Medicinal Cannabis:
The Evidence

Peter Reynolds, 27th February 2015

CLEAR Cannabis Law Reform
42-46 Bethel Street
Norwich
NR2 1NR

www.clear-uk.org

Contents

Abstract

This paper reviews the evidence in support of the safety and efficacy of using raw herbal cannabis as medicine.

It is widely claimed that there is insufficient evidence to support medicinal use but this is not borne out by the facts, let alone 10,000 years of human history. In fact, there is so much evidence available for so many conditions that this paper is restricted to conditions for which cannabis appears to have the most beneficial effects.

Side effects and risks of medicinal cannabis are very well documented in the literature, much of which is focused on identifying harms of recreational use. The risks are extremely low in a therapeutic context compared with pharmaceutical medicines.

Alzheimer's Disease	The evidence is strong that regular, moderate use of cannabis helps to delay the onset and progression of Alzheimer's disease and other neurodegenerative conditions.
Cancer	On balance, while there is excellent evidence of anti cancer properties in vitro (human cell lines) and in vivo (animal) studies, there is little evidence of actual results in humans except in the treatment of basal cell carcinoma. However, few would disagree that the palliative value of cannabis is of great benefit to many cancer patients.
Chronic Pain	There is a large quantity of good quality evidence, including clinical trials with placebo controls, that demonstrate the efficacy and safety of cannabis in treating chronic pain.
Crohn's Disease	Recent clinical trials have produced dramatic results with 50% of Crohn's patients achieving complete remission and over 90% achieving substantial improvement. The evidence for the use of cannabis in Crohn's, ulcerative colitis and other forms of inflammatory bowel disease (IBD) is conclusive.
Multiple Sclerosis	There is a clear consensus amongst scientists and doctors that cannabis is safe and effective as a palliative treatment for MS. Further promising research is underway into whether cannabis may have a curative effect by promoting repair of the myelin sheath

Conclusion

Cannabis clearly offers significant therapeutic benefits for a wide range of conditions without substantial risks or unmanageable side effects.

Cannabis should be transferred from schedule 1 to schedule 2 of the Misuse of Drugs Regulations.

Current MHRA policies and fees on traditional herbal products and marketing authorisations are an unnecessary obstacle to making medicinal cannabis available. The only practical solution is for doctors to prescribe Bedrocan products as unlicensed medicines.

What Evidence Is Available?

Published, peer-reviewed studies and clinical trials

PubMed references over 20,000 published studies or reviews under the search terms cannabis, cannabinoid or marijuana, nearly half of which were published within the last five years. (1)

By comparison, few pharmaceutical medicines are tested in multiple, large-scale clinical trials or have thousands of years of actual experience behind them. A recent analysis showed that in the USA about a third of pharmaceutical medicines won approval on the basis of a single clinical trial and many trials were of very few subjects over a short duration. (2) It is also now well established that both in the USA and UK, pharmaceutical companies cherry pick trial data for licence/marketing authorisation applications. (3,4)

The reality, therefore, is a massive amount of evidence on cannabis, which supports its relative safety when used as medicine to a far more rigorous and comprehensive standard than for most pharmaceutical products. Archaeological evidence also indicates that mankind has been using psychoactive cannabis for at least 10,000 years. (5) Recorded history first documents psychoactive cannabis approximately 5,000 years ago. (6)

Evidence on efficacy of medicinal cannabis is mixed, strong for some conditions and weaker in others. The long history of use and widespread reform in the last 20 years demonstrates that, subjectively, patients value it and believe it works.

Experience in other countries

Aside from the scientific evidence itself, many jurisdictions have already carried out in depth reviews and concluded that medicinal cannabis should be available.

Medicinal cannabis is now available on prescription in Austria, Canada, the Czech Republic, Finland, Germany, Israel, Italy, the Netherlands, Portugal and Spain (7).

Doctors in the USA can issue ‘recommendations’ rather than prescriptions. 34 states and the District of Columbia now have some form of medicinal cannabis access. (8)

Therefore, currently more than 500 million people in the ‘First World’ have legal access to medicinal cannabis. The UK is notable for its failure to give any serious consideration to such reform since 1998, despite reasonable estimates of up to one million British people using cannabis for medicinal purposes. (9)

Europe:	250 million
USA:	209 million
Canada:	35 million
Israel:	8 million

(See Table A for full details)

Regulation Of Medicinal Cannabis

Raw herbal cannabis cannot be regulated in the same way as single-molecule pharmaceutical medicines. Cannabis contains 400 – 500 individual compounds, including cannabinoids, terpenes and flavonoids, all of which work together in synergy to create 'the entourage effect'. This is shown to be vital to the beneficial and therapeutic qualities of cannabis. (10,11,12)

As a generic medicine, based on the evidence set out in this paper, there is a strong case for transferring cannabis from schedule 1 to schedule 2 of the Misuse of Drugs Regulations. (13) It is manifestly incorrect that cannabis has no medicinal value.

However, the extraordinarily high cost of applying for an MHRA marketing authorisation (initial fee of up to £103,059), is likely to inhibit such applications. (14) This is an unnecessary and disproportionate obstacle to bringing the benefits of medicinal cannabis to the UK. Traditional herbal registration is also inappropriate as cannabis will be used to treat major health conditions under medical supervision. With regulation is as onerous as this, doctors will need to take personal responsibility and prescribe cannabis as an unlicensed medicine.

In 1998, the House of Lords Science and Technology Committee recommended that doctors should be permitted to prescribe cannabis for medicinal use. (15) However, in direct contradiction, two years later, by the Misuse of Drugs (Designation) Order 2001 (16), the government explicitly removed medical practitioners' prescribing rights in respect of cannabis. Cannabis is the only substance in widespread current use and with many thousands of years of historical use, to which such a sanction has been applied. There is no rationale, explanation or evidence for this prohibition.

In January 2015, Prof. D.G. Penington argued that due to variations in compounds, potency and actions, cannabis is not suitable for medical prescription and should be "decided by the patient". (17)

However, medical professionals have a role to play in diagnosis of conditions and assessment of the risk/benefit equation for individual patients. With experience and suitable training, medical professionals can understand and advise on the benefits of particular strains and methods of ingestion.

In December 2014, the College of Family Physicians of Canada published its preliminary recommendations for physicians on smoked cannabis for chronic non-cancer pain. (18) The Netherlands Office of Medicinal Cannabis has also published guidelines for healthcare professionals (19)

Sativex (nabiximols)

The MHRA has granted a marketing authorisation for Sativex (nabiximols), a whole plant extract of cannabis, blended from different strains to contain a 1:1 ratio of THC:CBD. All the other cannabinoids, terpenes, flavonoids are regarded by the MHRA as "unspecified impurities" even though GW Pharmaceuticals, the manufacturer, considers them vital to "the entourage effect" (20,21)

Sativex is approved for treatment of spasticity in multiple sclerosis although many prescriptions have been written 'off label' for other conditions. However, its extraordinarily high cost has meant few Clinical Commissioning Groups (CCG) have been prepared to

fund it. Recently NICE recommended against its use “because it is not a cost effective treatment” (22)

Bedrocan

Bedrocan (23) is the exclusive contractor to the Netherlands government for the production of medicinal cannabis. It is also now a licensed contractor to Health Canada. (24) It produces a range of raw herbal cannabis products with varying ratios of THC:CBD. Aside from Sativex, it is the only prescribable form of cannabis in Europe because it is produced to quality standards, contains consistent levels of cannabinoids and is regulated by the Netherlands Office for Medicinal Cannabis (25). Its production complies with EU Good Manufacturing Practice (GMP) and Good Agricultural Practice (GAP) protocols.

Bedrocan products are available at lower cost than Sativex for equivalent cannabinoid content. Depending on the product selected, Bedrocan costs between approximately 5% and 20% of the cost of Sativex. (26)

Methods of Ingestion

Cannabis does not have to be smoked. By far the preferred method of ingestion for medicinal users is vapourisation. This involves a device that blows hot air through finely ground cannabis at a specified temperature that will vapourise the medicinal compounds. (27,28) This avoids inhaling toxic products of combustion but still provides accurate self-titration of dose.

However, for people with serious illness, smoking of cannabis (without tobacco), may still be a valid route of ingestion when the risks are outweighed by the benefits.

Consumption by eating, drinking an infusion or the insertion of suppositories are other useful methods depending on the condition and the effect required. (29)

Side Effects and Risks

Cannabis is not without side effects, principally its psychoactivity. Evidence of harm from smoking or vapourising is weak when adjusted for tobacco use and some studies suggest a protective effect against cancer and COPD (30,31,32).

Evidence of correlation with psychosis is very well documented, particularly in recreational use at early age of first use but the risks are extremely low (33) in a therapeutic context compared with pharmaceutical medicines.

Side effects and risks are very well documented in the literature, most of which is focused on identifying harms of recreational use. However, compared to the side effects and risks of pharmaceuticals, likely to be prescribed for the specified conditions, cannabis is low risk. In this context its side effects and risks need to be compared to anti-psychotics, opioids, NSAIDs, anti-epileptics, etc.

Studies And Clinical Trials

Alzheimer's disease

Cannabis has proven anti-inflammatory and neuroprotective properties. Inflammation plays a major role in not only Alzheimer's, but motor neurone disease, Parkinson's, AIDS, dementia, multiple sclerosis, autism, schizophrenia, etc.

The evidence is strong that regular, moderate use of cannabis helps to delay the onset and progression of Alzheimer's disease and other neurodegenerative conditions.

2003. The US government holds patent US6630507, 'Cannabinoids as antioxidants and neuroprotectants**'**:

*"**…**for example in limiting neurological damage following ischemic insults, such as stroke and trauma, or in the treatment of neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease and HIV dementia."* (34)

2006. THC has been shown to inhibit the progression of Alzheimer's more effectively than any currently prescribed pharmaceutical product. (35)

2007. British Journal of Pharmacology:

"Cannabinoids offer a multi-faceted approach for the treatment of Alzheimer's disease by providing neuroprotection and reducing neuroinflammation, whilst simultaneously supporting the brain's intrinsic repair mechanisms..." (36)

2012. Andras Bilkei-Gorzo of the University of Bonn:

"…elevation of cannabinoid receptor activity either by pharmacological blockade of the degradation of cannabinoids or by receptor agonists could be a promising strategy for slowing down the progression of brain ageing and for alleviating the symptoms of neurodegenerative disorders." (37)2012. Journal of Neuroinflammation:

"The chronic administration of non-selective cannabinoids may delay the onset of cognitive deficits in AD patients; this will dramatically reduce the socio-economic burden of AD and improve the quality of life of the patients and their families." (38)

2014. Professor Gary Wenk, of Ohio State University:

"…using low doses of marijuana for prolonged periods of time at some point in your life, possibly when you're middle-aged to late middle-aged, is probably going to slow the onset or development of dementia, to the point where you'll most likely die of old age before you get Alzheimer's." (39)

2014. Steven Fagan of the University of Dublin:

"Pharmacological modulation of the endocannabinoid system has been shown to reduce chronic activation of the neuroinflammatory response, aid in Ca^{2+} homeostasis, reduce oxidative stress, mitochondrial dysfunction and the resulting proapoptotic cascade, while promoting neurotrophic support." (40)

2014. Chuanhai Cao of the University of South Florida:

“These sets of data strongly suggest that THC could be a potential therapeutic treatment option for Alzheimer's disease through multiple functions and pathways.” (41)

Studies And Clinical Trials

Cancer

The anti cancer properties of THC, CBD, CBG and other cannabinoids are well established. Scientists have been investigating them since the early 1970s and more than 1100 papers on cannabinoids and cancer have been published. (42)

It is also well established that cannabis helps with the side effects of cancer treatments, particularly nausea and lack of appetite. (43,44,45,46)

Cannabis may also help alleviate anxiety, depression, insomnia and mood disorders in cancer patients. However, some patients may find exactly the opposite results (47)

A very large quantity of anecdotal reports detail remarkable results with cannabis oil on many different forms of cancer. (48) One of the most important properties of cannabis as a cancer therapy is that it is non-toxic and even if little therapeutic effect is achieved, it causes little harm.

On balance, while there is good evidence of anti cancer properties in vitro (human cell lines) and in vivo (animal) studies, there is little evidence of actual results in humans except in the treatment of basal cell carcinoma (49). However, few would disagree that the palliative value of cannabis is of great benefit to many cancer patients. (50)

Clinical trials are underway on cancer pain (51) and the treatment of glioma brain cancer (52).

These selected studies indicate the evidence currently available.

Cannabinoids and cancer: potential for colorectal cancer therapy. Biochem Soc Trans. 2005. http://www.ncbi.nlm.nih.gov/pubmed/16042581 (53)

A pilot clinical study of Δ9-tetrahydrocannabinol in patients with recurrent glioblastoma multiforme, British Journal of Cancer, 2006
http://www.nature.com/bjc/journal/v95/n2/full/6603236a.html (54)

Cannabinoids for Cancer Treatment: Progress and Promise. Cancer Res. 2008.
http://cancerres.aacrjournals.org/content/68/2/339 (55)

Cannabidiol Induces Programmed Cell Death in Breast Cancer Cells by Coordinating the Cross-talk between Apoptosis and Autophagy. Mol Cancer Ther., 2011.
http://mct.aacrjournals.org/content/10/7/1161.long (56)

The intersection between cannabis and cancer in the United States. CROH, 2011.
http://www.croh-online.com/article/S1040-8428(11)00231-9/fulltext (57)

Cannabinoids: a new hope for breast cancer therapy? Cancer Treat Rev. 2012
http://www.ncbi.nlm.nih.gov/pubmed/22776349 (58)

Towards the use of cannabinoids as antitumour agents. Nat Rev Cancer. 2012
http://www.ncbi.nlm.nih.gov/pubmed/22555283 (59)

Cannabis Extract Treatment for Terminal Acute Lymphoblastic Leukemia with a Philadelphia Chromosome Mutation. Case Rep Oncol. 2013. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3901602/ (60)

Non-hallucinogenic cannabinoids are effective anti-cancer drugs. Anticancer Research, 2013. http://www.sgul.ac.uk/news/news/study-shows-non-hallucinogenic-cannabinoids-are-effective-anti-cancer-drugs (61)

Cannabidiol as potential anticancer drug. Br J Clin Pharmacol. 2013. http://www.ncbi.nlm.nih.gov/pubmed/22506672%20 (62)

Cannabis, cannabinoids and cancer – the evidence so far. Cancer Research UK, 2014. http://scienceblog.cancerresearchuk.org/2012/07/25/cannabis-cannabinoids-and-cancer-the-evidence-so-far/ (63)

The Combination of Cannabidiol and Δ9-Tetrahydrocannabinol Enhances the Anticancer Effects of Radiation in an Orthotopic Murine Glioma Model. Mol.Cancer.Ther. 2014. http://mct.aacrjournals.org/content/13/12/2955 (64)

Studies And Clinical Trials

Chronic Pain

Chronic pain is the condition for which cannabis is most widely used. It seems to be particularly effective in neuropathic pain for which opioids, NSAIDs and other pharmaceutical medicines are not effective. It also appears to reduce the required dose when used in conjunction with opioids. (65)

THC, CBD and other cannabinoids each have different effects both as analgesics and in the perception of pain. Patients commonly report that even if pain is not eliminated, cannabis helps them to deal with it by altering their perception and allowing them to focus elsewhere.

There is a large quantity of good quality evidence, including clinical trials with placebo controls, that demonstrate the efficacy and safety of cannabis in treating chronic pain.

2007, Neurology

"…52% of patients who smoked marijuana had a greater than 30% reduction in pain compared to 24% in the placebo group. In this study, smoked marijuana was well tolerated and effectively relieved chronic neuropathic pain…" (66)

2007. Journal of Pain.

"This study adds to a growing body of evidence that cannabis may be effective at ameliorating neuropathic pain, and may be an alternative for patients who do not respond to, or cannot tolerate, other drugs." (67)

2008. Neuropsychopharmacology

"Smoked cannabis was generally well-tolerated and effective when added to concomitant analgesic therapy…" (68)

2010. Canadian Medical Association Journal

"Our results support the claim that smoked cannabis reduces pain, improves mood and helps sleep." (69)

2013. Neuropsychopharmacolgy

"This study is the first to demonstrate the dose- and route-dependent analgesic effectiveness of cannabinoids for acute experimentally-induced pain in a pain-free population, evidence that supports the role of cannabinoids for the management of pain." (70)

Studies And Clinical Trials

Crohn's disease

Crohn's disease, ulcerative colitis and other forms of inflammatory bowel disease (IBD) are widely and successfully treated with cannabis. (71)

A clinical trial using cannabis extract to treat ulcerative colitis was concluded by GW Pharmaceuticals in 2014. (72)

Anecdotally, there are many reports of dramatic improvements in symptoms shortly after cannabis use, e.g. cessation of rectal bleeding, increased appetite.

Recent clinical trials have produced dramatic results with 50% of Crohn's patients achieving complete remission and over 90% achieving substantial improvement. The evidence for the use of cannabis in Crohn's and other forms of IBD is conclusive.

2012. Digestion

"Three months' treatment with inhaled cannabis improves quality of life measurements, disease activity index, and causes weight gain and rise in BMI in long-standing IBD patients." (73)

2013. Clinical Gastroenterology and Hepatology

"In this trial, cannabis induced clinical remission in 50% of patients. Taking into account that our participants had longstanding Crohn's disease, with 80% nonresponse or intolerance to anti–TNF-a, this result is impressive." (74)

2014. Pharmacology

"Cannabis sativa has lived up to expectations and proved to be highly efficient in cases of inflammatory bowel diseases… cannabis produces significant clinical benefits in patients with Crohn's disease." (75)

Studies And Clinical Trials

Multiple Sclerosis

MS is the condition which has most commonly been associated with the therapeutic use of cannabis. It was the increasing illicit use of cannabis to treat MS that led to the House of Lords Science and Technology Committee inquiry in 1998 (76). The approval of Sativex (nabiximols) for the treatment of spasticity in MS is the first licensed cannabis medicine in modern times. (77)

Most MS patients also suffer from chronic pain, for which evidence in respect of medicinal cannabis is set out above.

A great deal of research has been carried out on cannabinoids in MS but much of it is fundamentally flawed by focusing on individual and/or synthetic cannabinoids, in particular the large scale CUPID trial used oral, synthetic THC (dronabinol). It is difficult to understand why this reductionist approach has been taken in view of evidence on the 'entourage effect' (10,11,12) and that these studies were inspired by anecdotal reports of using whole plant cannabis.

There is a clear consensus amongst scientists and doctors that cannabis is safe and effective as a palliative treatment for MS (78,79,80). Further promising research is underway into whether cannabinoids may have a curative effect by promoting repair of the myelin sheath (81,82,83)

Other Evidence

The International Association for Cannabinoid Medicines (IACM) maintains a database of clinical studies and case reports from 1970 to 2013.
http://www.cannabis-med.org/studies/study.php (84)

105 Peer-Reviewed Studies on Medical Marijuana. Medical Studies Involving Cannabis and Cannabis Extracts (1990 - 2012)
http://medicalmarijuana.procon.org/view.resource.php?resourceID=000884 (85)

The Medicalization of Cannabis. Wellcome Trust Witness Seminar, 2010
http://www.histmodbiomed.org/sites/default/files/44870.pdf (86)

Emerging Clinical Applications For Cannabis & Cannabinoids. A Review of the Recent Scientific Literature. NORML, 2014.
http://norml.org/pdf_files/NORML_Clinical_Applications_for_Cannabis_and_Cannabinoids.pdf (87)

What does marijuana do? It rebalances everything. Vipperman, 2014
https://michaelvipperman.wordpress.com/2014/04/20/what-does-marijuana-do-it-rebalances-everything/ (88)

Table A – Populations with legal access to medicinal cannabis

Jurisdiction	Population (millions)
Austria	8.47
Belgium	11.2
Czech Republic	10.52
Finland	5.43
Germany	80.62
Italy	59.83
Netherlands	16.8
Portugal	10.46
Spain	47.27
EUROPE TOTAL	250.61
Alabama	4.84
Alaska	0.73
Arizona	6.73
California	38.8
Colorado	5.35
Connecticut	3.59
Delaware	0.93
District of Colombia	0.65
Florida	19.89
Hawaii	1.42
Illinois	12.88
Iowa	3.10
Kentucky	4.41
Maine	1.33
Maryland	5.97
Massachusetts	6.74
Michigan	9.91
Minnesota	5.45
Mississippi	2.99
Missouri	6.06
Montana	1.02
Nevada	2.83
New Hampshire	1.32
New Jersey	8.93
New Mexico	2.08
New York	8.40
North Carolina	9.94
Oregon	3.97
Rhode Island	1.05
Tennessee	6.55
South Carolina	4.83
Utah	2.94
Vermont	0.62
Washington	7.06
Wisconsin	5.76
USA TOTAL	209.21
CANADA TOTAL	35.16
ISRAEL TOTAL	8.06
WORLDWIDE	503.04

References

1. PubMed Central http://www.ncbi.nlm.nih.gov/pmc/
2. Clinical Trial Evidence Supporting FDA Approval of Novel Therapeutic Agents, 2005-2012. JAMA 2014. http://jama.jamanetwork.com/article.aspx?articleid=1817794
3. All Trials campaign http://www.alltrials.net/find-out-more/
4. Extent of Non-Publication in Cohorts of Studies Approved by Research Ethics Committees or Included in Trial Registries. PLOS 2014 http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0114023
5. Archaeological Evidence for the Tradition of Psychoactive Plant Use in the Old World. Table 1. Economic Botany, 2003. http://www.jstor.org/stable/4256701?origin=JSTOR-pdf
6. Phytochemical and genetic analyses of ancient cannabis from Central Asia. J. Exp. Bot., 2008. http://jxb.oxfordjournals.org/content/59/15/4171.full
7. Medical Cannabis, Wikipedia http://en.wikipedia.org/wiki/Medical_cannabis
8. Medical Marijuana Access In The US, Americans for Safe Access, 2014 https://d3n8a8pro7vhmx.cloudfront.net/americansforsafeaccess/pages/121/attachments/original/1421349447/state_report_web_wAHPA.pdf
9. Taxing the UK Cannabis Market. IDMU, 2011. https://peterreynolds.files.wordpress.com/2015/02/taxukcan.pdf
10. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. Ethan B Russo. 2011 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3165946/#b42
11. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. Russo E, Guy GW. 2006 http://www.ncbi.nlm.nih.gov/pubmed/16209908/
12. Terpenoids, 'minor' cannabinoids, contribute to 'entourage effect' of Cannabis-based medicines. F. Gardner 2011 http://www.beyondthc.com/wp-content/uploads/2012/08/EntourageEffect.pdf
13. The Misuse of Drugs Regulations 2001. http://www.legislation.gov.uk/uksi/2001/3998/contents/made
14. MHRA fees 2014/15. https://www.gov.uk/government/publications/mhra-fees-201415/mhra-fees-201415#licence-applications-marketing-authorisations-including-extension-applications-fees
15. Cannabis: The Scientific and Medical Evidence. House of Lords Select Committee on Science and Technology, Ninth Report http://www.parliament.the-stationery-office.co.uk/pa/ld199798/ldselect/ldsctech/151/15102.htm
16. The Misuse of Drugs (Designation) Order 2001 http://www.legislation.gov.uk/uksi/2001/3997/made
17. Medical cannabis: time for clear thinking. D.G. Penington 2015 https://www.mja.com.au/journal/2015/202/2/medical-cannabis-time-clear-thinking
18. Prescribing smoked cannabis for chronic noncancer pain. Canadian Family Physician, 2014. http://www.cfp.ca/content/60/12/1083.long
19. Information for Health Care Professionals. Netherlands Office of Medicinal Cannabis, 2013. http://www.cannabisbureau.nl/en/doc/pdf/Information%20for%20Health%20Care%20Professionals%20(version%20October%202013)_18980.pdf
20. Cannabis company enjoys major growth, Cambridge News, 2012 http://www.cambridge-news.co.uk/Cannabis-company-enjoys-major-growth/story-22509041-detail/story.html
21. Cannabinoid Science. Mechanism of Action. GW Pharma. http://www.gwpharm.com/mechanism-of-action.aspx
22. Multiple Sclerosis Guidelines, 1.5.23, NICE, 2014 http://www.nice.org.uk/guidance/cg186/chapter/1-recommendations
23. Bedrocan BV website http://www.bedrocan.nl/english/home.html
24. Bedrocan Canada website https://bedrocan.ca/
25. Office for Medicinal Cannabis website http://cannabisbureau.nl/en/
26. Fascinating Facts About The Sativex Rip Off, CLEAR, 2013. http://clear-uk.org/fascinating-facts-about-the-sativex-rip-off/
27. The Volcano Medic Vapouriser. CCIC, 2009. http://www.ccic.net/index.php?id=132,744,0,0,1,0
28. Vaporization as a "Smokeless" Cannabis Delivery System. Clin. Pharmacol Ther., 2007. http://www.cmcr.ucsd.edu/index.php?option=com_content&view=article&id=149:vaporization-as-a-gsmokelessg-cannabis-delivery-system&catid=41:research-studies&Itemid=135
29. The medicinal use of cannabis and cannabinoids--an international cross-sectional survey on administration forms. J Psychoactive Drugs. 2013. http://www.ncbi.nlm.nih.gov/pubmed/24175484
30. Marijuana Use and Lung Cancer: Results of a Case-Control Study. American Thoracic Society International Conference, 2006. http://www.ukcia.org/research/MjUseAndLungCancer.php
31. Study Shows No Increased Risk for Even the Heaviest Marijuana Smokers. WebMD, 2006. http://www.webmd.com/lung-cancer/news/20060523/pot-smoking-not-linked-to-lung-cancer
32. Association Between Marijuana Exposure and Pulmonary Function Over 20 Years. JAMA, 2012. http://jama.jamanetwork.com/article.aspx?articleid=1104848

33. If cannabis caused schizophrenia--how many cannabis users may need to be prevented in order to prevent one case of schizophrenia? Addiction, 2009. http://www.ncbi.nlm.nih.gov/pubmed/19832786
34. Patent: Cannabinoids as antioxidants and neuroprotectants, US 6630507 B1, 2003. http://www.google.co.uk/patents/US6630507
35. A molecular link between the active component of marijuana and Alzheimer's disease pathology. Mol Pharm. 2006 http://www.ncbi.nlm.nih.gov/pubmed/17140265
36. Alzheimer's disease; taking the edge off with cannabinoids? BJP, 2007. http://onlinelibrary.wiley.com/doi/10.1038/sj.bjp.0707446/abstract
37. The endocannabinoid system in normal and pathological brain ageing, Phil.Trans.R.Soc.B, 2012. http://www.medicinalgenomics.com/wp-content/uploads/2011/12/Cannabinoids-and-Brain-Ageing.pdf
38. Can the benefits of cannabinoid receptor stimulation on neuroinflammation, neurogenesis and memory during normal aging be useful in AD prevention? J Neuroinflammation. 2012. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3284401/
39. How Smoking Marijuana Might Be The Best Way To Prevent Alzheimer's Disease, Leaf Science, 2014. http://www.leafscience.com/2014/01/30/smoking-marijuana-might-best-way-prevent-alzheimers-disease/
40. The influence of cannabinoids on generic traits of neurodegeneration. British Journal of Pharmacology, 2014. http://onlinelibrary.wiley.com/doi/10.1111/bph.12492/full
41. The potential therapeutic effects of THC on Alzheimer's disease. J Alzheimers Dis. 2014. http://www.ncbi.nlm.nih.gov/pubmed/25024327#
42. PubMed search term 'cannabinoid cancer' http://www.ncbi.nlm.nih.gov/pubmed?term=cannabinoid%20cancer
43. Cannabis and Cannabinoids. National Cancer Institute, 2014 http://www.cancer.gov/cancertopics/pdq/cam/cannabis/healthprofessional/page5
44. Cannabinoids in medicine: A review of their therapeutic potential. JEthPharm, 2006. http://www.ww.ufcw770.org/sites/all/themes/danland/files/CannabinoidsMedMetaAnalysis06.pdf
45. Review on clinical studies with cannabis and cannabinoids 2005-2009. IACM 2010. http://www.cannabis-med.org/data/pdf/en_2010_01_special.pdf
46. Medical marijuana for cancer. CA: A Cancer Journal for Clinicians, 2014. http://onlinelibrary.wiley.com/doi/10.3322/caac.21260/abstract
47. Cannabis and Cannabinoids. National Cancer Institute, 2014 http://www.cancer.gov/cancertopics/pdq/cam/cannabis/healthprofessional/page5
48. Cannabis Oil Testimonials. Cure Your Own Cancer, 2014. http://www.cureyourowncancer.org/testimonials.html
49. Physician's documentation confirms successful treatment of basal cell carcinoma resulted from the application of a topical cannabis extract. Cannabis Science, 2011. http://www.cannabisscience.com/2011/499-cannabis-science-provides-physician-s-documentation-that-confirms-successful-treatment-of-skin-cancer
50. Cannabis in Palliative Medicine: Improving Care and Reducing Opioid-Related Morbidity. AM J HOSP PALLIAT CARE, 2011. http://ajh.sagepub.com/content/28/5/297
51. Third phase III Sativex cancer pain trial commences http://www.gwpharm.com/Third%20phase%20III%20Sativex%20cancer%20pain%20trial%20commences.aspx
52. GW Pharmaceuticals Commences Phase 1b/2a Clinical Trial for the Treatment of Glioblastoma Multiforme (GBM) http://www.gwpharm.com/GW%20Pharmaceuticals%20Commences%20Phase%201b2a%20Clinical%20Trial%20%20for%20the%20Treatment%20of%20Glioblastoma%20Multiforme%20GBM.aspx
53. Cannabinoids and cancer: potential for colorectal cancer therapy. Biochem Soc Trans. 2005. http://www.ncbi.nlm.nih.gov/pubmed/16042581
54. A pilot clinical study of Δ9-tetrahydrocannabinol in patients with recurrent glioblastoma multiforme, British Journal of Cancer, 2006 http://www.nature.com/bjc/journal/v95/n2/full/6603236a.html
55. Cannabinoids for Cancer Treatment: Progress and Promise. Cancer Res. 2008. http://cancerres.aacrjournals.org/content/68/2/339
56. Cannabidiol Induces Programmed Cell Death in Breast Cancer Cells by Coordinating the Cross-talk between Apoptosis and Autophagy. Mol Cancer Ther., 2011. http://mct.aacrjournals.org/content/10/7/1161.long
57. The intersection between cannabis and cancer in the United States. CROH, 2011. http://www.croh-online.com/article/S1040-8428(11)00231-9/fulltext
58. Cannabinoids: a new hope for breast cancer therapy? Cancer Treat Rev. 2012 http://www.ncbi.nlm.nih.gov/pubmed/22776349
59. Towards the use of cannabinoids as antitumour agents. Nat Rev Cancer. 2012 http://www.ncbi.nlm.nih.gov/pubmed/22555283

60. Cannabis Extract Treatment for Terminal Acute Lymphoblastic Leukemia with a Philadelphia Chromosome Mutation. Case Rep Oncol. 2013. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3901602/
61. Non-hallucinogenic cannabinoids are effective anti-cancer drugs. Anticancer Research, 2013. http://www.sgul.ac.uk/news/news/study-shows-non-hallucinogenic-cannabinoids-are-effective-anti-cancer-drugs
62. Cannabidiol as potential anticancer drug. Br J Clin Pharmacol. 2013. http://www.ncbi.nlm.nih.gov/pubmed/22506672%20
63. Cannabis, cannabinoids and cancer – the evidence so far. Cancer Research UK, 2014. http://scienceblog.cancerresearchuk.org/2012/07/25/cannabis-cannabinoids-and-cancer-the-evidence-so-far/
64. The Combination of Cannabidiol and Δ9-Tetrahydrocannabinol Enhances the Anticancer Effects of Radiation in an Orthotopic Murine Glioma Model. Mol.Cancer.Ther. 2014. http://mct.aacrjournals.org/content/13/12/2955
65. Medical Marijuana: Clearing Away the Smoke. Open Neurol J. 2012. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3358713/
66. Cannabis in painful HIV-associated sensory neuropathy: A randomized placebo-controlled trial. Neurology, 2007. http://www.cmcr.ucsd.edu/images/pdfs/Abrams_2007.pdf
67. A Randomized, Placebo Controlled Cross-Over Trial of Cannabis Cigarettes in Neuropathic Pain. J.Pain, 2007. http://www.cmcr.ucsd.edu/images/pdfs/Wilsey_2008.pdf
68. Smoked Medicinal Cannabis for Neuropathic Pain in HIV: A randomized, cross-over clinical trial. Neuropsychopharmacology, 2008. http://www.cmcr.ucsd.edu/images/pdfs/Ellis_2008.pdf
69. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. CMAJ, 2010. http://www.cmaj.ca/content/182/14/E694.full.pdf+html
70. Comparison of the Analgesic Effects of Dronabinol and Smoked Marijuana in Daily Marijuana Smokers. Neuropsychopharmacology, 2013. http://www.nature.com/npp/journal/v38/n10/full/npp201397a.html
71. Cannabis use amongst patients with inflammatory bowel disease. Eur J Gastroenterol Hepatol. 2011. http://www.ncbi.nlm.nih.gov/pubmed/21795981
72. A Pilot Study of GWP42003 in the Symptomatic Treatment of Ulcerative Colitis. GW Pharma, 2014. https://clinicaltrials.gov/ct2/show/NCT01562314
73. Impact of Cannabis Treatment on the Quality of Life, Weight and Clinical Disease Activity in Inflammatory Bowel Disease Patients: A Pilot Prospective Study. Digestion, 2012. http://www.karger.com/Article/Abstract/332079
74. Cannabis Induces a Clinical Response in Patients With Crohn's Disease: A Prospective Placebo-Controlled Study. Clin Gastroenterol Hepatol. 2013. http://www.cghjournal.org/article/S1542-3565(13)00604-6/pdf
75. Cannabis Finds Its Way into Treatment of Crohn's Disease. Pharmacology, 2014. http://www.karger.com/Article/Pdf/356512
76. Cannabis: The Scientific and Medical Evidence. House of Lords Select Committee on Science and Technology, Ninth Report http://www.parliament.the-stationery-office.co.uk/pa/ld199798/ldselect/ldsctech/151/15102.htm
77. Sativex (nabiximols) - factsheet. MS Trust, 2014. http://www.mstrust.org.uk/information/publications/factsheets/sativex.jsp
78. Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients. Mult Scler, 2004. http://msj.sagepub.com/content/10/4/434.short
79. Efficacy, safety and tolerability of an orally administered cannabis extract in the treatment of spasticity in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled, crossover study. Mult Scler. 2004. http://www.ncbi.nlm.nih.gov/pubmed/15327040
80. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology, 2005. http://www.neurology.org/content/65/6/812.short
81. Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up. J Neurol Neurosurg Psychiatry, 2005. http://jnnp.bmj.com/content/76/12/1664.short
82. Strategies for Protecting Oligodendrocytes and Enhancing Remyelination in Multiple Sclerosis. Discov Med, 2013. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3970909/
83. Role of cannabinoids in multiple sclerosis. CNS Drugs, 2011. http://www.ncbi.nlm.nih.gov/pubmed/21323391/
84. The International Association for Cannabinoid Medicines (IACM) maintains a database of clinical studies and case reports from 1970 to 2013. http://www.cannabis-med.org/studies/study.php
85. 105 Peer-Reviewed Studies on Medical Marijuana. Medical Studies Involving Cannabis and Cannabis Extracts (1990 - 2012) http://medicalmarijuana.procon.org/view.resource.php?resourceID=000884

86. The Medicalization of Cannabis. Wellcome Trust Witness Seminar, 2010 http://www.histmodbiomed.org/sites/default/files/44870.pdf
87. Emerging Clinical Applications For Cannabis & Cannabinoids. A Review of the Recent Scientific Literature. NORML, 2014. http://norml.org/pdf_files/NORML_Clinical_Applications_for_Cannabis_and_Cannabinoids.pdf
88. What does marijuana do? It rebalances everything. Vipperman, 2014 https://michaelvipperman.wordpress.com/2014/04/20/what-does-marijuana-do-it-rebalances-everything/