS) is associated with secondary processes related to the disease such as diarrhea, vomiting, and a loss of appetite, resulting in a significant reduction of body weight. The Food and Drug Administration in the United States has approved the use of Marinol as an appetite stimulant for the treatment of wasting in AIDS patients. There is a lack of clinical evidence to support the efficacy of synthetic THC in appetite stimulation, despite its continued frequent use.<sup>12</sup> The only cannabinoid that has been evaluated in controlled clinical trials is Marinol, and these studies generally support its effectiveness in treatment. However, it is not more effective than the traditional treatment, a synthetic derivative of progesterone.<sup>13</sup>

THC may be an effective treatment option in medical conditions such as AIDS where multiple symptoms exist (nausea, vomiting, appetite loss, anxiety) that can be alleviated by the use of one treatment, rather than offering separate medications for each symptom. One possible disadvantage is that CB2 cannabinoid receptors located outside the CNS have been linked to immune functions, and marijuana smoke has been shown to have immunosuppressive effects mediated by these receptors.<sup>14</sup> The effect of oral THC and other cannabinoids as compared to smoking marijuana on the immune system is not known, and requires further study in patients whose immune system is already compromised.

### Other treatment indications

Other applications for the use of prescription THC are being studied. Animal research has shown that THC is a powerful analgesic (pain reducer), however studies with humans have produced conflicting and inconsistent results.<sup>15</sup> In cases where traditional treatment with opiate analgesics is ineffective, THC may be useful as an alternative or in combination with opiates. There is evidence that the control of pain with these two drugs is not mediated through the same neurological pathways,<sup>16</sup> and it is possible that combining them could result in a synergistic and more powerful effect. Further

research will determine if this is a viable treatment option.

Cannabinoid receptors are densely localized in brain areas that are involved in motor control. Animal studies have shown that THC acts directly on the motor areas of the brain, producing changes in movement<sup>17</sup>. Individuals with multiple sclerosis often report relief from muscle spasticity with the use of smoking marijuana.<sup>18</sup> Although the research to date has not produced strong evidence for the use of THC in this condition, there is a need for more controlled clinical trials before any conclusions can be made.

### Side effects

It has been shown that side effects occur significantly more often with cannabinoids.<sup>19</sup> Side effects noted include things like drowsiness, sedation, euphoria and feeling 'high', dizziness, depression, hallucination, paranoia and hypotension. In 19 of the 30 trials examined in the chemotherapy review, the number of patients withdrawing from the study due to adverse side effects was significantly higher with cannabinoids (11%) compared to the traditional treatments and placebo conditions (2%).

### Abuse potential

There is the additional concern with synthetic THC, as with other prescription drugs that have psychoactive effects, that it could become a drug of abuse. However, many of the side effects reported are aversive, such as dizziness and depression, which would decrease the likelihood that the drug would be abused widely. Additionally, the effect of oral ingestion slows the process of drug absorption into the body, which results in less intense psychoactive effects. In a study supported by the pharmaceutical company responsible for manufacturing Marinol in the United States, no evidence of abuse or diversion of Marinol was found.<sup>20</sup> Before any firm conclusions can be made, however, more research is needed in the area of abuse potential of Marinol and Cesamet.

It is also not clear what effect prior experience with smoking marijuana has on individual susceptibility to abuse. However, there is

evidence that prior use can influence patients' expectations of a positive outcome with synthetic THC treatment. In one trial included in the chemotherapy review, over half of the patients were regular marijuana users. Of these, 94% believed that cannabinoids would reduce their nausea and vomiting symptoms.<sup>21</sup>

### Policy

In Canada, marijuana and its synthetic derivatives fall under schedule II of the *Controlled Drugs and Substances Act*. The rules regarding their legal distribution are outlined in the *Narcotic Control Regulations*. At present, Marinol and Cesamet are approved for the management of severe nausea and vomiting associated with chemotherapy, and Marinol is approved for the treatment of anorexia in patients with AIDS.<sup>22</sup>

The Correctional Service of Canada does not have a national policy regarding the use of prescription THC. Each of the five regions across Canada has a Pharmacy and Therapeutics Committee, whose role is to develop and maintain a regional drug formulary and pharmacy policy.<sup>23</sup> The policy regarding the use of prescription THC varies by region. For example, in the Atlantic region, prescription THC has not been approved for use with offenders. In the Pacific region it has been used in the past to treat AIDS patients, however there are no offenders currently receiving treatment with THC.

### Conclusion

There is some evidence that synthetic THC may be an option for treatment of secondary symptoms in certain medical conditions. At this time, evidence is lacking that would favor using synthetic THC over currently available treatments, with the possible exception of circumstances where traditional treatments were not effective. It has been shown that synthetic THC can produce a variety of unwanted side effects along with its desired effects. As our understanding of the endogenous cannabinoid system grows, it may be possible to develop specific and selective drugs that target receptor subtypes which enhance the desired effects, while lessening the unwanted side effects that now limit its clinical usefulness. ■

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