



European Monitoring Centre  
for Drugs and Drug Addiction

# EMCDDA

---

# MONOGRAPHS

A cannabis reader: global issues and local  
experiences

Perspectives on cannabis controversies, treatment and  
regulation in Europe

**Editors**

Sharon Rödner Sznitman, Börje Olsson, Robin Room

8  
VOLUME I

## Legal notice

This publication of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) is protected by copyright. The EMCDDA accepts no responsibility or liability for any consequences arising from the use of the data contained in this document. The contents of this publication do not necessarily reflect the official opinions of the EMCDDA's partners, any EU Member State or any agency or institution of the European Union or European Communities.

A great deal of additional information on the European Union is available on the Internet. It can be accessed through the Europa server (<http://europa.eu>).

Europe Direct is a service to help you find answers to your questions about the European Union

Freephone number:

**00 800 6 7 8 9 10 11**

This publication should be referenced as:

EMCDDA (2008), A cannabis reader: global issues and local experiences, Monograph series 8, Volume 1, European Monitoring Centre for Drugs and Drug Addiction, Lisbon.

References to chapters in this monograph should include, where relevant, references to the authors of each chapter, together with a reference to the wider publication. For example: Corrigan, D. (2008), 'The pharmacology of cannabis: issues for understanding its use', in: A cannabis reader: global issues and local experiences, Monograph series 8, Volume 1, European Monitoring Centre for Drugs and Drug Addiction, Lisbon.

The publication is available on the Internet at:

<http://www.emcdda.europa.eu/publications/monographs/cannabis>

Cataloguing data can be found at the end of this publication.

Luxembourg: Office for Official Publications of the European Communities, 2008

ISBN 978-92-9168-311-6

© European Monitoring Centre for Drugs and Drug Addiction, 2008

Reproduction is authorised provided the source is acknowledged.

*Printed in Belgium*



European Monitoring Centre  
for Drugs and Drug Addiction

Rua da Cruz de Santa Apolónia 23–25, P-1149-045 Lisbon  
Tel. (351) 21 811 30 00 • Fax (351) 21 813 17 11  
[info@emcdda.europa.eu](mailto:info@emcdda.europa.eu) • <http://www.emcdda.europa.eu>

# Chapter 2

## The re-emergence of the therapeutic use of cannabis products: recent developments and future prospects

**Keywords:** cannabinoid – cannabis – dronabinol – medicinal use – medicines – multiple sclerosis – pharmaceutical – pharmacology – pharmacy – Sativex – therapeutics – therapy

### Setting the context

The previous chapter looked at the history of medicinal use of cannabis. It is interesting to consider that, a century ago, the patent medicine J. Collis Browne's *Chlorodyne* (a mixture of laudanum, tincture of cannabis, and chloroform) could be purchased at chemists and was marketed as 'the most wonderful and remarkable remedy ever discovered' <sup>(1)</sup>. Yet historical anecdotes about medicinal use of cannabis are gradually being displaced by a wealth of international research on cannabinoids and their role in therapeutics. This brief chapter — which may be perceived as a postscript to the previous one — provides a summary of recent developments in medicinal cannabis.

Researchers in this area are highly productive, and so this chapter is likely to suffer from almost instant obsolescence. Nonetheless, the chapter reveals that, at the time of writing in late 2007, there are relatively few cannabis-derived medicines that have received regulatory approval. Forecasts dating from the early 2000s that cannabinoids may become the new blockbuster branch of the pharmaceutical industry seem to be premature. Yet a recent market report by Visiongain <sup>(2)</sup> remains upbeat, valuing the global cannabis medicines market at USD 700 million. Besides interest from the pharmaceutical industry, there is an increasing body of research on 'self-medication' using herbal cannabis. The knowledge base is increasing, following relaxation of legislation relating to medicinal use of cannabis in some US states and the Netherlands, together with grassroots organisations focusing on medicinal use of herbal cannabis in Canada and several European countries.

<sup>(1)</sup> Advertisement for J. Collis Browne's *Chlorodyne*, 1891.

<sup>(2)</sup> [www.visiongainintelligence.com/reportDetail.aspx?reportId=1359](http://www.visiongainintelligence.com/reportDetail.aspx?reportId=1359)

## Further reading

- Grotenhermen, F. (2005), *Cannabis und Cannabinoide: Pharmakologie, Toxikologie und therapeutisches Potenzial*, Huber, Bern.
- Hall, W., Pacula, R. (2003), *Cannabis use and dependence: public health and public policy*, Cambridge University Press.
- Icon Group International (2003), *Cannabis: a medical dictionary, bibliography, and annotated research guide to Internet references*, Health Publica Icon Health Publications, San Diego.
- Mechoulam, R. (ed.) (2005), *Cannabinoids as therapeutics, milestones in drug therapy*, Springer Verlag, Berlin.

## Websites

The International Association for Cannabis as Medicine (IACM)

[www.acmed.org](http://www.acmed.org)

The International Cannabinoid Research Society

[www.cannabinoidsociety.org](http://www.cannabinoidsociety.org)

Sociedad Española de Investigación Sobre Cannabinoides

[www.ucm.es/info/seic-web/](http://www.ucm.es/info/seic-web/)

See also the grey literature list in the Appendix to Volume 1 of this monograph (p.300).

---

# The re-emergence of the therapeutic use of cannabis products: recent developments and future prospects

**John Witton**

The past two decades have seen renewed and concerted interest in the therapeutic potential of cannabis. Tetrahydrocannabinol (THC), the active and most significant constituent of cannabis, and other closely related compounds were identified in the 1960s. However, it was not until the mid-1980s and 1990s that research accelerated, when understanding increased of the biology of the body's endocannabinoid system and how cannabis works on the brain. These discoveries opened up possibilities to exploit cannabis-based products for medical use. This renewed scientific interest in the cannabinoids is evidenced by (i) the increase in the number of research papers on the biology of cannabinoids, from 200–300 per year through the 1970s to nearly 6 000 in 2004, and (ii) the number of cannabinoid drugs under pharmaceutical development, rising from 2 in 1995 to 27 in 2004 (Pacher et al., 2006).

The identification of a natural cannabinoid receptor–neuromodulator system in the body was the key to pharmacological and therapeutic developments. Receptors are the sites of action for brain chemicals, called neurotransmitters, and often the sites of action of drugs. Binding of the neurotransmitter or drug to the brain cell receptor causes a response in the cell. Two cannabis receptors (termed CB1 and CB2) have been found (Pertwee, 1997). CB1 receptors are distributed in discrete areas of the brain, particularly concentrated in the hippocampus and cerebral cortex (areas concerned with memory and cognition), olfactory areas, basal ganglia and cerebellum (areas concerned with motor activity and posture control) and the spinal cord. CB2 receptors are found peripherally and are closely linked with cells in the immune system (Kumar et al., 2001). With the discovery of cannabis receptors it became possible to develop cannabinoid agonists or antagonists — that is, agents that activate or bind but do not activate the receptors — that might act as therapeutic tools or help determine the roles of the cannabinoid receptors and the body's own endogenous cannabinoids (British Medical Association, 1997). Two major endocannabinoids have been identified and isolated: anandamide and 2-arachidonoyl glycerol. This endogenous cannabinoid system is

involved in analgesia, cognition, memory, locomotor activity, appetite, vomiting and immune control (Kumar et al., 2001).

As the structure–activity relationships of the cannabis receptors and endocannabinoid system unfolded, the potential for cannabis-based medicines became clearer. But in a review of these developments, a leading neuropharmacologist, Professor Leslie Iversen, suggested that pharmaceutical companies faced a range of substantial obstacles in developing cannabis-based medications. These obstacles were: development costs would be high; only synthetic cannabinoids could be patented rather than the natural product; products would be likely to be niche drugs rather than ‘blockbuster’ drugs used to treat common health problems; there were already medicines available to treat the problems that cannabinoids might be used for; and finally, the vast US marketplace would be difficult to enter, with the US having strict regulatory requirements to introduce a drug that is derived from or chemically related to a prohibited substance (Iversen, 2003).

Over the last 30 years, widely reported use of illicitly smoked cannabis for self-medication for a range of illnesses has brought normally law-abiding citizens into conflict with their country’s legal system. Surveys have found that the common indications for cannabis use include depression, multiple sclerosis, pain, migraine, asthma and cancer-related anorexia/cachexia (Schnelle et al., 1999; Gorter et al., 2005). The ethical dilemmas surrounding this issue were among the factors that led to a number of enquiries examining the therapeutic potential of cannabis products. The British Medical Association’s 1997 report *Therapeutic Uses of Cannabis* and the 1998 report *Cannabis: the Scientific and Medical Evidence* from a Select Committee of the House of Lords both called for the setting up of clinical trials to evaluate the potential therapeutic use of cannabinoids. The prestigious US Institute of Medicine published its report *Medical Use of Marijuana* in 1999. Together, these reports established the evidence base to support the further examination of cannabis products for medical use. Medical and political interest intensified in several European countries and the medical use of cannabis was legalised in the Netherlands in 2003 (Grotenhermen and Russo, 2002; Gorter et al., 2005) and extended for a five-year period in 2007.

Naturally, cannabis products are subject to the same rigorous clinical testing and regulatory processes as any other potential medicine. Clinical trials for new medications normally follow three phases. In phase I the safety of the drug is established. In phase II the efficacy of the drug is established through giving the medication to a small group of potential patients who have the condition targeted by the medication. Finally, phase III trials use large studies involving hundreds of patients.

Two synthetic cannabinoid receptor agonists, dronabinol and nabilone, have already passed these stringent tests. They have been available and approved for medical use since the 1980s. However, neither has been widely prescribed. The effective dose for these cannabinoids is close to a dose that causes sedation or intoxication, limiting the amount of the drug that can be given to patients (Iversen, 2000). Moreover, their therapeutic potential has been superseded by more powerful medications.

Dronabinol is the non-proprietary name for tetrahydrocannabinol. Marinol capsules containing dronabinol were approved for use by the US Food and Drug administration for nausea and vomiting associated with cancer chemotherapy for patients who had not responded to conventional antiemetic medications. Marinol was also approved for use in anorexia associated with weight loss in patients with AIDS. Dronabinol is also available on prescription in a number of countries outside the USA. Dronabinol is manufactured by two German companies, THC Pharm and Delta 9 Pharma, and may be bought by pharmacies to produce dronabinol capsules or solutions. The second cannabinoid receptor agonist, nabilone, a synthetic derivative of dronabinol, was also approved by the FDA in 1986 for use in treatment of nausea and vomiting associated with chemotherapy. It is delivered in the form of Cesamet capsules. Nabilone was originally developed by Eli Lilly in the USA but was not marketed there, but is available in the UK and other European countries.

Two more cannabis-related drugs have become available more recently. The British biotech firm GW Pharmaceuticals has developed Sativex, a cannabis plant extract, consisting of equal amounts of dronabinol (THC) and cannabidiol, another important cannabinoid. Sativex is delivered as an oral spray. Using a spray for delivery provides a consistent quality to the medication and enables doctors to set standard dosages. The spray technique also avoids the carcinogenic smoke normally associated with cannabis use. It also allows for flexible dosing, important when people with MS experience variable amounts of pain.

In 2005 Sativex received approval as an adjunctive treatment for the relief of symptomatic pain related to muscular sclerosis in Canada through the governmental Health Canada's Notice of Compliance with Conditions policy. This policy is applied to products which Health Canada considers as addressing a serious medical condition for which there are no currently approved products and where data from clinical trials to date appear to be promising. The condition to be satisfied is a need for confirmatory phase II study to further verify the clinical benefit of the product. In June 2007 Sativex was approved by the Canadian regulatory authority for use in cancer-related pain. More recently, GW has reached an agreement with the Japanese pharmaceutical firm Otsuka to develop and market Sativex in the USA, where it will be initially trialled for cancer pain.

In Europe, in November 2005 Sativex and the Catalan Health Authority reached agreement to supply Sativex to up to 600 patients suffering from multiple sclerosis under a compassionate access programme. Initial results from a patient study suggested that 65% of the patients had experienced an improvement in quality of life and a decrease in pain. In the UK, the Home Office permitted the prescription of Sativex to individual patients as an unlicensed medicine. Thus, Sativex can be supplied on a named patient basis from the drug's manufacturing site and dispensed by local pharmacies to patients. At the time of writing (end of 2007), Sativex is awaiting approval as a prescription drug for multiple sclerosis in Spain, Denmark and the Netherlands.

The second new drug, the cannabinoid receptor antagonist rimonabant, received a positive recommendation for approval by the European Medicines Agency in 2006. Available in the United Kingdom for the treatment of obesity under the name Acomplia, a Cochrane review found rimonabant use with diet and exercise led to modest weight loss at one year follow-up in the four studies under review. However the review authors suggested caution in interpreting the results of their review because of methodological shortcomings in the studies reviewed, high drop-out rates among participants and the need for longer term follow-up (Curioni and André, 2007). In the USA, rimonabant (planned to be marketed under the name Zimulti) was rejected by the Food and Drug Administration in June 2007. The FDA cited concerns on side-effects such as depression, anxiety and sleep problems when taking the drug.

Another cannabis-related product under investigation in clinical trials is Cannador, containing dronabinol and other cannabinoids. Studies have examined Cannador's value in treating spasticity and other symptoms related to multiple sclerosis and post-operative pain (Holdcroft et al., 2006; Zajicek et al., 2006). Further trials with Cannador have been undertaken at the Institute for Clinical Research in Berlin. There has been some interest in investigating the potential of cannabidiol as an antipsychotic (Zuardi et al., 2006).

Away from pharmaceutical cannabis-related preparations, the use of its natural form for medicinal purposes has also progressed recently. While cannabis remains illegal under federal law in the US, 13 states have made available the medical use of cannabis under their state laws. The latest to legalise medical use of cannabis is New Mexico, where 1 742 patients are authorised to possess dried cannabis as a medication. 1 040 are licensed to grow their own cannabis and 167 people are licensed to grow cannabis for the use of authorised patients. Here the state's health ministry buys the cannabis from these licensed growers and sells it on to the patient.

In terms of very recent developments, in Finland the Ministry of Social Affairs and Health in December 2007 sought to clarify legislation on prescribing cannabis to sufferers of chronic pain, based on the implications of a test case involving an individual who had obtained special permission from the ministry for using cannabis for pain relief. A Canadian pharmaceutical research company called Cannasat Therapeutics is developing three candidate medicines, named CAT 210, CAT 310 and CAT 320, for which it forecast Phase II testing for the lead candidate, CAT 310, 'by the end of 2008'. In late 2007, a Dutch company called Echo Pharmaceuticals, based in Weesp, announced funding aimed at developing a cannabis-based pill called Namisol, targeting numerous therapeutic applications. The company is partnering with the cannabis grower Bedrocan, as well as the companies Farmalyse and Feyecon, to develop a pill.

## Bibliography

- British Medical Association (1997), *Therapeutic uses of cannabis*, British Medical Association Board of Science and Education, Harwood Academic Publishers, Reading.
- Curioni, C., André, C. (2007), 'Rimonabant for overweight or obesity', *Cochrane Database of Systematic Reviews 2007, Issue 3*.
- Gorter, R., Butorac, M., Pulido Cobian, E., van der Sluis, W. (2005), 'Medical use of cannabis in the Netherlands', *Neurology* 64: 917–919.
- Grotenhermen, F., Russo, E. (eds) (2002), *Cannabis and cannabinoids: pharmacology, toxicology, and therapeutic potential*, Haworth Press, Binghamton.
- Holdcroft, A., Maze, M., Doré, C., Tebbs, S., Thompson, S. (2006), 'A multicenter dose-escalation study of the analgesic and adverse effects of an oral cannabis extract (Cannador) for postoperative pain management', *Anesthesiology* 104(5): 1040–1046.
- House of Lords, Select Committee on Science and Technology (1998), *Cannabis: the scientific and medical evidence (ninth report)*, Home Office, London.
- Iversen, L. (2000), *The science of marijuana*, Oxford University Press, Oxford.
- Iversen, L. (2003), 'Cannabis and the brain', *Brain* 126: 1252–1270.
- Joy, J., Watson, S. and Benson, J. (1999), *Marijuana and medicine: assessing the science base*, Division of Neuroscience and Behavioral Research, Institute of Medicine, National Academy Press, Washington.
- Kumar, R., Chambers, W., Pertwee, R. (2001), 'Pharmacological actions and therapeutic uses of cannabis and cannabinoids', *Anaesthesia* 56: 1059–1068.
- Pacher, P., Bátkai, S., Kunos, G. (2006), 'The endocannabinoid system as an emerging target of pharmacotherapy', *Pharmacological Reviews* 58: 389–462.
- Pertwee, R. (1997), 'Pharmacology of cannabinoid CB1 and CB2 receptors', *Pharmacology and Therapeutics* 74: 129–180.
- Schnelle, M., Grotenhermen, F., Reif, M., Gorter, R. (1999), 'Ergebnisse einer standardisierten Umfrage zur medizinischen Verwendung von Cannabisprodukten im deutschen Sprachraum', [Results of a standardized survey on the medical use of cannabis products in the German-speaking area], *Forsch Komplementarmed* 6 (Suppl. 3): 28–36.

- Zajicek, J., Sanders, H., Wright, D., Vickery, P., Ingram, W., Reilly, S., Nunn, A., Teare, L., Fox, P., Thompson, A. (2006), 'Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up', *Journal of Neurol Neurosurg Psychiatry* 76(12): 1664–1669.
- Zuardi, A., Hallak, J., Murat Dursun, S., Morais, S., Sanches, R., Musty, R., Crippa, J. (2006), 'Cannabidiol monotherapy for treatment-resistant schizophrenia', *Journal of Psychopharmacology* 20(5): 683–686.