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Cannabinoid Therapies

Therapeutics turning a corner

Edison themes

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Despite the fact that cannabis has been used for medical purposes for thousands of years, there are only a handful of therapeutics containing cannabis that have been approved by regulatory authorities, with worldwide sales of just $53m in 2018 according to Evaluate Pharma. GW Pharma's Epidiolex (cannabidiol, CBD) is a potential game changer and is likely to be the largest FDA-approved cannabinoid drug in history. However, the pipeline of cannabinoids for regulatory approval after Epidiolex is relatively sparse and generally consists of reformulations rather than anything truly novel or innovative, with a heavy focus on pain indications as that is one of the areas in which data on the efficacy of cannabis are the strongest.

Few approvals historically

Prior to 2018, the FDA had only approved three cannabinoid products (two of them based on the same active ingredient, dronabinol) with all of them being synthetic compounds. Marinol and Cesamet were both approved by the FDA in 1985 and were the first cannabinoids to gain approval, though Cesamet was withdrawn in 1989 for commercial reasons (it was resuscitated by Valeant, which regained approval for the drug in 2006). There were no additional US approvals until 2016 when Syndros, a reformulation of dronabinol into a liquid, was approved. The approvals have typically been in relatively niche areas, such as chemotherapy-related nausea as well as to improve the appetite of those with HIV.

Epidiolex leading the way

In June 2018, the FDA approved Epidiolex from GW Pharma for the treatment of certain rare epilepsies. Consensus estimates expect sales of $1.7bn in 2024, which would make it the largest cannabis-related FDA approved drug in history (it is also the first plant-based cannabinoid to gain approval). Epidiolex is a natural pharmaceutical-grade version of CBD and was able to demonstrate efficacy in a heavily pre-treated refractory population suffering from a debilitating disease. The US pediatric epilepsy population alone is over 466,000 patients, with the uncontrolled pediatric population is between 93,000 to 140,000 in total.

Likely winners…

- **Biotech/Pharma:** GW Pharma, Arena, Corbus
- **Consumers:** Patients with a variety of ailments including epilepsy and pain

Likely losers…

- **Opioid-focused specialty pharma:** Purdue, Insys, Endo, Teva
- **Alcohol companies:** AB InBev, Heineken, Molson Coors

Winners and losers/The companies shown above do not translate into buys and sells as other themes (and valuation parameters) may conflict.

From the street

Most cannabinoids are non-euphoric and many of them provide therapeutic benefits. Furthermore, they interact with our endocannabinoid system (ECS) in ways that are beginning to reshape our understanding of health and wellness. The ECS is one of the most ubiquitous networks of receptors in the human body and a retrograde signaling system that helps to regulate neurotransmissions. Science is teaching us that by targeting the right receptors with the right cannabinoids, a multitude of wellness indications, applications and potentially groundbreaking medical breakthroughs are not only plausible, but probable (source: CB1 Capital).

Edison themes

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Cannabinoids as therapeutics

Cannabis is thought to be one of the oldest plants cultivated by humans with multiple medicinal uses (including problems with the eyes, gynecological disorders as well as to fight inflammation) documented in ancient Egyptian texts. In all, cannabis was used to treat a wide variety of different indications, including pain, spasticity, cancer, epilepsy, nausea, anorexia and infectious disease.[1]

But despite the fact that cannabis has been used for various medical purposes for thousands of years (and has a safety profile that is superior to alcohol in many respects),[2] there are surprisingly few therapeutics containing cannabis that have been approved by major regulatory authorities, with worldwide sales totaling only around $53m in 2018 according to Evaluate Pharma. However, Epidiolex was only launched at the end of 2018 and is expected to have $1.7bn in sales in 2024 based on consensus forecasts. Also the World Health Organization, in January of 2019, called on a rescheduling of cannabis to facilitate trade for medicinal and scientific purposes.

Exhibit 1: Cannabis therapeutics currently authorized by regulators

Brand name	Originator	Description	Indications	Form	Location of approvals
Sativex (nabiximols)	GW	Extract of cannabis: mix of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), 1:1 ratio	Multiple sclerosis-related spasticity	Sublingual spray	25 countries in Europe, Latin America, North America and Australasia. Not approved in the US
Marinol (dronabinol)	Unimed	Synthetic delta-9-THC	Loss of appetite in people with AIDS and nausea and vomiting caused by chemotherapy	Capsules	US, Canada, Germany, Australia and New Zealand
Syndros (dronabinol)	Insys	Synthetic delta-9-THC	Loss of appetite in people with AIDS and nausea and vomiting caused by chemotherapy	Liquid	US
Cesamet (nabilone)	Lilly	Synthetic cannabinoid similar to THC	Nausea and vomiting caused by chemotherapy	Capsules	US, Canada, Europe, Australia
Bedrocan (dried cannabis flower tips)	Bedrocan	Medical grade cannabis	Various	Cannabis flower tips	Certain countries within Europe where medical cannabis is legal
Epidiolex	GW	Cannabidiol (CBD)	Dravet and Lennox-Gastaut syndromes (pediatric epilepsies)	Liquid	US

Source: European Monitoring Centre for Drugs and Addiction, FDA, drug labels, company reports

Marinol and Cesamet were both approved by the FDA in 1985 and were the first cannabinoids to gain approval though Cesamet was withdrawn in 1989 for commercial reasons (it was resuscitated by Valeant, which regained approval for the drug in 2006). There were no additional US approvals until 2016 when Syndros, a reformulation of dronabinol into a liquid, was approved and then Epidiolex (CBD) was approved for Dravet and Lennox-Gastaut (LGS) syndromes in 2018. Sativex, an extract of the cannabis plant, was first approved in the UK in 2010 but never approved in the US.

The pipeline of cannabinoids for regulatory approval is relatively sparse and generally consists of reformulations of phytocannabinoids (defined as cannabinoids derived from plants), CBD and/or THC rather than anything truly novel or innovative (see Exhibit 2), with a heavy focus on pain indications as that is one of the areas in which data on the efficacy of cannabis are the strongest.

1 Russo et al., History of Cannabis and Its Preparations in Saga, Science, and Sobriquet. *Chemistry and Biodiversity* – Vol. 4 (2007) 1614-1648)

2 Lachenmeier et al., Comparative risk assessment of alcohol, tobacco, cannabis and other illicit drugs using the margin of exposure approach. *Scientific Reports*. 5:8126, 1-7.

Exhibit 2: Select clinical-stage cannabinoid programs

Company	Product	Generic name	Phase	Indication
Insys Therapeutics	Cannabidiol	Cannabidiol	III	Epilepsy, Prader-Willi syndrome
Tilray	Cannabidiol oil capsule	Cannabidiol;	III	Anxiety
Corbus	Lenabasum	Ajulemic acid	III	Systemic sclerosis, dermatomyositis, lupus, cystic fibrosis
Tetra Bio-Pharma	PPP005	Cannabidiol; tetrahydrocannabinol	II/III	Cancer pain
Zynerba	ZYN002	Cannabidiol	II/III	Fragile X
Arena	APD371	Olorinab	II	Gastrointestinal pain
Therapix Biosciences	THX-110	Dronabinol; palmitoylethanolamide	II	Tourette syndrome, obstructive sleep apnea and pain
CMXTwenty	CMX-020	CMX-020	II	Pain
Tilray	Cannabis (vaporized)	Cannabidiol; tetrahydrocannabinol	II	PTSD
Tilray	TN-TC19LM	Cannabidiol; tetrahydrocannabinol	II	HIV
Tetra Bio-Pharma	PPP001	Cannabidiol; tetrahydrocannabinol	II	Cancer pain
GW Pharmaceuticals	GWP42006	Cannabidivarin	II	Epilepsy, autism, Rett syndrome
GW Pharmaceuticals	GWP42002	Cannabidiol; tetrahydrocannabinol	II	Glioblastoma
GW Pharmaceuticals	GWP42003	Cannabidiol	II	schizophrenia, neonatal hypoxic-ischemic encephalopathy
Kalytera Therapeutics	CBD	Cannabidiol	II	GvHD
Botanix	BTX 1503	Cannabidiol	II	Acne
Botanix	BTX 1204	Cannabidiol	II	Atopic dermatitis
MGC Pharma	CannEpil	Cannabidiol	II	Epilepsy
MGC Pharma	CogniCann	Cannabidiol; tetrahydrocannabinol	II	Mild dementia and Alzheimer's disease
Tilray	TN-TC11G	Cannabidiol; tetrahydrocannabinol	I/II	Glioblastoma
Intec Pharma	AP-CBD	Cannabidiol	I	Pain
Intec Pharma	AP-THC	Tetrahydrocannabinol	I	Pain
Artelo Biosciences	ART27.13	ART27.13	I	Anorexia
Bird Rock Bio	Nimacimab	Nimacimab	I	NASH, diabetic kidney disease
Veritas Pharma	CTL-X	Undisclosed	I	Acute pain

Source: EvaluatePharma, company reports, clinicaltrials.gov

One big issue with developing an FDA-approved cannabinoid product is that while the clinical trial process is no shorter, the period of exclusivity is especially short if the product is simply a reformulation of THC or CBD. First, Hatch-Waxman exclusivity is only three years for a product that is not a new chemical entity. Second, any patents in this area will likely be particularly narrow due to the high level of prior art affecting patentability of THC and CBD formulations. And any granted patents will likely be challenged once the Hatch-Waxman exclusivity expires. This challenging intellectual property landscape is likely a major reason that larger biotechnology and pharmaceutical companies have not involved themselves in this space.

One strategy that could get around this intellectual property issue would be to develop one of the 100+ minor cannabinoids that exist in cannabis plants into a drug as the level of actual invention would be far higher than with THC and CBD. Besides the possibility of cleaner and broader intellectual property, these cannabinoids may also have a differentiated efficacy and toxicity profile (see Exhibit 3). Research into these minor cannabinoids is still in relatively early days due to the expense of harvesting them, but new synthetic processes promise to make them available at a lower cost, which would encourage additional research.

Targeting the endocannabinoid system (a group of molecules and receptors in the brain that mediates the effects of cannabis) with novel synthetic compounds, such as Lenabasum from Corbus or APD371 from Arena, would be another strategy as they would be associated with new composition of matter patents, a key selling point for any large pharmaceutical partner. Both of these compounds are agonists of the cannabinoid receptor type 2 (CB2), which is mainly expressed in the periphery in immune cells and has a role in inflammation. The cannabinoid receptor type 1 (CB1), which is highly expressed in the brain, is the one associated with the psychoactive effects

and has been a troublesome target for pharmaceutical development while either activating it (agonism), due to those psychoactive effects, or blocking its activation (antagonism), as this can lead to increased risk of suicidality as seen with Sanofi's Acomplia (rimonabant).

Exhibit 3: Select cannabinoids and what they do

Name	Abbreviation	Comments
Tetrahydrocannabinol	THC	Most abundant cannabinoid in cannabis. Responsible for the euphoric feeling. A synthetic version is FDA approved for treating anorexia in AIDS patients and to treat nausea in cancer patients. Believed to potentially have efficacy with regards to pain, anxiety, depression, nausea, spasms and certain cancers. CB1 agonist (central nervous system disorders).
Cannabidiol	CBD	Second most abundant cannabinoid. Not psychoactive. A natural version has been approved by the FDA for refractory epilepsy. Also thought to work against pain, anxiety, depression, nausea, insomnia, spasms, psychosis and certain cancers. Antagonist of CB1/CB2 agonists, CB2 inverse agonist (anti-inflammatory), positive allosteric modulator (pain), TRPA1 agonist (pain), TRPM8 antagonist (prostate cancer), TRPV1 agonist (psychosis, pain).
Cannabichromene	CBC	Third most abundant cannabinoid. Not psychoactive. Preliminary studies indicate a potential to treat acne, diarrhea, pain, inflammation, depression, anxiety, multiple sclerosis and increase bone growth. Anandamide reuptake inhibitor (various neurological conditions).
Cannabigerol	CBG	Cannabis plants usually contain less than 1% CBG. Not psychoactive. Potential to treat pain, bacterial and fungal infections, cancers and depression. CB1 and CB2 partial agonist (neurological conditions), anandamide reuptake inhibitor (neurological conditions), TRPA1 agonist (pain), TRPV1 agonist (pain), TRPM8 antagonist (prostate cancer).
Cannabigerolic acid	CBGA	Precursor to all other cannabinoids. Not psychoactive. May have applications in pain and inflammation.
Cannabinol	CBN	Produced through the degradation of THC and typically plants contain less than 1% CBN. Minor psychoactive effects. Potential against bacteria, epilepsy, inflammation, anorexia, cancer, insomnia, glaucoma, bone healing and pain.
Delta-9-Tetrahydrocannabinolic acid	THCA	Precursor to THC, which turns into THC when burned or vaporized. Not-psychoactive. Potential to treat inflammation, nausea, cancers and act as a neuroprotective. TRPA1 partial agonist (pain), TRPM8 antagonist (prostate cancer).
Cannabidiolic acid	CBDA	Precursor to CBD, suggested to have efficacy in cancer, pain, nausea and inflammation. TRPA1 partial agonist (pain), TRPV1 agonist (pain), TRPM8 (prostate cancer), COX-2 inhibitor (pain/inflammation).
Tetrahydrocannabivarin	THCV	Works very differently from THC. Potential to treat obesity, diabetes, anxiety, Alzheimer's disease, epilepsy and stimulate bone growth. CB1 antagonism (epilepsy).

Source: Izzo et al., Non-psychotropic plant cannabinoids, *Trends in Pharmacological Sciences*. 2009 Oct;30(10):515–27. 2018 Cannabis Investment Report by Ackrell Capital

Cannabinoids for epilepsy

Earlier last year, the most monumental approval of a cannabinoid occurred in the neurologic realm, specifically for the treatment of epilepsy. In June of 2018, the FDA approved Epidiolex for the treatment of a pair of pediatric epilepsies, namely Dravet and LGS. Epidiolex is a natural pharmaceutical-grade version of CBD and was able to demonstrate efficacy in a heavily pre-treated refractory population suffering from a debilitating disease (see Exhibit 4).

Exhibit 4: Epidiolex trial data in Dravet and LGS

Indication	Doses tested	Number of patients	Average age	Average number of AEDs currently prescribed	Number of previously tried AEDs	Median baseline seizure frequency	Epidiolex seizure reduction	Placebo seizure reduction	p value	Dropouts due to AEs
Dravet	20mg/kg	120	10	3	4	13 convulsive seizures	-39% (20mg/kg)	-13%	0.0123	13%
LGS Trial 1	20mg/kg	171	15	3	6	74 drop seizures	-44% (20mg/kg)	-22%	0.0135	14%
LGS Trial 2	20mg/kg and 10mg/kg	225	16	3	7	85 drop seizures	-42% (20mg/kg), -37% (10mg/kg)	-17%	0.0047 (20mg/kg), 0.0016 (10mg/kg)	8% (20mg/kg), 1% (10mg/kg)

Source: GW Pharmaceuticals

Dravet syndrome is an extremely malignant form of childhood epilepsy that typically presents itself within the first year of life with prolonged febrile and afebrile, generalized clonic or hemiclonic epileptic seizures in otherwise normally developing children. Around 10–14% of Dravet patients end up dying, typically around the age of six or seven.[3] Besides the risk of death, by the time the children are teenagers they exhibit either severe or profound learning disabilities. In one study of 31

3 Sakauchi et al. 2011 *Epilepsia*, 52(6): 1,144–1,149.

typical and borderline Dravet patients (14 were typical Dravet, 17 were borderline) who were followed until adulthood, 22.6% could speak no words at all, 29% could speak several words, 29% could make primitive conversation and 16.1% could make simple conversation and read to some extent. Only one (3.2%) with borderline Dravet could lead an independent life, although he developed psychosis.[4] The incidence of Dravet ranges from 1:20,000 to 1:40,000 births, which suggests an overall disease prevalence of 5,500 patients in the US and 6,700 European patients.[5]

LGS, like Dravet, is a rare form of epilepsy, although it typically starts later in life, at between two and eight years of age vs six months for Dravet. As with Dravet, outcomes are extremely poor for these patients, with 90% becoming mentally handicapped with a progressive reduction in IQ. The mortality rate is high, although the exact percentage varies based on the study and ranges between 3% and 25%.[6] Incidence estimates for LGS vary, but it accounts for approximately 2–5% of all childhood epilepsies. This suggests 16,000 pediatric patients with LGS in the US and 24,000 in Europe with prevalence potentially doubling if including adult LGS patients according to the LGS Foundation.

With regards to the total pediatric epilepsy market, it is estimated that 20–30%[7] of those treated for epilepsy are considered to be uncontrolled, with seizure free rates plummeting dramatically after failing the first drug. As the US pediatric epilepsy population alone is over 466,000 patients,[8] the uncontrolled pediatric population is between 93,000 to 140,000 in total. With an average annual price for Epidiolex at $32,500, this suggests a $3bn to $4.5bn addressable market in the US alone (note that in Europe the submission is under review, with approval for Epidiolex expected around the middle of 2019), assuming expansion beyond Dravet and LGS to other uncontrolled pediatric epilepsy patients.

As caregivers discuss the possibility of substituting cheaper, non-standardized grade CBD products for Epidiolex, it is important to remember the fate of ZYN002, a synthetic transdermal cannabidiol that was being developed for adult epilepsy patients with focal seizures by Zynerba. In its Phase II trial, the drug failed to show significance in any of the primary or secondary endpoints. While Epidiolex was able to show a ~40% reduction in seizure frequency in its three Phase III trials (in a pediatric population), ZYN002 was only able to show an 18.4% reduction in the low dose and a 14.0% reduction in the high dose (both in adults). Simply put, not all CBD products are the same and the high-quality data from GW has set a very high bar.

Cannabinoids in other approved indications

Marinol and Cesamet have been approved for chemotherapy-related nausea and a review of data from 23 trials indicates that cannabinoids are superior to placebo and approximately in line with other anti-emetic therapies, though the cannabinoids were associated with dizziness, dysphoria, euphoria and sedation.[9]

Both Marinol and Cesamet have also been approved to improve the appetite of those with HIV, which makes sense as smoking cannabis has been associated with 40% greater caloric intake.[10] In a review of four studies with 255 participants, one review concluded that “there was some evidence

4 Akiyama M et al. 2010, *Epilepsia*, 51(6): 1043–1052.

5 Brunklaus A et al. *Brain* 2012: 135; 2329–2336.

6 Rijckevorsel, K. *Neuropsychiatric Disease and Treatment* 2008:4(6) 1001–1019.

7 French J et al., *Neurology* 2004;62;1261–1273.

8 Russ et al., *Pediatrics* 129, 2, February 2012.

9 Smith et al., Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy (Review). *Cochrane Database of Systematic Reviews* 2015, 11

10 Foltin et al., Effects of smoked marijuana on food intake and body weight of humans living in a residential laboratory. *Appetite* 11(1):1–14

that dronabinol is associated with an increase in weight when compared to placebo. More limited evidence suggested that it may also be associated with increased appetite, greater percentage of body fat, reduced nausea and improved functional status."[11]

Sativex is also approved in 25 countries (though not the US) for spasticity due to multiple sclerosis (MS), a condition that affects approximately 60% of MS patients (there are an estimated 900,000 MS sufferers in the US according to the National Multiple Sclerosis Society and 400,000 in the EU according to European Union estimates). Data are mixed. In a large 337-patient trial sponsored by GW Pharma, on an intent to treat basis, Sativex improved the spasticity numeric rating scale score by 1.05 points, compared to 0.82 points for placebo (p=0.219), a not statistically significant result. However, in a per-protocol analysis, which excluded 21% of patients who had protocol violations, Sativex improved spasticity scores by 1.3 points compared to 0.84 points for placebo (p=0.035), a statistically significant result. None of the 15 other secondary endpoints were positive on an intent to treat basis but three were positive on a per protocol basis. Needless to say, Sativex's market adoption has been limited with only $30m in worldwide sales in 2018.

Cannabinoids for pain

After epilepsy, pain is probably the area with the highest quantity of evidence associated with the efficacy of cannabinoids and is simply an enormous market. According to the Centers for Disease Control, 20.4% of adults in the US (around 50 million people) have chronic pain, with around 40% of those (around 19.6 million people) experiencing high-impact chronic pain. In Europe, the prevalence of moderate to severe pain in the adult population is estimated to be similarly high at 19%[12] (around 80 million people). However, while pain is a very promising and large market for cannabinoids, the clinical data have been a little inconsistent. In a review of 28 studies covering 2,454 patients, the authors concluded "studies generally suggested improvements in pain measured associated with cannabinoids but these did not reach statistical significant in most individual studies".[13] In one of the few high-grade clinical trials in the space, which was sponsored by GW Pharmaceuticals, Sativex was tested versus placebo in 298 patients with pain due to diabetic neuropathy, but only showed a minor benefit that did not reach significance with a p value of 0.63. However, usage data from states that have legalized medical cannabis indicates that patients are using it for pain and this has led to less opioid use. In one survey of 244 medical cannabis patients in Michigan, cannabis use was associated with a 64% decline in opioid use,[14] a tremendous decrease that would speak to at least some efficacy for the drug. Also, in an analysis of Medicare Part D data, medical cannabis legalization was associated with a statistically significant 11.4% reduction in the use of prescription pain medication statewide.[15]

One of the most advanced therapeutic programs in pain belongs to Arena Pharmaceuticals, which is developing a full CB2 agonist (due to CB2's effect on microglial activation and inflammation) for the treatment of pain associated with irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD), two highly prevalent indications. According to the International Foundation for Gastrointestinal Disorders, between 25 and 45 million people in the US suffer from IBS, while the Centers for Disease Control estimates that 1.0–1.3 million Americans have IBD. Around 30% of IBD

11 Whiting et al., Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 313(24):2456-2473

12 Breivik et al., Survey of chronic pain in Europe: Prevalence, impact on daily life and treatment. *European Journal of Pain 10* (2006) 287-333

13 Whiting et al., Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 313(24):2456-2473

14 Boehnke et al., Medical cannabis use is associated with decreased opiate medication use in a retrospective cross-sectional survey of patients with chronic pain. *Journal of Pain* 17(6):739-744

15 Bradford et al., Medical Marijuana Laws Reduce Prescription Medication Use in Medicare Part D. *Health Affairs* 35, no. 7 (2016):1230-1236.

patients[16] and 35% of IBS patients[17] receive opiates for their pain. The company conducted a 14-patient Phase IIa trial in adults with Crohn's disease where patients received either 25mg or 100mg three times daily. At peak effect, 85% of those with evaluable data at week four (13 of the 14 patients) and 100% of those with evaluable data at week eight demonstrated a greater than 30% change from baseline in their average abdominal pain scores (AAPS) with the data being consistent at both doses. Importantly, there were no psychotropic effects and no discontinuations due to adverse events. The company is currently preparing for a Phase IIb study.

Exhibit 5: Cannabinoid pipeline in pain

Company	Product	Generic name	Phase	Comments
Tetra Bio-Pharma	PPP001	Cannabidiol; tetrahydrocannabinol	II/III	Smokable cannabis pellets for cancer pain. Only data so far have been Phase I study in healthy volunteers. Phase III program ongoing.
Arena	APD371	Olorinab	II	CB2 agonist for the treatment of GI-based visceral pain. In a Phase IIa in 14 patients, 79% had clinically relevant reductions in pain at weeks four and eight. Preparing for Phase IIb.
Therapix Biosciences	THX-110	Dronabinol; palmitoylethanolamide	II	Dronabinol and PEA for chronic low back pain. No data yet. Phase IIa ongoing.
CMXTwenty	CMX-020	CMX-020	II	Oral and intravenous cannabinoid. Current status uncertain.
Tetra Bio-Pharma	PPP005	Cannabidiol; tetrahydrocannabinol	II	Cannabis oil for cancer pain. No data so far.
Intec Pharma	AP-CBD	Cannabidiol	I	Sustained release CBD for low back pain, neuropathic pain and fibromyalgia. In Phase I.
Intec Pharma	AP-THC	Tetrahydrocannabinol	I	Sustained release THC for low back pain, neuropathic pain and fibromyalgia. In Phase I.
Veritas Pharma	CTL-X	Undisclosed	I	Undisclosed cannabinoid product for acute pain.

Source: EvaluatePharma, company reports, clinicaltrials.gov

Cannabinoids in other neurological disorders

Cannabinoids have been tested in a variety of problems including Tourette's, anxiety and post-traumatic stress syndrome (PTSD), though the evidence of efficacy so far is rather limited as there have been few large trials.

Two small-scale randomized, controlled clinical studies have been performed examining dronabinol for the treatment of Tourette's. In the US, the CDC estimates that 138,000 children are diagnosed with the disease,[18] while the National Institute of Neurological Disorders and Stroke estimates that there are 200,000 children and adults with Tourette's.[19] The first study was a randomized crossover trial of 12 individuals, and it showed a 22% improvement in the Yale Global Tic Severity Scale (YGTSS), although it did not reach statistical significance.[20] However, a statistical improvement was seen for complex motor tics ($p=0.015$) and for patient reported symptoms ($p=0.015$). The second study examined 24 patients in placebo and dose escalation cohorts (ranging from 2.5mg to 10mg of dronabinol per day). It reached similar results, showing improvement in symptom ratings of motor tics ($p=0.04$) and patient reported symptoms ($p<0.05$), but failed to reach statistical significance in the overall YGTSS.[21] Also, in 2018, Therapix, which is combining dronabinol with palmitoylethanolamide (PEA), saw a 21% reduction in tic severity ($p=0.002$) in a trial of 16 Tourette's patients.

In anxiety, in a 24-patient trial in which patients either received 600mg of CBD or placebo and then had to conduct simulated public speaking, the CBD arm saw a greater improvement in anxiety

16 Burr et al., Increasing Prescription of Opiates and Mortality in Patients with Inflammatory Bowel Diseases in England. *Clinical Gastroenterology and Hepatology* 2018;16:534-541

17 Camilleri et al., Opioids in Gastroenterology: Treating Adverse Effects and Creating Therapeutic Benefits. *Clinical Gastroenterology and Hepatology* 2017;15:1338-1349

18 Tourette Syndrome (TS), Data and Statistics. *Centers for Disease Control and Prevention.*

19 Tourette Syndrome Fact Sheet. *National Institute of Neurological Disorders*

20 Müller-Vahl KR (2002) Treatment of Tourette's Syndrome with Δ9-Tetrahydrocannabinol (THC): A Randomized Crossover Trial. *Pharmacopsychiatry* 35, 57-61.

21 Müller-Vahl KR et al. (2003) Delta 9-Tetrahydrocannabinol (THC) is Effective in the Treatment of Tics in Tourette Syndrome: a 6-Week Randomized Trial. *J. Clin. Psychiatry* 64, 459-465.

compared to placebo. This data is likely the basis of a 50-patient, eight-week trial being sponsored by Tilray studying CBD oil capsules in patients with anxiety. Data is expected in Q420. As a reminder, anxiety disorders are highly prevalent, with 19.1% of adults suffering from them on an annual basis according to the National Comorbidity Survey conducted by Harvard Medical School.

With regards to PTSD, in a trial in 10 Canadian military personnel in which the participants alternated between receiving Cesamet and placebo, patients on Cesamet saw a statistically significant reduction in nightmares (p=0.03) as well as a general improvement in Clinical Global Impression of Change (p=0.05) in seven of 10 patients compared to only two of 10 on placebo.[22] While small, this is an interesting signal as military-related PTSD is notoriously difficult to treat. Only 20% of military-related PTSD patients were effectively treated in previous SSRI studies (the current standard of care).[23] And if you count both civilian and military PTSD, it is a rather large indication. Based on the results of a national comorbidity survey, 3.5% of the adult population have PTSD.[24] Tilray is conducting a 42-patient trial of vaporized dried cannabis in patients with PTSD with data expected in Q220.

There is also some data related to using cannabinoids in the treatment of recurrent glioblastoma. In a 21-patient trial in recurrent glioblastoma sponsored by GW Pharmaceuticals, patients who received a combination of CBD and THC had an 83% one-year survival rate, compared to 44% for patients on placebo (p=0.042). Median survival was also 662 days in the CBD/THC combination group compared to 369 days for patients in the control arm. According to the Central Brain Tumor Registry of the United States, glioblastoma represents 15% of all brain and central nervous system tumors, amounting to approximately 11,000 new cases per year.[25] GW is continuing the program and Tilray is involved with a 30-patient glioblastoma trial for another CBD and THC combination product, TN-TC11G, with data expected around the middle of 2020.

22 Jetly et al., The efficacy of nabilone, a synthetic cannabinoid, in the treatment of PTSD-associated nightmares: A preliminary randomized, double-blind, placebo-controlled cross-over design study. *Psychoneuroendocrinology* 51:585-588.

23 Walter Alexander, Pharmacotherapy for Post-traumatic Stress Disorder in Combat Veterans, *P&T*, January 2012.

24 Kessler et al, *Arch Gen Psych* 2005;62:617-627

25 Ostrom et al., CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2008-2012. *Neuro-Oncology*, 17(suppl 4), iv1-iv62.

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