Cannabis: The Evidence for Medical Use

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Executive Summary

Cannabis has been used as a medical product for many centuries. In recent decades it has been discovered that the human brain and other organs contain naturally occurring cannabinoid receptors as well chemicals that bind to those receptors. This is called the endocannabinoid system. It is known that the endocannabinoid system has a range of important natural functions, including modulation of pain, control of movement, protection of nerve cells and a role in natural brain adaptability (plasticity), as well as a role in various metabolic, immune and inflammatory processes and a possible role in the control of tumour growth. Plant cannabis probably works in man by "mimicking" the effects of the human endocannabinoid system. The main plant cannabinoids (phytocannabinoids) studied, and thought to be the most important in terms of efficacy, are tetrahydrocannabinol (THC) and cannabidiol (CBD), although many others exist and a role for them may become clearer in due course.

In this paper we have analysed and graded the evidence for efficacy of cannabis and various licenced cannabis products for a number of different indications. We have found **good** evidence for one or more of the cannabis products or "natural" cannabis in; the management of chronic pain, including neuropathic pain; spasticity; nausea and vomiting, particularly in the context of chemotherapy; and in the management of anxiety. We have found **moderate** evidence in; sleep disorders; appetite stimulation in the context of chemotherapy; fibromyalgia; post-traumatic stress disorder; and for

some symptoms of Parkinson's disease. We have found **some** limited evidence of efficacy, but further studies are required, in; the management of agitation in dementia; epilepsy, particularly drug resistant childhood epilepsies; bladder dysfunction; glaucoma; and in Tourette's syndrome. We have found that there is a theoretical basis, but so far **no** convincing evidence of efficacy; for the management of dystonia; Huntington's disease; headache; brain protection in the context of traumatic brain injury; depression; obsessive compulsive disorder; gastrointestinal disorders; anti-psychotic agent (CBD); and a role in cancer/tumour control.

We have summarised the short term effects of cannabis, which are generally mild and well tolerated. We have looked at the evidence for a causal link between cannabis use and schizophrenia and find that there is probably a link in those who start using cannabis at an early age and also if the individual has a genetic predisposition to psychosis. Thus we recommend caution with regard to prescription of cannabis for such individuals. We found there is a small dependency rate with cannabis at around 9%, which needs to be taken seriously but compares to a rate of around 32% for dependency in tobacco use and 15% dependency with regard to alcohol. There may be a, as yet unproven, risk of respiratory cancer for smoked cannabis but nevertheless this route of administration is not recommended. The evidence for cognitive impairment in long term users is not clear but it is wise to be cautious in prescribing cannabis to younger people, given the possible susceptibility of the developing brain.

Overall, we conclude there is considerable literature demonstrating the efficacy of cannabis and/or available cannabis products in a number of important indications.

Clearly there needs to be much further work with regard to the formulation of cannabis and the best THC:CBD ratio for different conditions and better and further studies are needed on both short and, more particularly, longer term effects. We consider that these studies will be facilitated by legalisation of cannabis for medical indications in strictly controlled circumstances with a quality-controlled product and a secure supply chain.

Cannabis: The Evidence for Medical Usage

1. Introduction

The authors have been asked by the All Party Parliamentary Group for Drug Policy Reform to carry out a review of the efficacy of cannabis for medical use. Specifically, we have been asked to –

- Examine those diseases and conditions where cannabis is identified as having an established or credibly potential treatment application.
- To assess and grade the quality of the research related to each of those diseases and conditions.
- To document the side effects of cannabis.
- To comment on the impact of potential legalisation of cannabis in the United Kingdom on potential medical use and supporting research.

The work was carried out in April and May 2016. The authors have received a small grant from the APPG for Drug Policy Reform for this work. The authors have received no other remuneration from any other source and have no commercial interests in cannabis or cannabis products. The work has been carried out in a personal capacity and the evidence collated in this paper and the views expressed are those of the authors alone and do not represent the views of Newcastle University or Northumberland, Tyne & Wear NHS Foundation Trust.

2. Search Criteria and Grading of Evidence

The authors have searched a number of established databases, including Medline, AMED, BNI, Cinahl, Embase and PsycINFO. The search terms were cannabis (also refined to medicinal cannabis), marijuana, endocannabinoids, phytocannabinoids tetrahydrocannabinol (THC), cannabidiol (CBD) and relevant specific drug names, including Nabiximols (Sativex), Nabilone (Cesanet), Dronabinol (Marinol) and Cannador. This search produced over 20,000 references although clearly there was significant overlap between the search terms. The relevant papers that describe efficacy / safety under the different headings were then analysed and graded.

The medicinal cannabis literature is far from satisfactory in that it contains many small scale studies as well as case reports and anecdotal evidence but very few good quality placebo-controlled double-blind trials. (this means that neither the investigator nor the participant knows whether they are taking the actual product or a placebo or other comparator). The authors recognise the difficulties of cannabis research, particularly given the illegality of cannabis in many countries. We also recognise the value, in the early phase of drug studies, of small scale trials that may point towards potential efficacy and pave the way for larger scale studies. However, in terms of the *current* strength of evidence we felt that it would be reasonable to adopt the grading system used by the American Academy of Neurology and used in the systematic review of medical marijuana for neurological conditions by the Academy (Koppel *et al* 2014). The American Academy's grading scheme (paraphrased) is as follows:

Class I study: a randomised, controlled clinical trial with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics of the participants should be presented and should be substantially equivalent among treatment groups (or there is appropriate statistical adjustment for differences). The following are also required:

a) Allocation to the groups in a blind fashion (so that neither the patient nor the investigator are aware of the allocation)
b) Primary outcome clearly defined
c) Exclusion / inclusion criteria clearly defined
d) Adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) with dropouts sufficiently low to have minimal potential for bias.
e) For non-inferiority or equivalence trials claiming to prove efficacy for one or both drugs, other criteria are also required (see Koppel *et al* 2014)

Class II study: a randomised, controlled clinical trial in a representative population with masked or objective outcome assessment that lacks one criterion a-e in Class I or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b-e in Class I. Relevant baseline characteristics are presented and substantially equivalent among treatment groups (or there is appropriate statistical adjustment for differences).

Class III study: All other controlled trials (including well-defined natural history controls or patients serving as their own controls) in a representative population,

where outcome is independently assessed, or independently derived by objective outcome measurements.

Class IV study: Studies not meeting Class I, II or III criteria, including consensus or expert opinion.

Overall, the authors felt it would be helpful to grade the evidence for each indication into “good”, “moderate” or “some”. We felt that it was reasonable to suggest that if there was evidence from at least two Class I studies for an indication backed up by a theoretical basis and other Class II/III/IV evidence then that would be deemed as being “**good**” evidence of efficacy. If there was one Class I study or at least two Class II studies, backed up by Class III/IV studies and a theoretical basis, then this would be “**moderate**” evidence of efficacy. If there were no Class I studies and only a single Class II study but there was evidence from Class III/IV studies and a theoretical basis, then this would be “**some**” evidence of efficacy. Lesser levels of evidence cannot lead to any recommendation. The authors wish to emphasise that “some” or “no” evidence of efficacy does not equate with poor efficacy but simply that there is currently insufficient data from studies to arrive at a definitive conclusion regarding the efficacy in that particular indication.

3. A Brief History of Medicinal Cannabis and its Regulation in the UK

It is not the purpose of this review to give a detailed history of cannabis as a medicine but nevertheless some background information may be of interest.

The medical use of cannabis dates back to around 4000 BCE in ancient China. It is also known to have been used in ancient Egypt. In addition, there is written documentation of use in India in at least the second millennium BCE.

It is also clear that ancient Greek and Roman cultures used cannabis. The first detailed account of the medical use of cannabis was in the first century CE when Dioscorides published his Materia Medica (Russo 2004a). Cannabis was recommended for the treatment of otalgia as well as for the use of joint pain, gout and burns. At this time the medicinal gastrointestinal effects of cannabis were noted.

Around the 10th century the use of cannabis was largely promulgated through the Arabic culture of the era. It was around this time that it was used as an analgesic agent, including migraine. However, cannabis went through periods when it was 'out of fashion'. Pope Innocent VIII in 1484 deemed it associated with witchcraft and cannabis consequently was less used. Another period of prohibition was attempted after the Napoleonic invasion of Egypt. However, by the late 19th century a number of cannabis indications were being explored and it was used throughout Europe for migraine, neuropathic and musculoskeletal pain and as an aid to childbirth.

Obviously the psychoactive properties were also known and it is felt that it contributed to the writings of a variety of authors, including Baudelaire and Dumas.

Around this time the significant physicians of the age supported medicinal use and indeed Sir John Russell Reynolds recommended it for various conditions ranging from insomnia to dysmenorrhea and indeed prescribed it to Queen Victoria.

By the end of the 19th century it was in widespread use and available in a number of formulations. However, in the 20th century it faced prohibitive legislation across the globe.

In the UK it actually remained clinically available until 1971 when it was reclassified and banned under the Misuse of Drugs Act. This Act made possession and supply of controlled drugs unlawful. Cannabis was included.

There are three Classes of controlled drugs under the Act and the Class determines the range of penalties for possession and supply. Class A drugs are deemed the most harmful with the highest penalties. That category includes morphine, diamorphine (heroin), cocaine and LSD. Class B drugs represent an intermediate category including amphetamines and barbiturates, as well as cannabis. Class C drugs are deemed to be the least harmful and thus carry a lesser penalty and include anabolic steroids, benzodiazepines and growth hormones.

The Misuse of Drugs Regulations 2001 define the categories of people authorised to supply and possess drugs controlled under this Act. Schedule 1, which includes drugs such as cannabis, are not conventionally used for medical purposes and *are deemed to have no medicinal value*. Possession and supply is prohibited without specific Home Office approval. Schedule 2 includes morphine and diamorphine and those drugs are subject to special requirements relating to their legal prescription, including safe custody and the need to maintain registers. Nabiximols (Sativex) is marketed under Schedule 4, which means that its prescription is not subject to special prescription or safe custody requirements. However, at the moment natural

cannabis is still Schedule 1 and remained a Class B drug until 2004 when the Advisory Council on the Misuse Drugs recommended it should be reclassified to Class C. In 2009 it was reclassified back to Class B. CBD in isolation is not proscribed. THC in certain formulations (nabilone and nabiximols) is also legally prescribable.

In 2006 the UK parliamentary Science and Technology Select Committee produced a report that said the present classification was arbitrary and unscientific and suggested improvements. There has not yet been a change in the law as a result of their recommendations

As a Schedule 1 drug it is very difficult, although not impossible, to undertake studies of cannabis and clearly, at least in the UK, this has hampered the progression of medical cannabis research.

Cannabis has also been restricted in many countries across the globe, although in recent years the medical prescription / use of cannabis has been made legal in a number of countries, including 11 European countries and currently 24 states in the USA. It is also legal, or partially legal, for medical use in Australia, Canada, Chile, Colombia, Ecuador, Israel, Paraguay, Peru, Puerto Rico and Uruguay.

4. The Scientific Rationale for Medicinal Cannabis

Whilst the medical benefits of cannabis have been known for many centuries, it is only in very recent years that a scientific rationale for the effects of cannabis on human bodily systems has been developed. In 1990 Matsuda and colleagues first described a cannabinoid receptor in several species, including man (Matsuda *et al*, 1990). Eventually this receptor was called the CB1 receptor and a few years later another receptor, called CB2, was also identified (Munro *et al* 1993). CB1 receptors are present throughout the central nervous system and in some peripheral tissues, including the immune system, reproductive and gastrointestinal systems and are also found in the heart, lung and bladder. The CB2 receptors are mainly expressed by immune cells. The discovery of these cannabinoid receptors led to significant further studies on what is now termed the endocannabinoid system (ECS). The endocannabinoid system is characterised by the two primary receptors, CB1 and CB2, and the chemicals (called lipid ligands) that bind to those receptors and the mechanism of their synthesis and metabolism. The key ligands are Anandamide and 2-Arachidonoylglycerol (2-AG), although others are known. It is thought that the phyto-cannabinoids found in the natural cannabis plant (see Section 5) mimic the effects of the human cannabinoid receptor ligands, particularly Anandamide and 2-Arachidonoylglycerol. (Skaper and Di Marzo 2012). The endocannabinoid system has now been identified in many bodily regions, not only the brain but also in the digestive tract and bladder (Izzo, *et al* 2015) and is now known to be involved in a number of metabolic (Gatta-Cherifi and Cota 2015) and endocrine (Hillard 2015) and immune (Cabral *et al* 2015) disorders. The ECS also seems to have a role in the regulation of tumour growth (Velasco *et al* 2015). In neurological terms, the

endocannabinoid system is involved in brain protection after damage, modulation of pain, regulation of motor activity and has a role in nerve formation (neuro-genesis), brain adaptability (plasticity) and the control of some aspects of memory processing (Pertwee 2015).

In summary, the medical effects of herbal cannabis in man are very likely to be modulated by the phyto-cannabinoids found in the cannabis plant which mimic the actions of the naturally occurring cannabinoid receptor ligands. There is, of course, much more to be learnt about the effects of the endocannabinoid system. It is likely that as our knowledge of the human endocannabinoid system develops then we will be in a better positon to develop strategies for improving the efficacy of cannabinoids. It may, for example, be possible to target specific cannabinoid receptors located outside the brain or receptors only expressed by a particular tissue. This may allow for better targeting of effects and limitation of side effects.

5. Cannabis – The Plant and the Phyto-Cannabinoids

Cannabis is a very hardy plant that grows throughout the world from the equator to at least 60^{o} north. It is thought to be present in three separate species – cannabis sativa, cannabis indica and cannabis ruderalis (Schultes *et al* 1974), although this is somewhat controversial in botanical circles. The plant probably originated in Central/Eastern Asia and, along with hops, is a member of the cannabaceae family. The plant produces natural cannabinoids called phyto-cannabinoids. The amount of phyto-cannabinoid varies among different strains. The phyto-cannabinoid concentration is not uniform throughout the plant. The phyto-cannabinoids are present in the leaves and stems but not the seeds and roots. However, phyto-cannabinoids are most abundant in the unfertilised female flower head. The plant stem and leaf is covered in small outgrowths containing resin (the glandular trichome) and these have the highest concentration of phyto-cannabinoids and indeed when harvested and compacted this constitutes 'hash'. The plant has a fibrous stem known as the hemp and indeed hemp has been cultivated for centuries as a source of building materials, paper and textiles. It is known from archaeological remains in China that hemp seed was being used between 3300 and 2300 BCE. Hemp seeds contain a high yield of protein and essential fatty acids.

In 1964 the main psychoactive component of cannabis, tetrahydrocannabinol (THC), was isolated and synthesised in Israel (Gaoni and Mechoulam 1964). This discovery was the followed by elucidation of many further phyto-cannabinoids in the plant. The most important, in terms of medical use, in addition to THC, is cannabidiol (CBD). There are now over 100 phyto-cannabinoids identified in the natural plant. Whilst it

seems clear that most of the psychoactive properties and some of the medicinal usage is secondary to THC, it is also clear that CBD has a number of potential medical usages. It is also possible, as are our knowledge of phyto-cannabinoids and human endocannabinoid system develops, that some of the other cannabinoids may also have a medical use. There is interaction between the phyto-cannabinoids and indeed it is known that CBD can reduce the psychoactive effects of THC. As an example, nabiximols (Sativex) has a 1:1 ratio of CBD:THC and does not manifest psychoactive properties, despite a high concentration of THC.

The ratio of THC:CBD appears to be quite important in terms of medicinal use and has a bearing on the side effect profile. It is also possible that the overall efficacy of the natural plant in medical terms depends not only on THC and CBD and the other phytocannabinoids but also on the “entourage effect” of the other plant chemicals that in themselves may not act on the CB receptors (Ben-Shabat *et al* 1998).

6. Cannabinoid Formulations Used in the Efficacy Studies

A major problem with cannabis studies is that a number of different formulations of cannabis are available. Basically, these formulations vary in terms of the relative proportion of THC and CBD. A few studies have used 'natural' smoked cannabis or a cannabis extract. However, most studies use the cannabis products that are commercially available. These are:

Nabiximols (Sativex) – GW Pharmaceuticals, UK

This is an oromucosal spray that contains an approximate 1:1 ratio of THC to CBD. It is approved in the United Kingdom and is a Schedule 4 Part I controlled drug that has been approved for use in patients with moderate to severe spasticity due to multiple sclerosis (MS) who have not yet responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity related systems during an initial trial of therapy. Nabiximols must be initiated and supervised by a physician with specialist expertise in treating that patient population. It is approved in a number of other European countries. It also has full regulatory approval for spasticity in New Zealand and is approved in Israel for MS spasticity and MS associated neuropathic pain. In Canada it is also approved for symptomatic relief from neuropathic pain and as an adjunctive analgesic treatment in patients with advanced cancer who still experience moderate to severe pain during the highest tolerated dose of strong opioid therapy.

GW Pharmaceuticals are also conducting studies in childhood resistant epilepsy (Dravets syndrome and Lennox-Gastaut syndrome). The product used in those studies is known as *Epidiolex* and consists purely of the cannabinoid CBD.

Nabilone (Cesamet) – Meda Pharmaceuticals, USA

Nabilone is a synthetic product that was approved (in 1985) by the US Food and Drug Administration for treatment of chemotherapy-induced nausea and vomiting that has not responded to conventional anti-emetics. It is also approved in Canada, UK and other countries for similar indications. It is a synthetic cannabinoid analogue of THC. It is formulated as a capsule.

Dronabinol (Marinol) – Solvay Pharmaceuticals, USA

Dronabinol is an isomer of THC and is synthetically manufactured. That means it has the same molecular formula but a different chemical structure. It is prescribable in the United States and is used to treat nausea and vomiting caused by chemotherapy but is also used to treat loss of appetite and weight loss in people who have acquired immunodeficiency syndrome (AIDS). It is formulated as a capsule. It is not legally prescribable in the UK.

Cannabis Extract (Cannador) – IKF, Germany

This is a whole plant extract with a standardised THC/CBD ratio of about 2:1. It is no longer widely available.

Bedrocan

This is medicinal grade cannabis and made under contract for the Dutch Ministry of Health and available for prescription in the Netherlands. It is also exported for medicinal use to various European countries and further afield, including Canada. It is recommended to be vaporised. The parent company, Bedrocan, has produced six strains of medicinal cannabis with varying THC/CBD levels. These are –

Bedrocan – standardised THC level of 22% with a CBD level below 1%. It is the most widely used cannabis offered by the Dutch Ministry.

Bedrobinol – this is standardised with a THC content of 13.5% with a CBD level below 1%.

Bediol – has a standardised THC content at 6.5% with a level of CBD at 8%. This is available in granulated form.

Bedica – has 14% THC with less than 1% CBD. It is made from a different variety of cannabis (cannabis indica) as opposed to the more usual cannabis sativa variety.

Bedrolite – this contains 9% CBD and 0.4% THC and is non-psychoactive.

Bedropuur – is a high THC cannabis indica variety with less than 1% CBD but is only available in Canada for research purposes.

The Bedrocan products are now widely known but have not been included in any major trials of efficacy.

Some studies have used other variable formulations of cannabis extract containing difference ratios of THC/CBD and indeed some containing just CBD.

7. Forms of Ingestion / Inhalation and Dosage

7.1 Ingestion /Inhalation

The other difficulty of studying cannabis is that, in addition to the different formulations, there are also different ways of using cannabis itself. As noted above, two of the licenced products, nabilone and dronabinol come in *capsular form*. Nabiximols is administered as an *oromucosal spray*. Natural cannabis is widely *smoked*. The dried flowers or leaves of the cannabis plant are smoked through a pipe, or rolled into a joint (as in a tobacco cigarette) or smoked using a water pipe (bong). However, for medical reasons smoking is not generally recommended as it is possible that carcinogens may be inhaled in a similar fashion to tobacco smoking (see Side Effect section and Melamede 2005).

Vaporising is a method that extracts the therapeutic ingredients of the cannabis plant at a much lower temperature than required for burning. The individual inhales the active ingredient as a vapour instead of smoke. Vaporising is a more efficient way of converting the plant matter into active ingredients and it is likely that more of the THC and other cannabinoids are available through vaporisation than through smoking.

Edible cannabis can be infused in butter or oil and cooked in food. The therapeutic effect is less certain and it usually takes longer for the effect to be recognised.

Cannabis can also be applied *topically* and includes availability in lotions, balms, sprays, oils and creams and also can be available as a *tincture* which is a concentrated form of medical cannabis in an alcohol solution.

Thus, when larger scale studies of cannabis become available with the wider legalisation of the plant, the studies will need to be controlled according to the method of ingestion/inhalation. The natural products will have different availabilities of the cannabinoids according to which method is used.

7.2 Dosage

The other variable in clinical studies is the dosage of cannabis. The doses used for the licenced products (nabilone, dronabinol and nabiximols) are normally quoted in the relevant efficacy papers.

However, the dosage of 'natural' cannabis will clearly vary according to the form of inhalation/ingestion as well as the strength and purity of the product. The studies using natural cannabis, particularly Class III / Class IV evidence, often do not quote the dosage taken by the subject. This clearly has a significant bearing on the efficacy of the product.

Smoking cannabis results in a more rapid onset of action and the effect is usually noticed within minutes. Smoking results in higher blood levels of cannabinoids and a shorter duration of effects compared to oral administration (Huestis 2007). Unfortunately, the amount of THC delivered from cannabis cigarettes is variable. There are factors that are difficult to control in a non-licensed setting, including source of the plant material and the actual composition of the cigarette - as well as the efficiency and method of smoking. Indeed, studies have demonstrated a large variation in bio-availability between 2 and 56% depending on depth of inhalation, puff duration and breath hold (Drotenhermen 2003).

Vaporising can also produce a wide variation of blood cannabis levels according to the amount and type of cannabis placed in the vaporiser, the vaporising temperature

and duration, and the volume of the balloon (in which the vapour is collected prior to inhalation).

Oral administration results in slower onset of action, lower peak blood levels of cannabinoids and a longer duration of effects compared to smoking or vaporisation. Unfortunately, the absorption is unreliable from an oral route. As an example, systemic availability of THC from a chocolate cannabis cookie has been estimated to be only between 4 and 12% (Agurell *et al* 1986). The time for peak THC concentration is usually 1-2 hours after ingestion but in some people it can take several hours for peak levels to be attained.

There is less information about topical (skin) application. Most cannabinoids are highly hydrophobic (dislike water) and that makes topical application across the aqueous layer of the skin difficult to achieve. However, topical application is a better method of administration for cannabidiol (CBD), as well as cannabinol (CBN), as it has a tenfold higher permeation than THC through the skin (Stinchcomb *et al* 2004).

Further information on pharmacokinetics and pharmacodynamics of cannabis and cannabinoids is found in a useful publication produced by Health Canada in 2013 (Health Canada 2013).

8. Efficacy of Cannabis

This section will review the efficacy of cannabis. We have reviewed several different conditions that have some published evidence and assessed the quality of that evidence for each condition. Each section starts with a brief overview of the rationale for cannabis use in that condition before a more detailed review of the evidence base.

We wish to emphasise that efficacy is likely to be specific, in evidential terms, to a particular cannabis formulation. If, for example, nabiximols is efficacious for spasticity this does not necessarily mean that other cannabis formulations will also be useful for spasticity. This will depend on many variables, particularly the THC:CBD ratio.

The authors draw attention to useful systematic reviews and meta-analyses of cannabinoids for medical use in recent publications (Whiting *et al* 2015; Koppel *et al* 2014; Hill 2015).

8.1 Pain

Chronic pain is extremely common and has been estimated that 8-46% of the population has chronic pain at some point, depending on the definition (Elliott *et al* 1999). Severe pain occurs in about 11% of adults and 8% of children. Severe chronic pain is known to have adverse effects on many aspects of life including employment, daily activities, relationships, mood, sleep and general health. Current treatment is often, but not always, effective but can be associated with serious side effects. This is particularly the case for the opioids, (see section 9.2) which carry very serious risks, including mortality.

Cannabis preparations have been used to treat pain for centuries. Indeed, in a recent survey undertaken for the APPG for Drug Policy Reform, it has been shown that pain is one of the leading reasons for medical use of cannabis in the UK. It is known that the endocannabinoid system is one of the key bodily systems that regulate pain sensation with actions at all stages of the pain processing pathway. Neural signalling through both CB1 and CB2 receptors has a key role in normal pain processing and considerable animal model and pre-clinical data on both patients and healthy volunteers confirm that modulation of the endocannabinoid system can reduce pain (Burston and Woodhams 2014; Woodhams *et al* 2015).

In terms of the clinical trials most have been carried out using the proprietary products nabilone, dronabinol and nabiximols. These have been used in studies both of chronic pain and neuropathic (nerve) pain and cannabis preparations seem to have a positive effect on both those pain modalities. The authors have decided to

discuss the clinical trials of cannabis and pain under different headings according to the specific available formulation – nabilone / dronabinol / nabiximols and 'natural' smoked cannabis. We have amalgamated the studies of chronic pain and neuropathic pain as there appears to be no significant difference in efficacy between these two pain modalities.

8.1.1 *Nabilone (Cesamet) and Pain*

One of the earliest studies of cannabis and pain was a simple description of the experience of 20 adult patients with chronic non-cancer pain published by Berlach and colleagues in 2006 (Berlach *et al* 2006). Fifteen of these patients reported subjective overall improvement with nabilone and nine reported reduced pain intensity. There were further beneficial effects on sleep and nausea. Intolerable side effects were experienced in three patients (palpitations, urinary retention and dry mouth). The authors concluded that nabilone may be a useful addition to pain management strategies and should be further evaluated in randomised controlled trials (Class IV).

In the same year Wissel and colleagues (2006) used 1mg per day of nabilone on spasticity-related pain in a placebo-controlled, double-blind, crossover trial involving just 13 patients – 11 of whom completed the study. The authors found significant decrease of pain with nabilone ($p<0.05$) with five patients reporting side effects, including drowsiness and transient weakness of the legs. This is a relatively underpowered study but nevertheless pointed towards the fact that nabilone could assist spasticity-related pain. Somewhat surprisingly, given the evidence of

effectiveness of cannabinoid products in spasticity (see Spasticity section), the authors found that spasticity itself did not change (Class II).

Pinsger and colleagues (2006) conducted a placebo-controlled, double-blind pilot study divided into a 14-week crossover period with two four-week medication phases plus washout phases followed by a 16-week medication switch period. The principal inclusion criterion was chronic therapy resistant pain. Pain intensity was assessed by a visual analogue scale and quality of life scales. Thirty patients were included and the authors found that nabilone treatment was superior to placebo with a decrease in the average spinal pain intensity as well as a decrease in average headache intensity, an increase in the number of days without headache as well as improvements in quality of life. Patients continued to take their standard treatment and the authors concluded that adding nabilone to standard pain treatment produced a further positive benefit (Class I).

Skrabek and colleagues (2008) showed improvement with nabilone on pain reduction and quality of life in 40 patients with fibromyalgia in a double-blind, placebo-controlled trial (see Fibromyalgia section).

Frank and colleagues (2008) conducted an interesting comparative study between nabilone and dihydrocodeine for chronic neuropathic pain. This Class II study involved 96 patients with chronic pain attending three hospitals in the United Kingdom. It was a straightforward randomised, double-blind, crossover trial of 14-weeks duration comparing dihydrocodeine and nabilone. Patients received a mean daily dose of 240mg of dihydrocodeine and 2mg of nabilone at the end of an

escalating treatment period of six weeks. There was a two-week washout period. The visual analogue scale results showed that nabilone was slightly inferior to dihydrocodeine – in other words dihydrocodeine provided somewhat better pain relief and had slightly fewer side effects, although there were no major adverse events for either drug.

Maida and colleagues (2008) carried out a Class III study using data from 112 patients and showed that pain scores in the nabilone treated patients were significantly lower than those in untreated patients and other parameters also improved, including less nausea, less anxiety and overall less distress. There was a borderline improvement in appetite in the nabilone group. Patients taking nabilone had a lower rate of using non-steroidal anti-inflammatory agents, tricyclic antidepressants, gabapentin, dexamethasone, metoclopramide and ondansetron, with a greater tendency to discontinue those drugs. Whilst this is not a well-designed study it does indicate that nabilone does have pain relieving properties but also other benefits, particularly less nausea. Indeed, it should be recalled that nabilone is licensed for the treatment of nausea and vomiting in the context of chemotherapy (see Nausea and Vomiting section).

In a slightly different context Bestard and Toth (2011) studied nabilone either as monotherapy or adjuvant therapy with the first line medication gabapentin in a patient population with painful peripheral neuropathy (a condition causing pain in the nerve endings in arms and legs). Patients were permitted to initiate either monotherapy (nabilone or gabapentin) or add one of these two medications to their existing pain treatment regime in a non-randomised open label study (Class III).

There appeared to be similar benefits between nabilone and gabapentin in terms of pain improvement, as well as sleep improvements, anxiety and depression scores and sleep adequacy. They concluded that nabilone appeared comparable to gabapentin for the management of such pain. The same authors, with others, also concluded that flexible dosing of nabilone (1-4mg per day) relieved symptoms in diabetic peripheral neuropathy as well as improving disturbed sleep, quality of life and overall status. Nabilone was well tolerated as an adjuvant treatment in such patients (Toth *et al* 2012) (Class II). Patients continued regular pain medications and were administered a single blinded adjuvant treatment with nabilone for four weeks. Those subjects achieving a >30% pain relief were then randomised and treated with either flexible dose nabilone or placebo in a further five-week double-blind treatment period. Greater than 30% pain relief is a standard measure of pain relief in pain trials and is thought to be a meaningful level of improvement for the patient.

In the further indication of headache, Pini and colleagues (2012) studied a total of 30 patients with medication overuse headache were enrolled in the study which was a randomised, double-blind, active-controlled, crossover comparing nabilone 0.5mg/ day and ibuprofen 400mg. Patients received treatment for eight weeks with a one-week washout period. Twenty-six patients completed the study. The results showed that nabilone was more effective than ibuprofen in reducing pain intensity and daily analgesic intake and nabilone also was the only drug able to reduce level of medication dependence and improve quality of life. Side effects were uncommon and mild and disappeared when nabilone was discontinued. This is a Class II study as the trial was somewhat underpowered to show a difference between the compounds (see also Headache section).

The most up to date study of nabilone was published in 2015 (Turcotte *et al* 2015). This was a randomised, double-blind, placebo-controlled study involving 15 relapsing/remitting patients with MS with MS-induced neuropathic pain. The study compared nabilone to gabapentin. Eligible patients with inadequate pain relief stabilised on gabapentin were then administered either nabilone or placebo titrated over four weeks followed by a five-week maintenance phase of 1mg oral nabilone or placebo twice daily. The authors concluded that nabilone as an adjunct to gabapentin was effective and well tolerated for multiple sclerosis induced neuropathic pain (Class II).

8.1.2 *Dronabinol (Marinol) and Pain*

There is less evidence of the efficacy of the other synthetic THC – dronabinol. In 2004 Svendsen and colleagues studied central neuropathic pain in multiple sclerosis in a randomised, double-blind, placebo-controlled crossover trial involving 24 patients (Svendsen *et al* 2004). Dronabinol was administered at 10mg daily or placebo for three weeks separated by a three-week washout period. Dronabinol showed an improvement in pain intensity compared to placebo as well as higher pain relief scores. On the SF-36 quality of life scale (an accepted quality of life measure) the bodily pain and mental health sub scores indicated benefits from dronabinol. The authors concluded that dronabinol had a modest but clinically relevant analgesic effect on central pain in patients with multiple sclerosis. There were some adverse events, including dizziness but these do not appear to be troublesome (Class II).

Dronabinol also seems to have a useful effect as an adjuvant treatment for those with chronic pain. Narang and colleagues (2008) studied 30 patients taking opioids for chronic pain. Phase 1 of the study was a randomised, single dose, double-blinded, placebo-controlled, crossover trial in which subjects were randomly administered either 10mg or 20mg of dronabinol or identical placebo. Phase II was an extended open-label titrated trial of dronabinol as add-on medication to those with stable doses of opioids. In phase 1, patients who received dronabinol experienced decreased pain intensity and increased satisfaction compared to placebo and there were no differences in benefit comparing the 10mg and 20mg dosage. In phase 2 titrated dronabinol contributed to significant relief of pain and increased satisfaction compared to baseline. Side effects were relatively mild and dose related (Class I).

8.1.3 *Nabiximols (Sativex) and Pain*

Nabiximols is licenced for pain relief in a number of countries, including Israel and Canada, for the symptomatic relief of neuropathic pain in multiple sclerosis and as an adjunctive analgesic treatment in patients with advanced cancer who experience moderate to severe pain during opioid therapy. Thus it is not surprising that there is reasonable evidence of efficacy, as the agent has passed regulatory hurdles.
One of the earlier studies was by Berman and colleagues in 2004 (Berman *et al* 2004). Brachial plexus root avulsion is considered a good human model of central neuropathic pain. (The brachial plexus is collection of nerves between the neck and shoulder and after trauma those nerves can damaged (avulsed). This is a very painful condition). In this study 48 patients with at least one avulsed nerve root were entered in a randomised, double-blind, placebo-controlled three period crossover

study comparing placebo with two formulations of cannabis – nabiximols and a further compound prepared by GW Pharmaceuticals (GW2000-02) which contained mainly THC. The primary outcome measure was a mean pain severity score during the last seven days of treatment and this outcome measure just failed to show the active compound to be significantly better than placebo. However, both the primary outcome measure and measures of sleep did show statistically significant improvements and the medications were well tolerated (Class I).

In the following year Rog and colleagues (2005), studied central pain in multiple sclerosis in a five-week randomised, double-blind, placebo-controlled, parallel group trial in 66 patients. They were treated with nabiximols as an adjunct to analgesic treatment, the dose of which could be self-titrated. The active product was superior to placebo in reducing the intensity of pain (p=0.005) and sleep disturbance (p=0.003) and was well tolerated (Class I).

In the only study we could identify in the context of pain caused by rheumatoid arthritis, Blake and colleagues published the results of a 2006 study (Blake *et al* 2006). The authors compared nabiximols to placebo in a randomised, double-blind, parallel group study in 58 patients over five weeks of treatment. In comparison to placebo nabiximols produced statistically significant improvements in pain on movement, pain at rest, quality of sleep and quality of life measures. Most of the adverse effects were mild to moderate and there were no adverse effect-related withdrawals or serious adverse events in the active group (Class I).

In a further context nabiximols was shown to improve pain characterised by allodynia in a randomised, double-blind, placebo-controlled trial (Nurmikko *et al* 2007). (Allodynia is an increased sensitivity to pain by a stimulus that normally would not cause pain). This study was in a good number of patients (125) and consisted of a five week randomised, double-blind, placebo-controlled, parallel design study with patients remaining on their existing stable analgesia. A reduction in pain intensity scores was greater in those receiving nabiximols compared to placebo. There were also improvements in the neuropathic pain scale, sleep, allodynia scores and the disability index. Sedative and gastrointestinal side effects were reported more commonly on those on active medication. In total of 18% of those on nabiximols and 3% of those on placebo withdrew from the study (Class I). An open label extension study showed that initial pain relief was maintained without dose escalation or toxicity for a further year.

In yet another context Johnson and colleagues (2010) demonstrated the efficacy of pain relief in patients with advanced cancer pain that was not fully relieved by strong opioids. This study involved a reasonable number of patients (177). They were entered into a two week multicentre, double-blind, randomised, placebo-controlled, parallel group trial and were randomised either to nabiximols (n=60), a THC extract (n=58) or placebo (n=59). A change from baseline in a mean pain numerical rating scale was statistically significant in favour of nabiximols compared to placebo whereas the THC group showed no significant change. Indeed, twice as many people taking nabiximols showed a reduction of more than 30% from baseline scores when compared to placebo. On the negative side there was a worsening in nausea

and vomiting with nabiximols compared to placebo but otherwise drug related adverse events were mild or moderate (Class I).

Similar positive results were found by Langford and colleagues in 2013 (Langford *et al* 2013*).* In this study nabiximols was compared to placebo in a double-blind, randomised, placebo-controlled, parallel group study in a total of 339 patients. These were individuals who failed to gain adequate analgesia from existing medications and they were treated with nabiximols spray or placebo as an add-on treatment in a double-blind manner for 14 weeks. The parallel group phase was then followed by an 18 week randomised withdrawal study to investigate time to treatment failure and show maintenance of efficacy. The primary endpoint of responder analysis at the 30% level at week 14 was not met - 50% of patients on nabiximols spray were classed as responders at 30% level compared to 45% of those on placebo. However, an interim analysis at week 10 did show a statistically significant treatment difference in favour of nabiximols spray. The primary endpoint of time to treatment failure in the randomised withdrawal phase was also in favour of the active spray. A change from baseline in pain numerical rating scale and sleep quality was also in favour of nabiximols compared to placebo (Class I).

Nabiximols has been shown to be a useful add-on analgesic for those with opioid refractory cancer pain and this was confirmed in a study by Portenoy and colleagues in 2012 (Portenoy *et al* 2012). This was a large scale study involving a total of 360 patients who were randomised in a double-blind, placebo-controlled, graded-dose study. The placebo group was compared to nabiximols at a low dose (1-4 sprays per day), medium dose (6-10 sprays per day) and high dose (11-16 sprays per day).

Once again the 30% responder pain primary analysis was not significant for nabiximols due to a high rate of placebo response. The secondary responder analysis of average daily pain from baseline to end of study did show that the proportion of patients reporting analgesia was greater for nabiximols than placebo overall and specifically in the low dose and medium dose groups. Adverse events appeared to be dose related and only the high dose group compared unfavourably with placebo. This was a useful study of efficacy but more particularly of safety and provided useful dose information for future studies (Class I).

8.1.4 *Smoked Cannabis and Pain*

In addition to the studies of the synthetic cannabinoids and of nabiximols there have been a few studies in the context of pain with 'natural' smoked cannabis. In 2007 Abrams and colleagues reported a study that involved 50 patients who completed the whole trial and used smoked cannabis with random assignment to either smoked cannabis (containing 3.56% THC) or identical placebo cigarettes with the cannabinoids extracted (Abrams *et al* 2007). Cigarettes were smoked three times daily for five days. Greater than 30% reduction of pain (the accepted measure of efficacy in pain trials) was reported in 52% in the cannabis and 24% in the placebo group. No serious adverse events were reported (Class II).

Wilsey and colleagues (2008) conducted a double-blind, placebo- controlled, crossover study evaluating analgesic efficacy of smoking cannabis for neuropathic pain. Thirty-eight patients with both central and peripheral neuropathic pain underwent a standardised procedure for smoking either a high dose (7%) or low

dose (3.5%) or placebo cannabis cigarettes. Pain intensity was a primary outcome measure and secondary outcome measures included evoked pain using a heat-pain threshold, sensitivity to light touch, psychoactive side effects and neuropsychological performance. The authors confirmed analgesic response to smoking cannabis with minimal psychoactive effects and good toleration but with some acute cognitive effects, particularly with regard to memory at high doses (Class II).

Ellis and colleagues (2009) studied the effect of smoked cannabis for neuropathic pain in HIV in a randomised, crossover clinical trial in patients with HIV-associated distal sensory predominant polyneuropathy (DSPN). (This is a painful nerve condition focussed in the arms and legs). The subjects had neuropathic pain refractory to at least two analgesic classes and they continued on their pre-study analgesic regime throughout the trial. The active cannabis ranged in potency from 1-8% THC and was smoked four times daily for five consecutive days during each of the two treatment weeks separated by a two-week washout period. The primary outcome was a change in pain intensity. Pain relief was greater with cannabis than placebo and the proportion achieving the 30% pain relief with cannabis was 46% compared to 18% in the placebo group. Mood and daily functioning were similar in both groups. Side effects were mild and self-limited (Class III).

A recent study with regard to smoked cannabis and pain was produced in 2010 by Ware and colleagues (2010b). This was a study in adults with post-traumatic or post-surgical neuropathic pain randomly assigned to receive cannabis at four potencies (0%, 2.5%, 6% and 9.4%) of THC over four 14 day periods in a crossover trial. Participants inhaled a single 25mg dose through a pipe three times daily for five days

followed by a nine-day washout period. Twenty-three patients were recruited and 21 completed the trial. The average daily pain intensity was lower at the 9.4% THC level compared to placebo. Preparations at the intermediate potency yielded intermediate but non-significant relief compared to placebo. Those at the higher THC dose also reported improved ability to fall asleep and improved quality of sleep. There were some drug related adverse events in the high THC group, including headaches, dry eyes, burning sensation in areas of neuropathic pain, dizziness, numbness and cough (Class III).

8.1.5 *Conclusion*

This is a difficult literature to summarise as a number of different formulations have been used and a number of different types of pain have been studied. The authors are also aware of the considerable literature in terms of anecdotal reports, case studies, questionnaires and uncontrolled trials that have also showed efficacy in various types of pain with various formulations.

However, nabilone, dronabinol, nabiximols and smoked marijuana have all been shown to be efficacious to varying extents in a variety of pain settings in good quality studies. We conclude that there is **good** evidence for efficacy of cannabis for pain relief in various formulations and in a number of settings.

8.2 Nausea and Vomiting in the Context of Chemotherapy

Patient experiences that smoked cannabis relieves chemotherapy-induced nausea and vomiting (CINV) are widely recognized, and increasing evidence suggests a role for the endocannabinoid system in the regulation of nausea and vomiting (Parker *et al* 2010). The mechanism of action seems to be different from other medications and so could be used in combination with other anti-emetics to enhance their effect or in cases that have not responded to other anti-emetics (Machado Rocha *et al* 2008).

According to Walsh and colleagues (2003), cannabinoids may be considered for controlling nausea and vomiting as a result of chemotherapy and may be effective in people with cancer who respond poorly to commonly used agents. They have been recommended in international anti-emetic guidelines for the prevention of chemotherapy-induced nausea and vomiting (CINV) (Gralla *et al* 1999).

A recent Cochrane Systematic Review (Smith *et al* 2015) examined 23 randomised controlled trials (RCTs) which compared a cannabis medication with either a placebo or with another anti-emetic in adults receiving chemotherapy. The literature showed that cannabinoids were more effective than placebo and were similar to conventional anti-emetics (metoclopramide and prochlorperazine) for treating chemotherapy-induced nausea and vomiting. However, participants were more likely to report adverse events with cannabinoids, such as dizziness, dysphoria and sedation. Smith and colleagues concluded that cannabinoids may be a useful therapeutic option for people with chemotherapy-induced nausea and vomiting who have not responded to other anti-emetics (Smith *et al* 2015).

Machado Rocha and colleagues (2008) conducted a literature review on this area and found that cannabinoids were significantly more effective than placebo in the control of CINV, and the evidence from randomized clinical trials suggested that cannabinoids were slightly better than conventional anti-emetics. These findings have been corroborated by a recent meta-analysis carried out by Whiting and colleagues (2015) that assessed 28 randomised clinical trials into CINV and cannabinoid treatment. Despite the adverse events reported in relation to cannabinoids, patients appeared to prefer them to conventional anti-emetics (Machado Rocha *et al* 2008), perhaps because of the sedation and euphoria effects, which may be valued by some patients whilst undergoing chemotherapy.

Meiri and colleagues (2007) conducted a randomised controlled trial, which was double-blind and placebo-controlled, looking at the efficacy of dronabinol alone and in combination with ondansetron (an accepted anti-nausea medication) versus ondansetron alone. They found that ondansetron and dronabinol were similarly effective for the treatment of CINV and combination therapy was not more effective than either agent alone. A limitation of this study is that it is somewhat underpowered with 66 participants (Class 1).

Duran and colleagues (2010) conducted a randomized, double-blind, placebo-controlled clinical trial which investigated the efficacy of medical cannabis (nabiximols in a spray form) in the treatment of CINV. Compared to placebo, nabiximols plus standard antiemetic therapy was well tolerated and significantly improved CINV. Despite its robust methodology, this study had small participant

numbers and therefore the results would need to be substantiated by studies that are higher powered (Class 1).

Another randomized, double-blind, parallel group, multicenter study tested dronabinol and prochlorperazine alone and in combination (Lane *et al* 1991). They found that the combination of drugs was significantly more effective than either single agent in controlling CINV. Only 29% of patients in the drug combination group experienced nausea after chemotherapy versus 47% in the dronabinol plus placebo group and 60% in the prochlorperazine plus placebo group. In addition, the median duration per episode and severity of nausea were significantly less with combination therapy (Class II).

Conclusion

In summary, cannabinoids for the management of nausea and vomiting with chemotherapy have been shown to produce some adverse effects but they are just as effective as established anti-emetics or actually slightly more effective (Whiting *et al* 2015). Medicinal cannabis could be a useful adjunctive treatment to consider for people on moderately or highly emetic chemotherapy who are not responding to other anti-emetic treatments (Smith *et al* 2015). We consider that there is **good** evidence for this indication.

8.3 Appetite Stimulation

The ability of cannabis to increase appetite and satiety has been documented for many centuries. It is also known from questionnaire based studies of recreational cannabis users that many people actively use cannabis to improve appetite. Indeed, controlled laboratory studies with healthy subjects show that inhalation or oral ingestion of THC correlates with increase in food consumption, caloric intake and body weight (Foltin *et al* 1988). There is now a reasonable theoretical basis following further elucidation of the endocannabinoid system. It is known there is a high concentration of CB1 receptors in brain areas associated with control of food intake and satiety. There is probably a role of the endocannabinoid system not only for modulating appetite, food palatability and intake but also a role in energy metabolism and modulation of both lipid and glucose metabolism (Farrimond *et al* 2011).

Studies have been carried out with regard to appetite stimulation and weight gain in HIV patients. There have also been studies to counteract anorexia in cancer patients and indeed there are some, albeit more theoretical, studies of use in anorexia nervosa.

Much of the work has been carried out with dronabinol, as appetite stimulation in various contexts is a licensed indication in some countries. In one study Haney and colleagues (2005) showed that experienced HIV+ cannabis smokers benefitted with regard to appetite from both dronabinol and also from smoked cannabis cigarettes three times per week for a total of eight sessions (Class IV).

In a subsequent (Class II) study by the same authors, higher doses of dronabinol (5 and 10 mg) were alternated with smoked marijuana (2% and 3.9% THC) four times per day for four days with a washout period between phases. Both groups showed substantial increases in food intake and body weight as well as improvements in mood but only the high dose marijuana produced improved sleep (Haney *et al* 2007).

On the other hand, Timpone and colleagues (1997) found that dronabinol only improved weight over 12 weeks of treatment in those with HIV associated wasting syndrome in combination with megestrol acetate (an appetite stimulant) but did not improve weight by itself (Class III).

The product monograph for dronabinol in Canada summarised a six week randomised, double-blind, placebo-controlled trial in 139 patients with AIDS related anorexia who received 2.5mg of dronabinol twice a day compared to placebo. Over the treatment period dronabinol significantly increased appetite with a trend towards improved body weight and mood as well as a decrease in nausea (Beal *et al* 1995) (Class I study). The main study was followed by an open-label 12-month follow-up that showed that dronabinol was safe and continued to be effective for long term use of anorexia in such patients. The dose of dronabinol was 2.5mg twice a day, although higher doses (20-40mg per day) have been used (Beal *et al* 1997).

In terms of cancer and appetite stimulation there have been surprisingly few studies. In two early studies (Class III), oral THC in the form of dronabinol did improve appetite and food intake in some patients undergoing cancer chemotherapy (Sallan *et al* 1980*).* In an open label study advanced cancer patients reported an increase in

appetite and food intake but limited weight gain (Nelson *et al* 1994). In a large study by Strasser and colleagues (2006) there were 289 patients screened and 243 were randomly assigned to three groups to receive either cannabis extract, THC or placebo twice daily for six weeks. Intention to treat analysis (analysis of all those entered into the study) showed no significant difference in the three arms for appetite, quality of life or cannabinoid related toxicity. However, increased appetite was reported by 73%, 58% and 69% of patients receiving cannabis extract, THC or placebo respectively. Indeed, the Independent Data Review Board recommended termination of recruitment because of insufficient differences between the study arms (Class II).

Furthermore, when dronabinol was compared with megestrol it was less efficacious in appetite improvement and weight gain for cancer patients (Jatoi *et al* 2002). However, despite relatively modest improvements in cancer patients as opposed to HIV patients, cannabinoids may help in terms of quality of life. A phase II randomised, double-blind, placebo-controlled 22-day pilot study (Class II) in adult patients with advanced cancer showed that the majority (73%) of dronabinol treated patients self-reported an increased overall appreciation of food compared to those receiving placebo (30%). A total of 64% of the dronabinol treated patients reported increased appetite whereas the majority of people in the placebo group reported decreased appetite (50%) or no change (20%). The patients were started at a low dose followed by a gradual dose escalation up to a maximum of 7.5mg of dronabinol daily (Brisbois *et al* 2011).

Despite the theoretical reason for manipulation of the endocannabinoid system in anorexia nervosa there have actually been very few studies, except in animal models or small uncontrolled trials in humans (Gross *et al* 1983).

Conclusion

In summary, we consider there is **moderate** evidence for improvement in appetite and for weight gain in AIDS patients. There is much less satisfactory evidence for similar improvements in cancer patients but nevertheless there is a little patchy evidence of efficacy but more and larger studies are required. There is no convincing evidence of efficacy for appetite stimulation in anorexia nervosa but adequate studies have not been done.

8.4 Spasticity

Spasticity is the second most researched indication for various cannabis formulations, after chronic pain. The cannabis-med.org website, for example, lists 53 spasticity studies using different formulations. Most of the work has been in the context of multiple sclerosis, although there are a few studies on the management of spasticity in other conditions, particularly spinal cord injury. The authors wish to emphasise that there is no particular difference in management of spasticity whatever the underlying neurological aetiology and if cannabis is deemed to be effective in spasticity in multiple sclerosis then there is no reason why it should not be effective in other neurological disorders that give rise to spasticity, such as spinal cord injury, traumatic brain injury and stroke.

In these cannabis studies we consider it worthwhile to differentiate between the different cannabis formulations. Most of the work has been carried out using nabiximols but other formulations have also been studied. Once again, the authors wish to emphasise that if, for example, there is good evidence of efficacy using nabiximols then it does not necessarily mean that any cannabis formulation would have the same effect on spasticity. It is likely that the efficacy of cannabis in this, and other indications, will depend on the relative ratio of the cannabinoids, particularly THC and CBD. Thus we have summarised the evidence for spasticity under the different cannabis formulations.

Spasticity is remarkably common, and a very disabling, symptom in the context of many neurological disorders, including multiple sclerosis, stroke, traumatic brain

injury, spinal cord injury, motor neurone disease and other neurological disorders. Indeed, spasticity can occur after any interruption to the upper motor neural pathways. It is characterised by muscle spasm, particularly in the legs but can also occur in the arms or other parts of the body, such as the trunk or neck. The muscle spasm impairs coordinated movement giving rise to, for example, difficulties with walking, use of the arms, etc. Often the condition is not only associated with incoordination but weakness of the involved muscles. The spasm can be unpredictable and is often painful. Thus cannabis has a potential dual action in patients with spasticity. It can relieve the muscle spasm but also reduce the pain associated with the spasm. There are many treatment modalities for spasticity. Physiotherapy is often essential along with provision of appropriate equipment. However, from a medical point of view, there are a number of antispastic drugs, such as Baclofen, Dantrium, Tizanidine and others. These are efficacious in terms of reduction of spasticity but can often be associated with significant and very unsatisfactory side effects, particularly fatigue and weakness. The underlying conditions are often already associated with fatigue and weakness and thus the antispastic drugs can make the overall situation worse. Focal treatment can be administered, which includes botulinum toxin as a muscle relaxant which is injected into the affected muscle. This is a useful treatment but it is less effective in more widespread spasticity, as the number of injections and the total dose of botulinum toxin has to be limited. There are surgical treatments, such as the use of intrathecal baclofen pumps or more aggressive surgical procedures. Thus whilst there is an array of treatments for spasticity none are entirely satisfactory and there is certainly room for additional therapy, either alone or in combination with the existing modalities (Barnes and Johnson 2008).

8.4.1 *Spasticity studies with nabiximols (Sativex)*

As we have noted, nabiximols is a licenced product in the UK under Schedule IV of the Misuse of Drugs Act. It is a 1:1 combination of THC and CBD. It is available as an oromucosal spray. The first randomised controlled study was conducted by Collin and others in 2007 (Collin *et al* 2007). A total of 189 subjects with multiple sclerosis and spasticity were randomised to receive daily doses of nabiximols or placebo in a double blind study over six weeks. The primary endpoint was a change of daily self-recorded Numerical Rating Scale in spasticity. Secondary endpoints included a more objective measure of spasticity (Ashworth Scale – which is an accepted objective measure of spasticity) and a subjective measure of spasm. Primary analysis on the intention-to-treat population (this is the population who entered the study and the whole group is analysed regardless of drop outs) showed nabiximols to be significantly superior. Secondary efficacy measures were in favour of nabiximols but did not achieve statistical significance. Overall, about 40% of subjects achieved a greater than 30% benefit (which is an accepted measure of clinically useful improvement). The product was associated with few serious side effects although there were eight withdrawals attributed to adverse events, six from the active preparation group and two on placebo (Class I).

The same lead author undertook further work with nabiximols (Collin *et al* 2010). This was a 15 week multicentre, double-blind, randomised, placebo-controlled, parallel group study (Class I) in 337 subjects with MS spasticity not fully relieved by their current anti spasticity medication. On this occasion the intention-to-treat analysis showed a non-significant improvement in the Numeric Rating Scale in

favour of nabiximols. The per-protocol (analysis of those who completed the study) population change in the score and the responder analysis (> or =30% improvement from baseline in spasticity) were both significantly superior for nabiximols compared to the placebo group. A carer “Global Impression of Change” (the carer view of the degree of improvement) also significantly improved, as did a timed 10 metre walk. The authors determined that if the patient was going to respond they had usually done so within the first four weeks of treatment.

As a result of this finding, Novotna and colleagues (2011) conducted a redesigned trial. This was a 19-week, follow-up, multicentre, double-blind, randomised, placebo-controlled, parallel-group study in subjects with multiple sclerosis with resistant spasticity. The subjects were treated with nabiximols as add-on therapy in a single blind manner for four weeks and those who achieved an improvement in their spasticity of greater than 20% progressed to a 12 week randomised, placebo-controlled, phase. The authors felt that this reflected clinical practice. A total of 272 out of 572 subjects achieved a greater than 20% improvement after the four week single blind phase and 241 were randomised. The intention-to-treat analysis showed a highly significant difference in favour of nabiximols (p=0.0002). Secondary endpoints were responder analysis, spasm frequency scores, sleep disturbance, Numeric Rating Scale and carer and clinician global impression of change were all significant in favour of nabiximols (Class I).

It is of interest that this preparation is one of the few cannabinoid formulations that have been studied for longer term use (Notcutt *et al* 2012). These authors showed maintenance of nabiximols efficacy over a mean duration of usage of 3.6 years with

a mean daily dose of 8.25 sprays of the compound. In a further long term use study Serpell and colleagues (2013) followed up, in an open label fashion, 146 patients with a mean treatment exposure of 334 days and the patients were administering an average of 7.3 sprays per day. A total of 36% of the patients withdrew in the first year, 14% due to side effects and 9% due to lack of efficacy. Most side effects were mild to moderate in severity and the commonest were dizziness and fatigue. There were five patients with more serious side effects, including two psychiatric events reported by one patient. However, no psychosis or withdrawal symptoms seemed to occur after abrupt cessation of treatment. In the long term the baseline spasticity did not deteriorate but was maintained to study completion in those who did not withdraw. There was no evidence of tolerance developing. However, this is an open-label study but nevertheless provides useful long term safety data (Class IV). Nabiximols have also been studied in a large patient group in Germany (Flachenecker *et al* 2014). The study involved 335 patients and 276 fitted the admission criteria and were included in the effectiveness analysis. After one month nabiximols provided relief of resistant spasticity in the patients in 74.6% of cases, as documented by a mean reduction of the spasticity Numerical Rating Scale. In this study after three months 55% of patients had continued to use nabiximols. A total of 17% of patients reported some adverse events although the treatment was well tolerated. This is a simple observational prospective study and thus limited conclusions can be drawn but nevertheless this further provides useful long term safety data and confirms longer term efficacy of the product (Class IV).

Similar results have been confirmed in other open-label long term follow up studies (Ferre *et al* 2016). Further long term evidence of continuing efficacy and safety was

recently published by Zettl and colleagues in 2016 (Zettl *et al* 2016). This study confirmed that dizziness and fatigue were the most common treatment related adverse events being mostly mild to moderate in severity. They confirmed continuing efficacy and safety in a total of 1600 patients with multiple sclerosis with a total of over 1500 patient years.

There are other studies of nabiximols but overall we consider there is **good** evidence of the efficacy of nabiximols for the management of spasticity in multiple sclerosis. Some of the studies were not initially convincing although all showed antispastic effects in favour of nabiximols. Later studies have involved analysis after a four-week open phase to determine responders, which we consider is a reasonable approach and reflects clinical practice. The studies confirm that nabiximols is generally well tolerated and efficacy has been shown to be long term, but not in all initial responders. A question arises in this and other cannabis studies of whether subjects can be truly blinded (unaware of which treatment they are taking) given that the active product is likely to give rise to a 'high' whereas placebo does not. This may be the case in studies of herbal cannabis or those with high THC content. However, CBD counteracts the effect of the THC 'high' and this appears to be the case in the nabiximols studies. Wright and colleagues reanalysed 666 patients, included in three phrase III placebo-controlled studies (Wright *et al* 2012*).* Two of the three trials have been referred to above (Collin *et al* 2007 and Collin *et al* 2010). The other study was an earlier nabiximols double-blind, randomised, placebo-controlled study by Wade and colleagues (2004). The authors concluded that there was no evidence to suggest the widespread unblinding to treatment allocation in those three studies and they found no evidence that if individuals did become unblinded then this

led to bias in the assessment of treatment difference between nabiximols and placebo for efficacy, adverse events or dosage. This is clearly reassuring but is obviously only likely to apply to drugs with a high proportion of CBD to THC.

8.4.2 *Spasticity Studies with Other Formulations*

Other authors have used different cannabis formulations. Indeed, studies date back to 1981 when Petro and Ellenberger described the first use of THC for human spasticity (Petro and Ellenberger 1981). Vaney and colleagues (2004) used cannabis extract capsules standardised to 2.5mg THC and 0.9mg CBD. Participants (50) received the active compound for 14 days followed by placebo or placebo for seven days and active treatment for 14 days. In the intention-to-treat analysis there was no statistically significant difference associated with active treatment compared to placebo but there was a trend in favour of active treatment for spasm frequency, mobility and getting to sleep. In the 37 patients who received at least 90% of their prescribed dose there were significant improvements in spasm frequency and mobility. Adverse effects seemed to be relatively minor (Class II).

In 2003, Zajicek and colleagues reported on a large study (Class I) of 33 UK centres giving oral cannabis extract or THC or placebo over a trial duration of 15 weeks (Zajicek *et al* 2003). The study noted no treatment effect of cannabinoids on the primary outcome measure which was a change in overall spasticity score using the Ashworth scale. There was evidence of treatment effect on patient reported spasticity and pain with improvement in spasticity reported in 61% of those on the cannabis extract and 60% of those on THC but only 46% of those on placebo.

In 2012 Zajicek and colleagues produced a further (Class I) study of oral cannabis extract or placebo in 22 UK centres in patients with stable multiple sclerosis and spasticity (Zajicek *et al* 2012). This was a double-blind, placebo-controlled phase III study with a two-week dose titration phase from 5mg to a maximum of 25mg of THC daily and a 10-week maintenance phase. The primary outcome measure in this study was a rating scale measuring patient reported change in muscle stiffness and further rating scales assessing body pain, spasms and sleep quality. The relief from muscle stiffness after 12 weeks was almost twice as high with cannabis extract than with placebo and similar results were found for the secondary outcome measures. The authors reported no new safety concerns.

There is one study of smoked marijuana in a randomised, placebo-controlled trial (Corey-Bloom *et al* 2012). Thirty-seven participants were randomised and 30 completed the study. The randomisation was either to smoked cannabis once daily for three days or placebo cigarettes. After a washout interval of 11 days participants crossed over to the other group. The primary outcome was a change in the Modified Ashworth Scale (similar to the Ashworth scale and still an accepted scale) with secondary outcomes of perception of pain, a timed walk, changes in cognitive function and ratings of fatigue. Treatment with smoked cannabis resulted in a reduction of patient scores by an average of 2.74 points compared to placebo (statistically significant at $p < 0.0001$). In addition, pain scores were significantly reduced, timed walking did not differ and there were no serious adverse events. However, this trial had few participants and there were issues with the study design and blinding (Class III).

8.4.3 *Spinal Cord Injury*

There have been few studies other than in multiple sclerosis. One study assessed the effect of nabilone on spasticity after spinal cord injury (Pooyania *et al* 2010). There have been other studies of the effect of cannabis formulations on pain in spinal cord injury and indeed in multiple sclerosis (see Pain section). The study by Pooyania and colleagues was a double-blind, placebo-controlled, crossover study that only involved 11 subjects who either received nabilone or placebo during a four-week period and after a two-week washout subjects were crossed to the opposite arm of the study. There was a significant decrease on active treatment for the Ashworth score in the most involved muscle as well as total Ashworth score. There were no significant differences in secondary measures which included the spasm frequency scale and the clinician's and subject's global impression of change. Side effects were mild and tolerable (Class III).

8.4.4 *Conclusion*

In summary, we consider there is **good** evidence for efficacy of nabiximols for reducing patient-reported spasticity symptoms, although there is not firm evidence for improvement in objective measures. We consider there is **good** evidence of safety in the long term and for continued efficacy. We also consider there is **moderate** evidence for the efficacy of oral cannabis extract for reducing patient-reported spasticity scores. There is insufficient evidence to make any recommendations with regard to other forms of cannabis.

8.5 Movement Disorders

8.5.1 *Parkinson's Disease*

Parkinson's disease is very common and occurs in about 30/10000 of the male population and 24/10000 of the female population. This means that there about 125000 people with Parkinson's in the UK – mainly, but not exclusively, in the older population. It is well known that the symptoms of Parkinson's disease are largely related to the loss of dopaminergic neurones in the basal ganglia of the brain. The basal ganglia is not only a site for dopamine receptors but also cannabinoid receptors and there is at least a potential role for the endocannabinoid system to control voluntary movement in Parkinson's disease (Fernandez-Ruis *et al* 2015). In an animal model, for example, a cannabinoid type 1 receptor agonist reduced movements induced by levodopa/carbidopa (dopamine products) or apomorphine (a dopamine agonist). It is also known that activation of the CB1 receptor can stimulate the dopaminergic system as well as the cannabinoid system and thus cannabinoids may have a role to play in the treatment of Parkinson's disease (Gilgun-Sherki *et al* 2003). The dynamics of the cannabinoid and the dopaminergic system in the human brain is further discussed in a useful article by Rodriguez De Fonseca and colleagues (2001). Anecdotal evidence has been available for some years and indeed in an anonymous questionnaire sent to patients attending the Prague Movement Disorder Centre it was shown that 25% of Parkinsonian patients (out of 339 respondents) had taken cannabis and just less than 50% of those described some benefit (Venderova *et al* 2004). However, few studies have more formally analysed the question of whether cannabis is useful in Parkinson's disease.

In 2004 Carroll and colleagues published a four-week dose escalation study which assessed the safety and tolerability of cannabis in six Parkinson's disease patients with levodopa induced dyskinesia (Carroll *et al* 2004). (Dyskinesia is a description for involuntary "writhing" movements induced by the dopamine therapy). After this pilot study a randomised, placebo-controlled, crossover study was performed in 19 Parkinson's disease patients randomised to receive either oral cannabis extract followed by placebo or vice versa. The treatment phase lasted four weeks for the two week intervening washout period. Seventeen patients completed the study and cannabis was well tolerated but there was no evidence for a treatment effect on levodopa induced dyskinesia as assessed by the Unified Parkinson's Disease Rating Scale (an accepted scale in Parkinson's disease studies) or any of the secondary outcome measures (Class II).

In a relatively small Class III study Lotan and colleagues (2014) studied 22 patients in a Parkinson's clinic both at baseline and after 30 minutes of smoking cannabis using a well-recognised Parkinson's symptom battery. The Unified Parkinson's Disease Rating Scale improved significantly over the period of time following cannabis consumption and analysis of specific motor symptoms also improved, including tremor, rigidity, bradykinesia (slowness of movement) and sleep and pain scores. No significant adverse effects were observed. The authors felt this study might indicate that cannabis has a place in the therapy of Parkinson's disease but admitted that larger, controlled studies were clearly needed. Other authors have analysed the effect of cannabidiol (CBD). Chagas and colleagues (2014) selected 21 Parkinson's disease patients without dementia and assigned them to three groups of seven subjects who were treated with placebo, cannabidiol (CBD) 75mg

daily or CBD 300mg daily. The authors found no statistically significant differences in the rating scores or other measures except there was a significant difference (in favour of CBD) between the placebo group and the CBD 300mg group with regard to a measure of wellbeing and quality of life (Class III).

Conclusion

In summary, whilst there is theoretical evidence that cannabis may assist some aspects of Parkinson's disease there is very limited good quality evidence and whilst further studies are justified at the moment there is just **some** evidence in this indication.

8.5.2 *Dystonia*

Dystonia is a condition characterised by prolonged muscle spasm. It most often occurs in just a few muscles, commonly the neck (called torticollis), the face (hemi-facial spasm) and the hand (writer's cramp) but sometimes involves the whole body. The prevalence is about 15 / 100000 population. The spasms can be painful and disabling. The endocannabinoid system is likely to be involved in movement control and thus there is a theoretical basis for manipulation of the ECS in the management of dystonia. However, there is very limited evidence for efficacy in human studies. There are a number of anecdotal and open label studies that suggest there may be some benefit using cannabis in dystonia (Consroe *et al* 1986; Chattergee *et al* 2002; Uribe Roca *et al* 2005). There are also some animal models that are similarly suggestive (Madsen *et al* 2011). However, there is only one Class III human study -

a randomised double-blind placebo-controlled trial (Fox *et al* 2002). This study used a synthetic cannabinoid receptor agonist (nabilone) in patients with generalised and segmental primary dystonia but it showed no significant reduction in dystonia following treatment. However, the study was underpowered to detect differences.

Conclusion

In dystonia, whilst there is anecdotal evidence, the data is insufficient to draw any conclusions.

8.5.3 *Huntington's Chorea*

Huntington's disease is quite rare (about 5/100000 population) and is a genetic disorder characterised by abnormal movements (chorea) and behavioural problems, often leading to dementia. Current treatment is very limited and really only manages to reduce some symptoms temporarily. Whilst there is a theoretical reason why the endocannabinoid system may be involved in Huntington's disease there is no convincing evidence of efficacy in the disorder (Sagredo *et al* 2011). In an early Class III study the authors found no effect of cannabidiol (10mg/kg/day for six weeks) compared to placebo in a double-blind, randomised, cross-over trial design. However, the study was underpowered and only involved 15 patients with Huntington's disease (Consroe *et al* 1991). Curtis and colleagues (2009b) studied the efficacy of nabilone in Huntington's disease and conducted a double-blind, placebo-controlled, crossover study versus placebo (Class 1). Forty-four patients were involved and either received nabilone 1 or 2 mg followed by placebo or vice

versa. Assessment of both doses of nabilone versus placebo showed a treatment difference in favour of nabilone for motor scores, chorea and cognition as well as behavioural scores. However, it was questionable whether the change noted was of clinical significance and the study was underpowered but nevertheless was promising and larger studies are merited.

Conclusion

In summary, the evidence is sparse for the efficacy of cannabinoids in Huntington's disease but with one modestly positive study and theoretical evidence, further studies are warranted.

8.5.4 *Tourette's Syndrome*

Tourette's syndrome is surprisingly common and thought, in variable presentations, to affect about 1% of the population at some time. It is characterised by sudden movements (tics) and vocal utterances. Treatment is very unsatisfactory.
The literature is sparse for the efficacy of cannabis in any form for the treatment of Tourette's syndrome. A single author produced two studies on the subject. One study can be classified as Class II (Muller-Vahl *et al* 2002) and the other study classified as Class III (Muller-Vahl *et al* 2003). There are earlier anecdotal reports but these provide very limited further information.

In 2002 Muller-Vahl and colleagues performed a randomised double-blind placebo-controlled crossover single dose trial of THC (in 5mg, 7.5mg or 10mg formulation)

(Muller-Vahl *et al* 2002). The study was carried out in 12 adult Tourette's syndrome (TS) patients. Tic severity was assessed using a self-rating scale and an examiner rating scale. These scales are generally accepted as valid measures of severity of symptoms. On one scale (Schapiro Tourette's Syndrome Symptom List) there was a significant improvement of tics ($p=0.015$) and also in obsessive compulsive behaviour ($p=0.041$) after treatment with THC compared to placebo. Examiner ratings also showed a significant difference with regard to the sub-scale for complex motor tics and a trend towards significant improvement for sub-scales of motor tics and vocal tics. There were no serious adverse reactions but five patients experienced mild and transient side effects. The authors concluded that the results suggested that a single dose treatment with THC was effective and safe in treating tics and obsessive compulsive behaviour in Tourette's syndrome but they recommended that further studies should be carried out to confirm the results. The subject numbers were small and it is lacking in statistical power for reliable conclusions to be drawn.

In a second study in 2003 Muller-Vahl and colleagues carried out a slightly larger scale study in a randomised double-blind placebo-controlled trial of 24 patients with TS who were treated over a six-week period with up to 10mg per day of THC (Muller-Vahl *et al* 2003). Tics were rated at six visits using a standardised Tourette Syndrome evaluative measure as well as a video-taped rating scale. Unfortunately, seven patients dropped out of the study or had to be excluded but only one of those was due to side effects. There were significant differences ($p<0.05$) or a trend towards a significant difference ($p<0.1$) between THC and placebo at visits two, three and four of the six-week treatment period on three of the Tourette's scales and on

the video rating scale. The authors concluded that this study provided more evidence that THC was effective and safe in the treatment of tics and further postulated that the central cannabinoid receptor system (the endocannabinoid system) might play a role in Tourette's syndrome pathology. However, the numbers in the study were still small and the seven patients dropping out of the study was also of some concern.

Conclusion

These two small studies do not provide sufficient evidence to either confirm or refute the suggestion that cannabis may be helpful for the treatment of this particular form of tic disorder. The studies were indicative that there may be a therapeutic possibility for this indication but clearly further and larger studies are needed. Overall, we suggest there is only **some** evidence of efficacy in Tourette's syndrome.

8.6 Headache

Headache is remarkably common. The lifetime prevalence of headache (including anybody with any form of headache), migraine, and tension-type headache is 93%, 8% and 69% in men; and 99%, 25% and 88% in women. There are satisfactory treatments but a minority of headache sufferers have persistent symptoms despite treatment.

Cannabis has been used for centuries for treatment of headache/migraine. After the discovery and elucidation of the endocannabinoid system there is now a theoretical basis for such treatment (Russo 1998). It is known that the serotonin system (a central neurotransmitter system involved in headache/migraine) can be affected by the endocannabinoid system. Anandamide (cannabinoid receptor ligand) also potentiates serotoninergic receptors and it is known that cannabinoids demonstrate dopamine blocking and anti-inflammatory properties which may also be relevant in terms of migraine. Indeed, Russo has postulated a clinical endocannabinoid deficiency syndrome to explain the therapeutic benefits of cannabis in migraine, as well as in fibromyalgia and irritable bowel syndrome (Russo 2008). This concept has been further confirmed by Smith and Wagner (2014).

However, despite this theoretical basis there are no Class I or Class II studies of the use of cannabis in headache or migraine. Robbins and colleagues published a single case study of the efficacy of recreational marijuana successfully used to abort cluster headache refractory to standard medication (Robbins *et al* 2009). The patient subsequently continued to use dronabinol which provided longer term effective pain

relief. Nevertheless, in a larger study of 139 patients with cluster headaches, although it was found that just over 45% of the patients had used cannabis, only just 25% reported efficacy and indeed 22% reported negative effects (Leroux *et al* 2013). A slightly more promising study has recently been published by Rhyne and colleagues (2016). One hundred and twenty-one adults with a primary diagnosis of migraine headache were recommended migraine treatment or prophylaxis with medical marijuana. Migraine headache frequency decreased from 10.4 to 4.6 headaches per month with the use of medical marijuana. This was a statistically significant. Inhaled forms of marijuana were most commonly used. Fourteen patients (11.6%) reported negative effects, including somnolence. The authors suggested that further prospective studies should be carried out (Class IV).

Conclusion

In summary, it is surprising that despite a long history of use in headache and migraine there are no good quality randomised clinical trials and thus no conclusion can be drawn.

8.7 Neuroprotection - Traumatic Brain Injury and Stroke

It is known that the endocannabinoid system is involved in protection of the nervous system (neuroprotection) after trauma and other insults. Thus there is a theoretical basis for the use of cannabis as a neuroprotective agent following trauma to the brain. However, there is little convincing evidence that this is the case. One study by Nguyen and colleagues in 2014 described a three-year retrospective review of registry data at a level one trauma centre of those who had been admitted with traumatic brain injury (Nguyen *et al* 2014). Children and patients with a suspected non-survivable injury were excluded. Those with a positive toxicology screen for THC were compared to a group who had no such positive toxicology. Overall there were 446 cases meeting the inclusion criteria. The incidence of a positive THC screen was 18.4% in this population. The mortality in the THC+ group (2 patients) were significantly decreased compared to the THC- group (42 patients). After adjusting for differences between the cohorts the THC+ screen was independently associated with better survival chances (Class IV). An early phase II study of a new cannabinoid receptor agonist (KN38-7271) has also shown that survival rates within one month of the traumatic brain injury were significantly better in the treatment group compared to a placebo group. However, this is a very early study and the agonist in question is not commercially available (Firsching *et al* 2012).

Traumatic brain injury - Conclusion

Overall, whilst there is a theoretical basis for cannabinoids to provide neuroprotection, there is limited evidence and not yet convincing evidence of efficacy in the context of traumatic brain injury.

There is no evidence of neuroprotective effect of cannabis after **stroke**. Indeed, there is some, albeit limited, evidence that there is a causal link between heavy recreational use of cannabis and stroke. A review in 2015 (Hackan 2015) had found 34 case reports on 64 patients and in most cases there appeared to be a temporal relationship between cannabis exposure and the stroke and 70% of the evaluation was sufficiently comprehensive to exclude other sources of stroke. About a quarter (22%) of patients had another stroke after a subsequent re-exposure to cannabis, although half of the patients had concomitant stroke risk factors, most commonly tobacco (34%) and alcohol (11%) consumption. Another literature review by Desbois and Cacoub (2013) has also shown that in anecdotal cases cannabis usage is associated with arterial disease, such as stroke, myocardial infarction and limb arteritis. A recent comprehensive study reviewed all patients in a Nationwide Inpatient Sample in 2004 to 2011 with a primary diagnosis of acute ischaemic stroke (Rumalla *et al* 2016). The authors found the incidence of acute ischaemic stroke was significantly greater among marijuana users compared to non-users with a relative risk of 1.13 (95% confidence intervals of 1.11-1.15). However, marijuana users were also more likely to use other illicit substances. The authors concluded that amongst young adults (marijuana use was most prevalent in younger males) recreational

marijuana usage was independently associated with a 17% increased likelihood of hospitalisation for acute ischaemic stroke.

Stroke - Conclusion

There is no evidence that there is any neuroprotection offered by cannabis in stroke and indeed some, limited, evidence that heavy recreational users have a slightly increased risk of stroke.

8.8 Dementia

Dementia is a very common chronic condition mainly affecting older adults. Indeed, around 750,000 people in the UK currently live with dementia and the prevalence is rising as the population ages. Current treatment modalities are generally unsatisfactory. As the chemical acetylcholine is known to be reduced in the brain in various dementias then drugs that can increase the concentration (cholinesterase inhibitor drugs) have been shown to improve cognitive symptoms, activities of daily living and some aspects of behaviour. However, the treatment effects are rather small and they tend to only delay a decline in cognitive functioning by a period of around one year.

In theory the cannabinoids may be helpful for the treatment of dementia. It is known that the cannabinoids are neuroprotective and thus may mitigate the effects of neurodegeneration (Gowran *et al* 2011). It is also known that some cannabinoid receptors can reduce neuro-inflammation, which is also implicated in the aetiology of dementia. Quite recently it was found that THC can reduce the aggregation of amyloid, which is a key pathological marker of Alzheimer's disease (Eubanks *et al* 2006). It has also been found that THC can inhibit the enzyme acetylcholinesterase and such drugs are known to have an, albeit modest, effect in slowing the progression of Alzheimer's disease.

Despite the theoretical basis for the use of cannabis and cannabinoids in dementia there is a paucity of literature on the subject. A recent Cochrane review (Volicer *et al* 1997) found only one placebo-controlled, crossover designed study, which examined

the effects of dronabinol on anorexia and disturbed behaviour in patients with Alzheimer's disease. However, this was obviously a symptomatic treatment rather than a treatment designed to study the effect on the disease process itself. Only 11 patients completed the study period. The authors found that body weight increased during the dronabinol treatment more than during the placebo period and the dronabinol treatment decreased the severity of disturbed behaviour and this effect persisted during the placebo period in patients who received dronabinol first. There were more adverse reactions in the dronabinol group, including euphoria, somnolence and tiredness. However, the study was unsatisfactory in many ways and can only be classified as a Class II study.

Recently Shelef and colleagues (2016) have conducted an open label, add-on pilot study of the use of medical cannabis oil for behavioural and psychological symptoms of dementia. Just 11 patients with Alzheimer's disease were recruited into this open label four-week study. Ten patients completed the trial. The authors noted significant improvement in aspects of cognition and behaviour, including decreases in delusions, agitation/aggression, irritability, apathy, sleep and caregiver distress. However, the study can only be classified as Class III.

In 2014 Woodward and colleagues reported on a retrospective systematic chart review of 40 inpatients with dementia in a neuropsychiatric facility (Woodward *et al* 2014). Dronabinol was added to the treatment regimes. The addition of dronabinol was associated with a significant decrease in agitation and significant improvements in global impression scores, sleep duration and percentage of meals consumed during the treatment periods. There were adverse events which were generally mild

and none lead to medication discontinuation. However, the study being uncontrolled cannot lead to firm conclusions but is simply indicative that dronabinol may be of some assistance in the alleviation of symptoms in this population (Class IV).

A similar effect on agitation was noted in just six patients with severe dementia treated with dronabinol (Walther 2006) (Class IV).

The only randomised controlled trial was conducted by van den Elsen and colleagues in 2015 (van den Elsen *et al* 2015). It was a randomised, double-blind, placebo-controlled study (Class I). Individuals were randomly assigned to either THC 1.5mg or matched placebo three times daily for three weeks. Twenty-four patients received THC and 26 received placebo. However, there was no significant difference from baseline between THC and placebo, although neuropsychiatric symptoms were reduced in both groups. There were no significant changes in scores for agitation or quality of life or activities of daily living. However, the THC was well tolerated. The authors concluded that oral THC at 4.5mg daily showed no benefit in neuropsychiatric symptomatology. The authors suggested that the reasonable tolerance of the compound in this population may lead to studies that look at whether higher doses are efficacious.

Conclusion

At the present time we find **some** evidence that cannabinoids are effective in improvement of disturbed behaviour and the treatment of other symptoms in dementia. This is in agreement with the Cochrane database systematic reviews on

this subject (Krishnan *et al* 2009). A useful up-to-date review has been published by Ahmed and colleagues (2015).

8.9 Epilepsy

Epilepsy affects around 1% of the population. Fortunately, there are a number of anticonvulsant drugs and indeed around 80% of epilepsy can be fully controlled using a single anticonvulsant. A minority of people have refractory epilepsy but nevertheless the majority of those individuals are controlled on two, or sometimes three, anticonvulsants. However, despite significant progress in anticonvulsant research and availability of the newer anticonvulsant drugs there is still a minority of individuals who have epilepsy refractory to the currently available compounds. This is particularly the case in various forms of severe childhood epilepsy, such as Dravet's syndrome and the Lennox-Gastaut syndrome. In addition, anti-epileptic drugs often have serious adverse effects, particularly if used in combination.

It has been known for many years that phytocannabinoids have anticonvulsant effects and this has been adequately demonstrated in pre-clinical studies and in animal models (Rosenberg *et al* 2015). However, the situation is complicated. THC appears to be anticonvulsant in some circumstances but in other circumstances seems to be pro-convulsant. The main phytocannabinoid with anticonvulsant properties is cannabidiol (CBD). Another phytocannabinoid, cannabidivarin, also shows promise as an anticonvulsant (Dos Santos 2015). Unfortunately, human studies are limited in number and quality but nevertheless there is emerging evidence of the usefulness of both cannabidiol and very early evidence of the efficacy of cannabidivarin. The mode of action of CBD is not known but it seems likely that it has effects both within and outside the endocannabinoid system. It is known that it can affect other brain receptors such as the vanilloid system, the

5HT1A receptor and the alpha 3 and alpha 1 glycine receptors. All these may have a role to play in the aetiology of epilepsy (Devinsky *et al* 2014).

A liquid formulation of pure plant derived cannabidiol has been developed by GW Pharmaceuticals under the name of Epidiolex. This compound has been granted Orphan Drug Designation by the FDA in the United States for the treatment of Dravet's syndrome and Lennox-Gastaut syndrome. There have been early results of the use of Epidiolex in patients with treatment-resistant epilepsy. Devinsky has recently published work in 2016 (Devinsky *et al* 2016). This is an open label trial with patients from 1 to 30 years with severe intractable childhood-onset treatment-resistant epilepsy who were receiving stable doses of anti-epileptic drugs before the study entry. Enrolment was in 11 epilepsy centres across the United States. Oral cannabidiol was given at 2-5mg per kg per day and then up titrated to intolerance or to a maximum dose of 25-50mg per kg. This was a large study and 214 patients were enrolled and 76% of them had at least 12 weeks of follow-up after the first dose of cannabidiol and 64% were included in the efficacy analysis. There were a number of different types of epilepsy but 33 patients had Dravet's syndrome and 31 patients had Lennox-Gastaut syndrome. The drug was reasonably well tolerated and adverse events reported in more than 10% of patients were somnolence, decreased appetite, diarrhoea, fatigue and convulsion (although the latter may have been simply part of the ongoing epilepsy). Just five patients discontinued treatment because of an adverse event. The median reduction in monthly motor seizures was 36.5%. The authors recommended that further randomised, controlled trials were warranted to further characterise both the safety profile and the efficacy (Class III).

This study was supported by an on-line survey of parents who had administered CBD enriched cannabis preparations for the treatment of their children's epilepsy. One hundred and seventeen parents of epileptic children were studied and 85% of all parents reported a reduction in seizure frequency and 14% reported complete seizure freedom. The cannabis preparation was mainly used in childhood resistant epilepsy, particularly Dravet's syndrome. The parents reported that the side effects were well tolerated and indeed some 'side effects' were useful, including improvement in sleep (53%), alertness (71%) and mood (63%) (Hussain *et al* 2015).

Tzadok and colleagues (2016) recently published the current Israeli experience of CBD enriched medical cannabis for intractable paediatric epilepsy. This was a retrospective study describing the effect of cannabidiol (CBD) enriched medical cannabis in children with epilepsy. There were 74 patients from 1 to 18 years with intractable epilepsy resistant to at least seven anti-epileptic drugs. All the patients used medical cannabis oil treatment for at least three months (average six months) and the selected formula contained CBD and THC at a ratio of 20:1, dissolved in olive oil. The treatment yielded significant positive effect on seizure load and most children (89%) reported a reduction in seizure frequency. Eighteen percent reported 75-100% reduction, 34% reported 50-75% reduction and 12% reported 25-50% reduction. Five patients (7%) reported aggravation of seizures which led to CBD withdrawal. Observations of improvement in behaviour and alertness, language, communication, motor skills and sleep were also observed. The drug seemed to be well tolerated with the adverse reactions including somnolence, fatigue, gastrointestinal disturbance and irritability leading to withdrawal in five cases (Class III).

The company is also developing a cannabidivarin (CBDV) cannabinoid treatment which, as documented above, has shown anti-epileptic properties in a range of pre-clinical models. It is now into a phase II study involving 130 patients with epilepsy. In a phase I study in 66 healthy subjects CBDV was tolerated even at the highest tested dose with no serious or severe adverse events or any withdrawals due to side effects (Hill *et al* 2012). The current designation of this compound is GWP42006 (www.gwpharm.com/epilepsy). GW Pharma estimates that the size of the intractable paediatric epilepsy population is approximately 140,000 people in the United States and 230,000 people in Europe and thus development of the paediatric epilepsy programme is potentially important and may have a significant impact. The company has also recently announced plans to develop epidiolex for a third target indication, Tuberous Sclerosis Complex, which is a rare paediatric genetic disorder which is associated with significant epilepsy issues.

Conclusion

In summary, whilst there is a theoretical basis and animal model studies and early human studies are promising, at the moment robust trials are lacking but further results are awaited. There is only limited evidence at the moment.

8.10 Sleep

Cannabis in different formulations can cause somnolence and fatigue. This is a well-known effect of the drug. There is a scientific foundation for this effect, as it is now known that the endocannabinoid system has a role to play in regulating sleep (Pava *et al* 2016). The side effects of fatigue and somnolence are well documented in many reports, as well as in the historical literature. However, there have been surprisingly few studies with the primary purpose of investigating the effect of cannabis on sleep disorders. There is one study which demonstrated the effects of nabilone on sleep in fibromyalgia (Ware *et al* 2010a). This study confirmed that nabilone was effective in improving sleep in people with fibromyalgia and was well tolerated in a randomised, double-blind, active control equivalency crossover trial, which compared nabilone to amitriptyline (Class I) – see also fibromyalgia section. Nabilone has also been studied for the treatment of post-traumatic stress disorder (PTSD) nightmares (see section on PTSD) (Jetly *et al* 2015). This small study (10 subjects – Class II) confirmed relief from PTSD-associated nightmares following the administration of nabilone in a double-blind treatment compared to placebo.

Sleep was documented as a secondary outcome (mainly using a numeric rating scale) in several of the nabiximols studies of spasticity in multiple sclerosis (see Spasticity section) and many reported positive results in terms of sleep.

The authors should also point out that sometimes difficulty sleeping and strange dreams are amongst the symptoms reported with both acute and sub-acute cannabis withdrawal. Nevertheless, except for the situation of cannabis withdrawal, cannabis

use seems to be clearly associated with sleepiness and facilitation of falling asleep (Schierenbeck *et al* 2008).

Conclusion

It is difficult to quantify and assess the evidence for sleep as it has been very rarely used as a primary outcome measure but nevertheless the authors feel that given the plethora of literature demonstrating that cannabis promotes somnolence, fatigue and sleep then there is **moderate** evidence that it is likely to be helpful in sleep disorders. All formulations of cannabis seem to have the same effect on sleep but obviously further research is required to elucidate which particular formulation may be more beneficial.

8.11 Bladder

A number of studies have demonstrated some efficacy with cannabinoids for the use of bladder symptoms in various conditions, particularly multiple sclerosis. The commonest difficulty with bladder functioning in neurological disease is urinary frequency and urgency, often associated with urinary incontinence. This is largely due to over-activity of the bladder (detrusor) muscle and often there is additional incoordination between bladder contraction and opening of the external urinary sphincter (detrusor sphincter dyssynergia). Bladder difficulties are very common in the context of most central nervous system diseases but particularly troublesome in multiple sclerosis and spinal cord injury. There is a scientific rationale for the use of cannabinoids on bladder systems as it is now known that both endocannabinoid receptors (CB1 and CB2) are located in the lower urinary tract tissues (Ruggieri 2011; Hedlund 2014).

In the early days of development of nabiximols Brady and colleagues (2004) undertook an open label pilot study on bladder dysfunction in advanced multiple sclerosis. Patients took cannabis extracts containing THC and cannabidiol for eight weeks followed by THC only for a further eight weeks and then entered a long term extension part of the study. Twenty-one patients were recruited and data for 15 were evaluated. Urinary urgency, the number and volume of incontinence episodes, frequency and nocturia (waking to urinate at night more than considered normal) all decreased significantly following treatment. Patient self-assessment of pain, spasticity and quality of sleep also improved. The authors reported few troublesome side effects (Class III).

This open pilot study has been followed in the literature by a randomised controlled trial (Kavia *et al* 2010). This was a 10-week double-blind, randomised placebo-controlled parallel group trial in 135 randomised subjects with multiple sclerosis and over-active bladder. The primary endpoint of the trial (reduction of daily number of urinary incontinence episodes) was not different between nabiximols and placebo. However, four of the seven secondary endpoints were significantly in favour of nabiximols. These were the number of episodes of nocturia, overall bladder condition, number of voids per day and the patient's global impression of change. The number of daytime voids was significantly reduced and in favour of nabiximols. The study provides some evidence of improvement in some symptoms associated with bladder dysfunction in multiple sclerosis (Class I).

Some other studies that have not been specifically focused on bladder symptoms as a primary endpoint have failed to show improvement (Wade *et al* 2004).

Another group of authors used cannabis extract. This was a sub-study in the work referred to in the spasticity section by Zajicek and colleagues (2003). The CAMS study randomised 630 patients to receive the oral cannabis extract or THC or placebo. All three groups showed a significant reduction in episodes of urge incontinence but both active treatment arms showed a further significant effect over placebo (cannabis extract p=0.005: THC p=0.039) (Freeman *et al* 2006).

In contrast other studies have shown no effect on self-reported bladder complaints (Vaney *et al* 2004).

Conclusion

Thus the evidence for efficacy of cannabis formulations on bladder dysfunction is not entirely clear. However, there does seem to be **some** evidence of efficacy of nabiximols and an oral cannabis extract but clearly further and better designed studies are required in larger groups of patients. Diagnoses other than multiple sclerosis also need to be studied.

8.12 Glaucoma

Glaucoma is an irreversible eye disease which can slowly progress to blindness due to progressive loss of the retinal cells. It is the second leading cause of blindness in the world. It is characterised by an increased pressure inside the eye and lowering of that intraocular pressure can result in reduced progression of the disorder.
It is now known that the endocannabinoid system is present throughout most ocular tissues and it is also known that the intraocular pressure can be lowered by use of cannabinoids (Cairns *et al* 2016). It has been known for many years that marijuana can reduce intraocular pressure and thus has a theoretical role in the management of glaucoma (Flom *et al* 1975). There was considerable interest in the scientific literature in the use of cannabis and cannabinoids for lowering of the intraocular pressure in glaucoma in the 1980s but there were very few properly conducted human studies. The subject was reviewed again in 2002 (Jarvinen *et al* 2002). The authors confirmed the potential efficacy of cannabis and cannabinoids for the treatment of glaucoma but proper therapeutic trials were still lacking. In 2004 Tomida and colleagues published a further review article (Tomida *et al* 2004). The article once again confirmed the potential efficacy of cannabis and cannabinoids in the management of glaucoma and summarised the numerous studies that had confirmed that different cannabinoids can reduce the intraocular pressure when administered both systemically and topically. However, controlled and longer term studies were still lacking. The same authors produced a small pilot study in 2006 (Tomida *et al* 2006). They performed a randomised, double-blind, placebo-controlled four-way crossover study using a cannabis-based medicinal extract of THC and CBD. Six patients received a single sublingual dose either of 5mg of THC or 20mg

or 40mg of CBD or placebo. They found that the administration of THC reduced intraocular pressure compared to placebo but CBD did not reduce the pressure and indeed the higher dose of CBD actually produced a transient elevation of intraocular pressure. The single dose was well tolerated. However, given the very small numbers this is not a satisfactory study and must be classified as Class III.

Conclusion

In summary, whilst there is a good theoretical basis for the use of cannabis and cannabinoids in the treatment of glaucoma there are no satisfactory studies of longer term use. There are a number of single dose studies confirming that the cannabinoids can reduce intraocular pressure. Thus at the present time there is only **some** evidence of efficacy in glaucoma.

8.13 Fibromyalgia and “Rheumatic” Diseases

Fibromyalgia is a remarkably common condition and thought to affect about 2-8% of the population with a female preponderance of around 8:1. It is characterised by chronic widespread pain with a heightened pain response to pressure. Other very common symptoms are overwhelming fatigue, difficulty sleeping and cognitive problems, particularly trouble with memory. It can be associated with a variety of other conditions, including irritable bowel syndrome and headaches. The cause is unknown but one hypothesis is that the individual has a lower threshold for pain because of increased reactivity of pain sensitive nerve cells. It is likely there is involvement of the endocannabinoid system. Undoubtedly other neurotransmitter systems are involved. Genetic factors may also have a role to play. The emerging concept of the endocannabinoid deficiency syndrome may provide a partial explanation for the aetiology, as discussed under Headache/Migraine (Russo 2004b). There is also evidence that the endocannabinoid system has some involvement in “trigger points” and may play a role in reducing inflammation in myofascial tissues, which in turn may give a theoretical basis for use of cannabinoids in fibromyalgia. However, the literature is limited.

Katchan and colleagues (2016) have recently undertaken a systematic review of the cannabinoid system and the effect on autoimmune disease and concluded that cannabinoids have promising potential as immunosuppresants and anti-fibrotic agents in therapy for autoimmune disorders, which includes fibromyalgia.

In one small pilot study nine patients with fibromyalgia underwent studies after administration of dronabinol (delta-9-tetrahydrocannabiol) (Schley *et al* 2006). Unfortunately, five of the nine patients withdrew due to adverse side effects. The remaining patients' daily recording of pain significantly reduced and electrically induced pain was significantly attenuated after doses of around 10-15mg of delta-9-THC. No particular conclusions can be drawn given the small numbers of participants (Class III).

In 2011 Fiz and colleagues conducted a questionnaire-based study with 28 fibromyalgia patients who were cannabis users and 28 non-users (Fiz *et al* 2011). After two hours of cannabis use (the majority were smokers) visual analogue scale scores showed a statistically significant reduction of pain and stiffness, enhancement of relaxation, increase in somnolence and feeling of well-being. However, whilst this study is of interest it is not strong evidence (Class III).

In the context of sleep disturbance in fibromyalgia Ware and colleagues (2010a) studied the use of nabilone. This was a randomised, double-blind, active control equivalency crossover trial that compared nabilone (0.5-1mg before bedtime) to amitriptyline in patients with fibromyalgia and chronic insomnia. Subjects received each drug for two weeks with a two-week washout period. The outcome was sleep quality measured by the Insomnia Severity Index and the Leeds Sleep Evaluation Questionnaire (standard measures). Thirty-one subjects were involved and 29 completed the study. Sleep was improved by both amitriptyline and nabilone but nabilone was superior to amitriptyline. No effects were found on pain, mood or quality of life. Side effects were mostly mild to moderate and the most common side

effects with nabilone were dizziness, nausea and dry mouth. The authors concluded that nabilone was effective in improving sleep in patients with fibromyalgia and was well tolerated. (Class I)

Nabilone has also been used for the treatment of pain in fibromyalgia (Skrabek *et al* 2008). This was a randomised, double-blind, placebo-controlled trial to determine the benefit of nabilone in pain management and quality of life improvements in 40 patients with fibromyalgia. Nabilone was titrated upwards to 1mg twice daily over four weeks or corresponding placebo. The outcome measure was a visual analogue scale for pain and with secondary measures, including the number of tender points, average tender point pain threshold and the Fibromyalgia Impact Questionnaire (a standard measure). The authors found significant decreases in the pain scores, the FIQ and anxiety scores in the nabilone treated group at four weeks and concluded that nabilone appeared to be beneficial and well tolerated for fibromyalgia with significant benefits in pain relief and functional improvement (Class I).

Fitzcharles and colleagues (2016) have undertaken a systematic review of randomised controlled trials in chronic pain associated with rheumatic diseases, which included fibromyalgia as well as back pain, osteoarthritis and rheumatoid arthritis. They found four studies that included a variety of aetiologies, including fibromyalgia. Unfortunately, the superiority of cannabinoids over controls was not consistent, although cannabinoids were generally well tolerated. They concluded there was insufficient evidence for recommendation of any cannabinoid preparation for symptom management in patients with chronic pain associated with rheumatic diseases.

Conclusion

Overall we consider there is **moderate** evidence of efficacy for cannabinoid usage in fibromyalgia in the context of pain management and sleep. There is insufficient evidence for recommendations to be made for other musculoskeletal disorders.

8.14 Gastrointestinal Disorders

There have been a few case reports and anecdotal studies of the use of cannabis in various gastrointestinal disorders. However, there have been very few controlled trials. The scientific rationale is the discovery of the involvement of the endocannabinoid system in the physiology and pathophysiology of the gastrointestinal tract. CB1 receptors are present in neurones of the enteric nervous system and in sensory terminals of the vagal and spinal neurones while CB2 receptors are located in the immune cells. Activation of CB1 receptors is known to modulate several functions in the gastrointestinal tract, including gastric secretion, gastric emptying and intestinal motility (Massa *et al* 2005).

8.14.1 *Crohn's Disease*

The first report of cannabis use in Crohn's disease in humans was published by Naftali and colleagues in 2011 (Naftali *et al* 2011). This was a retrospective observational study in 30 patients who used cannabis. Of those 30 patients, 21 improved significantly after treatment with cannabis and the need for other medication was significantly reduced. Little evidence can be drawn from this study other than that larger studies are warranted (Class IV).

In a study by Lal and colleagues (2011) a total of 100 patients with ulcerative colitis and 191 patients with Crohn's disease attending an outpatient clinic completed a questionnaire on cannabis usage and usage of other alternative medicines. A significant number of ulcerative colitis and Crohn's disease patients reported lifetime

(51%) or current (12%) usage of cannabis, particularly those with a history of abdominal surgery or chronic abdominal pain and/or a low quality of life index. Obviously little can be extrapolated from this study except to note that presumably cannabis has some therapeutic benefit in those who use the drug (Class IV).

We are not aware of any other studies.

8.14.2 *Ulcerative Colitis*

The study referred to under the Crohn's disease section above (Lal *et al* 2011) confirms significant use of cannabis amongst patients with ulcerative colitis but provides no further useful information. Thus we can draw no conclusions.

8.14.3 *Irritable Bowel Syndrome*

In the paper by Lal (see above Lal *et al* 2011) it was seen that people with Crohn's disease used cannabis to relieve irritable bowel symptoms, including abdominal pain, diarrhoea and reduced appetite. The authors felt that the therapeutic benefits of cannabinoid derivatives in irritable bowel disease may warrant further exploration. A paper by Lahat and colleagues in 2012 reported a study that included 13 patients with irritable bowel disease who completed two questionnaires on quality of life and disease activity (Lahat *et al* 2012). The patients were advised to smoke cannabis cigarettes whenever they felt pain and were provided with 50g of dry cannabis per month for this on-demand treatment. After three months unspecified treatment, patients reported improvement in general health, social functioning, ability to work,

physical pain and depression. However, the study is small, uncontrolled and does not provide adequate evidence for any recommendation (Class IV).

8.14.4 *Gastrointestinal Disorders Conclusion*

In summary, there is theoretical evidence of the potential use of cannabis formulations in gastrointestinal disease but at the present time there are no satisfactory studies that can lead to any recommendation on the subject.

8.15 Mental Health Disorders

8.15.1 *Anxiety*

Cannabis use can both increase and decrease anxiety in humans. CBD has been shown to reduce anxiety whereas THC usually has the converse effect. The precise mechanism by which CBD exerts its anxiety-reducing effects is not well established. It may act either by decreasing blood flow to brain regions associated with the processing of anxiety or fear-based stimuli, or possibly through the modulation of serotonergic neurotransmission (Gomes FV *et al* 2011). Limited clinical evidence indicates that cannabinoid medications may be effective in the treatment of primary anxiety or anxiety secondary to chronic illness. Effective doses of CBD have not been established. However, it does have an adequate safety profile, it has no psychoactive effects and does not affect cognition (Schier *et al* 2012).

Fusar-Poli and colleagues (2009) carried out a randomized, double-blind, placebo-controlled trial (Class 1) in which participants were studied through functional magnetic resonance imaging (fMRI) scanning and electrodermal activity monitoring whilst viewing faces that that elicited different levels of anxiety following administration of THC, CBD, or a placebo. CBD was found to reduce autonomic arousal and subjective anxiety whilst THC was found to increase anxiety. The same participants were used on three occasions and so treatment groups were equivalent on baseline characteristics. The results cannot be generalised to females as they used a male sample.

A recent double-blind, randomized, placebo-controlled clinical study (Class 1) showed that orally-administered CBD was associated with a significant reduction in anxiety, cognitive impairment, and discomfort in patients suffering from generalized social anxiety disorder subjected to a simulated public-speaking test (Bergamaschi *et al* 2011).

A further study carried out by Crippa and colleagues (2011) looked at the effect of CBD on anxiety and the brain mechanisms involved (Class1). This double-blind, randomized, placebo-controlled study found that CBD significantly decreased anxiety and that this was related to its effects on the limbic and paralimbic brain areas.

Woolridge and colleagues (2005) recruited HIV-positive individuals attending a large clinic into an anonymous cross-sectional questionnaire study (Class III). Ninety-three percent of individuals who completed the questionnaire reported an improvement in anxiety levels. Improved anxiety levels have also been reported in patients suffering from chronic neuropathic pain (Ware *et al* 2010b)

Conclusion

Overall, we consider there is **good** evidence for CBD use in anxiety.

8.15.2 Depression

As reported under the Anxiety section, there is good preclinical and clinical evidence that supports an important role for the endocannabinoid system in both anxiety and depression. Animal studies using CB1 receptor agonists show reduced anxiety-like behaviour and antidepressant-like responses (Witkin *et al* 2005). CB1 receptor agonists are also known to enhance central serotonergic and noradrenergic neurotransmission, which is similar to the actions of antidepressant medication (Bambico and Gobbi 2008). However, the clinical situation is not entirely clear, as some studies have demonstrated that recreational users are at a slightly higher risk than controls for developing depression. The odds ratio for cannabis users for developing depression was marginally elevated compared to controls at 1.17 in a longitudinal study that screened 57 cannabis articles and included 14 in the final analysis with a total of 76,058 subjects. The odds ratio for heavy cannabis users for developing depression was higher at 1.62 compared to non-users or light users. The authors concluded that heavy cannabis use may be associated with an increased risk of developing depressive disorders (Lev-Ran *et al* 2014). However, other explanations are possible. It is conceivable, for example, that some cannabis users may have tried the effect of cannabis for pre-existing depression or at least low mood. On the other hand, improvement of mood is a common reason for taking recreational or indeed medicinal cannabis. In a survey conducted for the APPG for Drug Policy Reform the commonest use of cannabis was for depression (10.8% of users) followed by taking of cannabis for anxiety (9% of users). This was previously backed up in a survey by Ware and colleagues (2005). Those authors studied 2969 questionnaires in people using cannabis for medical purposes and found that

depression was the main use reported by patients (22%) after chronic pain (25%) and at a similar level to use for multiple sclerosis (22%).

In terms of clinical trials in a study of HIV+ patients 93% felt there was an improvement in anxiety and 86% an improvement in depression (Woolridge *et al* 2005). (Class IV). Some improvements of mood have been reported in studies primarily looking at other indications for cannabis, such as multiple sclerosis and chronic neuropathic pain (see relevant sections). It is also possible, and indeed likely, that there is alleviation of mood if individuals use cannabis formulations for pain, as chronic pain is clearly associated with depression and thus alleviation of pain may well produce an improvement in mood. There is also a tendency for the relief of anxiety symptoms to be associated with relief of depression in those suffering from both disorders.

Conclusion

Overall, there is still much work to be done in terms of clinical trials to study the effect of cannabis formulations on depression. It is likely that the THC:CBD ratio is important in such studies given that THC in isolation can induce anxiety whereas CBD in isolation can alleviate anxiety. At the moment whilst there is considerable anecdotal and survey evidence of the use of cannabis formulations for the alleviation of depression there is very little convincing trial data on the topic. We can make no recommendation.

8.15.3 *Obsessive Compulsive Disorder*

According to research, 40-60% of individuals with obsessive compulsive disorder (OCD) do not respond to first-line treatments (Schindler *et al* 2008). Schindler and colleagues (2008) documented two cases in which the cannabinoid dronabinol was used and successfully treated OCD symptoms. However, this is Class IV research and, whilst of clinical importance, further research needs to be conducted in this area in order to corroborate these findings. In addition, there is some anecdotal evidence that THC may be effective in treating obsessive compulsive behaviour in individuals with Gilles de la Tourette Syndrome (GTS) (Curtis *et al* 2009a). However, this is specific to obsessive compulsive behaviours which may not constitute the OCD diagnosis. No recommendation can be made.

8.15.4 *Post-Traumatic Stress Disorder*

Research suggests that people suffering from PTSD use cannabis in order to regulate their symptoms (Bujarski *et al* 2012). Evidence is accumulating that cannabinoids may play a role in fear extinction (Passie *et al* 2012). PTSD is thought to be maintained by the amygdala becoming overactive. Cannabis may reduce the strength of traumatic memories, “calming” the amygdala and making it easier for individuals with PTSD to sleep and causing them to feel less anxious when experiencing flashback memories (Passie *et al* 2012; Neumeister *et al* 2013). Furthermore, endocannabinoids exert an amnesic effect, which may play an important part in the extinction of aversive memories (Marco and Viveros 2009).

Trezza and Campolongo (2013) suggest the existence of a link between endocannabinoids and maladaptive brain changes after trauma exposure. The authors note that although SSRIs are the preferred first line to treat the anxiety symptoms of PTSD, a large proportion of patients fail to respond to these medications. Furthermore, no suitable treatment is currently available to treat the maladaptive cognitive features of PTSD and/or to prevent its development. They suggest that endocannabinoid degradation inhibitors may be an ideal therapeutic approach to simultaneously treat the emotional and cognitive features of PTSD.

Rabinak and colleagues (2014) conducted an fMRI study using a randomized, double-blind, placebo-controlled, between-subjects design (n=14 per group) in order to investigate the effect of cannabinoids (oral dronabinol) on extinction memory recall in humans (Class II). Results suggested that pre-extinction administration of THC facilitates recall of extinction, as demonstrated 24 hours after extinction learning. The fMRI scanning showed that the brain areas involved in fear extinction were more active during extinction memory recall in the individuals who had received the THC. This study represents the first evidence that dronabinol modulates the neural circuits involved in fear extinction in humans.

Jetly and colleagues (2015) investigated male Canadian military personnel with PTSD in 2015 using a double-blind, placebo-controlled, between-subjects (at one time point) and also within-subjects (at two time points) design (n = 10 per group). They found that nabilone significantly decreased trauma-related nightmares when compared to the placebo group, and the nabilone group had significant global improvement (as measured by the Clinical Global Impression-Improvement (CGI-I)

scale) and general well-being as compared to placebo. These findings need to be replicated in a larger cohort but the study does support nabilone as a clinically effective treatment for PTSD (Class II). Further research needs to establish whether nabilone can alleviate other symptoms of PTSD, such as flashbacks and hypervigilance, in addition to nightmares.

Cougle and colleagues (2011) conducted a large survey of adults (n = 5,672) from the United States in order to look at the relationship between PTSD and cannabis use. They found that individuals with PTSD had a significantly increased use of cannabis even when the data were adjusted for confounding variables. The authors reported that there was a strong correlation between severity of PTSD symptoms and the amount of cannabis use. The literature suggests that individuals with PTSD are self-medicating with cannabis. However, this study was cross-sectional and so cannot address issues of causality regarding the relationship between cannabis use and PTSD (Class III).

Reznik (2012) carried out a naturalistic observational study with the aim of assessing and monitoring the effectiveness and safety of medical cannabis use in approximately 80 PTSD patients. The medical cannabis used was mostly of the *sativa* species and was supplied from several companies. The results showed good tolerability, an increase in quality of life scores, and improvements in trauma symptoms and in CGI-I scores, especially in patients with either pain and/or depression comorbidity (Class III).

A recent clinical trial to evaluate the effects of nabilone on treatment-resistant nightmares in 47 PTSD patients demonstrated that the majority of patients (72%) receiving nabilone experienced either cessation of nightmares or a significant reduction in nightmare intensity (Fraser 2009). Subjective improvement in sleep time, the quality of sleep, and the reduction of daytime flashbacks were also noted by some patients. The author relied on self-report measures which have inherent limitations, nevertheless the study represents promising results for future investigation (Class III).

Cameron and colleagues (2014) conducted a retrospective study of 104 male inmates with serious mental illness prescribed nabilone and results indicated a significant improvement in symptoms of PTSD. Although specific to the prison population, this study supports the use of nabilone as a safe, effective treatment for PTSD (Class III). Betthauser and colleagues (2015) reviewed the evidence for the use of cannabinoids in military veterans with PTSD and found a further four Class III studies in support of their use within this population.

Passie and colleagues (2012) described a case in which a male managed and reduced his symptoms of PTSD through smoking cannabis (Class IV).

Conclusion

Further larger scale research studies are required within this area in order to substantiate observational data and to determine the correct doses, most effective method of administration and timing of the exposure in relation to the traumatic event

that caused the PTSD. The studies to date represent encouraging possibilities for the use of medical cannabis in the treatment of this debilitating and often hard to treat mental disorder. We consider there is **moderate** evidence of efficacy in PTSD for nabilone and dronabinol and **some** evidence for the use of “natural” cannabis.

8.16 Cancer

It has been known for many years that cannabinoids can have antineoplastic (anti-cancer) activity. One of the very early papers was published as long ago as 1975 when it was demonstrated that lung adenocarcinoma cancer growth was retarded by the oral administration of THC and other cannabinoids in animal models (Munson *et al* 1975). It is, of course, likely that cannabinoids will not affect all forms of cancer but only specific types and very little is known about the mechanism of action at the present time. In some cases, cannabinoids can appear to kill specific tumour cells, particularly the glioma cells in a specific brain tumour, glioblastoma multiforme (Velasco *et al* 2004). Another potential specific effect seems to be on prostate cancer cells (Sarfaraz *et al* 2005). However, it is of some potential concern that depending on drug concentration cannabinoids can seem to inhibit or stimulate cancer cell proliferation. Thus it is clear that there is still a great deal to be learnt about the effect of cannabinoids on different tumour cell types (Bifulco *et al* 2006).

Another promising line of treatment is the use of cannabinoid receptor agonists in the treatment of oestrogen receptor negative breast cancer (Alexander *et al 2009*). A reasonably up to date review of the potential use of cannabinoids in cancer management has been published by Cridge and Rosengren (2013). Nikan and colleagues (2016) further reviewed how modulation of the endocannabinoid system may be appropriate treatment for several cancer subtypes.

Despite this theoretical anticancer effect there have been very few studies. In one study by Liang and colleagues (2009) the authors studied the relationship between

marijuana use and the induction of head and neck squamous cell carcinoma and found that 10-20 years of marijuana usage was associated with a significantly reduced risk of such cancer.

In humans the most promising therapeutic strategy at the moment seems to be the use of THC in patients with recurrent glioblastoma multiforme (a rare and aggressive form of brain tumour). A pilot phase 1 trial of nine patients with recurrent glioblastoma multiforme was conducted by Guzman and colleagues in 2006 (Guzman *et al* 2006). These patients had previously failed standard therapy, including surgery and radiotherapy, and had clear evidence of tumour progression. THC was administered directly to the tumour. The delivery was safe and there were no overt psychoactive effects. The main aim of the study was to determine safety rather than efficacy and the technique was deemed safe and may indicate one method of improving survival in this aggressive condition.

Conclusion

At the present time there is a reasonable evidence base for the anticancer properties of cannabinoids but very limited evidence of actual efficacy in human populations. Further studies are needed before any recommendation can be made.
We emphasise that cannabinoids have a significant role to play in the management of appetite loss and nausea and vomiting in the context of cancer chemotherapy.

8.17 Other Indications

There are a number of other case reports and anecdotal reports in a variety of other indications. However, none of these indications provide any firm evidence for efficacy but nevertheless may point the way to possible future uses. The indications that have been reported in the literature are:

- Attention Deficit Hyperactivity Disorder (ADHD) (Aharonovich *et al* 2006)
- Trichotillomania (Grant *et al* 2011)
- Tinnitus (Raby *et al* 2006)
- Pruritus (Stander *et al* 2006)
- Night sweats (Maida V 2008)
- Isaac's syndrome (Meyniel *et al* 2011)
- Night vision (Russo *et al* 2004)
- Asthma (Tashkin *et al* 1977)
- Breathlessness (Pickering *et al* 2011)
- Hiccups (Gilson and Busalacchi 1998)
- Amyotrophic lateral sclerosis (motor neurone disease) (Carter and Rosen 2001)
- Anti-psychotic effect (CBD) (Iseger and Bossong 2015)

9. Side Effects

The majority of the clinical studies discussed in this paper confirm that the side effects of cannabis in various formulations are in general mild and well tolerated. Many papers have listed the side effects encountered in trials. We have attempted to amalgamate the commonest side effects but we do not claim that this is a definitive review of all possible side effects, as a number of rarer problems will arise and have been reported. We felt it was reasonable to differentiate between short term effects of cannabis ingestion or inhalation on the one hand and potential longer term effects of cannabis on the other hand. The latter includes a discussion regarding concerns of triggering schizophrenia or schizophrenic-like illness in longer term users. We have also discussed the potential cognitive problems that might be encountered in the long term. We include a brief section on driving and cannabis, as continued driving in modern society is clearly an important factor for the medical usage of cannabis. We briefly review studies that may show some loss of brain volume in long term usage. We also discuss the possibility of respiratory cancers in relation to smoked marijuana. However, we should emphasise in that context that most of the publications on medical usage do not use or recommend smoked marijuana.

9.1 Short Term Effects

Ingestion and inhalation of cannabis is commonly associated with a number of effects. Most studies confirm that these effects are mild and well tolerated and the dropout rate from cannabis studies is quite low – usually less than 10%. This compares, for example, to dropout rate in studies of opioids from unacceptable side effects of around 33%. In the systematic review by Koppel and colleagues in 2014 the authors analysed 1619 patients who received cannabinoids for less than six months (Koppel *et al* 2014). Meta-analysis showed that 6.9% stopped medication because of adverse effects. This compared to 2.2% of the placebo patients in these studies that also stopped because of adverse events. The authors list adverse events that occurred in at least two studies as:

- Nausea
- Increased weakness
- Behavioural or mood change or both
- Suicidal ideation or hallucinations or both
- Dizziness or vasovagal symptoms or both
- Fatigue
- Feelings of intoxication

They also reported psychosis, dysphoria (general dissatisfaction, restlessness, low mood) and anxiety were generally associated with higher concentrations of THC but these side effects were not typical of the studies analysed.

The authors point out that there is no definite case of death as a result of overdose of cannabis in any formulation. The paper cites one death 'possibly related' to treatment which included a seizure followed by fatal aspiration pneumonia.

A further systematic review paper also looked at adverse events reported in 62 studies (Whiting *et al* 2015). These authors produced a useful meta-analysis for the number of participants in the studies experiencing any adverse event when compared with controls. The authors point out that no study has evaluated long term adverse events of cannabinoids and this is a significant problem with the current literature. The authors obviously confirm that there were more adverse events with cannabinoid treatments than with placebo but this is not surprising. The authors list the 'top 20' individual adverse events with odds ratio for developing such an event in comparison to placebo or with active comparator. The odds ratio is a measure of the increased (or decreased) chance of an event occurring compared to a comparator – in this case usually placebo. These 'leading' adverse events are as follows –

- Disorientation (Odds ratio (OR) 5.41 – in other words there is a 5.41 increased chance of disorientation compared to placebo)
- Dizziness (OR 5.09)
- Euphoria (OR 4.08)
- Confusion (OR 4.03)
- Drowsiness (OR 3.68)
- Dry mouth (OR 3.50)
- Somnolence (drowsiness or sleepiness) (OR 2.83)

- Balance problems (OR 2.62)
- Hallucination (OR 2.19)
- Nausea (OR 2.08)
- Paranoia (OR 2.05)
- Asthenia (OR 2.03)
- Fatigue (OR 2.00)
- Anxiety (OR 1.98)
- Vomiting (OR 1.67)
- Diarrhoea (OR 1.65)
- Depression (OR 1.32)
- Psychosis (OR 1.09)

Two adverse events (dyspnoea and seizures) were actually less common in the cannabinoid treatment group than the placebo or active comparator group. This list of the commonest 'short term' adverse events is entirely compatible with the authors' own analysis of the literature but we have not carried out our own calculation of the odds ratios.

Although there were only two studies in their review that evaluated native herbal cannabis they found no evidence that the effects of herbal cannabis differed from other cannabinoid formulations (such as nabiximols, dronabinol and nabilone) with similar THC proportions.

The literature is clear that the 'high' associated with cannabis, and one of the main reasons for recreational use, is associated with the main psychoactive component –

THC. Formulations that have a high THC will tend to have more psychoactive side effects. It is also known that CBD will to some extent counteract the effect of THC and thus formulations with a relatively high CBD level will have no or few psychoactive side effects. A case in point is nabiximols that has a 1:1 ratio of THC:CBD. This relatively high proportion of CBD will counteract the effect of an equally high proportion of THC and users of nabiximols do not experience a ‘high’. Thus we must emphasise again that the above side effect profile is characteristic of THC. Other formulations, particularly those higher in CBD would not carry this profile – as in discussed in several sections of this paper.

9.2 Comparison with Opioids

As one of the key uses of cannabis and cannabinoids is for chronic pain relief, then the authors have been asked to compare the side effect profile of cannabis and different cannabinoid formulations with the side effects of opioids. Opioids have been used for many years to relieve pain. Opioid is a term that historically refers to drugs derived from opium, including morphine. Other opioids have been produced synthetically such as hydrocodone, oxycodone and fentanyl. Opioids are powerful substances and overdose, deliberate or accidental, particularly with concurrent use of other depressant drugs, will commonly result in death from respiratory depression. Common adverse events include sedation, nausea, vomiting, constipation, urinary retention and falls. Thus there are significant risks in the older populations who may be at risk of falls, urinary retention and constipation in any case, as well as the risk associated with respiratory depression in the older age group. Overall, studies indicate approximately 0.2% per annum risk of death amongst patients prescribed opioids for non-cancer pain over a 10-year period (Gomes T *et al* 2011). Other, less serious, effects include itch, drowsiness, dry mouth, dizziness and other problems such as impaired sexual functioning, irregular menstruation, negative effects on the immune system and depression. The opioids are also known for significant withdrawal symptoms after cessation of therapy, including severe dysphoria, irritability, sweating, nausea, tremor, vomiting and muscle pain, which can often be followed by a long phase of depression and insomnia. Addiction is also a problem with opioids. More infrequent adverse events can also occur, including confusion, hallucinations, delirium, changes in body temperature and heart rate, headache and muscle spasm. There is no doubt that opioids are of significant use in medicine,

particularly in advanced and chronic pain, but nevertheless there are very significant risks associated with opioid therapy. In general terms there are significantly less risks associated with cannabis and cannabis formulations, particularly with regard to the very severe side effect of respiratory depression with risk of death.

9.3 Long Term Effects

9.3.1 *Side Effects in Relation to Schizophrenia and Psychosis*

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), the diagnosis of schizophrenia involves not only positive symptoms (hallucinations, delusional thinking, paranoia, thought disorder), but also negative symptoms (apathy, poverty of thought, flattened affect and social withdrawal) as well as cognitive impairment (impairment in memory function, attention and executive functioning) (American Psychiatric Association, 2013). The majority of the research into cannabis and schizophrenia has focused upon the positive symptoms of schizophrenia. Therefore, this is a limitation of the research base as a whole. There also needs to be clarity around whether we are talking about psychotic symptoms or the clinical diagnosis of schizophrenia. The authors will describe the research detailing both of these outcomes in relation to side effects of cannabis use. The following research is described in categories relating to the classification scheme used throughout the report.

Class IV research

D'Souza and colleagues (2009) carried out a literature review on this topic and suggested that cannabis use can cause some transient (minutes to hours) psychotic symptoms in mentally well individuals. The research that D'Souza and colleagues drew these conclusions from was anecdotal evidence, case reports and surveys and

so would fall into Class IV (D'Souza *et al* 2009). Furthermore, the research base that D'Souza and colleagues used was quite dated and ranged from 1968-1984.

Reilly and colleagues (1998) surveyed 268 long-term cannabis users using a structured interview and found that 21% of users reported anxiety, paranoia, and depressive symptoms, and 21% reported tiredness, lack of motivation and low energy levels. Although paranoia can be seen as a positive symptom of schizophrenia and lack of motivation could be seen as a negative symptom, the study had various limitations. The majority of the participants were regularly drinking alcohol and quarter had taken other drugs within the previous month so it is hard to ascertain causality of the reported affects. Furthermore, the participants were from a rural area of Australia and so the findings may not generalise to other geographical areas. In addition, the study used a "snowball" sampling method rather than random sampling meaning that they may have similar characteristics as they were associates of each other. Another factor that complicated the results was that the participants differed in their frequency of use and method of administration. Despite these reported negative effects of cannabis, 61% of the sample reported that the main reason that they used cannabis was for its positive effect of relaxation.

Another study within Class IV has been carried out by Thomas (1996) in which 200 New Zealanders (aged 18-35 years) completed a self-report questionnaire about their experiences of the adverse effects of cannabis use. Fifteen percent of this sample reported psychotic symptoms following usage. However, the chemical content of herbal cannabis can vary and the dosage and frequency of usage varied

across the sample. Furthermore, self-report data has inherent limitations as it is dependent upon the degree of insight and social desirability within the individual.

The issue of causality between cannabis use and the onset of schizophrenia and psychotic symptoms is complex and involves many factors. McLoughlin and colleagues (2014) suggest that other factors need to be considered such as social class, additional drug use, and reverse causality whereby an individual starts to use cannabis as a means of coping with prodromal symptoms of schizophrenia, such as low mood, and consequently the cannabis use is attributed as the cause when the illness may have started prior to this drug use (the self-medication hypothesis). However, even when taking these factors into account, cannabis has still been associated with an increased risk of developing schizophrenia (Matheson *et al* 2011). Despite this increased risk, Hill (2014) points out that within the Western world there was a dramatic increase in cannabis use in the 1960s and 1970s and yet the prevalence of schizophrenia has largely remained stable.

Henquet and colleagues (2005a) carried out a meta-analysis of seven prospective studies into the role of cannabis use and psychosis and they reported an overall odds ratio of 2.1. Within these prospective studies, baseline cannabis use consistently increased the risk for psychosis at follow-up. This effect was not due to confounding variables since all studies included in the meta-analysis had adjustments made to account for confounding variables. Confounding variables included age, sex, social class, ethnic group, family history of psychiatric illness, urbanicity, and use of other drugs. Henquet and colleagues (2005a) also concluded that the association was not due to reverse causality because four of the studies

included in the analysis had addressed this issue by either excluding or adjusting for participants with predisposition to psychosis or using statistical modelling to distinguish the likelihood of causality. However, a predisposition to psychosis has been shown to predict future use of cannabis (Ferdinand *et al* 2005) and so may partly explain the association between cannabis and psychosis. Therefore, both the self-medication hypothesis and the causal hypothesis may be true. Henquet and colleagues (2005a) states that "Causality is generally thought to be plausible if studies (i) report an association between the exposure and the outcome consistently and with a strong effect size, (ii) show dose-response relationships between the exposure and the outcome, (iii) show that the exposure precedes the outcome, and (iv) show that there is a plausible biological mechanism linking the exposure and the outcome". Criteria i-iii were fulfilled by the studies included in the meta-analysis with the exception of the large effect size needed to confirm causality.

Various authors have proposed biological mechanisms by which cannabis may cause psychosis in terms of neurodevelopment in adolescence (Schneider and Koch 2003; Veen *et al* 2004) and dopamine sensitivity (Howes *et al* 2004). However, this is far from established and needs further research. A limitation of the meta-analysis carried out by Henquet and colleagues (2005a) was that the studies included did not measure cognitive functioning, which is a core component of the schizophrenia diagnosis.

Another large meta-analysis was conducted by Moore and colleagues in 2007 which analysed seven longitudinal, population based, studies (Moore *et al* 2007). The authors found a dose-response effect in that there was a greater risk of developing

psychosis in people who used cannabis more frequently. The pooled odds ratio was 1.41 which had been adjusted for confounding variables and which was independent of transient intoxication effects. The studies attempted to limit reverse causation through adjusting for psychotic symptoms or predisposition to psychosis, and excluding participants with psychosis at baseline. Attrition rates were included for six out of the seven studies and a limitation of the meta-analysis may have been that attrition rates had a small effect on the results. The authors note that attrition rates are higher in individuals who use drugs and in those who develop mental health problems and so this would have the effect of underestimating the strength of association. Based on the odds ratio of 1.4, Moore and colleagues (2007) estimated that 14% of psychosis cases within the UK were due to cannabis use.

Class III Research

Leweke and colleagues (1999) reported the effects of oral synthetic THC in 17 healthy males under controlled laboratory conditions. Reactions amongst the participants ranged from mild euphoria to feelings of loss of self-control and body distortion suggestive of psychotic symptoms. One subject went into a two-hour psychotic episode and experienced paranoia, persecutory delusions, and delusions of thought insertion. These findings cannot be generalised to the female population, a control group was not used, and a standardised outcome measure of psychosis was not used.

In 2004 D'Souza and colleagues carried out a randomised, double-blind, placebo-controlled study of 22 healthy control participants (D'Souza *et al* 2004). The authors

found that THC produced transient positive symptoms of schizophrenia (paranoia, perceptual alterations, grandiose delusions, feelings of unreality, depersonalisation and derealisation, and disordered thinking), symptoms that are similar to the negative symptoms of schizophrenia (blunted affect, psychomotor retardation, and a lack of spontaneity), and cognitive difficulties such as impaired immediate and delayed verbal memory recall. Participants were screened for psychiatric disorders and family history of those disorders. Outcomes were assessed by standardised measures of psychosis (the Positive And Negative Symptom Scale, PANSS), perceptual alterations (the Clinician Administered Dissociative Symptoms Scale) and verbal learning and recall (Hopkins Verbal Learning Test, HVLT). Baseline characteristics were not presented in the form of comparison of the different groups so we cannot presume that these were equivalent. In addition, the study did not account for attrition rates.

Degenhardt and colleagues (2007) carried out a 10-month prospective study in 2007 that looked at the relationship between cannabis use and symptoms of psychosis in 101 individuals with a current diagnosis of schizophrenia. They found that cannabis use predicted a small but significant increase in symptoms of psychosis in the following month after increased cannabis use. This effect was present even when confounding variables of age, gender, other drug use, medication compliance and symptoms of depression were controlled for. Outcomes were measured using standardised assessments but the study was slightly underpowered due to its limited sample size. Despite this small effect, this study indicates that there is a risk of increased symptoms within individuals already suffering from schizophrenia following cannabis use.

Conversely, Casadio and colleagues (2011) found a significant clinical improvement in psychotic symptoms following cannabidiol therapy.

Cannabis is often used as a form of self-medication amongst people suffering from psychosis with the belief that it reduces psychotic symptoms or reduces the unpleasant side-effects of antipsychotic medication (Dixon *et al* 1990); and the prevalence rates of cannabis usage in people diagnosed with schizophrenia are much higher than the general population at 40% (McLoughlin *et al* 2014). In 2005 D'Souza and colleagues conducted another randomised, double-blind, placebo-controlled study similar to the one they carried out in 2004 but this time with a population suffering from schizophrenia (D'Souza *et al* 2005). They found that THC caused a transient increase in positive and negative symptoms of schizophrenia as well as cognitive difficulties. These effects occurred despite the participants being stable and compliant with taking antipsychotic medication. Compared to their 2004 study on healthy individuals, patients diagnosed with schizophrenia appeared to be more sensitive to THC effects as measured by the PANSS and HVLT. However, confounding variables may be the effect of the course of the illness itself and its impact upon cognitive ability, and the complex effect of some antipsychotics upon cognition. Further research is needed into this population of individuals suffering from schizophrenia who are using cannabis in order to ascertain the effects upon their positive, negative and cognitive symptoms. This is particularly merited given the increase in THC within street preparations of the drug and a decreasing age of first-time exposure to cannabis (Casadio *et al* 2011)

De Hert and colleagues (2011) investigated the influence of cannabis on the age of onset of schizophrenia using a regression analysis. They found that cannabis use was associated with a decrease in the age of onset by an average of 1.5 years, which was representative of both males and females. Another study by Ongur and colleagues (2009) concluded that lifetime cannabis use was associated with a significantly earlier age of onset of psychosis by 3.1 years when compared to non-users.

A Swedish cohort study carried out over 35 years found an odds ratio of 3.7 for schizophrenia, 2.2 for brief psychosis, and 2.0 for non-affective psychoses when they compared frequent cannabis users with non-users. (Manrique-Garcia *et al* 2012) The study involved 41,943 male Swedes conscripted between the years 1969-1970, and so cannot be generalised to the female population. This risk declined over time for moderate users but much less so for frequent users, and the associations were stronger within the highest consumption category. The study looks at hospitalisation for psychosis and so may have missed those who had still experienced psychosis but had managed to function without inpatient care (through accessing community mental health services, for example). The data was adjusted for confounding variables which are likely to be related to cannabis use and schizophrenia including psychiatric diagnosis at conscription, low IQ, urbanicity, cigarette smoking, and 'disturbed behaviour' (such as truancy and contact with the Police). However, the study did not account for the confounding variable of other drug use. The authors described 60% of the cases of schizophrenia occurring in the first decade compared with 45% in non-users of cannabis, which supports the proposition that cannabis can trigger an earlier onset of this mental illness.

However, a limitation of this study is that they only have data regarding cannabis use at and prior to the date of conscription when the participants were on average 18 years old and so we do not have information on consumption in subsequent years. Furthermore, self-report data is limited because it is reliant on accurate disclosure by the individual and conscripts may have under-reported drug use or even over-reported in an attempt to avoid conscription.

Manrique-Garcia and colleagues (2014) analysed the same data from Swedish conscripts as in their 2012 study, in order to determine whether cannabis users had a different prognosis compared to non-users. Data from 357 participants were analysed. They found that prognosis was worse in cannabis users in terms of significantly longer inpatient stays, a higher rate of readmission to hospital, as well as being more likely to have inpatient stays of longer than two years. Confounding variables were controlled for but a limitation of the study is that substance use is often associated with poor medication compliance, which would affect the prognosis of the illness.

Another longitudinal study by Arseneault and colleagues (2002) found evidence in agreement with the Swedish study described above in that using cannabis in adolescence increases the likelihood of experiencing symptoms of schizophrenia in adulthood. They looked at a birth cohort of 759 individuals born in New Zealand between 1972-1973 and assessed their psychotic symptoms at age 11, their drug use at ages 15 and 18 and re-assessed these outcomes at age 26. This study controlled for psychosis preceding the cannabis use, which suggests that the cannabis use is not secondary to a pre-existing psychosis (evidence against the self-

medication hypothesis). In addition, the risk was specific to cannabis use rather than to other drugs such as glue, cocaine and opiates. Furthermore, this research found that earlier onset of cannabis use (by age 15) causes a greater risk of later developing schizophrenia; indeed they are four times more likely to have this diagnosis than controls. However, Moore and colleagues (2007) points out that the increase risk of psychosis if cannabis is used from a younger age may be due to increased exposure at this age rather than a sensitive period per se.

Henquet and colleagues (2005b) found that the effect of cannabis use was much stronger in those individuals with previous experience of psychotic symptoms than in those without this previous experience. The authors analysed data from 2437 young participants aged 14-24 years over a four-year period. The sample was randomly drawn from the registry offices of Munich giving a representative population based sample. Psychotic symptoms were measured by diagnostic interview carried out by trained psychologists and self-report measures. They found that cannabis use at baseline increased the incidence of psychotic symptoms at follow up four years later after confounding variables were controlled for such as age, sex, socioeconomic status, urbanicity, childhood trauma, use of other drugs, tobacco, alcohol use, and also a predisposition for psychosis at baseline. These data did not support the self-medication hypothesis since baseline predisposition for psychosis did not predict cannabis use at follow-up.

In terms of studies looking at genetic risk, McGuire and colleagues (1995) found that the first degree relatives of patients with psychosis who used cannabis had a 10 times higher risk for developing schizophrenia (at 7.1%) than the relatives of patients

who were non-users (at 0.7%). The findings suggested that the development of psychosis in the context of cannabis use may be associated with a genetic predisposition to schizophrenia. In support of this finding, Henquet and colleagues (2005b) reported that the risk of developing psychotic symptoms was 21% in individuals without genetic predisposition to psychosis and 51% in individuals with a genetic predisposition, with both groups using cannabis (more detail of this study is described above). Power and colleagues (2014) studied the genetics of 2082 healthy individuals and suggested that the association between schizophrenia and cannabis is due to a shared genetic aetiology; the same genes that increase psychosis risk may also increase risk of cannabis use. Their results suggested that individuals with an increased predisposition to schizophrenia are more likely to use cannabis. This study implied that the association between cannabis use and psychosis could be bidirectional, in which case the risks of cannabis use in causing schizophrenia could be overestimated within the research. Indeed, a recent study by Giordano and colleagues (2015) indicated that population-based estimates of cannabis-schizophrenia comorbidity substantially overestimate their causal association. There is strong evidence for genetic contributions to both schizophrenia and cannabis use (Giordano *et al* 2015), and so part of this association may be confounded by genetics. The authors studied a sibling-pair group who were discordant in their cannabis use alongside a general population sample in order to control for this potential confounder variable. Sibling pairs are a natural experiment; they share 50% of their parents' genes and often share similar environmental factors. Once familial confounding was controlled for, the risk of later developing schizophrenia substantially reduced within the cannabis users. Although this latest research supports the earlier findings that cannabis use has a causal impact on the

risk for developing schizophrenia, this risk is likely to have been overestimated in the previous literature and when familial confounding is controlled for, this risk reduces by approximately two thirds. A limitation of the Giordano and colleagues (2015) study is that it used individuals admitted to hospital or convicted of cannabis use and so their findings may not generalise to individuals with lower levels of cannabis use and less severe psychosis.

Class I and II Research

Randomised controlled trials of cannabis and schizophrenia are clearly difficult to undertake. This is partly because the synthetic preparations of the drug differ from the recreational drug and therefore studies using synthetic (legal) cannabinoids may not help to address the issue of causality. The relatively short follow-up period of randomised controlled trials may also limit the results.

Conclusion

We have seen that cannabinoids can induce transient symptoms similar to the positive, negative, and cognitive symptoms of schizophrenia in healthy individuals. However, these are short-lived symptoms and do not constitute a psychiatric condition. The research suggests that cannabinoids can exacerbate symptoms within individuals already suffering from psychosis and the use of herbal cannabis has been shown to reduce the age of onset of psychosis. In addition to these findings, the prognosis of the course of the illness has been shown to be worse within individuals who have used cannabis, as indicated by longer inpatient stays

and more readmissions. Furthermore, people who have a genetic predisposition to developing psychosis are more likely to develop psychotic symptoms following cannabis use.

However, the direction of the causal link between cannabis use and psychosis has not been fully established as yet and this association is likely to have been overestimated in the earlier research papers. Hickman and colleagues (2009) considered how many cannabis users would need to stop the habit in order to prevent one case of schizophrenia or psychosis. These estimates are considerable, ranging, for men aged 20–24, from 2800 for heavy cannabis users to more than 10000 for light cannabis users; and, for women aged 20–24, from 7700 for heavy cannabis users to 29000 for light cannabis users. These figures demonstrate that the actual clinical risk of cannabis causing schizophrenia is very low and this needs to be considered, holding in mind the risks and benefits that all pharmaceutical medicines share.

A limitation of the research base in this area is that studies do not often measure cognitive functioning or negative symptoms, which are core components of the schizophrenia diagnosis, and rather the focus has been on positive symptoms. Furthermore, the literature needs to be clear about whether we are hypothesising a link between cannabis and the symptoms of psychosis or the diagnosis of schizophrenia, or both. In addition, the literature would benefit from a consistent way of measuring either psychosis or schizophrenia; the DSM-5 has rarely been used in these studies as a standardised clinical diagnostic tool. Another difficulty within this area of research is that it is impossible to ascertain the balance of THC and CBD

within the herbal recreational cannabis that the participants consumed. The more recent studies are also more likely to include individuals who have used herbal cannabis with a higher level of THC since street preparations are increasingly using a higher concentration of this chemical (Casadio *et al* 2011).

In conclusion, the majority of the literature gives support for a causal hypothesis between cannabis use and psychosis, particularly if usage starts at an early age (young adolescence) and if the individual has a genetic predisposition to psychosis. We know that it is unlikely that any one environmental factor (such as cannabis use) or any one gene can cause schizophrenia on its own. It appears that cannabis is a component cause in the development of symptoms of schizophrenia and the onset of this mental illness depends upon many interacting factors. However, it is also important to remember that most people who use cannabis do not develop schizophrenia, and most people with schizophrenia have never used cannabis.

The authors wish to emphasise that it is likely that THC is the main cannabinoid which triggers schizophrenia and psychosis. CBD on the other hand is known to be anti-psychotic and may have a therapeutic role as an anti-psychotic agent although further studies are required (Iseger and Bossong 2015).

9.3.2 *Dependence*

Dependence on cannabis is actually quite unusual and the generally accepted figure is that about 9% of those who use cannabis develop dependence. Most of the studies have been done in recreational users. Dependence has been defined in the

International Classification of Diseases and Health Problems (ICD10) as ‘a cluster of physiological, behavioural, and cognitive phenomena in which the use of a substance or a class of substances takes on a much higher priority for a given individual than other behaviours that once had greater value’. A central characteristic is a strong desire or sense of compulsion to take the substance. There are difficulties in controlling the substance-taking behaviour and a physiological withdrawal state on cessation of the drug is also characteristic. In an article in the Lancet in 2007 a scale was developed to assess the harm of drugs of potential misuse (Nutt *et al* 2007). Heroin was highest on the list of both psychological and physical dependence following by cocaine, tobacco, barbiturates, alcohol, benzodiazepines and amphetamine. Cannabis was eighth on this list. The dependency rate of around 9% compares to a dependence rate of alcohol of around 15%, cocaine of around 17%, heroin 23% and tobacco 32%. We do not wish to underplay the potential problem of dependency in some individuals but nevertheless the risk is reasonably small and is less likely to be the case in medical usage, as prescription, formulation and use is likely to be more controlled than in recreational usage.

9.3.3 *Driving and Cannabis*

Driving is an important component of modern society. Individuals taking cannabis for medical reasons will need to be given advice on whether they should or should not drive whilst taking the drug. Such advice is, of course, common in prescriptions of all psychoactive drugs. Studies tend to confirm that a single ‘dose’ of cannabis does impair driving and indeed that effect is exaggerated when combined with alcohol.

THC has been shown to impair both psychomotor function and actual driving performance in a dose related manner (Ramaekers *et al* 2004). The degree of impairment of performance in experimental studies has shown that a dose of THC of up to 300 mcg / kg produces equivalent impairment to alcohol concentration of 0.05g/dl which is the legal limit for driving in many European countries. Studies have also shown that detectable THC in the blood at the time of accident means that those drivers are three to seven times more likely to be responsible for their crash compared to drivers who do not use drugs or alcohol. However, the authors wish to emphasise that such studies have mainly been carried out on illegal cannabis users and the cannabis attained is likely to be high in THC and may contain impurities. We also point out that non-psychoactive cannabinoids, such as CBD, are not likely to carry any risk with regard to driving. The importance of determining the safety in regard to the specific formulation is confirmed in a study by Friedel and colleagues (Friedel *et al* 2015) which showed no effect on driving performance in relation to nabiximols.

Thus there should be no ‘blanket’ ban on driving with concomitant cannabis medicinal usage but it would be dependent on the circumstances and type of cannabis taken. However, doctors prescribing cannabis should be aware of the need to caution patients with regard to driving (and probably using machinery) whilst taking the medication.

A useful summary article on the effects of cannabis and driving skills has recently been published by Hartman and Huestis (2013).

9.3.4 *Respiratory Cancer and Cannabis*

The commonest form of recreational intake of cannabis is by smoking. However, the great majority of cannabis trials for medical use do not involve smoking the natural product. Either the product is taken in capsular form (nabilone and dronabinol) or by oromucosal spray (nabiximols) or if cannabis extract/herbal cannabis is used then other forms of ingestion/inhalation are recommended, such as vaporisation. Thus the number of studies of medicinal use by smoking cannabis is very limited. If cannabis is legalised in the UK for medical use, then smoking is unlikely to be the recommended route and thus the risk of lung cancer is minimal. The problem with epidemiological studies on this subject is that many recreational cannabis smokers also smoke tobacco which is, of course, a known carcinogen for lung and upper respiratory/throat/mouth cancers. Some studies have shown no connection between marijuana smoking and lung (or colorectal cancer) and indeed some studies have shown that compounds found in cannabis have an anticancer effect (see Cancer section above). Thus the effect of cannabinoids is complex and indeed sometimes contradictory. Nevertheless, smoke from both tobacco and cannabis contains many of the same carcinogens. In a review of the subject (Melamede 2005) the author concludes that both tobacco smoke and cannabis smoke contain carcinogens but the THC inhibits the enzyme necessary to activate some of the carcinogens found in the smoke. The author points out a number of other differences between tobacco smoke and cannabis smoke and concludes that the current evidence does not suggest that cannabis smoke will have a carcinogenic potential comparable to that resulting from exposure to tobacco smoke. He also makes the point that

development of cannabis vaporisers largely eliminates the carcinogenic potential of smoking cannabis.

As long as smoked cannabis is not the recommended route then the risk of respiratory cancer seems very small or non-existent.

9.3.5 *Cognition and Cannabis Use*

A number of conditions that may benefit from cannabis prescription are associated with cognitive deficits – such as multiple sclerosis, traumatic brain injury, Parkinson's disease, etc. Thus if cannabis in any formulation caused additional cognitive impairment then this would be of some concern. There is a considerable literature on this subject and it is not the purpose of this paper to review that literature in detail. Most of the neuropsychological studies have been carried out on recreational cannabis users and thus, whilst of relevance, are not necessarily applicable to those who use cannabis in more controlled form for medical reasons.

There are many studies of the neuropsychological effect on acute intoxication with cannabis, usually in the form of the smoked product. The evidence is reasonably clear that cannabis, particularly the THC component, impairs psychomotor performance and cognition. Most attention has focused on deficits of episodic memory. (episodic memory is autobiographical memory for time, places, associated emotions, etc.) There are also deficits noted in attention and concentration and some elements of higher executive functioning, including decision making and abstract

reasoning (Crane *et al* 2013). As we have seen the short term effects are usually mild.

In terms of the longer term medical usage, it is more relevant to look at the potential cumulative cognitive effects of cannabis intake. Some studies have indicated residual effects after several hours to several days of abstinence and some studies have shown longer term effects after several weeks of abstinence whilst other studies have shown no clear evidence for residual or long term neuropsychological deficits amongst cannabis users (Crean *et al* 2011). Studies differ on whether there are long term effects on attention, concentration and working memory. Some confirm that there are documentable deficits after weeks of abstinence whilst others refute the suggestion. There is some evidence that the neurocognitive deficits have a greater impact if cannabis is started at a young age (during adolescence) when relevant parts of the brain are still developing. There is also evidence that the effect is dose related in that heavy users have more cognitive deficits than lighter users. In terms of patient use there is some evidence that, in multiple sclerosis, cannabis use can worsen the cognitive deficits that already exist in such patients (Pavisian *et al* 2014). There is further evidence that the THC component in cannabis has more negative neurocognitive effects than the cannabis formulations relatively high in CBD. The formulation of cannabis is very likely to be important. A study by Vachova and colleagues (Vachova *et al* 2014), for example, has shown no long term cognitive effects following nearly one year of nabiximols usage in 121 patients in a placebo controlled, double blind study in MS spasticity.

There are very few studies indeed that have followed individuals in the longer term and studied their ongoing cognitive functioning. At the present time the authors conclude there is no firm evidence that would suggest that the possible cognitive problems of cannabis use are of sufficient severity to give rise to concern but it may be sensible to suggest that prescription in adolescence should be given with more caution than in adults, given the probable susceptibility of the developing brain (Jacobus and Tapert 2014).

The historical literature on cannabis has emphasised that an “amotivational” syndrome can occur in cannabis users. This syndrome is well known in neuropsychological terms and usually, but not always, reflects specific damage to the frontal lobe of the brain. It is characterised by lack of initiation, apathy, passivity and, incorrectly, is often labelled as “laziness”. It is quite common after traumatic brain injury. It is still thought by some to be a cannabis-related issue and indeed features in a recent publication by the National Institute of Drug Abuse in the US (US Department of Health and Human Services 2014). However, there is no convincing evidence that this is the case. A thorough review (Barnwell, Earleywine and Wilcox 2006) failed to show any difference in motivation between cannabis users and non-users. In the short term, cannabis can induce a state of “relaxation” and indeed this is the desired result in many recreational, and medicinal, users. Some actually find this effect helpful in terms of their ability to cope in stressful social situations (Buckner and Zvolensky 2014). However, we find no convincing evidence of longer term social detriment.

Clearly more studies are required, particularly in a medical population that may already have cognitive deficits, in order to determine the longer term possible cognitive deficits and whether brains already damaged by various pathologies are more prone to further damage from cannabis use or whether there is no such correlation.

9.3.6 *Brain Volume and Cannabis*

There has been some concern in the literature that cannabis may give rise to reduced brain volume, particularly in long term heavy recreational users. In one study 15 long term (> 10 years) and heavy (> five joints daily) users showed bilateral reduced volume of the hippocampus and the amygdala (central parts of the brain - Yucel *et al* 2008). Other neuroimaging studies have failed to show such change. In a review by Lorenzetti *et al* (2010) the authors identified 13 structural neuroimaging studies and found that no study noted global structural change in cannabis users but six studies reported regional alterations, particularly in the hippocampus and the para-hippocampal region. However, these findings were inconsistent across the studies. The authors suggested that the overall evidence was that THC exposure does affect brain morphology but given the small literature and the limitation of the studies further research was required. Those studies that have shown changes in the hippocampus have tended to be in the heavy recreational user.

The main problem with these studies is that even if it is shown that regional brain volume is affected in long term users, then the importance of such findings is entirely unknown. Is such a reduced volume of relevance in the long term and might it lead,

for example, to cognitive decline or mental health issues? At the moment there is no evidence that brain volume loss, if it occurs, is associated with any such longer term issue. Recent authors have shown a lack of such brain volume changes with regard to CBD usage and have suggested that if THC is associated with loss of volume then such potential harm is minimised by the additional use of CBD and that such changes can be reversed by extended periods of abstinence (Yucel *et al* 2016).

10. Impact of Potential Legalisation of Cannabis in the United Kingdom

The authors see a number of potential benefits of legalisation of cannabis in the United Kingdom but one also has to recognise some potential drawbacks.

It is clear from the literature and from presentations to the APPG for Drug Policy Reform that there is widespread use of cannabis in the United Kingdom for medicinal purposes. Legalisation would take many tens of thousands of people, currently using cannabis for medical purposes, out of the criminal justice system. At the moment such individuals are exposed to the illegal trade with the concern of putting potentially vulnerable people in potentially hazardous situations – and risking prosecution.

Cannabis obtained illegally can be highly variable in terms of the quality of the product. We see, from a medical point of view, that a significant advantage of legalisation is that there could be far better quality control. Such quality control now occurs in a number of US states. In many states there are licenced producers who are subject to strict quality control measures. The supply by the Dutch Ministry of Health of the various bedrocan products is a further example of an improvement in quality control that can be obtained through a legal system.

It is also clear from the evidence presented in this paper that a key factor in the efficacy of cannabis is the ratio between the THC content and the CBD content. If the products are produced by licenced and quality checked growers, then this ratio

can also be controlled. This is the case with the various bedrocan products and also the case with the nabiximols oromucosal spray.

The authors recognise that even if production is controlled then there is a risk of diversion of the product into the recreational market. This is known to be the case in some of the US states, such as Oregon. Indeed, Oregon growers produce a total of approximately 408,000lbs of medical marijuana each year, yet it has been estimated that Oregon's medical marijuana patients should only require about 85,000lbs per year (Privateer Holdings 2015). The authors of that paper assume that the excess production is diverted into the illegal market. However, in states where the supply chain is fully controlled, then the diversion rate is much less. An early study in Colorado in 2012 demonstrated that 74% of adolescents had used someone else's medical marijuana (Salomonsen-Sautel *et al* 2012). This study, as well as other political and social pressures, led to tightening of the supply chain in Colorado with the creation of licenced pharmacy premises. In most of the US states which have legalised marijuana, a physician has to approve an individual patient as being able to access the product – usually against a number of allowed medical indications. This also reduces the diversion rate and secures the supply chain as far as possible.

The authors particularly recognise the benefit of legalisation of cannabis in terms of improving the evidence base for the efficacy and safety of the product. As will have been clear from this paper, many of the studies into the efficacy of cannabis have, not surprisingly, involved only the licenced products nabilone, dronabinol and nabiximols. There is limited evidence of efficacy, at least in formal academic studies, of the efficacy of the 'natural' product. Legalisation would allow such studies to be

undertaken in large and meaningful numbers for the different indications and in a controlled format. This paper has demonstrated there are many applications that have a theoretical basis and have some evidence of efficacy but such evidence is limited. Legalisation, over a period of time, would clearly correct this defect in our knowledge. The other key factor that could be properly studied is the incidence of the short and long term side effects of the product. Most of the studies of side effects of cannabis have been in recreational users and have not been properly controlled in the medical context. It is just as important to determine the short and long term safety of the product as it is to determine the overall evidence of efficacy in different indications. Indeed, it would be possible, as was the case for disease modifying drugs in multiple sclerosis, for medical users to be automatically entered into an appropriate long term study, particularly with regard to side effect profile.

Have we seen advantages, from a medical viewpoint, of legalisation in US States? Obviously, at a personal level many individuals will have been assisted by the medical legalisation process in many US States. However, it would appear that these States have not initiated any coordinated research programme to monitor the impact, in medical terms, of such legalisation. Formal studies are hampered by the fact that the US Food and Drug Administration (FDA) still views cannabis as an illegal drug under the Controlled Substances Act, whereas 24 states and the District of Columbia approve and regulate its medical use. This confusion makes coordinated research difficult as it is the FDA that has to approve the safety and efficacy of any prescription drug. There is wide variation between States in the conditions approved and in the production chain. Some States allow growth of the plant by the individual whereas others only allow production by licensed growers and supply through

licensed dispensaries. It so far appears that the opportunity for proper, large scale studies of efficacy and safety is being missed in the US, although some studies are underway and results are awaited.

In summary, from the patient point of view, legalisation of medical cannabis would take individuals outside the criminal justice system. It seems preferable for the growth and supply of cannabis to be formally regulated so that the quality of the product, and particularly the THC:CBD ratio, can be controlled. The supply chain should be secured as far as possible to reduce diversion into the recreational market. Patients using cannabis could be entered into proper studies both of the efficacy of the product and also of the short and long term side effects.

11. Conclusions

Cannabis has been used as a medicinal product for centuries. However, it is only in recent decades that neuroscientists have discovered that humans have natural cannabinoid receptors and natural chemicals that bind to those receptors. This is known as the endocannabinoid system. It is now known the endocannabinoid system is not only found throughout the brain but also in many other regions of the body, including the digestive tract, the bladder and the metabolic, endocrine and immune systems. The endocannabinoid system is involved in modulation of pain, regulation of motor activity and has a role to play in brain plasticity, protection of brain cells and aspects of memory processing. It seems to have a role in the regulation of tumour growth. Our knowledge of the endocannabinoid system is rapidly expanding and it is clear that it is an important regulator of many bodily functions. It is also becoming clear that manipulation of the endocannabinoid system can have an important role in the management of many common diseases and disorders.

It is thought that the natural phytocannabinoids found in the cannabis plant are able to interact with the human endocannabinoid system and thus modulate the effects of that system. Thus there is now a good scientific rationale for the mode of action of cannabis in many diseases.

This paper has demonstrated the depth and breadth of evidence for cannabis in a number of different disease states. The scientific literature has focussed on the cannabis products that are legally available. In the UK nabilone (Cesamet) is legally

prescribable for nausea and vomiting and nabiximols (Sativex) is legally prescribable for management of resistant spasticity. The former is a synthetic form of THC, which is the most widely occurring phytocannabinoid. The latter is 1:1 mixture of THC and the second most common phytocannabinoid – cannabidiol (CBD). In the United States further work has been carried out on another synthetic form of THC – dronabinol (Marinol). The studies on 'natural' cannabis and cannabis extracts are not surprisingly limited by the fact that in most countries the product is illegal. However, despite these difficulties there is evidence for the efficacy of cannabis in a number of different indications.

This paper has shown that there is **good** evidence for the efficacy of at least one formulation of cannabis in:

- Pain – both chronic pain and neuropathic pain
- Spasticity – mainly in multiple sclerosis but there is no reason why it should not be just as efficacious in spasticity secondary to other neurological disorders
- Nausea and vomiting – particularly in the context of chemotherapy
- Anxiety

We find there is **moderate** evidence for efficacy in:

- Parkinson's disease
- Sleep disorders
- Fibromyalgia
- Post-traumatic stress disorder
- Appetite stimulation – most of that evidence in the context of HIV infection

There is **some** limited evidence of efficacy, but clearly further studies are required, in:

- Epilepsy (particularly the drug resistant childhood epilepsies)
- Bladder dysfunction in the context of neurological disorders, especially multiple sclerosis
- Glaucoma
- Control of agitation in dementia
- Tourette's syndrome

We have found that there is a reasonable theoretical base but so far **no** convincing evidence for efficacy in dystonia, a neuroprotective effect in traumatic brain injury, Huntington's disease, headache, depression, obsessive compulsive disorder, gastrointestinal disorders, as an anti-psychotic agent (CBD). We find no convincing evidence so far for an effect on cancer.

Obviously some of these recommendations are drug specific, as the studies have only been done in the context of the licenced products.

There is clearly a considerable amount of work yet to be done to further determine the efficacy in these, and probably other, indications and also to determine the best dose of the product and, in particular, which type of cannabis, especially in terms of the THC:CBD ratio, best helps each specific condition.

We know a considerable amount about the short term effects of cannabis, which are generally mild and well tolerated. We know less about long term effects. The most

studied possible long term effect is with regard to schizophrenia. Our conclusion is that the majority of literature gives support for a causal link between cannabis use and psychosis in certain circumstances, particularly if usage starts in adolescence and if the individual has a genetic predisposition to psychosis. If cannabis is legalised it may be preferable for caution to be exercised in prescription for those with a personal history or family history of schizophrenia. There is a small risk of dependency with “natural” cannabis use in the order of 9% but this favourably compares to higher levels of dependency in, for example, alcohol and tobacco users. Caution needs to be expressed with regard to using cannabis in the context of driving or using heavy machinery but we consider from the evidence there should be no overall ban on driving with concomitant cannabis medical usage, as it depends on the circumstances and the type of cannabis taken. There may be, although far from proven, a carcinogenic risk from smoking cannabis but nevertheless the medical recommendation would be that cannabis should not be taken as a smoked product as there are safer ways of administration, such as vaporisation, oromucosal spray or taken in food or even topically applied. Further studies are clearly required on the best route of administration. We have documented some cognitive difficulties, at least in the short term and, in a similar fashion to prescription in schizophrenia, it may be wise to avoid prescription in adolescence given the probable susceptibility of the developing brain.

Most of the side effects are secondary to the THC component. CBD has less side effects and indeed may counteract some of the THC effects.

We should not forget that whilst there are alternative medications for most of the indications we have studied in this paper, many of the alternative medical treatments do give rise to significant, and often troublesome, side effects. This is particularly the case with regard to the prescription of opioids for pain.

Overall, there is good evidence for the use of cannabis in many important conditions that effect many thousands of disabled people in the UK. Generally, cannabis and cannabis products are safe and well tolerated. It is clear from this review that cannabis does have medicinal value and continuing placement of cannabis under Schedule 1 of the Misuse of Drugs Act, which thus states it is of no medicinal value, is inaccurate and misleading. We consider that the evidence firmly suggests that cannabis should be a legal product for medicinal use, as long as the quality of the product is guaranteed and the supply chain secured and that medical users are, as far as possible and practicable, entered into proper long term studies of both efficacy and side effects.

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