Cannabinoids as Therapeutics
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The development of Sativex® – a natural cannabis-based medicine

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History of the development

Cannabis has been used medicinally for 4000 years [1–4] in a variety of cultures and was re-introduced into British medicine in 1842 by W. O'Shaughnessy [5]. It remained in the British pharmacopaeia until 1932, when cannabis, extract of cannabis and tincture of cannabis were among 400 medicines removed, though all three remained in the British Pharmaceutical Codex of 1949 [5].

However, following the 1961 UN Single Convention on Narcotic Drugs, cannabis and cannabis derivatives became scheduled products and were subject to special measures of control and parties could ban their use altogether. Following the 1971 UN Convention on Psychotropic Substances, the UK enacted the Misuse of Drugs Act 1971. Cannabinol and its derivatives, including Δ^9-tetrahydrocannabinol (Δ^9-THC), appeared in Schedule I to the Convention, and their regular medical use was prohibited. The introduction of the Misuse of Drugs Regulations in the UK in 1973 listed cannabis and cannabis products in Schedule 4 (now Schedule I in current legislation), thereby prohibiting medical use altogether [5].

Early research

Although the medicinal properties of cannabis had been well documented for a number of years, the constituent(s) responsible for therapeutic efficacy had, until recently, not been identified. The discovery, isolation (and subsequent synthesis) of the principal cannabinoid present in cannabis, Δ^9-THC, by Raphael Mechoulam and Yehiel Gaoni in 1964 [6] ensured that interest in cannabinoid chemistry remained and led to an expansion of cannabinoid research.

Despite the scheduling and prohibition of cannabis and the ban on medical use of cannabis-based products in the 1970s, research into the pharmacology and toxicology of Δ^9-THC continued through the 1970s and 1980s, mainly by the National Institute of Health (NIH) in the USA.

However, much of the work concentrated solely on Δ^9-THC (NTP program, NIH) [7]. In many cases, the investigation of the pharmacokinetics of cannabis components involved the delivery of smoked marijuana, and the measurement of Δ^9-THC levels and its primary metabolite, 11-hydroxy-tetrahydrocannabinol (11-OH-THC).

Recent research and development of a cannabis-based medicine

In January 1997, the White House Office of National Drug Control Policy (ONDCP) asked the Institute of Medicine (IOM) to conduct a review of the scientific evidence to assess the potential health benefits and risks of marijuana and its constituent cannabinoids. That review began in August 1997 and resulted in the report published in 1999 [8]. Reports were also published in August 1997 by the US NIH [9] and in December 1997 by the American Medical Association (AMA) [10].

In parallel with the timing of the IOM review, a number of expert bodies in the UK were asked to review the medical and scientific evidence for and against the use of cannabis as a medicine. The British Medical Association (BMA) published a report on the topic in 1997 [11]. The UK Department of Health commissioned three literature reviews on cannabis, at the request of the Advisory Council on the Misuse of Drugs (ACMD); and these were reviewed by the House of Lords Select Committee on Science and Technology in 1998. The authors of the report all gave evidence to the House of Lords inquiry [12–14].

Dr Geoffrey Guy was also invited to submit evidence to the House of Lords enquiry, and subsequently GW Pharmaceuticals Ltd was founded in the UK in early 1998. As GW's Executive Chairman, Dr Guy successfully floated the company (GW Pharmaceuticals plc) on the Alternative Investment Market (AIM) of the UK Stock Exchange in June 2001. The first UK Home Office licenses received by GW were to cultivate, possess and supply cannabis for research purposes were received in June 1998 and cultivation began in August 1998.

In November 1998, the House of Lords Select Committee on Science and Technology published its report *Cannabis: The Scientific and Medical Evidence* [15], which recommended that clinical trials of cannabis medicines should be carried out as a matter of urgency. The Committee warmly welcomed GW's research programme.

September 1999 saw the start of GW's first phase I clinical trials in healthy volunteers and in March 2000 GW received authorization from the Medicines Control Agency (MCA; now the Medicines and Healthcare Products Regulatory Agency, MHRA) to start phase II clinical trials in patients.

In March 2001, the same House of Lords Select Committee published a follow-up report, *Therapeutic Uses of Cannabis* [16], which confirmed the UK Government's intention to permit the prescription of cannabis-based medicines (CBMs) subject to the approval of the MHRA.

GW entered into its pivotal phase III clinical trials programme in March 2001. The initial phase III studies involved patients with multiple sclerosis (MS), neuropathic pain and cancer pain. The results of the first four phase III studies were reported in November 2002, and six of the trials have now been completed, yielding positive results, and a further three are due to report in 2005.

In March 2003 GW submitted an application to the MHRA for its first product, Sativex®.

In May 2003 GW entered into an exclusive UK marketing agreement for Sativex® with the German pharmaceutical company Bayer AG. This agreement was extended in November 2003, to add the Canadian market.

In May 2004 GW submitted a New Drug Submission for Sativex® to the Canadian regulatory authorities, Health Canada.

The endogenous cannabinoid system

The discovery and chemical synthesis of Δ^9-THC initiated the modern era of cannabis research because it enabled investigation of the effects and mode of action of individual cannabinoids in laboratory models [17]. The production of synthetic analogues of Δ^9-THC enabled structure – activity relationships of Δ^9-THC to be established. Further, pharmacological investigation of Δ^9-THC indicated that it might exert its effects by interacting with a specific receptor protein in the brain [18, 19]. The conclusion from this work was that the so-called cannabinoid receptor was a G-protein-coupled receptor. Once a CB receptor agonist, CP-55,940, was synthesized, radiolabelled binding studies were performed [20], and the distribution of CP-55,940-binding sites were found to be similar to those coded for by cDNA for another G-protein-coupled receptor, SKR6, a receptor without a known ligand (an orphan receptor). Further investigation using cannabinoid-binding assays revealed that SKR6 was indeed a cannabinoid receptor identified in rat brain [21]. Soon afterwards a human G-protein receptor was identified that had an amino acid sequence 98% identical to the SKR6 receptor in rat brain.

In 1993, a second G-protein-coupled cannabinoid receptor sequence (CX5) was identified among cDNAs from the human promyelocytic leukaemic cell line HL60 [22].

Munro et al. [22] suggested that the brain receptor be referred to as CB_1 and that the second receptor, which is expressed by cells of the immune system, be referred to as CB_2.

It has since become widely accepted that CB_1 receptors are widely distributed but are particularly abundant in some areas of the brain, including those concerned with movement and postural control, pain and sensory perception, memory, cognition and emotion, and autonomic and endocrine functions [23, 24]. They are also prevalent in the gut, testes and uterus. The role of the second type of receptor, CB_2 receptor, is still under investigation but it is believed to mediate the immunological effects of cannabinoids [23, 24].

In the meantime, Mechoulam and Devane isolated and elucidated the structure of a brain constituent that bound to the cannabinoid receptor [25]: arachidonylethanolamide (AEA, anandamide). During subsequent investigation of several lipid fractions collected from rat brain, it was discovered that the fractions also contained materials that bound to cannabinoid receptors [26]. Characterization of these fractions revealed that some contained polyunsaturated acid ethanolamides (similar to AEA), but others contained a distinct lipid component, 2-arachidonoyl glycerol (2-AG).

AEA is found to be a partial agonist at CB_1 receptors; whereas 2-AG binds to CB_1 and CB_2 with similar affinities, and is a full agonist at CB_1. 2-AG occurs in concentrations in the brain that are 170 times higher than those of AEA [26].

The role of these endogenous cannabinoids (so-called endocannabinoids) is currently unclear, and others have subsequently been identified: noladin ether [27], virodhamine [28], *N*-arachidonoyl-dopamine (NADA) [29] and arachidonoyl-serine (ARA-S) [30]. The identification of AEA and 2-AG has led to a resurgence of interest in the field of cannabinoid medicine, especially within the pharmaceutical industry, as they may represent potential molecular targets for the treatment of a number of disorders.

Cannabinoid receptor ligands

In the wake of widespread availability of synthetic CB receptor-specific ligands, research into the identification of potential sites of action of cannabinoids has increased around the world. However, until recently, the lack of significant available quantities of pure cannabinoids other than Δ^9-THC and cannabidiol (CBD) has been a constant source of frustration for researchers.

To date, of the synthetic research receptor ligands, only SR-141716A (CB_1 receptor antagonist) has shown sufficient potential to be developed into a pharmaceutical product (Rimonabant). A number of other synthetic cannabinoids have been developed into pharmaceuticals including Marinol®, Synhexyl, Nabilone and Levonantradol. However, regulatory approval of these products varies between territories and, as a result, they are not currently widely used or accepted.

Classification of cannabinoids

The existence of the various types of cannabinoid molecule available and their source has led to the proposal of four distinct classes of cannabinoids:

1. phytocannabinoids: those which occur naturally in the plant;
2. endocannabinoids: those that occur naturally in the body (AEA, 2-AG, etc.);
3. synthetic cannabinoids: cannabinomimetic compounds resulting from chemical synthesis (e.g. dronabinol, nabilone, HU-210, CP-55,940, SR-141716A);

4. fatty acid amide hydrolase (FAAH) inhibitors: compounds that affect AEA production, release, metabolism and re-uptake.

Production of cannabis-based medicines

Cannabis-based medicines may be produced according to the regulatory requirements in a variety of ways:

- isolation and purification of individual molecules from plant sources;
- chemical synthesis of required molecular components;
- extraction of required plant components;
- selective delivery of required components.

Rationale for the development of a cannabis-based medicine as a whole-plant extract

The cannabinoids that are currently of most interest and have received the most scientific interest to date are the principal components of cannabis, Δ^9-THC and CBD. Both have important pharmacology [31, 32]. Δ^9-THC has analgesic, anti-spasmodic, anti-tremor, anti-inflammatory, appetite-stimulant and anti-emetic properties; CBD has anti-inflammatory, anti-convulsant, anti-psychotic, anti-oxidant, neuroprotective and immunomodulatory effects. CBD is not intoxicating and indeed it has been postulated that the presence of CBD in cannabis may alleviate some of the potentially unwanted side effects of Δ^9-THC.

It is postulated that the beneficial therapeutic effects of cannabis result from the interaction of different cannabinoids [31]. This may explain why cannabis-based medicines made from whole-plant extracts may be more effective than single cannabinoid products, as the extracts consist of multiple cannabinoids in defined, specific ratios. Different ratios of cannabinoids may be effective in treating different diseases or conditions across a number of therapeutic areas.

Although research has focused primarily on the two principal cannabinoids, Δ^9-THC and CBD, it is possible that other components within the plant are also important, which is why GW Pharmaceuticals' medicines are made from whole-plant extracts. McPartland and Russo [31] cite a number of literature reports, which support this theory. Mechoulam et al. [33] suggested that other compounds present in herbal cannabis might influence Δ^9-THC activity. Carlini et al. [34] determined that cannabis extracts produced effects "two or four times greater than that expected from their THC content." Similarly, Fairbairn and Pickens [35] detected the presence of unidentified "powerful synergists" in cannabis extracts causing 330% greater activity in mice than Δ^9-THC alone.

Other compounds in cannabis may ameliorate the side effects of Δ^9-THC [31]. Whole cannabis causes fewer psychological side effects than synthetic

Δ^9-THC, seen as symptoms of dysphoria, depersonalization, anxiety, panic reactions and paranoia [36].

It is possible that the observed difference in side-effect profiles may also be due, in part, to differences in routes of administration: orally administered Δ^9-THC undergoes 'first-pass metabolism' in the small intestine and liver, to 11-OH-THC; and the metabolite has been reported to be psychoactive, albeit on the basis of limited evidence [37]. Inhaled Δ^9-THC undergoes little first-pass metabolism, so less 11-OH-THC is formed [38, 39]. The effect of the route of administration on tolerability has been known for years. Walton, in 1938, remarked that "smoking cannabis is a satisfactory expedient in combating fatigue, headache and exhaustion, whereas the oral ingestion of cannabis results chiefly in a narcotic effect which may cause serious alarm" [40].

The other classes of compounds present in cannabis also have their own pharmacology (e.g. terpenoids, flavonoids) [31, 32]. The potential for interaction and synergy between compounds within the plant may play a role in the therapeutic potential of cannabis as a medicine. This may explain why a cannabis-based medicine using extracts containing multiple cannabinoids, in defined ratios, and other non-cannabinoid fractions, may provide better therapeutic success and be better tolerated than the single synthetic cannabinoid medicines currently available.

CBD, as a non-psychoactive cannabinoid, is currently the cannabinoid of considerable interest. CBD, along with Δ^9-THC, has been demonstrated to have a wide range of pharmacological activity, with the potential to be developed for a number of therapeutic areas [41]. It is likely that other cannabinoids, present in small amounts in *Cannabis sativa* L., may also have interesting pharmacological properties, for example tetrahydrocannabivarin (THC-V), cannabichromene (CBC) and cannabigerol (CBG) [31, 32, 39].

Regulatory requirements

The pharmaceutical development of cannabis-based medicines is well documented [42, 43]. For cannabinoids to be made into pharmaceuticals, licensed by the regulatory bodies around the world, they must reach strict requirements laid down in terms of the product's quality, safety and efficacy and increasingly the healthcare industry requirement of cost-effectiveness. Such standards are achieved by adhering to the industry and regulatory standards of Good Laboratory Practice (GLP), Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP), according to the guidance documents provided by the International Conference on Harmonisation [44]. All requirements are now implemented through European Union and national legislation. In the case of plant-based medicines they must also adhere to Good Agricultural Practice (GAP) standards.

As a result, quality control is required throughout the whole of the manufacturing chain, including the production of raw materials. For pharmaceuti-

cals produced from plants, the regulatory authorities have produced their own guidelines on the production of botanical drug products (BDPs) [45]. As botanical pharmaceuticals have more than a single chemical entity present, their control is paramount, and hence detailed characterization and specification is required.

Breeding of cannabis plants for generation of cannabis extracts

Cannabis is in most cases a dioecious plant; that is to say, the species produces separate male (staminate) and female (pistillate) plants [46].

Analysis of the various parts of the plant confirms that the major source of cannabinoids is the female flower. Cannabinoids are not detected in the roots. The richest sources of the principal cannabinoids Δ^9-THC and CBD are the leaves and flowers and hence these plant components are selected for the production of Δ^9-THC- and CBD-based medicines.

In the wild, *Cannabis* is a short-day-length plant. This means that the plant grows vegetatively through the long days of summer. Only when the day length falls, signalling the end of summer, does the female plant start to flower and hence the cannabinoids are produced. As an annual herb in the field, normally only one crop per year would be produced.

It is during the last few weeks of life that the female plant is most active in the production of cannabinoids and terpenes. The plant will produce variable inflorescences, these being complex clusters of flowers and bracts. Each flower consists of a furled specialized single leaf – the calyx – within which is housed the ovary. Each calyx is covered in minute sticky organelles – the stalked glandular trichomes. When viewed through a hand lens, each trichome resembles a golf ball (the resin head, also known as the glandular head) sitting on a tee (the trichome's stalk; Fig. 1)

The particular day length that induces flowering is termed the 'critical day length'. This will differ according to the geographical and genetic origin of the plant in question. Thus, flowering in response to exposure to a defined amount of light may be achieved through selective breeding.

Cannabinoid content varies in different varieties but the high cannabinoid content of modern varieties is purely due to plant breeding.

However, by growing under glass in controlled conditions, a succession of crops can be planned to meet production requirements. To be suitable for long-term commercial use, plants must have selected characteristics. Plants that are selectively bred for their characteristics are termed chemovars. In order to be commercially useful, they must possess the following characteristics:

- high rate of cannabinoid production;
- high yield of cannabinoid per unit area;
- high level of purity of the desired cannabinoid (purity as used here defines the consistency of cannabinoid content as a ratio);

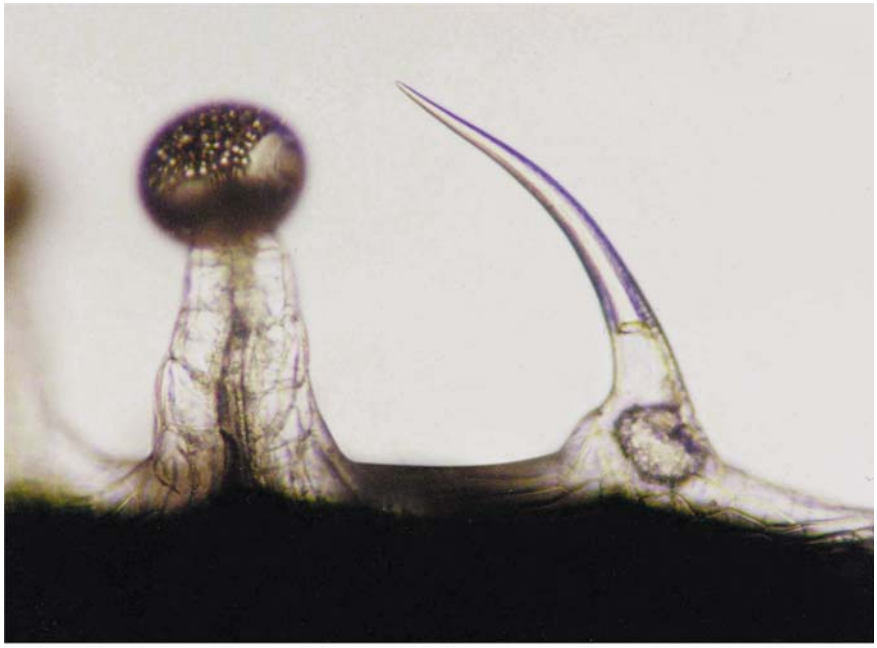

Figure 1. A glandular trichome from *C. sativa* L. (left) alongside a non-glandular trichome (right). The head on the glandular trichome is the main site of cannabinoid biosynthesis.

- high inflorescence-to-leaf ratio (the harvest index);
- natural resistance to pests and diseases;
- sturdy growth capable of bulk plant handling;
- ease of harvesting;
- minimal production of anthers on female plants.

The production of uniform high-quality botanical raw material (BRM) of defined composition is dependent upon the bulk production of cloned plants; that is to say, all plants are derived from cuttings taken from a few select mother plants. Being genetically identical, all the cloned plants have the potential to replicate exactly the characteristics of the mother plant.

BRM is obtained from distinct varieties of *C. sativa* plant hybrids to maximize the output of specific cannabinoids. The chemovars used are the result of an extensive breeding programme spanning more than 15 years.

GW's cannabis-based medicines are pharmaceutically formulated whole-plant extracts of chemovars of *C. sativa* produced by selective breeding to give a high content of defined cannabinoids, optimum habit and early flowering. A wide range of chemovars of *C. sativa* has been selectively bred by GW Pharmaceuticals. Each of these chemovars has a different cannabinoid profile, and the chemovars have been specifically bred to produce the required

level of specified cannabinoids. From this range, two separate chemovars, one that produces Δ^9-THC as the principal cannabinoid and one that produces CBD as the principal cannabinoid, have been selected for production of Sativex®.

Cultivation of chemovars for generation of cannabis extracts

Crops are produced from cuttings, which ensures that the genotype is fixed, giving a constant ratio of cannabinoid content. Cannabinoid content may be selectively bred to produce defined ratios of principal and other minor cannabinoids. By further careful, selective breeding, it is possible to cultivate chemovars which produce minor cannabinoids (CBC, CBG, THC-V, etc.) in greater amounts than have been observed to date in wild-type cannabis plants or in varieties produces by recreational growers. The pharmacology of the minor cannabinoids has yet to be clearly established, but may yet provide a whole new range of therapeutic options for both patient and clinician.

Mother plants

Potter [46] has described the use of "mother plants" to maintain the genotype for each subsequent generation of plants (rooted cuttings, termed "clones"). Once potted up and grown in continuous bright light [75 W/m^2 PAR (photosynthetically active radiation)] at 25 °C in optimized compost, a rooted cutting will reach a height of 2 m in 12 weeks. This plant is then capable of being heavily pruned; the removed branches being cut up to produce up to 80 cuttings per mother plant. If well kept, over the next 10–15 weeks the trimmed mother plant will regrow to produce at least two more flushes of cuttings. The vigour of the mother plant then wanes, and the plant is destroyed to make way for younger mothers.

Clones

Branches of the mother plant are removed where there are sufficient numbers of axial buds developing, these being the new growths that eventually develop into mature plants. Each branch is then cut into sections, each supporting only one axial bud. The cutting is then placed in rooting powder and immediately transferred into a very moist peat plug. In the correct environment, roots begin to appear after 7 days, and the cuttings allowed to acclimatize to their surroundings before they are potted up.

Rooted cuttings are transferred into large pots, filled with a proprietary growing media, which contains sufficient fertilizer to stimulate vegetative growth and flower production.

For the first 3 weeks after potting, plants are grown in continuous bright light. With no night-time breaks during this period the plant grows to around 50 cm and establishes a healthy root system.

After 3 weeks the lighting is switched to a 12-h light/12-h dark cycle. Having established themselves in a 24-h daylight environment in subtropical temperatures, the plants suddenly detect the change in light exposure, as if they had experienced the immediate arrival of the autumn equinox. For a short-day plant (i.e. late summer/autumn flowering) like cannabis, the response is dramatic. The GW chemovars flower within 5 days of the photoperiod switch. The inflorescences (flowers) increase in size over the next 6 weeks, becoming white with myriad receptive stigmas. The unfertilized stigmas then start to senesce to an orange/brown colour. After 8 weeks in flower, the bulk of stigmas have senesced and the rate of cannabinoid biosynthesis in the selected varieties slows rapidly. At this point, the crop is harvested.

Mother plants, seedlings and mature clones are produced under glass, which allows a very high degree of control of growing conditions to be exercised. The controls significantly exceed the controls possible for field-grown crops. In particular:

- proprietary compost is used, warranted free of artificial pesticides and herbicides by the supplier;
- the compost contains sufficient fertilizer to ensure optimum vegetative growth and eventual flowering;
- stringent hygiene conditions reduce ingressive pests and diseases – adventitious infestation is controlled biologically with predatory mites;
- fresh potable water, rather than stored or untreated water, is used for the irrigation of the plants; this reduces the potential for contamination with water-borne organisms;
- during growing, the plants are inspected regularly, and plants showing male characteristics are removed to avoid fertilization of plants;
- growing conditions are strictly controlled via computer technology to ensure that optimal cultivation conditions are maintained at all times in terms of light, temperature, humidity, airflow, etc.

Drying

At harvest, the entire plant is cut and dried in a temperature- and humidity-controlled environment until it meets the specification for loss on drying. Leaves and flowers are stripped from the larger stems to provide the BRM, which is stored in suitable containers protected from light under controlled conditions.

Drying the crop as quickly as possible reduces the cannabinoid losses, and this is achieved by keeping the plants in a stream of dehumidified air. Plants are crisp to the touch in less than 7 days.

As part of GAP and GMP, the BRM must conform to a specification. The specification for BRM includes tests for identification, extraneous matter and identification and assay for cannabinoids and cannabinoic acids, confirmatory thin-layer chromatography (TLC) and loss on drying. Additionally, BRM is tested for aflatoxins and microbial bioburden. The growing parameters employed have been selected to minimize the conditions that would be expected to result in microbial and fungal spoilage.

Extraction

Cannabinoids are present in the plant as the corresponding carboxylic acid and it is necessary to decarboxylate material before extraction. The conditions for efficient decarboxylation have been optimized to maximize decarboxylation and minimize oxidation. The process is time- and temperature-dependent and a criterion of not less than 95% efficiency was adopted for BRM used in subsequent manufacture of botanical drug substance (BDS; whole-plant extract).

Development work has shown that efficient extraction can be carried out using patented extraction technology. The conditions of the extraction have been carefully assessed during development and are essential to ensure the optimum conditions and hence the correct composition of the extract produced. The extraction produces a whole-plant extract, from which the BDS is prepared.

The whole-plant extract is subject to further processing (covered by intellectual proprietary rights) to remove unwanted materials from the extract. The exact content of the BDS is defined by a specific BDS specification. BDS is transferred to sealed, stainless steel containers and stored at -20 ± 5 °C to maintain stability.

A schematic diagram of the process flow from cultivation to final processing and quality-control release of the pharmaceutical product is detailed in Figure 2.

BDS content

Using any defined BRM, a corresponding BDS may be created using the above GW proprietary process. The contents of the BDS will depend on the genetically defined content of the BRM, and the technology used to extract the active constituents. Thus, BDSs may be produced which have defined levels of principal cannabinoids, other cannabinoids and other non-cannabinoid constituents. Thus a series of individual BDSs may be described.

Each BDS contains a cannabinoid fraction and a non-cannabinoid fraction. GW describes its BDSs individually as each BDS generated has a unique composition. The two BDSs used to generate Sativex® are Tetranabinex®, an extract of a chemically and genetically characterized cannabis plant, contain-

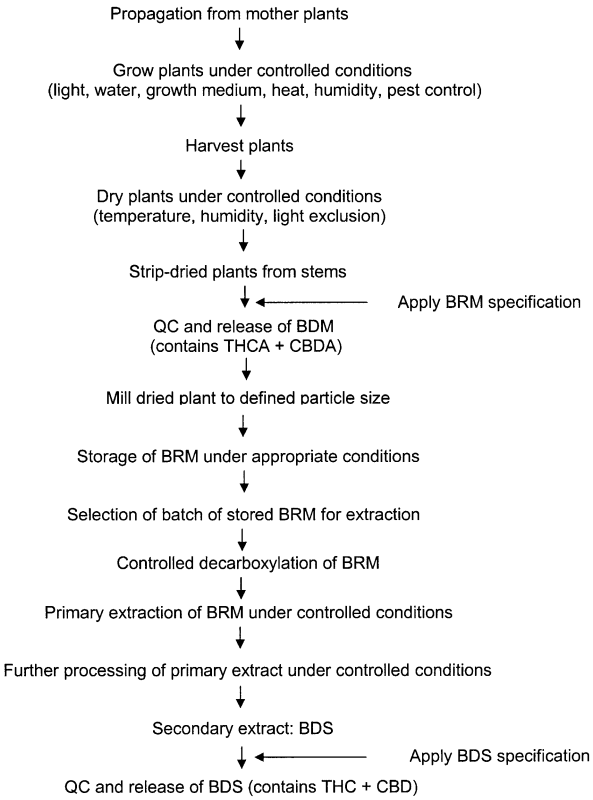

Figure 2. Schematic flow diagram of the production of GW Pharmaceuticals' BDSs. CBDA, cannabidiolic acid; QC, quality control; THCA, tetrahydrocannabinolic acid.

ing Δ^9-THC as the principal cannabinoid, and Nabidiolex®, an extract of a chemically and genetically characterized cannabis plant containing CBD as the principal cannabinoid. Other BDSs may be generated from extracts high in CBC, CBG, THC-V, cannabidivarin (CBD-V), etc.

Cannabinoid fraction

In addition to the principal cannabinoids present, each BDS contains other cannabinoids that may contribute to the activity of the whole extract.

Non-cannabinoid fraction

Each BDS also contains a non-cannabinoid fraction, which contains terpenes, sterols, fatty acids, anti-oxidants and flavonoids.

Characterization, control and specification of BDS

The ranges for the principal cannabinoids and other cannabinoids are defined in the BDS specification, as are the levels of non-cannabinoid compounds. The minor cannabinoids and non-cannabinoids are considered to be adjuvants to the principal cannabinoid rather than impurities. The non-cannabinoid fraction may be regarded as a diluent, rather than an impurity, making up the difference between assayed percentage of cannabinoids and 100% of the extract.

For regulatory approval, tight control of the content of the BRM, BDS and BDP is essential. Even though the pharmaceutical product is a botanical product, rather than a new chemical entity, characterization of more than 90% of the composition of the whole extract is required. GW has achieved this.

Stability

Stability studies are ongoing to assess the stability of Tetranabinex®, Nabidiolex® and the finished product Sativex® in order to establish a suitable shelf-life for the product. Such studies include temperature cycling and photostability, in compliance with international regulatory (International Conference on Harmonisation) conditions. Additionally, studies are being performed to investigate forced degradation.

Profile of a BDS

Typically, a GW Pharmaceuticals BDS contains the following.

- Principal cannabinoids
  Δ^9-THC (>90% of the cannabinoid fraction in THC BDS)
  CBD (>85% of the cannabinoid fraction in CBD BDS)
- Minor cannabinoids
  Cannabichromene (CBC)
  Cannabigerol (CBG)
  Cannabinol (CBN)
  Tetrahydrocannabivarin (THC-V)
  Cannabidivarin (CBD-V)
  Tetrahydrocannabinolic acid (THCA)
  Cannabidiolic acid (CBDA)
  Cannabicyclol (CBL)
  Cannabitriol (CBO)
  Cannabielsoin (CBE)
  Cannabichromivarin (CBC-V)
- Terpenes
  Monoterpenes: myrcene, limonene, linalool, α-pinene
  Sequiterpenoids: *trans*-caryophyllene, α-caryophyllene, caryophyllene

oxide, *cis*-nerolidol, *trans*-nerolidol
Diterpenoids: phytol
Triterpenoids: squalene

- Fatty acids
  Linolenic acid, palmitoleic acid, linoleic acid, palmitic acid, oleic acid, stearic acid, myristic acid, arachidic acid and behenic acid
- Sterols
  β-Sitosterol, Campesterol and Stigmasterol
- Carotenoids
  β-Carotene, lutein
- Chlorophylls and related compounds
  Phaeophytin
- Vitamins
  Vitamin E
- Phenolic compounds
  Flavonoids, coumarins, cinnamic acids and psoralens

Finished product – BDP: formulation and filling

The dosage form for Sativex® is a solution, consisting of a vehicle of ethanol, propylene glycol and peppermint, containing Tetranabinex® and Nabidiolex® extracts, that is sprayed into the oral cavity, on to the oromucosal surface.

Sativex® contains Tetranabinex® and Nabidiolex® extracts of *C. sativa* equivalent to 27 mg/ml Δ^9-THC and 25 mg/ml CBD per actuation. The container is an amber Type I glass vial, with a sealed pump, designed to deliver a uniform 100 μl volume. An actuator is used to produce the spray (Fig. 3).

Administration of Sativex®: achieving the therapeutic window

Appropriate delivery of the active components of a cannabis-based medicine is important in terms of patient acceptability, and achieving optimal and predictable effect. The rate of delivery of constituents to the site of action is as important as the amount delivered. Hence, the formulation selected to deliver cannabinoids is very important. The fact that cannabinoids are extremely lipophilic compounds limits the number of excipients that may be used to formulate cannabis-based medicines.

Sativex® is self-titrated by patients. Its frequency of use is determined by the type, severity and frequency of symptoms that patients endure. As patients vary enormously in terms of the symptoms they exhibit upon presentation to their physician, the administration of Sativex® is unique in each individual patient.

The ability of Sativex® to relieve a variety of single primary symptoms across different patient populations, coupled with its ability to relieve ‘clus-

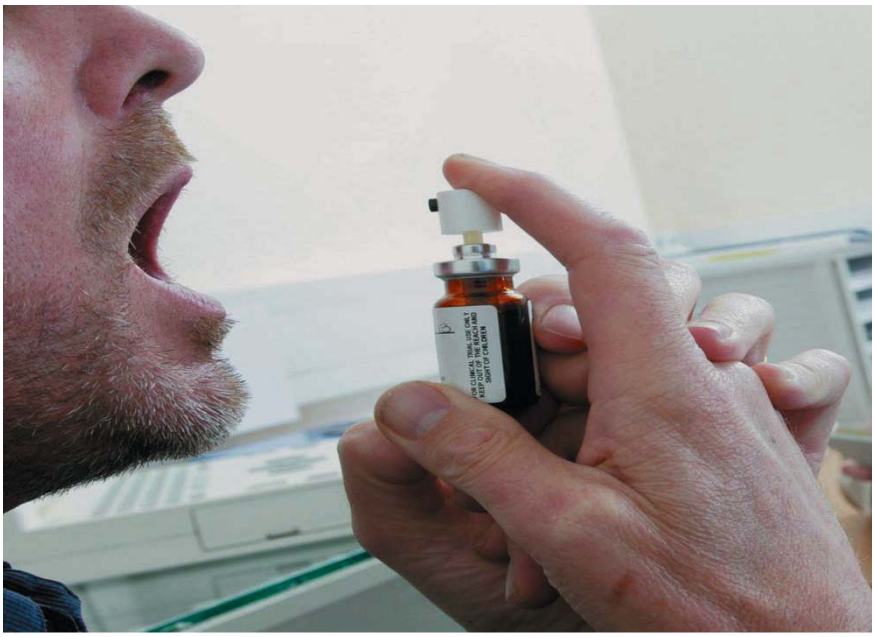

Figure 3. Administration of Sativex®.

ters' of symptoms in individual patients as reported in GW's clinical programme, demonstrates the real strength and potential of Sativex® as a medicine. These beneficial effects are not only due to the pharmacological actions of the medicine but also due to the flexibility of dosing that the medicine offers. It accommodates inter-individual variation, but also allows each patient to establish a dose regimen that provides patient benefits with minimal unwanted side effects. It allows patients the opportunity to develop their own dosing regimen, including dosing interval and acceptable dose range, and also enables them to assess the time course of symptom relief, using their own personal endpoints as markers of efficacy and tolerability. In this way, the patient is able to optimize the relief of their symptoms, while minimising and resolving the occurrence of any side effects that they may experience (i.e. patiens can target the therapeutic window).

By utilizing this approach, a number of significant clinical benefits of Sativex® have been reported in GW's clinical trial programme.

Clinical effects of Sativex®

The clinical effects of Sativex® have undergone investigation in an international clinical trials programme, with centres in UK, Romania, Belgium,

Ireland and Canada. More than 1400 subjects have participated in the clinical programme, which has initially targeted MS patients who have symptoms, and patients with neuropathic pain.

A summary of the programme is presented in Table 1. A total of 13 phase I studies have been undertaken to investigate the pharmacokinetics of Sativex®

Table 1. GW clinical programme, wave 1

Study number	Study population	Number enrolled	Study status
Acute studies			
Phase II studies			
GWN19901A	Various symptoms in MS and SCI[#]	34	C
GWN19902	Various symptoms in MS[#]	25	C
GWN19904	Various symptoms in MS, RA and SCI[#]	29	C
GWCRI016	Pain and stiffness caused by RA[*]	58	C
GWQSCBME01	Bladder dysfunction in MS[†]	21	C
Phase III studies			
GWMS0106	Spasticity in MS[*]	189	C
GWNP0101	Peripheral neuropathic pain characterized by allodynia[*]	125	C
GWMS0001	Multiple symptoms in MS[*]	160	C
GWPS0105	Chronic refractory pain in MS and other defects of neurological function[*]	70	C
GWMS0107	Neuropathic pain in MS[*]	66	C
GWBP0101	Pain in brachial plexus avulsion[#]	48	C
GWCA0101	Cancer pain[*]	176	O
GWMS0208	Bladder dysfunction in MS[*]	130[‡]	O
GWSC0101	Neuropathic pain in SCI[*]	120[‡]	O
Long-term extension studies			
Phase II			
GWN19901A	Various symptoms in MS and SCI[#]	29	O
GWN19902	Various symptoms in MS[#]	20	O
GWN19904	Various symptoms in MS, RA and SCI[#]	22	O
GWCRI016	Pain and stiffness caused by RA[*]	35	O
GWQSCBME01	Bladder dysfunction in MS[†]	16	C
Phase III			
GWEXT0101	Cancer pain[†]	40	O
GWMS0001 EXT	Multiple symptoms in MS[†]	137	O
GWEXT0102	Neuropathic pain and bladder dysfunction in MS[†]	494	O

C, complete; O, ongoing; MS, multiple sclerosis; SCI, spinal cord injury; RA, rheumatoid arthritis.
[#] Randomized, double-blind, placebo-controlled crossover study.
[*] Randomized, double-blind, placebo-controlled parallel group study.
[†] Open-label study.
[‡] Target recruitment figure.

and other formulations/products of GW's portfolio. To date, the results from three pharmacokinetic studies have been published [47–49].

Clinical programme results

Of the 11 efficacy studies completed to date (five phase II; six phase III), all 11 have yielded a range of positive results [50–60]. An additional three phase III trials commenced in 2002 and are due to complete in 2005.

In all studies all patients remained on the best current therapy available for their condition. However, they still had sufficient residual symptom-severity scores for them to seek further treatment (i.e. there was still a high clinical unmet need despite best available therapy). Sativex® was added to all their other medications, which were kept stable during the baseline/run-in periods and throughout the study period. The subsequent improvement in symptoms that was observed following treatment with Sativex® was *in addition* to any benefit they had previously derived from their existing therapy.

Phase II data

In phase II studies the following effects were seen:

- relief of neuropathic pain [50];
- improvement in spasticity [51, 52];
- improvement in muscle spasms [51, 53];
- improvement in bladder-related symptoms [52];
- improvement in sleep, mood and overall sense of well-being [50–52];
- improvement in morning pain in rheumatoid arthritis [54];
- opiate sparing effects

Phase III data

In randomized, double-blind, placebo controlled, phase III studies the following effects were seen:

- relief of central neuropathic pain (CNP) in MS [55] (see Fig. 4);
- relief of CNP in brachial plexus avulsion [56] (see Fig. 5);
- relief of chronic refractory pain of neurological origin [57];
- relief of spasticity in MS [58, 59] (see Figs 6 and 7);
- relief of peripheral neuropathic pain [60];
- relief of relief of sleep disturbance and improvement in sleep quality [55–58, 60] (see Fig. 8);
- improvement in patients quality of life [55, 60].

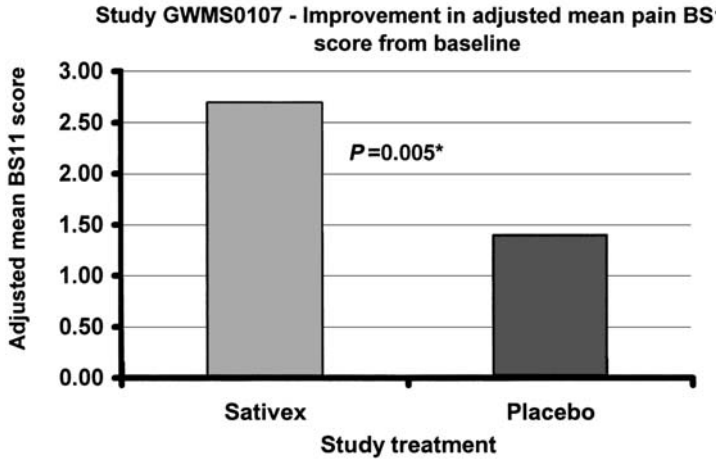

Figure 4. Relief of central neuropathic pain in MS [55]. BS11, Box Scale 11. Adapted from Rog and Young [55].

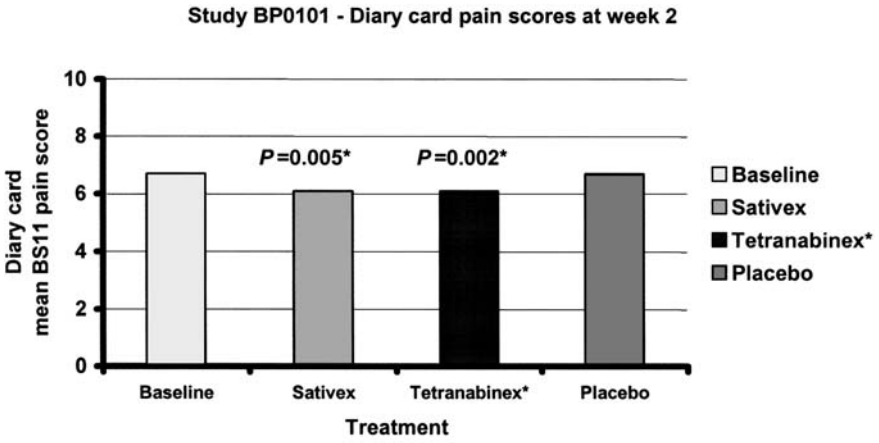

Figure 5. Relief of neuropathic pain in brachial plexus avulsion [56]. BS11, Box Scale 11. Adapted from Berman et al. [56].

Figures 4–8 present the primary efficacy data for Sativex®, from a number of the randomized, double-blind, placebo-controlled, phase III clinical studies conducted and presented to date.

Figure 9 presents the long-term data from patients who have reported pain as a symptom. The results encompass data from patients with a variety of pain syndromes who have completed the randomized studies and have elected to continue on the medicine long-term.

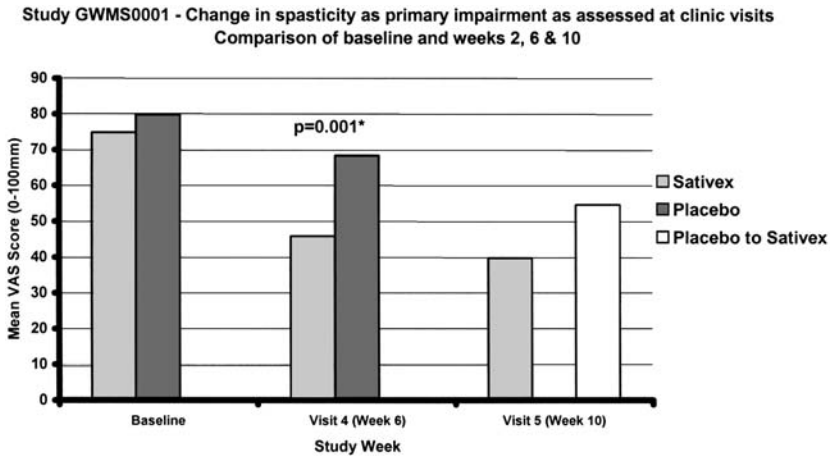

Figure 6. Relief of spasticity in MS (clinic assessments) [58]. Placebo was crossed over to Sativex® in weeks 7–10. Adapted from Wade et al. [58].

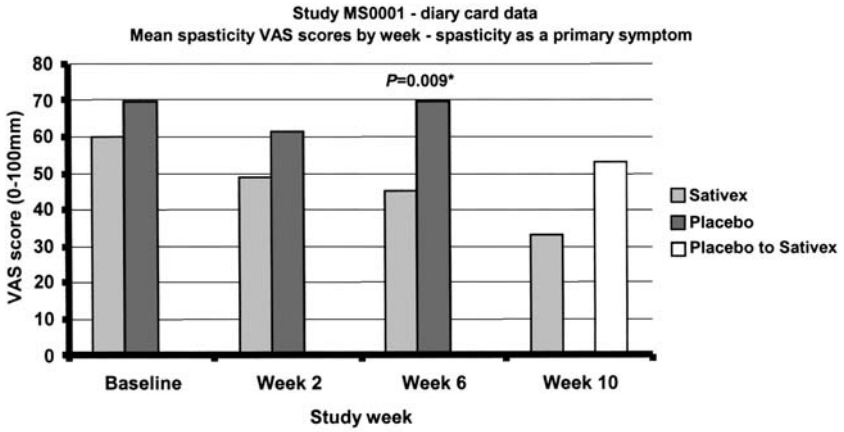

Figure 7. Relief of spasticity in MS (diary cards) [58]. Placebo crossed over to Sativex® in weeks 7–10. Adapted from Wade et al. [58].

Neuropathic pain in MS

Sativex® has been investigated for its effects on neuropathic pain from a variety of aetiologies. A study evaluating its effects in CNP in MS was undertaken in 2002 [55]. Following a baseline period during which their pain scores were assessed, 66 patients with CNP were randomized to receive either Sativex® or placebo for 4 weeks. The primary endpoint of the study was pain scores as measured on a patient diary card using an 11-point Numerical Rating

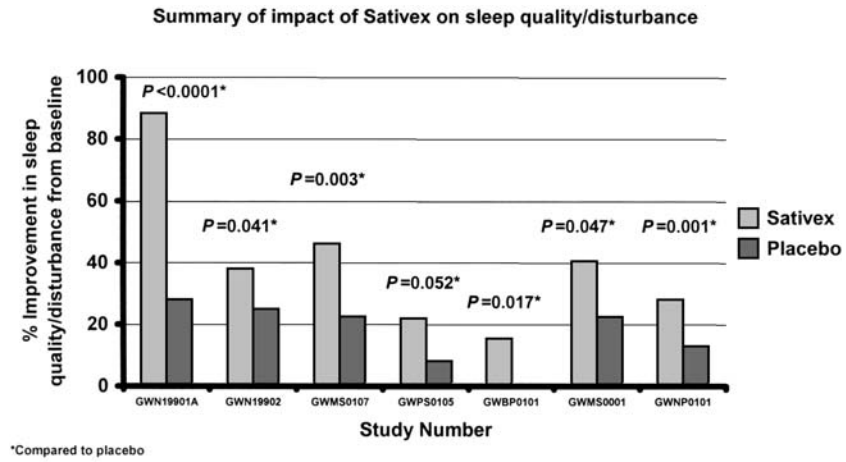

Figure 8. Relief of sleep disturbance [50, 51, 55–58, 60]

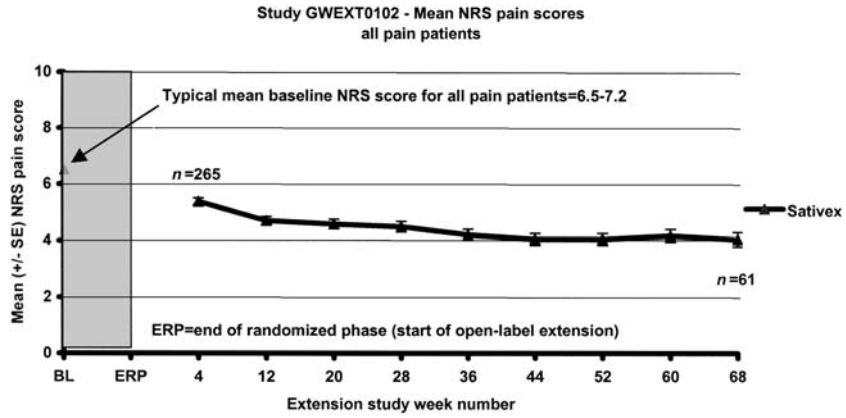

Figure 9. Sustained relief of neuropathic pain [64]

Scale (range 0–10). A summary of the results is given below, and the primary endpoint presented in Figure 4.

Sixty-four patients (96.9%) completed the trial. Fourteen patients were male, mean age 49.2 years (range 26.9–71.4, SD 8.3), mean expanded disability status scale (EDSS) 5.9 (range 2.0–8.5, SD 1.3) and mean duration of MS since diagnosis 11.5 years (range 1–36, SD 7.7).

The mean number of daily sprays taken in the final week of treatment was 9.6 of Sativex® (range 2–25, SD 6.1) and 19.1 of placebo (range 1–47, SD 12.9).

Thirty patients (88.2%) on Sativex® and 22 (68.8%) on placebo had at least one adverse event, none of which were serious. There was a statistically significant mean reduction in pain in favour of Sativex®, as measured using the

11-point numerical rating scale (NRS; 0 = none, 10 = worst), which was the primary outcome of the study [–1.25; 95% confidence interval (CI), –2.11, –0.39; $p = 0.005$].

There was a statistically significant improvement in mean sleep disturbance in favour of Sativex® (–1.39; 95% CI, –2.27, –0.50; $p = 0.003$). A significant mean reduction in pain with Sativex® compared with placebo was also demonstrated using the 10-item, 100-point neuropathic pain scale (–6.82; 95% CI, –13.28, –0.37; $p = 0.039$). On a seven-point Patient's Global Impression of Change (PGIC), those treated with cannabis-based medicine extracts were 3.9 times more likely (95% CI, 1.51, 10.06; $p = 0.005$) to feel "much" or "very much" improved than those receiving placebo, and no patient felt "much" or "very much" worse at the end of either treatment. No significant mean differences were found between treatment groups prior to treatment.

Neuropathic pain in brachial plexus avulsion

A further study evaluating the effects of Sativex® on CNP was undertaken in patients with brachial plexus avulsion [56]. Brachial plexus avulsion is a relatively uncommon condition but is characterized by severe, intractable neuropathic pain, which is difficult to treat. Due to the low numbers of patients available, even at the national treatment centre in the UK, the study was performed as a crossover study rather than to a parallel group design.

Following a baseline period during which their pain scores were assessed, 48 patients with brachial plexus avulsion were randomized to receive Sativex®, a formulated Δ^9-THC-rich extract (formulated Tetranabinex®), or placebo, each for a period of 2 weeks. The primary endpoint of the study was pain scores as measured on a patient diary card using an 11-point NRS (range 0–10). A summary of the results is given below, and the primary endpoint presented in Figure 5.

Forty-eight patients were enrolled. They all had at least one brachial plexus root avulsion for at least 18 months. They also had pain of at least 4 on an 11-point NRS at the time of enrolment. The study was a randomized, double-blind, crossover design consisting of three 2-week periods following a run-in period of 7–24 days. Patients continued on all previous stable medications including analgesics. During each 2-week period subjects received, in random order, either placebo, formulated Tetranabinex® or Sativex®. These were given as patient-activated oromucosal 100 µl sprays.

Efficacy endpoints were: 11 point NRSs for pain and sleep, short-form McGill (McGill Pain Questionnaire), General Health Questionnaire-12 (GHQ-12) and sleep quality and sleep disturbance were all recorded.

The mean number of daily sprays taken in the final week of treatment was 6.93 for Sativex®(range 1.1–22.2, SD 4.79), 7.26 for Tetranabinex® (range 1.2–21.6, SD 5.04) and 9.15 for placebo (range 2.0–35.6, SD 7.30). The results for the efficacy endpoints are shown in Table 2.

Table 2. Study GWBP0101 efficacy results

	Baseline	Placebo	Formulated Tetranabinex®	Sativex®
Pain NRS Score	6.7	6.7	6.1 ($P = 0.002$)	6.1 ($P = 0.005$)
McGill Pain Questionnaire (total intensity)	17.3	15.5	13.4 ($P = 0.04$)	13.8 ($P = 0.15$)
McGill (Part II) Pain-intensity VAS score	60.9	52.9	43.6 ($P = 0.04$)	45.1 ($P = 0.09$)
Sleep-quality NRS	4.8	5.2	6.0 ($P = 0.001$)	5.9 ($P = 0.02$)
GHQ-12	13.4	13.5	12.3 ($P = 0.18$)	10.9 ($P = 0.02$)

VAS, Visual Analogue Scale; GHQ-12, General Health Questionnaire-12.

These two studies [55, 56] and a third reported by Sharief [57] demonstrate that Sativex® has a significant analgesic effect in CNP. A further study yet to be fully reported also demonstrated a significant improvement in peripheral neuropathic pain characterized by allodynia [60]. These results are consistent with a recent report of dronabinol being effective in CNP in MS [61].

Symptoms of MS

In addition to reports of Sativex® being effective in the treatment of neuropathic pain, early studies indicated that it had a broad spectrum of activity across a variety of other symptoms in MS such as spasm, spasticity and bladder dysfunction [51–53]. In order to test the breadth of effect of the medicine, a study was undertaken evaluating a range of nominated primary symptoms in MS [58].

Patients chose one of five symptoms (pain, spasm spasticity, tremor or bladder dysfunction) as their nominated primary symptom. Despite their existing treatment prior to study entry, patients were required to have a symptom severity rated as >50 mm on a 100-mm VAS scale in order to be eligible. Other secondary impairments/symptoms (if present) were also monitored during the study.

A total of 160 patients entered a baseline period (14 days maximum); followed by a 6-week randomized, double-blind, placebo-controlled parallel-group comparison of Sativex® with placebo. Patients self-titrated to symptom resolution or maximum tolerated dose. Existing medication continued at a constant dose.

Primary efficacy comparisons were made between symptom scores recorded during baseline and scores recorded at the end of the 6-week parallel group period.

Patients then entered weeks 7–10 and all patients were re-titrated on to Sativex® and received open-label treatment for 4 weeks.

The results of the study are presented below and the outcome on the symptom of spasticity is presented in Figures 6 and 7.

Thirty-nine patients ($n = 19$ for Sativex®, $n = 18$ for the placebo) who nominated spasticity as their primary impairment showed a statistically significant improvement in their spasticity VAS scores as assessed at either their clinic visits or as recorded on their daily diary cards.

When the changes in each of the clinic visit spasticity VAS scores (in patients with spasticity as a primary impairment) were analysed, there was a highly statistically significant treatment difference of 22.79 mm in spasticity in favour of Sativex® ($P = 0.001$).

When the changes in each of the diary card spasticity VAS scores (in patients with spasticity as a primary impairment) were analysed, there was a highly statistically significant treatment difference of 18.41 mm in spasticity in favour of Sativex® ($P = 0.009$).

Effect on sleep

The most consistent endpoint in terms of response to Sativex® (measured in all GW studies except GWMS0106) has been the improvement in sleep quality/sleep disturbance reported by patients which chronic symptoms, irrespective of the aetiology. Patients with chronic refractory pain of neurological origin, CNP (from conditions such as MS and brachial plexus avulsion), peripheral neuropathic pain, and other symptoms of MS such as spasm, spasticity and bladder dysfunction have all reported statistically significant improvements in sleep (Fig. 8).

It is well accepted that sleep quality has a major impact on the quality of life of patients with chronic conditions. In the above clinical studies, Sativex® has not only produced statistically and clinically significant improvements in the patients primary symptoms, but also the ability to gain rest as a result of the relief of those symptoms. On average across the studies Sativex® has produced a 40% improvement in sleep quality/disturbance.

However, the effect of Sativex® on sleep is not due to a direct hypnotic effect of the medicine. The effect of Sativex® on the sleep process was investigated in a sleep laboratory study [62].

Nicholson et al. have reported the effects of Sativex® and formulated Tetranabinex® on nocturnal sleep and early-morning behaviour in young adults [62]. The effects of the medicines on nocturnal sleep, early-morning performance, memory and sleepiness were studied in eight healthy volunteers.

The study was double-blind and placebo-controlled with a four-way crossover design. The four treatments were placebo, Sativex® (six sprays, delivering a total dose of 15 mg of Δ^9-THC and 15 mg of CBD), formulated Tetranabinex® (six sprays, delivering a 15 mg dose of Δ^9-THC), and a "low-dose" Sativex® formulation (six sprays delivering a total dose of 5 mg of Δ^9-THC and 5 mg of CBD; i.e. identical to Sativex® formulation, but one-third

of the potency). Electroencephalogram (EEG) recordings made during the sleep period (11:00 PM to 7:00 AM). Performance, sleep latency and subjective assessments of sleepiness and mood were measured from 8:30 AM (10 h after drug administration).

There were no effects of 15 mg of Δ^9-THC (Tetranabinex®) on nocturnal sleep. Low-dose Sativex® (5 mg of Δ^9-THC and 5 mg of CBD) and Sativex® (15 mg of Δ^9-THC and 15 mg of CBD), produced a decrease in stage 3 sleep, but interestingly with Sativex® (15 mg) wakefulness was increased.

The next day, with Tetranabinex® (15 mg of Δ^9-THC), memory was impaired, sleep latency was reduced and the subjects reported increased sleepiness and changes in mood. However, interestingly, when 15 mg of CBD was added to the 15 mg of Δ^9-THC (i.e. following administration of 15 mg of Sativex®) there was no observed effect on daytime sleep latency and memory.

From this study, at the doses investigated, it appears that Δ^9-THC appears to have sedative properties, while CBD (present in Sativex®) appears to have alerting properties as it increased awake activity during sleep of patients taking Sativex® and counteracted the residual sedative activity of 15 mg of Δ^9-THC.

Thus Sativex® appears to promote sleep without changing the sleep architecture, but minimizes the residual effects that may be present if a Δ^9-THC-rich medicine (without the presence of CBD) is used.

What do patients want?

In a number of GW's clinical studies, patients have reported good overall improvement with Sativex®, as measured using the PGIC. Even small changes in symptom relief appear to be important to the patients, with a subset of the patients gaining large and sustained responses (e.g. ≥50% improvement from baseline).

This is reflected in reports from a number of patient groups. In the MS Society's (the UK's largest charity for people affected by MS) submission to the UK's National Institute for Clinical Excellence (NICE), the importance of small improvements in symptoms and sleep quality has been emphasized.

For example, the following quotes were included in their submission:

> "If cannabinoid-based medicines provide even minor symptom relief they could still have a major impact on people's quality of life and boost their self esteem."

> "An ideal treatment for spasticity would be short-acting so that it could reduce nocturnal spasms and aid sleep, but not compromise functioning during the daytime. Many of the existing treatments have long-term effects. Cannabinoid-based medicines have the advantage that they are short acting – they could therefore allow much better control of symptoms."

> *"Q*: What is it like to have MS?
> *Person with MS*: Get somebody to stay awake for 48 hours, make them drink loads of coffee so they just can't sleep, put weights on their ankles, a pack on their back, make them wear two lots of rubber gloves, the whole thing. Tell them it's for the rest of their life, because that's the most important thing."

> "…Others obtained pain relief or found that the drug (cannabis) simply helped them to sleep. Sleepless nights caused by spasms and nocturia can make the extreme fatigue in MS even worse. The importance of a good night's sleep cannot be overestimated. It has a major impact on Quality of Life."

Long-term data

The majority of patients (>70%) who participated in the GW randomized studies elected to receive the drug in long-term, open-label extension studies (>750 patients) [63, 64]. Efficacy with respect to a variety of symptoms has been maintained over an extended period of time (>1 year). To date, more than 200 patients have remained on treatment for more than 1 year, and a significant number have remained on treatment for more than 2 years (the maximum is 814 days as of November 2003), with no evidence of tolerance developing. Dosing has remained steady over the same period, and only minimal levels of intoxication have been reported using a 0–100 mm VAS scale (scores up to a maximum of approximately 20 upon initial exposure, diminishing over time). This, coupled with the low number of serious adverse reactions reported, demonstrates the tolerability of the product.

The effects observed in the randomized clinical studies have been sustained over the long-term (Fig. 9).

At baseline, patients in the randomized, placebo-controlled phase had the following NRS scores: brachial plexus injury, 6.8; neuropathic pain in MS, 6.5; peripheral neuropathic pain, 7.2; spinal cord injury (data not available, study ongoing).

Safety

GW has now generated more than 800 patient-years of exposure to Sativex® since the year 2000. By June 2004, more than 200 patients had been exposed to Sativex® for at least 1 year.

The most common adverse events reported during clinical studies were generally non-serious in nature and are mainly due to application site reactions (oral pain, dry mouth, oral mucosal disorder, tooth discolouration, mouth ulceration, oral discomfort, application-site pain, dysgeusia) or intoxication-like

reactions (fatigue, feeling drunk, lethargy, dizziness, somnolence, disturbance in attention, memory impairment, euphoric mood, disorientation).

Other common adverse events reported were nausea, vomiting, diarrhoea, constipation, dyspepsia, weakness and headache.

Intoxication

The long-standing concern regarding the development of cannabis-based medicines has been the psychoactivity of Δ^9-THC. Until now, this has been perceived as a major barrier to the safety and tolerability of such medicines. To date, patients have often reported that they are often unable to tolerate the synthetic cannabinoid medications currently available to them due to their side effects. The main concern for many patients regarding the use of cannabis-based medicines is the symptom of intoxication. Patients do not wish to get high and actively seek to avoid this as it interferes with their daily life, which in many cases has already been compromised by their symptoms and/or underlying condition. This is not a situation that is unique to cannabinoid medicines, as many other classes of licensed pharmaceuticals may produce intoxication-like effects (e.g. opioids, benzodiazepines, tricyclic antidepressants, etc.). Indeed, many patients suitable for treatment with cannabis-based medicines are already experiencing polypharmacy with such products.

The range of intoxication like reactions reported by patients taking Sativex® in clinical trials has consistently been reported [50–60, 63, 64]. Safety data have been collected in randomized, double-blind studies and in long-term open-label extension studies. Safety data from more than 500 patients in the long-term extension studies are now available, where patients were allowed to take up to 48 sprays per day (maximum Δ^9-THC dose = 130 mg/day). The most common intoxication like reaction reported is dizziness, reported initially in approx. 35% of patients. However, this includes patients who are new to the medication and are titrating their initial dose. In long-term use the incidence of such an event is approximately 25%. All other intoxication-like reactions are reported at incidences of less than 5% (with the exception of somnolence, 7%).

However, the most important issue regarding intoxication is not the incidence, but the severity of any intoxication-like reactions. This is where the composition of the medicine and its delivery become important. Sativex® not only produces a low incidence of intoxication, but when experienced by patients it is generally very low in severity. The ability of the patient to self-titrate with Sativex® makes it easier to target the therapeutic window, and makes the occurrence of any such side effects much more manageable, as the dose and dosage interval can be tailored to each patient's needs as required according to their daily circumstances.

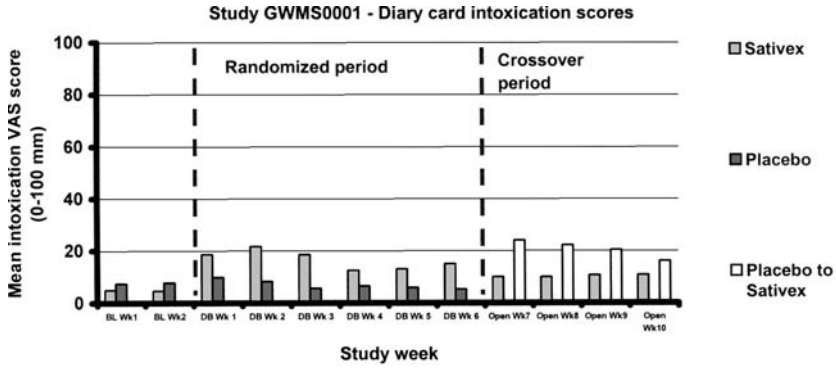

Figure 10. Intoxication produced by Sativex® [58]. BL, baseline; DB, randomized, double-blind period (weeks 1–6). Placebo crossed over to Sativex® in weeks 7–10. Adapted from Wade et al. [58].

As can be seen from Figure 10, the maximum severity of intoxication experienced by patients (measured using a VAS) was only approximately 20 out of 100 mm following initial exposure to Sativex®. This severity occurs early on in their initial titration period (within the first 2 weeks) and rapidly diminishes over time to scores less than 5 out of 100 mm. Figure 10 also shows that the picture is repeated in placebo patients who were then switched over to Sativex®. The long-term intoxication data presented in Table 3 also support this (see also Fig. 11).

So, although a relatively small amount of intoxication may occur initially in patients who use Sativex®, it subsides over time, and may be easily managed using patient self-titration, to minimize levels even further.

Table 3. Long-term intoxication produced by Sativex® [64]

Study week	No. of patients	Mean VAS score	SD	Median	Minimum	Maximum
4	330	4.84	11.69	1	0	75
12	268	3.08	8.33	0	0	62
20	211	2.04	4.75	0	0	35
28	205	2.46	6.26	0	0	42
36	184	2.83	6.77	0	0	45
44	150	3.69	10.54	0	0	77
52	121	2.26	7.29	0	0	50
60	90	1.37	6.02	0	0	53
68	62	1.92	8.94	0	0	69

VAS scale is 0–100 mm, where 0 means no intoxication and 100 is extreme intoxication.

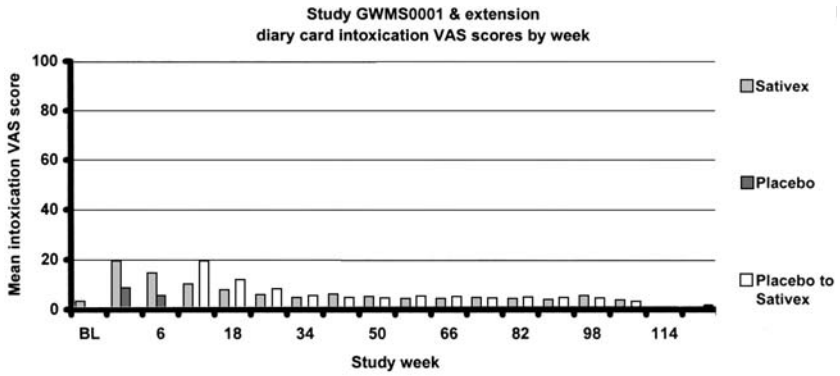

Figure 11. Long-term intoxication produced by Sativex® [63]. BL, baseline. Adapted from Wade et al. [63].

Dosing

The review of the efficacy and safety information above clearly demonstrates that there is a therapeutic window for Sativex® between the level at which patients can receive significant benefit without significant adverse effects, and the dose which may produce intoxicating effects. There is no evidence of tolerance, it can be seen that improvements in symptoms can be maintained while on a stable dose (Fig. 12).

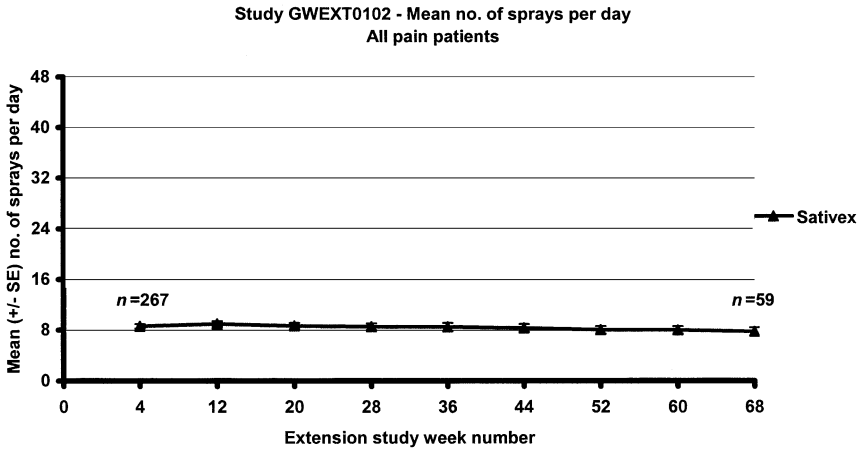

Figure 12. Long-term dosing of Sativex® in neuropathic pain [64]

Conclusion

There has been great debate with regard to merits of cannabis-based medicines with little scientific and clinical evidence to substantiate the anecdotal efficacy and safety. The discovery of the endogenous cannabinoid receptors and endocannabinoids such as AEA, 2-AG, noladin ether and NADA has spawned resurgence in the search for therapeutic agents to treat severe and chronic conditions.

To date, medicines made from single synthetic cannabinoid molecules have yet to be widely used, mainly due to their side-effect profiles. The development of a new product, Sativex®, made from whole-plant extracts of cannabis, may change the way cannabis is viewed, its therapeutic potential maximized and its universal approval as a medicine granted.

Sativex® is produced from botanical raw materials that have been specifically grown for their defined cannabinoid ratios. It is a blend of defined extracts, which ensure batch-to-batch reproducibility is attained. The other components of the extracts, in addition to the principal cannabinoids add to the benefits of the medicine.

Clinical studies with Sativex® have focused initially on symptom relief in chronic conditions, such as MS, neuropathic pain and rheumatoid arthritis, but it may have further potential as a disease-modifying agent in such conditions. Further clinical studies will be necessary to investigate this.

The clinical efficacy of Sativex® has been demonstrated in the largest programme of clinical studies of a cannabis-based medicine ever undertaken. Positive benefits have been observed in all 11 studies completed to date by GW. Dosing at levels of 8–15 sprays per day have produced significant improvements in central and peripheral neuropathic pain and improvement in a number of symptoms of MS (neuropathic pain, spasm, spasticity and bladder dysfunction) have also been reported. Further, the first study of cannabinoids in rheumatoid arthritis has demonstrated that Sativex® may have potential in relieving not only symptoms of rheumatoid arthritis, but it also may have a modulating effect on the disease process. A characteristic, which accompanies the symptom relief achieved with Sativex®, is an improvement in sleep quality.

Sativex® appears to improve symptom relief in the most difficult groups of patients – i.e. those who have significant residual symptoms even after best available therapy has been implemented. The benefits it confers are in addition to any relief patients may previously have attained with other medications. Patient groups continue to clamour for the approval of a cannabis-based medicine and have indicated that even a small reduction in symptoms is of major importance to patients, their quality of life and their overall sense of well being.

In addition to its considerable and sustained efficacy, Sativex®, in clinical studies, has a very acceptable safety and tolerability profile. It is generally well tolerated, and the flexibility offered to patients ensures they can quickly and

easily self-titrate to optimum benefit. Intoxication is not usually a limiting factor for the majority of patients, and any low levels of intoxication upon the patient's initial exposure to the medicine are further reduced as they become familiar with the medicine and the process of self-titration. Side effects experienced are usually mild or moderate in severity, and there have been few withdrawals from treatment in the clinical studies to date due to undesirable effects. Most adverse effects resolve without treatment, and some on a reduction of dosage of the medicine.

Long-term dosing with Sativex® maintains the clinical benefits initially observed in the acute setting, over prolonged periods. There is no evidence that tolerance to the beneficial effects develops. In some cases the benefits achieved with Sativex® have allowed patients to reduce the doses of, or even stop taking, other medications.

The approval of Sativex® as a pharmaceutical medicine by regulatory authorities around the world will represent a milestone in modern medicine and may catalyse a new era of BDPs.

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