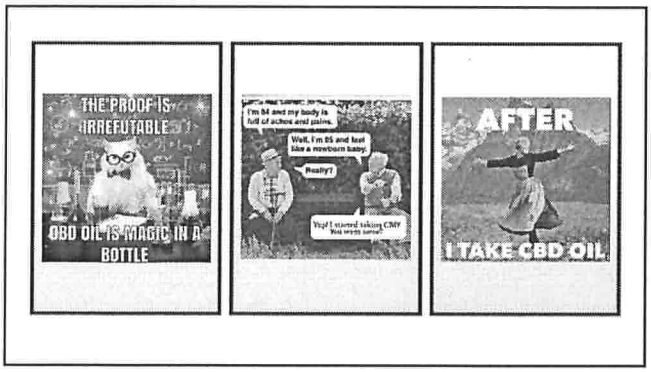
# CBD-infused preparations- effective or not, safe or dangerous: what is the evidence?

Marcus Debiasi, DDS, MS-BMS, MSN,PMH-NP

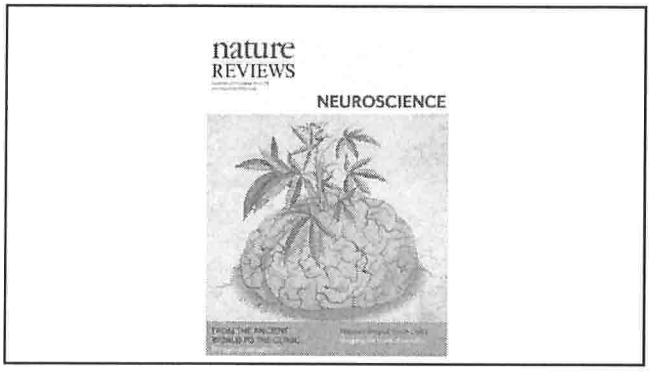


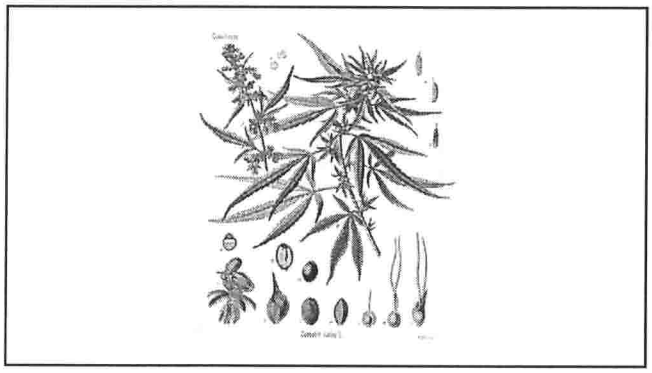

"...modulating endocannabinoid activity may have therapeutic potential

in almost all diseases affecting humans,

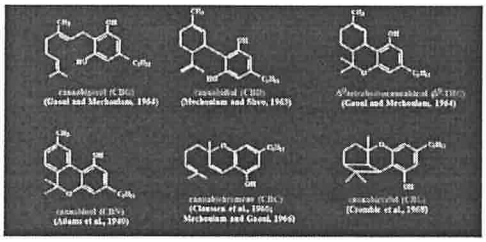
including obesity/metabolic syndrome, diabetes and diabetic complications, neurodegenerative, inflammatory, cardiovascular, liver, gastrointestinal, skin diseases, pain, psychiatric disorders, cachexia, cancer, chemotherapy-induced nausea and vomiting, among many others."

Pacher and Kunos review, FEBS, 2013

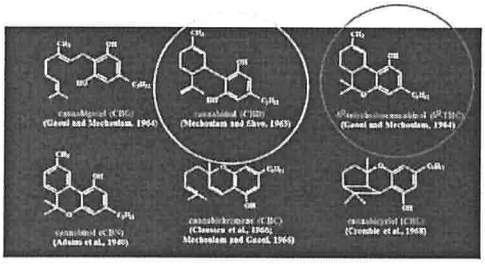


Identification of components from *Cannabis sativa*



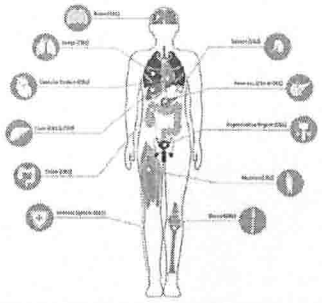
## PHYTOCANNABINOIDS



## THE BODY'S ENDOCANNABINOID SYSTEM

The "ENDOCANNABINOID" system

- Wide-spread through the body
- Regulation of homeostasis
- Involvement in inflammatory and immune processes, anxiety



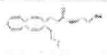
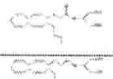
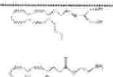
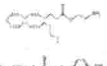
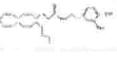
## PHYSIOLOGICAL SYSTEM AND CONDITIONS AFFECTED BY CANNABINOIDS

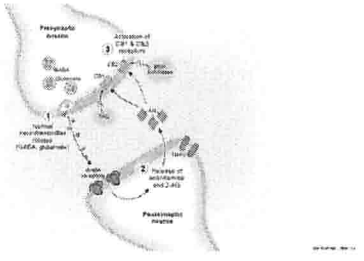
| | |
|---|---|
| Anxiety | Inflammation |
| Appetite/feeding | Memory |
| Blood pressure | Mood |
| Bone formation | Movement |
| Cerebral blood flow | Neuroprotection |
| Digestive system | Pain |
| Emesis and nausea | Reproduction |
| Immune system | Stress |

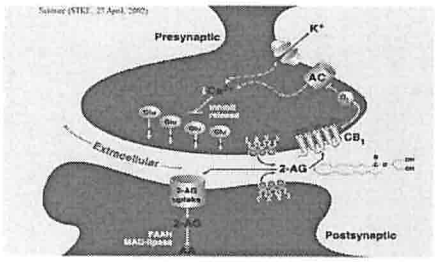
## ENDOCANNABINOID SYSTEM

| Brain regions in which cannabinoid receptors are abundant | |
|---|---|
| Basal ganglia | Movement control |
| Substantia nigra pars reticulata | |
| Entopeduncular nucleus | |
| Globus pallidus | |
| Putamen | |
| Cerebellum | Body-movement coordination |
| Hippocampus | Learning and memory, stress |
| Cerebral cortex, especially cingulate, frontal, and parietal regions | Higher cognitive function |
| Intrabulbar anterior commissure | Link between cerebral hemispheres |
| Nucleus accumbens | Reward pathway |

## ENDOCANNABINOID SYSTEM

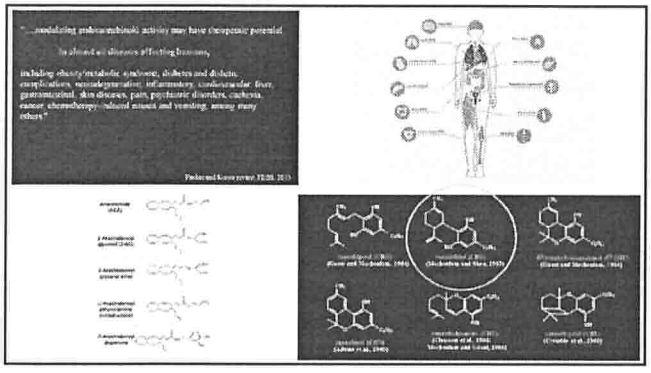
| | | | |
|---|---|---|---|
| Anandamide (AEA) |  | $CB_1$ >> $CB_2$ agonist TRPV1 agonist | Mechoulam et al., 1995; Arnold et al., 1996; Schwarzer et al., 1996; Felder et al., 1999; Zygmunt et al., 1999 |
| 2-Arachidonoyl glycerol (2-AG) |  | $CB_1$ = $CB_2$ agonist | Mechoulam et al., 1995; Ben-Shabat et al., 1998 |
| 2-Arachidonoyl glyceryl ether |  | $CB_1$ >> $CB_2$ agonist | Hanus et al., 2001 |
| O-Arachidonoyl ethanolamine (virodhamine) |  | $CB_1$ >> $CB_2$ agonist | Porter et al., 2002 |
| N-Arachidonoyl dopamine |  | $CB_1$ >> $CB_2$ agonist TRPV1 agonist | Bisogno et al., 2000; Huang et al., 2002 |






## THE ENDOCANNABINOID SYSTEM

- Endocannabinoids: anandamide and 2-arachidonoyl-glycerol [2-AG]
- Receptors: CBD-1 and CBD-2
- Enzymes



## CBD biochemical effects

- Inhibits endocannabinoid re-uptake
- Increases SEROTONIN 5-HT-1A activity
- Activation of transient potential receptor vanniloid-1
- Activation of G-protein-coupled receptor 55

(Harrison, J et al., 2019)

- Likely inverse agonist of CBD-2 receptor (Lunn CA et al., 2006)

## EPILEPSY

Double blind.
Drug: CBD in capsules
Patients: 15 epileptic patients, who did not benefit from known antiepileptic drugs.
Dose: 200-300 mg/day for 4.5 months.
Results: 4 patients (out of 8) remained almost completely free of seizures.
3 patients had partial improvement
1 patient showed no improvement
Placebo patients: only one showed improvement

Cunha, Carlini, Mechoulan, 1980

## CBD as adjunct treatment of epilepsy

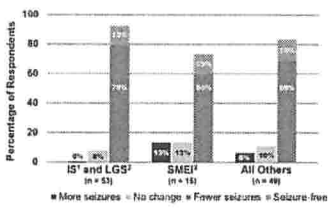



Fig. 1. Perceived response to CBD exposure. [1]Infantile spasms. [2]Lennox-Gastaut syndrome. [3]Severe myoclonic epilepsy of infancy (Dravet syndrome).

Hussain, SA et al. (2015)

## CBD as adjunct treatment of epilepsy

Table 2
Perceived side effects before CBD exposure and during CBD exposure.

| Side effect | Before CBD | During CBD |
|---|---|---|
| Fatigue, % | 70.1 | 9.4 |
| Drowsiness, % | 70.9 | 12.8 |
| Nausea, % | 15.8 | 6.8 |
| Vomiting, % | 23.9 | 2.6 |
| Rash, % | 10.3 | 0.9 |
| Increased appetite, % | 12.8 | 25.6 |
| Decreased appetite, % | 40.2 | 6.8 |
| Weight loss, % | 25.9 | 4.3 |
| Weight gain, % | 17.9 | 29.1 |
| Irritability, % | 29.9 | 9.4 |
| Diarrhoea, % | 15.9 | 6.0 |
| Anxiety, % | 15.9 | 3.4 |
| Insomnia, % | 47.6 | 5.1 |
| Confusion, % | 15.0 | 0.9 |
| Obsessive behavior, % | 23.9 | 2.6 |
| Aggressive behavior, % | 6.0 | 4.3 |
| Total number of adverse effects reported* | 5 (2–10) | 1 (0–2) |

* Median, interquartile range

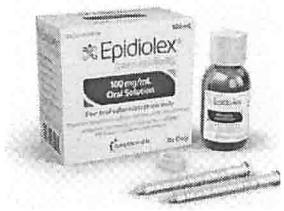
Hussain, SA et al. (2015)

## EPILEPSY

Pure- CBD Tincture 2000mg
~~$159.00~~ $139.00

Double blind.
Drug: CBD in capsules
Patients: 15 epileptic patients, who did not t
antiepileptic drugs.
Dose: 200-300 mg/day for 4.5 months.
Results: 4 patients (out of 8) remained almo
seizures.
3 patients had partial improvement
1 patient showed no improvement
Placebo patients: only one showed improve

## Epidiolex®
(cannabidiol) ℃



## Epidiolex®
(cannabidiol)

- FDA-approved treatment for seizures associated with Lennox-Gastaut or Dravet syndromes ( > 2 years old).
- 2.5 mg / kg BID initially, after 1 week increase to 5 mg / kg BID.
- Max. dose – 10 mg / kg BID.
- Monitor liver enzymes.

** Some participants tested positive for THC**

## Clinical trials in the works for Epidiolex®
(cannabidiol)

- Autism Spectrum Disorder (Phase 2) = irritability and anxiety.
- Anxiety disorders (8-week pilot study)
- Adjunct treatment for Bipolar Disorder (Phase 2)
- Sub-Lingual for anxiety (Phase 2)

## IMMUNE SYSTEM

## GRAFT-VERSUS-HOST DISEASE

**Graft-versus-host disease**

Graft-versus-host disease (GVHD) is a complication that can occur after a bone marrow transplant in which the newly transplanted donor cells attack the transplant recipient's body.

M. Yeshurun et al., (2014) administered CBD (300mg/day) to 46 patients with hematological malignancies for 30 days and followed them for 8 months.

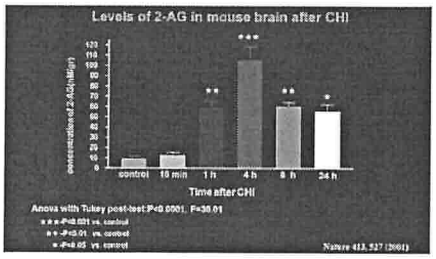
## CHRONIC GVHD (after 100 days)

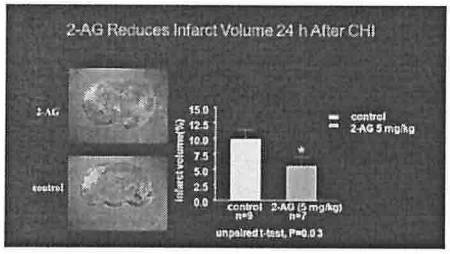
**Chronic GVHD (after 100 days)**

| | 101 patients control | 46 patients (with CBD) |
|---|---|---|
| 2-4 grade | 46% | 12% |
| 3-4 grade | 10% | 5% |

M. Yeshurun et al., 2014

## INFLAMMATORY PROCESSES




## CHRONIC PAIN

- "Based on the available literature, it is difficult to make a recommendation for the use of CBD in chronic pain management".

  (Boyaji et al., 2020)

- Sativex [ THC:CBD = 1:1] approved for chronic pain / spastic pain in the United Kingdom, Europe and Canada.

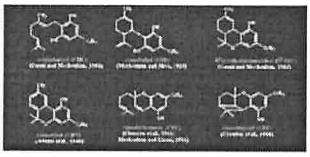
## CBD and ANXIETY

- Some evidence from animal models (Devinsky et al., 2014).
- Results are mostly inconclusive: low statistical power, healthy volunteers used in all but 3 studies ( White, CM, 2019).
- Social Phobia: reduced anxiety during a simulated public speaking test

(Bergamaschi MM, 2011; Zuardi et al, 2017) -600 mg / 300 mg prior to event.

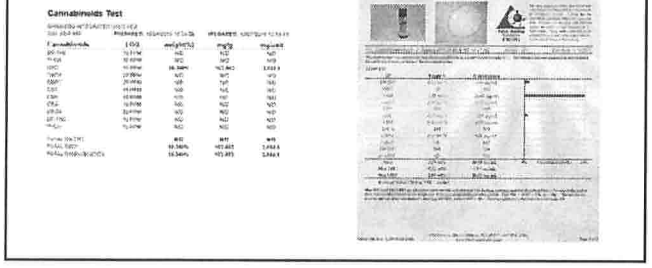
## CBD oil

- One of the many components isolated from the CANNABIS plant.
- Relatively abundant, highly lipophilic.
- Commercially available as "full spectrum" or "pure".
- May be derived from Hemp or Marijuana strains of *Cannabis sativa.*



## FULL SPECTRUM vs. PURE CBD OIL

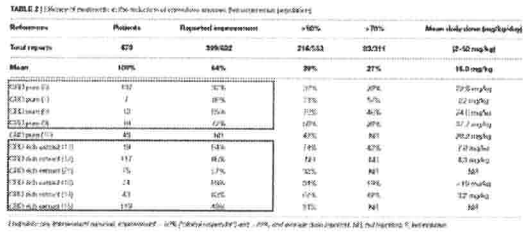

## FULL-SPECTRUM VS. PURE CBD OIL (HEMP)


Cannabinoids Test


PROVERDE

KANIBI

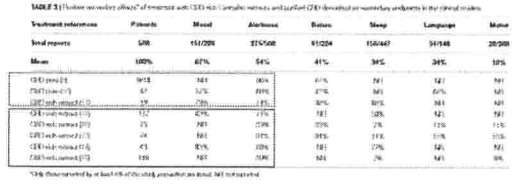
## FULL-SPECTRUM VS. PURE CBD OIL: REDUCTION OF SEIZURES



| Reference | Patients | Reported improvement | >50% | >70% | Mean daily dose (mg/kg/day) |
|---|---|---|---|---|---|
| Total reports | 670 | 399/622 | 214/553 | 83/311 | 2–50 mg/kg |
| Mean | 100% | 64% | 39% | 27% | 16.0 mg/kg |
| CBD pure [3] | 137 | 92% | 69% | 69% | 22.6 mg/kg |
| CBD pure [1] | 7 | 86% | 71% | 57% | 22 mg/kg |
| CBD pure [2] | 12 | 75% | 75% | 42% | 24 [1 mg/kg |
| CBD pure [4] | 84 | 77% | 69% | 39% | 17.7 mg/kg |
| CBD pure [5] | 49 | NR | 49% | NR | 20.2 mg/kg |
| CBD rich extract [11] | 59 | 54% | 14% | 42% | 7.8 mg/kg |
| CBD rich extract [6] | 117 | 48% | NR | NR | 8.3 mg/kg |
| CBD rich extract [21] | 75 | 17% | 12% | NR | NR |
| CBD rich extract [10] | 24 | 46% | 04% | 13% | ~15 mg/kg |
| CBD rich extract [14] | 43 | 60% | 49% | 49% | 37 mg/kg |
| CBD rich extract [15] | 172 | 49% | 31% | NR | NR |

Pamplona et al., 2015

## FULL-SPECTRUM VS. PURE CBD OIL SECONDARY POSITIVE EFFECTS

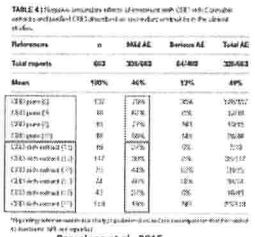


| Treatment reference | Patients | Mood | Alertness | Better | Sleep | Language | Motor |
|---|---|---|---|---|---|---|---|
| Total reports | 670 | 151/205 | 274/508 | 91/204 | 158/447 | 34/148 | 20/205 |
| Mean | 100% | 67% | 54% | 44% | 34% | 24% | 10% |
| CBD pure [3] | 9/15 | NR | 46% | 44% | NR | NR | NR |
| CBD pure [1] | 6/7 | 57% | 86% | 57% | NR | 67% | NR |
| CBD pure [2] | 1/2 | 0% | 0% | 50% | 50% | NR | NR |
| CBD rich extract [11] | 7/12 | 42% | 17% | NR | 42% | NR | NR |
| CBD rich extract [21] | 2% | NR | 13% | 33% | 2% | 11% | 11% |
| CBD rich extract [6] | 4/4 | NR | 0% | 25% | 11% | 11% | 11% |
| CBD rich extract [10] | 4/5 | 80% | 80% | NR | 27% | NR | NR |
| CBD rich extract [14] | 1/20 | NR | 20% | NR | 2% | NR | 0% |

Pamplona et al., 2015

## FULL-SPECTRUM VS. PURE CBD OIL: NEGATIVE SIDE-EFFECTS OF SEIZURE TREATMENTS

* POTENTIAL FOR IMPROVED TOLERABILITY OF ANTI-CONVULSANTS USED OFF-LABEL IN MENTAL HEALTH DISORDERS

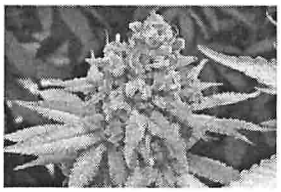


Pamplona et al., 2015

## HEMP vs. MARIJUANA OIL

**HEMP**

**MARIJUANA**



## HEMP vs. MARIJUANA OIL

**FULL-SPECTRUM**

- Marijuana: high THC content, available in states with medical-regulated programs.
- Hemp: negligible THC content, higher CBD content, available in all states with cannabis program

**CBD-ISOLATE**

- No appreciable difference in composition.
- Marijuana-derived classified as schedule I.
- Hemp-derived de-classified under the 2018 "Farm Bill".

## HEMP SEED OIL


- Rich in omega-3, 6 and 9 fatty-acids
- No appreciable CBD present.
- Often sold as "Hemp Oil"
- Not the same as "Full spectrum" Hemp Oil.

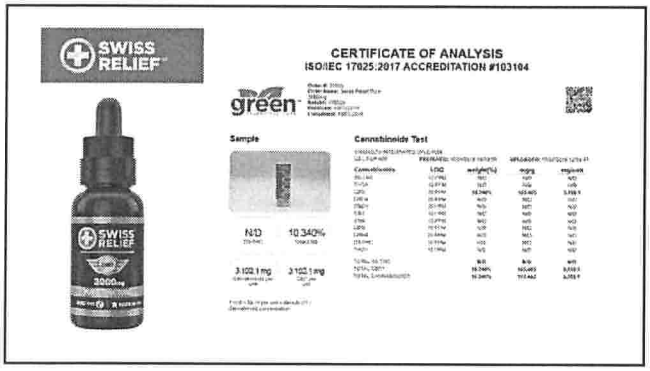
## SAFETY

- 84 samples tested from 31 companies, only 26 labeled accurately.
- Excessive THC in 18 samples (potential for intoxication in children or testing positive for marijuana). (Bonn-Miller at al., 2017)
- Warning letters sent to 22 companies by the FDA in 2019
- Potential for liver toxicity.

## WHERE TO BUY?

| TABLE 3. Checklist for Finding a High-Quality Cannabidiol and Hemp Oil Product |
|---|
| 1. Does it meet the following quality standards?<br>a. Current Good Manufacturing Practices (CGMP) certification from the US Food and Drug Administration<br>b. European Union (EU), Australian (AUS), or Canadian (CFIA) organic certification<br>c. National Science Foundation (NSF) International certification |
| 2. Does the company have an independent adverse event reporting program? |
| 3. Is the product certified organic or ecofarmed? |
| 4. Have their products been laboratory tested by batch to confirm tetrahydrocannabinol levels <0.3% and no pesticides or heavy metals? |

(Harrison J, 2019)




## FEDERAL-LEVEL LEGAL ASPECTS OF CANNABINOID USE AND COMMERCE

### "FARM BILL" of 2018

- Hemp derivatives with 0.3% w/w THC or less no longer classified as "marihuana".
- Jurisdiction from DEA over to USDA / FDA.
- Full effect from Bill far from immediate.
- Many regulatory barriers still in place.

## Legal Considerations: interstate commerce

## STATE-LEVEL LEGAL ASPECTS OF CANNABINOID USE AND COMMERCE


(National Conference of State Legislatures)

## DRUG-DRUG INTERACTIONS

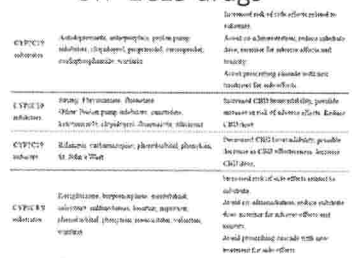
- Main CYP-450 enzymes affected are 3A4 and 2C19 (Jiang R et al., 2011)

## DRUG-DRUG INTERACTIONS
## CYP-3A4 drugs

| | | |
|---|---|---|
| CYP3A4 substrates | Immunosuppressants, chemotherapeutics, antidepressants, antipsychotics, opioids, benzodiazepines, z-hypnotics, statins, calcium channel blockers, others | Increased risk of side effects related to substrate<br>Avoid co-administration, reduce substrate dose, monitor for adverse effects and toxicity.<br>Avoid prescribing cascade with new treatment for side effects. |
| CYP3A4 inhibitors | Strong: Protease inhibitors, ketoconazole, itraconazole, nefazodone<br>Moderate: Amiodarone, verapamil, cimetidine, aprepitant, imatinib | Increased CBD bioavailability, possible increase in risk of adverse effects. Reduce CBD dose. |
| CYP3A4 inducers | Strong: Enzalutamide, phenytoin<br>Moderate: Carbamazepine, topiramate, phenobarbital, rifampicin, efavirenz, modafinil | Decreased CBD bioavailability, possible decrease in CBD effectiveness. Increase CBD dose. |

(Brown, JD and Winterstein, A, 2019)

## DRUG-DRUG INTERACTIONS
## CYP-2C19 drugs



(Brown, JD and Winterstein, A, 2019)

## ADVERSE EFFECTS OF CBD OIL

- Transaminase elevation (Epidolex prescribing information, 2020)
- Unclear if may cause somnolence, sedation, insomnia, weight loss, suicidality (Brown, JD and Winterstein, A, 2019).

## FINAL CONSIDERATIONS

- Manipulation of the endocannabinoid system holds great promise for therapeutic interventions.
- CBD oil, as a main constituent of the cannabis plant, is now object of intense scientific scrutiny.
- Pure CBD has been granted approval for treatment of epilepsy.
- CBD with THC has been granted approval (in other countries) in chronic pain, muscle.
- Commercially available CBD varies in purity / label reliability.
- Liver enzyme elevation needs to be considered.
- Patients may test positive for marijuana.
- Potential for interactions with other drugs needs to be considered.