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# Cannabinoid-Based Medicines for Neurological Disorders—Clinical Evidence

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**Abstract** Whereas the cannabis plant has a long history of medicinal use, it is only in recent years that a sufficient understanding of the pharmacology of the main plant constituents has allowed for a better understanding of the most rational therapeutic targets. The distribution of cannabinoid receptors, both within the nervous system and without, and the development of pharmacological tools to investigate their function has lead to a substantial increase in efforts to develop cannabinoids as therapeutic agents. Concomitant with these efforts, the understanding of the pharmacology of plant cannabinoids at receptor and other systems distinct from the cannabinoid receptors suggests that the therapeutic applications of plant-derived cannabinoids (and presumably their synthetic derivatives also) may be diverse. This review aims to discuss the clinical evidence investigating the use of medicines derived, directly or indirectly, from plant cannabinoids with special reference to neurological disorders. Published studies suggest that the oral administration of cannabinoids may not be the preferred route of administration and that plant extracts show greater evidence of efficacy than synthetic compounds. One of these, Sativex® (GW Pharmaceuticals), was approved as a prescription medicine in Canada in 2005 and is currently under regulatory review in the EU.

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## Introduction

The history of modern analgesics is the history of plant-based medicines. An extract of willow bark was described by Hippocrates in the fifth century B.C., and subsequently, the isolation of salicylic acid and its subsequent chemical modification may be said to represent the beginnings of the modern pharmaceutical industry, subsequently resulting in the nonsteroidal anti-inflammatory agents as well as aspirin. Similarly, seeds of the opium poppy had been used for analgesic purposes for many centuries when morphine was isolated in 1806. Morphine remains the most commonly used analgesic opioid, although a range of other analgesics based on the same pharmacologic principle now exist.

The Cannabis (marijuana) plant has an equally long history as a therapeutic agent, especially in the area of analgesia. It was the publications of William O'Shaugnessy [1] that led to an expansion of the medicinal uses of cannabis, to the extent that it became a part of both the US and UK pharmacopeia. The case can be made with medicines derived from cannabis, as with medicines derived from opium, that the challenge of producing synthetic analogues of naturally occurring cannabinoids may be greater than the challenge of producing a modern medicine from a plant extract.

It is a prerequisite of contemporary drug development that the therapeutic agent be highly characterized and that the process of manufacturing should result in a medicine that meets strict quality standards. The history of the pharmaceutical industry in the 20th century and indeed of modern therapeutics has been the history of highly targeted single molecules based particularly on the objective of

obtaining a 'clean' pharmacological profile, thus reducing side effects and improving risk/benefit. This holy grail has not been proved achievable to date: Adverse drug reactions are the fourth leading cause of death in the USA and cause approximately 25,000 deaths per annum in the UK [2]. The associated healthcare costs are huge.

One response to this paradox is to consider again the use of plant extracts as medicines, especially where those plant extracts have a long history of vernacular use with an apparently low risk of serious adverse reactions. Cannabinoids provide an excellent example of where this approach marries with the requirements of regulatory authorities for high standards of quality. The fact that a single plant species can be the source of a single plant medicine facilitates the production of a uniform extract and makes full characterization of the composition a realistic objective. This approach has been used by several investigators into the therapeutic potential of cannabinoids.

Another equally valid approach to the development of therapeutic cannabinoids has become more approachable after the characterization of the endocannabinoid system as elaborated elsewhere in this journal. Whereas an understanding of structure-activity relationships with cannabinoids is still at an early stage, nonetheless, a traditional medicinal chemistry approach to synthesizing molecules with activity at cannabinoid receptors or which impact on the production, action and metabolism of endocannabinoids is now more realistic.

Whereas paying due respect to the many studies exploring the therapeutic applications of unprocessed herbal cannabis, this review will restrict itself to looking at the clinical evidence for plant-derived and synthetic cannabinoids in the treatment of neurological disorders and will not consider evidence for therapeutic benefit derived from studies with smoked or inhaled whole cannabis.

## The Composition of *Cannabis sativa L*

The literature regarding the pharmacology and especially the neuropharmacology of plant-derived and synthetic cannabinoids has been dominated by that of the principle cannabinoid, delta-9-tetrahydrocannabinol (THC), and that of its synthetic analogue, nabilone. However, it is clear that other plant cannabinoids also have a pharmacology potentially relevant to therapeutic applications within neuroscience.

Within the plant, THC is synthesized in its carboxylic acid form from its immediate precursor, cannabigerol (CBG), via the enzyme THC acid synthase. There are two alternative synthetic routes from CBG, one involving the enzyme cannabidiol acid synthase, resulting in the production within the plant of cannabidiol acid (CBDA), and another resulting in the production of cannabichromene acid (CBCA). As the plant reaches maturity, CBC production declines and is more or less 'switched off', but THC acid and CBD acid production goes on, resulting in plants with variable ratios of these two. Left to their own reproductive devices, the genetics of the synthase enzymes means that a plant colony of Cannabis would express the two principal cannabinoids in a ratio of approximately 1:1 [3]. The relative contribution of the two cannabinoids to the therapeutic effect of cannabis extracts has been the subject of some discussion, and it has become much clearer in recent years that CBD has a rich pharmacology, which is likely to contribute to the effect of plant extracts.

## Pharmacological Considerations

The described pharmacology of the principal cannabinoids is the pharmacology of the decarboxylated forms. Decarboxylation is usually accomplished by the application of heat. In the native acid form, both THC and CBD are considered to be more or less pharmacologically inactive.

These observations raise the intriguing prospect that the therapeutic uses of the cannabis plant described after its vernacular use may be due in part to the pharmacology of CBD, as well as to those of THC. It is not the purpose of this review to dwell at length on the pharmacology of the two principal cannabinoids—the reader is referred to earlier contributions in this journal—but it is clear that the activity of CBD on the TRPV1 receptor [4], as an inhibitor of adenosine uptake [5], as an inhibitor of neutrophil chemotaxis [6], and with clear neuroprotective and antiepileptic properties [7], are unlikely to be irrelevant to therapeutic effects of plant extracts.

An awareness of the contribution that CBD may make to the effects of cannabis extracts is important in understanding the results of clinical studies, especially because there is now considerable evidence that there are constructive pharmacological and pharmacodynamic interactions between THC and CBD [8, 9]. It has become apparent in the therapeutics of many neurological disorders that polypharmacy is desirable, provided that it is a polypharmacy based on a rational appreciation of the pharmacodynamics of each medicinal component of a combination of compounds. In fact, the majority of chronic neurological disorders are already treated with a 'cocktail' of medicines, each targeting one or other aspects of the pathology. The presence of two relevant pharmacologies within a single product, as is the case with an extract of Cannabis containing THC and CBD, allows for the application of relevant pharmacologies without some of the drawbacks of administering several different products simultaneously.

As a consequence of the greater level of knowledge about the pharmacology of THC and of the $CB_1$ and $CB_2$

receptor systems, the therapeutic targets for cannabinoids to date have tended to reflect this known pharmacology. In addition, because cannabis, which has been cultivated for recreational purposes, will tend to contain relatively little CBD, contemporary reports of beneficial medical effects from recreational cannabis may tend to reflect the effects of THC more than those of CBD. The emerging pharmacology of CBD may change this with therapeutic targets which reflect the pharmacology of CBD more closely.

## Pharmacokinetic and Metabolic Considerations

Naturally occurring cannabinoids are highly lipophilic and are subject to extensive first-pass metabolic effects. This provides significant challenges for formulation and suggests that the oral route may not be the optimal route of administration. It also has the consequence that oral THC is poorly bioavailable, with somewhere between 6 and 20% of an oral dose reaching the systemic circulation [10]. This means that a single fixed dose given to a group of people will produce markedly different plasma concentrations in that group, with the result that a predictable therapeutic effect may be hard to identify. When the between-subject pharmacodynamic variability is added to this between-subject pharmacokinetic variability, it is hard to avoid the conclusion that the oral route of administration may not be appropriate for chronic administration. Because of this, cannabis extracts may be more reliably delivered by a route that avoids the first-pass effect. For chronic administration, the most suitable of these routes is the sublingual route [11], although rectal administration of cannabinoids has been shown to have favorable pharmacokinetics as well [12]. To date, only one synthetic cannabinoid—nabilone—has been approved as a medicine. This is a structural analogue of THC, with apparently similar pharmacodynamic effects, active at $CB_1$ and $CB_2$ receptors. There is little information available on its pharmacokinetics, but oral absorption appears to be good.

Metabolism of cannabinoids is complex, and although they are substrates for the Cytochrome P450 system, there are no clinically significant drug–drug interactions yet identified with any therapeutic cannabinoids. As yet, the pharmacology of the primary metabolites of all cannabinoids used therapeutically has not been well-defined, and it may emerge that some of the major metabolites will have useful effects and may contribute to the clinical utility of the cannabinoids.

## Clinical Studies

The pharmacology of both the principal components of *Cannabis sativa* suggests therapeutic potential in several particular areas: firstly, in pain—specifically neuropathic pain, in movement disorders, and in several other areas of neurotherapeutics. In reviewing the available clinical data, this paper will first look at the data available from studies with synthetic cannabinoids and then review the data available with plant extracts.

### With Synthetic Cannabinoids

The two synthetic cannabinoids so far approved as medicines are approved for the treatment of chemotherapy-induced nausea and vomiting (dronabinol and nabilone) and for appetite stimulation in HIV-AIDS (dronabinol). This review will not discuss the clinical study evidence of their efficacy in these indications. Other investigational cannabinoids, which have been studied for neurological disorders, are listed below along with those studies that have investigated dronabinol or nabilone in the relief of various types of pain. Early studies with synthetic analogues of THC, notably levonantrodol and benzopyranoperidine, have not lead to any subsequent large-scale clinical studies, although the more recent emergence of ajulemic acid (CT-3) may offer new promise for synthetic THC analogues. Ajulemic acid is based on the immediate metabolite of THC, 11-OH-THC, formed in vivo as a result of Phase I oxidative metabolism. As yet, a clear pharmacologic basis for an analgesic effect of this compound is lacking, as it appears not to have appreciable affinity for either $CB_1$ or $CB_2$ receptors, and results from larger clinical trials are clearly needed (Table 1).

All of the published studies have had relatively short exposure periods, none approaching the current requirement of the EU regulatory guidelines that studies in pain should be at least 12 weeks in duration post dose stabilization. It is of note that so many of the published randomized studies have used a crossover design, perhaps because the numbers of patients have been relatively small in these studies, and the investigators have been trying to increase the power of the study by adopting the crossover approach. This can sometimes make the statistics difficult to interpret [26]. Whereas there are consistent indications that oral THC has some analgesic efficacy, it is not possible to conclude that the case for oral THC as an effective analgesic has been proven. As several reviewers have noted, it remains the case that more high quality clinical trials data are required before firm conclusions can be drawn [27].

It is of course feasible that THC genuinely has no analgesic effect as Campbell et al. [27] have asserted. However, this would seem to be wholly inconsistent with our extensive knowledge of the pharmacology of the $CB_1$ and $CB_2$ receptors. Furthermore, there is a wealth of uncontrolled anecdotal data from studies using smoked cannabis that attest to its efficacy in bringing relief from pain (and other symptoms [28]). Instead, we should consider

**Table 1** Published clinical studies of synthetic cannabinoids in pain

| Cannabinoid | Indication | Study design | Reference |
|---|---|---|---|
| Benzopyranoperidine (synthetic THC analogue) | Cancer pain | RCT (crossover) | Stacquet et al. [13] |
| Benzopyranoperidine | Cancer pain | RCT (crossover) | Stacquet et al. [13] |
| Benzopyranoperidine | Cancer pain | RCT (crossover) | Jochimsen et al. [14] |
| Levonantrodol | Postoperative and trauma pain | RCT | Jain et al. [15] |
| Cannabidiol | Chronic neuropathic pain | RCT (crossover) | Lindstrom et al. [16] |
| CT-3 (ajulemic acid—synthetic analogue of 11-OH-THC) | Chronic neuropathic pain | RCT (crossover) | Karst et al. [17]<br>Salim et al. [18] |
| Dronabinol | Cancer pain | RCT (crossover) | Noyes et al. [19]<br>Noyes et al. [20] |
| Intravenous THC | Dental pain | RCT (crossover) | Raft et al. [21] |
| Dronabinol | Postop pain | RCT | Buggy et al. [22] |
| Dronabinol | Experimental pain | RCT (crossover) | Naef et al. [23] |
| Dronabinol | Spinal cord injury | N of 1 | Maurer et al. [24] |
| Dronabinol | Neuropathic pain in multiple sclerosis | RCT (crossover) | Svendsen et al. [25] |

whether there are other factors that may account for these generally unimpressive results (with notable exceptions). The answer may lie in the pharmacokinetic and pharmacodynamics of THC. With such poor oral bioavailability, a well-described pharmacodynamic variability between subjects, and the unopposed psychoactivity of THC, reflected in the adverse event profile in these studies, the drug would generally be considered a poor candidate for clinical development unless delivered by an alternative route and perhaps in combination with additional compounds, which reduce the psychoactivity of THC. An alternative approach would be to identify compounds that somehow separate the undesirable psychoactivity of $CB_1$ receptor agonism from the more desirable therapeutic effects.

## Other Neurological Disorders

Synthetic cannabinoids have also been studied in a variety of other neurological disorders notable in multiple sclerosis (MS), spasticity, and pain because of spinal cord injury in Tourette syndrome, Parkinson's Disease, and dystonia. This wide range of conditions reflects the ubiquity of $CB_1$ receptor distribution, as well as being a reflection of the significant unmet need for new therapeutic agents that clearly exists within chronic disorders of the nervous system. These studies are outlined in Table 2.

In contrast to the studies exploring the role of THC as an analgesic, the studies looking at spasticity and at bladder symptoms, whether in MS or spinal cord injury, have generally shown positive results. In general, it seems as though the studies with the positive results have used larger doses of THC than those studies with negative results but were limited to short treatment periods or even single doses.

Similarly, in Tourette syndrome, both studies (by the same authors) have shown a decrease in tic frequency first in a single dose study, and then over a 6-week treatment period as well as an improvement in obsessive-compulsive behaviour, and in the 6-week study; the dose of THC used was relatively low at up to 10 mg daily.

In Parkinson's disease, Sieradzan et al. [35] reported that nabilone produced a reduction in L-DOPA-induced dyskinesia. In all of these studies, the adverse event profile, although characterized by psychoactive effects, has been

**Table 2** Studies of synthetic cannabinoids in the treatment of neurological disease

| Cannabinoid | Indication | Study design | Reference |
|---|---|---|---|
| Dronabinol | Spasticity in MS | RCT crossover | Petro and Ellenberger [29] |
| Dronabinol | MS symptoms | Single-blind, placebo-controlled, parallel group | Clifford [30] |
| Dronabinol | Spasticity in MS | RCT crossover | Ungerleider et al. [31] |
| Nabilone | Symptoms in MS | RCT crossover | Martyn et al. [32] |
| Dronabinol | Spasticity in spinal cord injury | RCT crossover | Hanigan et al. [33] |
| Dronabinol | Symptoms in spinal cord injury | Open label comparison | Hagenbach et al. [34] |
| Nabilone | Parkinson's disease | RCT crossover | Sieradzan et al. [35] |
| Nabilone | Dystonia | RCT crossover | Fox et al. [36] |
| Dronabinol | Tourette syndrome | RCT crossover | Muller-Vahl [37, 38] |
| Dexanabinol | Traumatic brain injury | RCT parallel group | Maas et al. [39] |

relatively benign, and serious adverse events seem to have been reported infrequently.

Perhaps the most high profile therapeutic failure of the synthetic cannabinoids is that of dexanabinol, an optical isomer of THC lacking affinity for cannabinoid receptors, but with activity at *N*-methyl-D-aspartate receptors, and an inhibitor of COX-2. It is difficult to extrapolate the disappointing results with dexanabinol in acute brain injury to an interpretation of the therapeutic potential of other cannabinoids, but the results should be included in a review of therapeutic cannabinoids.

## Plant Extracts

There are more than 60 cannabinoids present in Cannabis sativa, and the great majority as yet have an unknown pharmacology [40]. The two cannabinoids present in the greatest quantities are THC and CBD. It has become increasingly apparent over the last few years that cannabidiol has a pharmacology that may be relevant to its use in the therapeutics of neurological disorders [41, 42]. In particular, CBD has antipsychotic activity in animal models and has been reported to show antipsychotic efficacy in humans [43, 44]. The case for using a plant extract that combines THC and CBD has recently been eloquently made by Russo and Guy [45], and a series of clinical trials have now been conducted that explore the efficacy and safety of plant extracts in neurological disease. In general, the therapeutic targets for plant extracts have been the same as those for synthetic cannabinoids, although the pharmacology of CBD might suggest that inflammatory diseases are also a rational target indication. The presence of CBD has also been shown to reduce THC-induced anxiety [46] and to modulate THC-induced postsleep cognitive impairment [47].

There is no reason to believe that the pharmacokinetics of orally administered cannabinoids is likely to be any different when they are plant-derived than when they are synthesized. Thus, the oral administration of THC and CBD is likely to be a poor choice for best exploring their therapeutic potential because of the high degree of between-subject variability in pharmacokinetics, which is inevitable with drugs of poor oral bioavailability. This has been addressed in the case of Sativex® (GW Pharmaceuticals, Salisbury, UK), which is formulated as a spray containing equal proportions of CBD and THC and administered via the sublingual and buccal mucosal surfaces, thus avoiding to some extent the first-pass effect associated with gastrointestinal delivery. The results of clinical studies with Sativex, both published and those published only as extracts, have been comprehensively reviewed recently by Perez [48]. The other extract most commonly used in published clinical studies is Cannador, which generally has a THC:CBD ratio of 2:1 and is delivered orally in capsule form.

The published studies, which have been done with extracts, are shown in Table 3 by indication.

It is easier to draw conclusions regarding the efficacy and safety of studies that have used cannabis extracts, because they have, in general, been larger, and there are fewer crossover studies. Those studies conducted with Sativex have also followed a more conventional drug development route with a series of Phase 1 studies,

**Table 3** Published clinical studies with cannabis extracts

| Extract | Indication | Study design | Reference |
|---|---|---|---|
| a. Sativex<br>b. THC rich<br>c. CBD rich | Neurogenic pain | 'N of 1' design in 34 subjects | Notcutt et al. [49] |
| a. Sativex<br>b. THC rich | Neuropathic pain because of brachial plexus avulsion | RCT crossover | Berman et al. [50] |
| Sativex | Neuropathic pain because of MS | RCT parallel groups | Rog et al. [51] |
| Sativex | Symptoms of MS | RCT crossover | Wade et al. [52] |
| Sativex | Symptoms of MS | RCT parallel groups and open label extension | Wade et al. [53, 54] |
| Sativex | Spasticity in MS | RCT parallel groups | Collin et al. [55] |
| Sativex | Bladder symptoms in MS | Open label pilot study | Brady et al. [56] |
| a. Cannador<br>b. THC | Spasticity in MS | RCT parallel groups | Zajicek et al. [57, 58] |
| a. Cannador<br>b. THC | Spasticity in MS | RCT crossover | Killestein et al. [59] |
| THC:CBD 3:1 extract | Spasticity in MS | RCT crossover | Vaney et al. [59] |
| Cannador | Parkinson's disease | RCT crossover | Carroll et al. [61] |

followed by Phase 2 studies aimed at identifying the preferred ratio of THC to CBD, and then Phase 3 studies using that ratio. They show significant efficacy for Sativex in relieving neuropathic pain because of brachial plexus avulsion and MS, and results have been presented elsewhere showing efficacy in the relief of peripheral neuropathic pain and cancer pain [47]. The results of the studies conducted with extracts have been more generally positive than those with synthetic THC analogues, suggesting that there are other components in cannabis that contribute to the therapeutic effect. One notable exception to this is the recently published long-term placebo-controlled study by Zajicek et al. [60], suggesting that THC itself may have long-term utility in relieving spasticity as assessed by the Ashworth score, whereas oral cannabis extract did not. In the earlier placebo-controlled study conducted by the same authors, both extract (Cannador) and oral dronabinol were shown to have no significant effect on the Ashworth score but did produce significant improvements in patient-reported outcomes. Aside from spasticity and pain in MS, cannabis extracts have shown promise in the relief of bladder symptoms, although studies have so far been restricted to people with MS. There have been no effects observed on the motor symptoms of Parkinson's disease nor on levodopa-induced dyskinesias with extract, unlike the earlier study with nabilone, and it is notable that tremor is a symptom that has not been seen to improve in patients with MS when treated with cannabinoids.

It is necessary when reviewing the published studies of cannabis extracts (or synthetic cannabinoids) to consider the patient population included in clinical studies. In all of the published studies with Sativex, the patient population is one that still has significant impairment despite the use of optimal existing treatment. During the studies, they stayed on the currently available therapy. This is a patient population in whom there would not otherwise be any prospect of substantial improvement. Showing efficacy in this patient population is likely to be more difficult than in a population of patients who were withdrawn from other treatments before being randomized to study drug or placebo.

On the basis of the published and unpublished data, Sativex was approved as a prescription medicine in Canada in 2005 for the treatment of neuropathic pain in MS and is currently under regulatory review in the EU as a treatment for the relief of spasticity in people with MS.

## Discussion

The pharmacology of the cannabinoids and a large volume of anecdotal data suggest that cannabinoids may have a role in a number of neurological diseases. The most obvious targets are pain, particularly neuropathic pain, and movement disorders. A review of the results of the published studies leads this reviewer to conclude that there is a general paucity of compelling evidence of efficacy for the synthetic cannabinoids perhaps with the exception of Tourette syndrome, where more work is needed. On the other hand, results with cannabis extracts, particularly with Sativex, are promising notably in the areas of neuropathic pain and spasticity in MS. Whereas this may be taken as evidence that there are elements within a plant extract that contribute to efficacy, in fact, it may also more simply be a consequence of clinical trial design and route of administration of the cannabinoids used in the clinical studies of synthetic compounds.

It is important when reviewing the clinical studies of cannabinoids to bear their complex pharmacology and their clinical pharmacokinetics in mind. There has been a tendency in the literature to attribute the apparent therapeutic benefits of smoked cannabis to THC alone and to assume that the $CB_1$ receptor is responsible for any efficacy. This has further resulted in a tendency to 'lump together' the results of all the studies using cannabinoids, whether synthetic or extracted as if each of the compounds used is identical. Whereas it seems likely that the CB1 receptor is in fact responsible for the most evident adverse effects, there is plentiful evidence, both from basic science but also from clinical studies, that other receptor and effector systems may play a role in the efficacy, particularly of extracts. In particular, the recently described effects of CBD on the vanilloid receptor system [4], on the uptake of nucleosides [6], and on the chemotaxis of immune active cells [5] all provide a coherent reason why this cannabinoid is likely to contribute to the therapeutic effects of extracts. The potential contribution of other cannabinoids remains to be determined as their pharmacology becomes more defined. For example, the presence of tetrahydrocannabivarin in extracts, a $CB_1$ and $CB_2$ antagonist at nanomolar concentrations [62], has the potential to modulate any effect of THC, unless its presence is carefully controlled in the extract used. Clinical studies of extracts should specify the presence and proportion of this compound in the material used.

Cannabinoids, at least THC and CBD, are not good drugs for use as an oral medicine. With very poor oral bioavailability and significant formulation challenges because of their poor water solubility, the oral route is not ideal. Again, when reviewing clinical studies, it is important to consider the route of administration. In the studies conducted with Sativex, administered by a within-patient dose titration approach using the sublingual route, the overall daily dose of THC is substantially greater than that achieved using the oral dosing route. Whereas this is predictable from a knowledge of the pharmacokinetics of cannabinoids, it is often overlooked by commentators.

Furthermore, the ratio of plasma THC to 11-OH-THC is generally higher with Sativex [63] than when THC is administered by the oral route, another factor of possible relevance in efficacy.

Although the pharmacology of the cannabinoids suggests that there are likely to be additional applications within neurological diseases, there have so far been few published large scale clinical studies. Using CBD, several small studies have shown it to have anxiolytic effects, which may be mediated by effects on the hypothalamic-pituitary-adrenal axis [64].

In conclusion, there appears to be little good evidence to date for meaningful efficacy of synthetic cannabinoids in the treatment of neurological diseases. This may be due to the paucity of large-scale clinical studies, and it must be noted that the single large, long-term study of dronabinol does show good evidence for an antispasticity effect. With extracts, the situation is different, and there is good evidence for a meaningful therapeutic effect, especially with an extract comprising equal proportions of CBD and THC and administered by the sublingual route. The recent approval in Canada of Sativex for the relief of neuropathic pain in MS suggests that the therapeutic role of cannabinoids will expand in the coming years.

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