Clinical evidence in cannabis medicine episode 1

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Body regeneration schedule

Body Regeneration Schedule:

- Intestinal lining: **2-30** days
- Skin: **21-30** days
- Red Blood Cells: **90-120** days
- Pancreas: **5-12** months
- Liver: **6** weeks-**3** months
- Muscles: **6** months- **3** years
- Tissues: **1- 7** years
- Bones: **8** months – **4** years
- Hair: Grows 1mm every **3** days - renews every **6** yrs
- Mouth's Lining: Every few hours
- Bladder: About **49** days
- Lung's Surface: **2-3** weeks
- Heart: **3-4** times over a lifetime

พยาธิสรีรวิทยาที่สัมพันธ์กับระบบ ECS

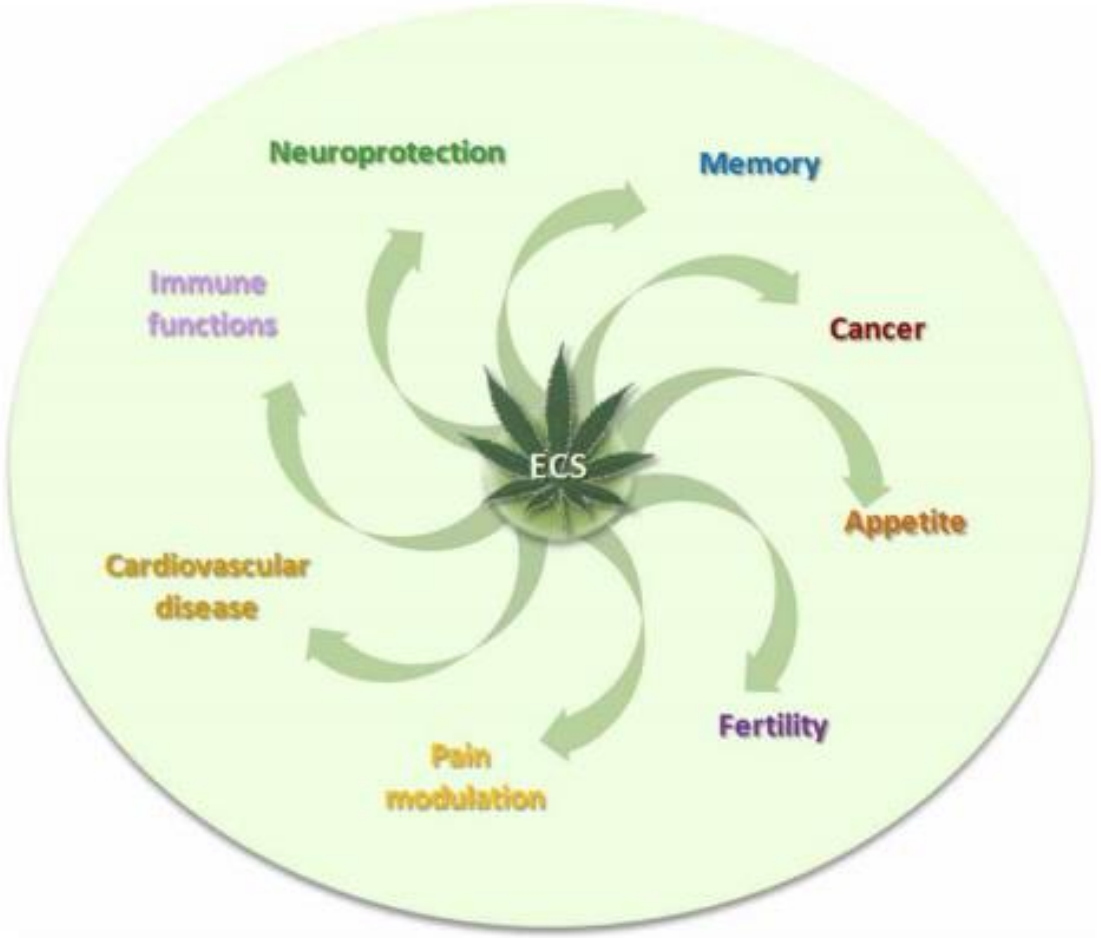

FIGURE 3 | The involvement of ECS in some pathophysiological conditions.

- ความผิดปกติของระบบเอนโดแคนนาบินอยด์ มีส่วนเกี่ยวข้องกับการเกิดโรคหลากหลาย เช่น

โรคมะเร็ง (cancer)

ระบบความจำ (memory)

โรคหัวใจ (cardiovascular disease)

อาการความเจ็บปวด (pain modulation)

ความอยากอาหาร (appetite) เป็นต้น

CB1 and CB2 pharmacology

- AEA กระตุ้น CB1 ทำให้กล้ามเนื้อเรียบของหลอดเลือดขยายตัว
- AEA กระตุ้น CB1 ทำให้กล้ามเนื้อกระเพาะอาหารคลายตัว
- AEA พบเพิ่ม ใน ผู้ป่วย fibrogenesis ของตับ (ยับยั้งการเกิดตับแข็งด้วยสารยับยั้ง CB1 (CB1 antagonist)
- กระตุ้น CB1 เพิ่ม fat storage ในเซลล์ไขมัน adipocytes
- 2-AG กระตุ้น CB1 เพิ่ม fatty acid synthase ทำให้เพิ่มระดับ triglyceride-rich apolipoproteins
- 2-AG กระตุ้น CB1 สังเคราะห์น้ำตาลที่ตับ (gluconeogenesis)
- ไขมันพอกตับ ชอบกินเหล้า เบียร์ ไวน์ หรือ อ้วนลงพุง จะใช้กัญชา เน้น สารสกัดรวม หรือ ถ้าไม่ได้ ก็เน้น สาร CBD เด่น ระวังการใช้สาร THC สูง ในระยะยาว

ภก.พงษ์ศักดิ์ สง่าศรี

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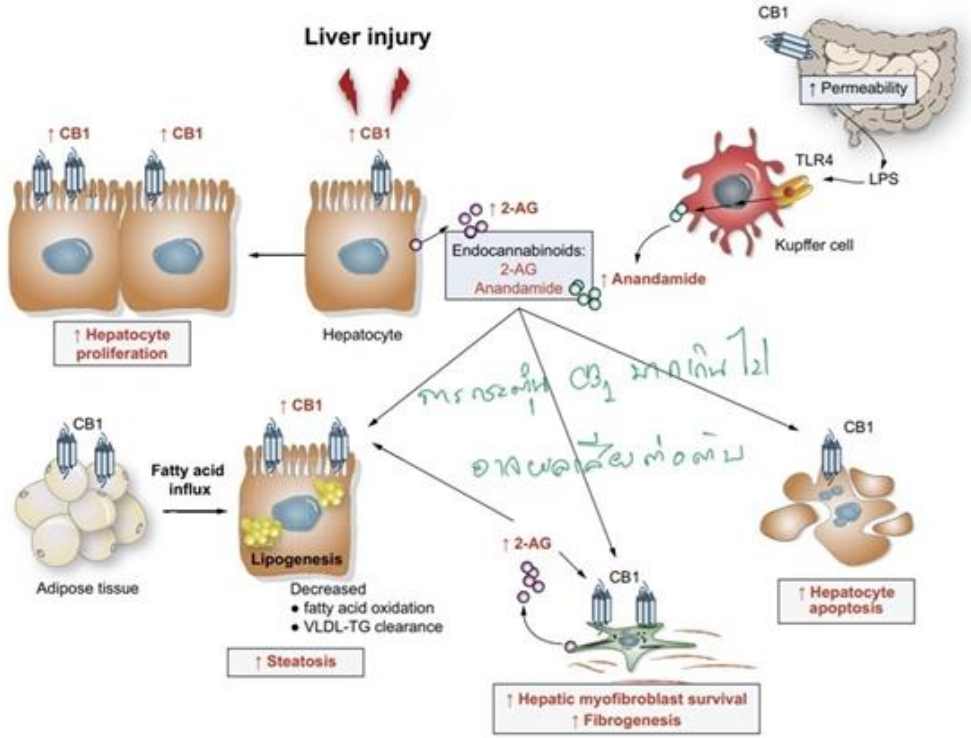
กัญชา กัญชง

แบบไหน ปลอดภัยต่อตับ



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Medical Cannabis for Chronic Pain

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Introduction

- Pain is the symptom that alarm of disease.
- There are no truly effective medicines for certain types of pain, and sometimes relief comes only at the expense of debilitating side effects.
- Thus, the search for new and better pain relievers, perhaps the oldest form of medicine, continues unabated.
- Early in that pursuit, people discovered the pain-relieving properties of marijuana. It has since been used to treat a wide variety of painful conditions, from headache to the pain of childbirth.
- The nerve signals that our brains interpret as pain originate in receptor-bearing cells that become activated by temperature, touch, movement, or chemical changes in their environment. Pain signals travel to the brain by one of three main pathways,
- People with chronic pain develop tolerance to opiates over months or years and so must continually increase their dosage.
- Clearly, better pain medications would be welcome.

Pain: Opioids and Marijuana

- Opioids are a class of drugs used to reduce pain and include prescription opioids, heroin, and synthetic opioids (like fentanyl).
- Although some research suggests that states that legalize marijuana use for medical purposes experience a reduction in opioid prescribing and opioid-related deaths,[4-7]
- the impact of medical marijuana policies over a longer period of time indicates marijuana legalization is not associated with decreases in opioid overdose deaths and that prior research findings could be coincidental.[8-9]
- Importantly, using marijuana either alone or in combination with opioids has been shown to increase risk for opioid misuse.[10,11]
- There is no evidence that marijuana works to treat opioid use disorder.
- Medicinal cannabis is not an FDA-approved medication, although a licensed practitioner can prescribe it.
- This activity highlights the mechanism of action, indications, contraindications, and pertinent clinical studies regarding the possible role of cannabis in the treatment of chronic pain and the importance of an interprofessional approach for the treatment of chronic pain.

Function

- Cannabis consists of a large number of compounds, to date, 568 unique molecules have been identified in cannabis
- most of which are 60 pharmacologically active cannabinoids that act on receptors in the body's endocannabinoid system (ECS).[14]
- This system plays a key role in endogenous pain control.[14-17]
- the primary compounds found in the highest concentration are tetrahydrocannabinol (THC) and cannabidiol (CBD).
- THC contributes to the psychoactive effects of marijuana, including euphoria and psychosis.
- CBD is not psychoactive and is considered to have anti-anxiety and anti-psychoactive properties.[3]
- The therapeutic effects of medicinal cannabis depend on both the concentration of THC and the THC to CBD ratio.
- other cannabinoids, terpenes, and flavonoid compounds, are thought to exhibit synergistic effects that promote pain relief.[16,17]
- Recreational cannabis tends to contain a higher concentration of THC, whereas medicinal cannabis contains a higher concentration of CBD to limit the psychoactive effects of the drug.

Function

- There are two primary types of endocannabinoid receptors: cannabinoid receptors type 1 (CB1) and cannabinoid receptors type 2 (CB2).
- Both receptors are classified as G-protein coupled receptors.
- CB1 receptors are located in the central and peripheral nervous system, specifically in the centers of the brain involved in pain modulation, the nociceptive pathways of the spinal cord, and peripheral nerves.[4]
- CB2 receptors are primarily located in the periphery, such as in the immune and hematological systems, and aid in decreasing inflammation.
- THC is a partial agonist at both CB1 and CB2 receptors and inhibits the release of glutamate (GABA), 5-hydroxytryptamine(5HT), and alters dopaminergic function, thereby affecting pain pathways.[5]
- CBD is a negative allosteric modulator of CB1 receptors and also acts on serotonin, vanilloid, and other receptors.

Positive Evidence

Clinical Significance

- The use of medical marijuana can be traced back to over 5000 years ago.

1. It was used by early Chinese physicians to treat pain associated with childbirth, rheumatic pain, malaria, and even constipation.[9]

- The study included 984 chronic pain patients, including those with neuropathic pain, back pain, arthritis, post-surgical pain, headaches, and abdominal pain.
- In this particular study, two-thirds of patients reported pain relief as the main benefit of marijuana use.

2 Improved sleep was the second most commonly reported benefit.

- Study showed a 64% reduction in opioid use amongst chronic pain patients who used medical marijuana.[12]
- These patients experienced fewer side effects and improved quality of life.
- Due to the ongoing opioid epidemic, medicinal cannabis as a possible alternative treatment has become increasingly important.
- Unlike opioids, marijuana does not cause respiratory depression leading to lesser mortality rates.

Clinical Significance

- A study analyzing the effects of marijuana dispensaries on the number of adverse outcomes due to opioid use demonstrated a 17% reduction in opioid-related fatalities.[13]
- Dispensaries also had a similar effect on opioid-related admissions to treatment centers, thereby highlighting the substitutability of medicinal marijuana.
- A different study highlighted the effectiveness of medical marijuana in treating chronic non-cancer pain, neuropathic pain, medication-rebound headache, and allodynia.
- However, it did not appear to have the same effectiveness as non-opioid analgesics for the treatment of acute pain. Furthermore, in this particular study, medicinal cannabis was no more effective than a placebo for treating visceral pain and only provided minimal analgesic effect in cancer pain.[14]
- In one specific study, experts across nine different countries developed three different treatment protocols for the dosing and administration of cannabis when treating patients with chronic pain.

Clinical Significance

- THC relieves pain but have also found that the drug has the opposite effect in painful shocks, heat, or pressure from a tourniquet reported that THC actually increased their sensitivity to pain.
- Pain signals arise and travel to the brain by one of three main pathways, each of which produces different pain sensations: somatic, visceral, and sensory.
- Pain may be acute—short lived and intense—or chronic, persisting for days to years.
- For acute pain, such as the discomfort that follows surgery, doctors typically prescribe opiates: narcotic drugs derived from, or chemically similar to, opium.
- Cannabinoids appear to peripheral nerves that detect pain sensations contain abundant receptors for cannabinoids, and cannabinoids appear to block peripheral nerve pain in experimental animals
- marijuana-based medicines could perhaps be combined with opiates to boost their pain-relieving power while limiting their side effects.

Clinical Significance: Doses form

- In the routine treatment protocol, it was agreed that a 5-milligram CBD-predominant strain of cannabis taken twice daily should be the initiating form of treatment due to its safety profile.
- If greater than or equal to 40 milligrams of CBD per day failed to provide adequate pain relief, a starting dose of 2.5 milligrams of THC was deemed appropriate.
- THC could be slowly titrated up to 2.5 milligrams every two to seven days until a maximum of 40 milligrams daily is reached.
- Expert consultation from a cannabinoid specialist or experienced medicinal cannabis clinical was recommended if the dosing as mentioned above failed to provide adequate pain relief.

Clinical Significance: Doses form

- In the conservative treatment protocol, the initiating CBD dose was 5 milligrams once or twice daily up to a maximum of 40 milligrams daily, followed by an initiating dose of 1 milligram of THC if the maximum CBD-predominant dose provided inadequate pain control.
- The THC dose could then be titrated up by 1 milligram every seven days to reach a maximum dosage of 40 milligrams daily.
- Lastly, the rapid protocol involved a balanced CBD to THC type of cannabis. The initial starting dose was 2.5 to 5 milligrams of each cannabinoid once or twice daily. The dosage could be titrated up by 2.5 to 5 milligrams every two to three days once or twice daily until a maximum dosage of 40 milligrams of THC was reached.[15]

Clinical Significance: Doses form

- Many of the studies that have been performed analyzing the potential benefit of medicinal cannabis in treating chronic pain have small sample sizes.
- further research needs to be performed to fully determine its true role in the world of pain management.
- The treatment of chronic pain requires an interprofessional approach. As with any patient encounter, a thorough history and physical exam are essential when delineating appropriate treatment options for chronic pain patients.
- The complexity of treating chronic pain patients is attributable to the subjective nature of pain, variability of pain tolerance amongst patients, and the psychosocial impact of chronic pain.

Clinical Significance: Doses form

- Therefore, effective collaboration amongst various disciplines, including physiatrists, physical therapists, psychologists, pain management physicians, neurologists, psychiatrists, social workers, is necessary to ensure the best possible outcome for patients.
- Questionnaires and other forms can be offered to patients to monitor symptomatic improvement in pain and quality of life after initiating cannabis use.
- Nonetheless, ongoing research and studies are required to determine the actual effectiveness of medicinal cannabis as a possible alternative treatment for chronic pain.

Treating Chronic Pain: How and why

- Cannabis has been employed to treat pain based on its action on both CB1 and CB2 receptors.[27]
- CB receptor agonists have been revealed to cause antinociceptive and antihyperalgesic effects by regulating neuronal and non-nervous system inflammatory activity.[27]
- One theory proposes that activation of CB1 receptors in mast cells elevates cyclic adenosine monophosphate and suppresses degranulation.[27]
- Analgesia may also result from CB1 receptor activation, causing negative modulation of the P2X3 receptor in primary afferent neurons.[28]
- Activation of CB2 receptors can hinder the release of proinflammatory factors, causing suppression of nerve growth factor–induced mast-cell degranulation and neutrophil accumulation.[27,28]

Anecdotal evidence

- cannabis for the relief of some types of chronic pain, including neuropathic pain, and spasticity associated with multiple sclerosis.14,29
- efficacy for cancer-related pain, migraines, fibromyalgia, and other pain conditions.14,30
- It has been suggested that these compounds may be valuable in other conditions, including rheumatoid arthritis, osteoarthritis, and various other types of acute and chronic musculoskeletal pain.31,32
- However, how different cannabis species, routes of administration, and doses differ in their effect is less clear, and more research is required.14

Negative Evidence

- Related to THC include anxiety, panic, disorientation, impaired attention, short-term memory, and driving performance.
- The most common acute side effect of CBD is diarrhea
- Has potential drug interactions with conventional pharmacotherapies as it interacts with cytochrome P450 (CYP 450) enzymes involved in drug metabolism.[8]
- Avoid medicinal cannabis in patients with psychiatric illnesses, such as schizophrenia, as it may exacerbate the condition.
- Associated with medicinal cannabis use amongst these patients were adverse effects of the medication and perceived bias against marijuana use.[11]
- the primary negative theme amongst these patients was the cost associated with medicinal cannabis.
- The average cost was about two thousand dollars per year, depending on the formulation and preferred route of administration.
- Unlike other medications, medicinal cannabis is not covered by insurance companies leading to increased costs.
- Regulations and medical CPG contributing to the difficulty in prescribing medicinal cannabis to patients suffering from chronic pain.
- Cannabis use continues to be a politically charged topic.

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