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Marijuana in Post Operative Pain

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Objectives

- Identifying/ Defining products from the Marijuana Plant
- The Endocannabinoid System/Receptors
- Role in Bone Health and Healing
- Uses and potential for marijuana plant products in postoperative pain management and recovery
- Complications of Use

Definitions

- Marijuana- dried leaves, flowers, stems, sees from the whole plant
- Cannabis- flowering tops and leaves of the plant. Hemp fiber, Hemp oils, medicinal purposes, recreational purposes
- Cannabinoids: molecules that come from the cannabis plant, most commonly Cannabidiol (CBD), 9-Tetrahydrocannabinol (THC)
- Hemp: C. Sativa high CBD very low THC
- C. Indica: high THC, low cbd

Method of Action- Endocannabinoid System

- Involved in the pain, appetite, memory, mood, sleep
- Similar to human cannabinoid receptors: CB1, CB-2, GPR55
- CB-1
  - CNS, bone, immune cells of the bone marrow
- CB-2
  - CNS, Immune system
  - neurodefense, reduction of inflammation
- GPR55
  - Osteoblasts ,osteoclasts, GI tract, adrenal glands

Endocannabinoid System: CB-1

- Bone metabolism action by affecting sympathetic nerves
  - Stimulation of CB-1→ increased osteoblast activity
  - Smaller quantity of CB-1 on bone cells
    - In Vivo: CB-1 Knockout mice showed initial increase in bone volume followed by accelerated age-related osteoporosis

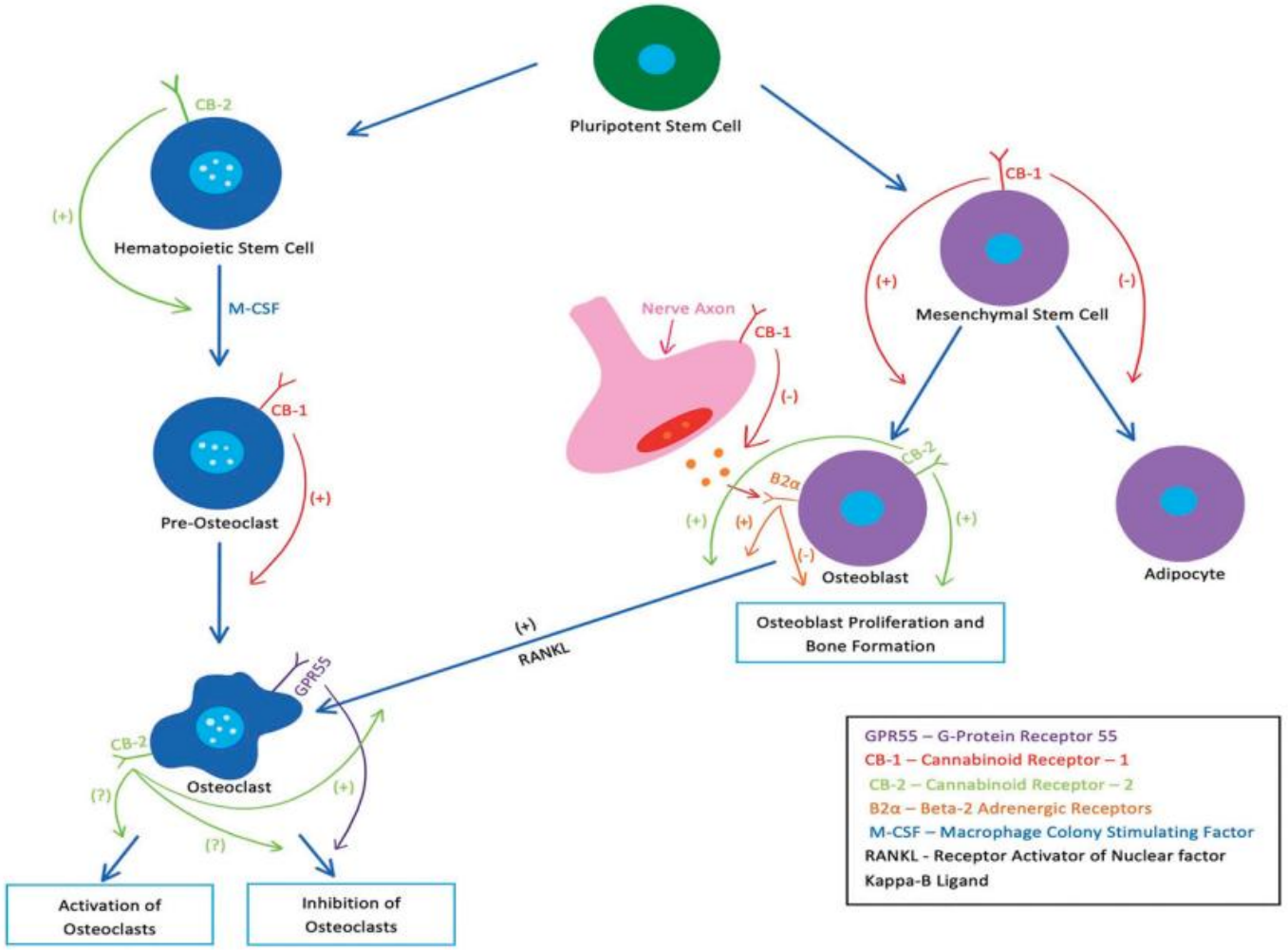
Endocannabinoid System: CB-2

- Increases osteogenic factors
- Increased osteoporosis
- Disputed opposing results in knockout

Endocannabinoid System: GPR55

- Primarily within the CNS, but also with osteoblasts and osteoclasts
- Stimulation decreases osteoclast formation
- increased trabecular bone and cartilage remnants at the growth plate

Endocannabinoid System: Bone Metabolism



Endocannabinoid System: Bone Metabolism

TABLE I Effects of CB-1, CB-2, and GPR55 on Bone Formation and Bone Resorption

Receptor	Bone Formation	Bone Resorption
CB-1	The primary effect is through stimulation of osteoblast formation and activity indirectly through peripheral nervous system beta-2 adrenergic receptors[16] and, less importantly, through direct osteoblast stimulation[18].	Inhibits RANKL stimulation through peripheral nervous system beta-2 adrenergic receptors[17].
CB-2	Stimulates osteoblast formation and bone formation directly as it is located in high quantities on osteoblasts[22]; stimulates other osteogenic factors[23].	Currently unknown due to conflicting studies[7,22,26].
GPR55	No effect has been established[19,24].	Inhibits osteoclast formation and activity directly[7].

Endocannabinoid Agonists

- THC
  - Partial agonist of CB-1 and CB-2
    - higher affinity for CB-1
    - Downregulates MSC differentiation to osteocytes
    - Induces Caspase-3 leading to osteocyte death
- CBD
  - GPR55, CB-2 antagonist
    - Less affinity for CB-1
  - Promising effects on bone healing and bone metabolism
  - Increasing bone bridging across fracture defects

Endocannabinoid System: Wound Healing

- Present throughout the skin and subcutaneous tissues
- Anti-inflammatory effects MAY help with wound healing
  - Some inflammation is helpful and required
  - Excessive inflammation inhibits wound healing
- CB-2 agonism results in decreased infiltration by neutrophils and macrophages and pro-Inflammatory cytokines
  - In Mice: topical CBD showed increased proliferation of Keratinocytes and increased re-epithelialization speed

Total Joint Arthroplasty

- Cannabis smoke has been demonstrated to decrease radiographic bone healing around titanium implants and rat models
- Retrospective Cohort study: Higher revision rate in Cannabis users (12.8%) vs non-users (9.1%)
  - higher prevalence due to injection, not well controlled
  - other studies refuted results but were smaller
  - Increased DVT and PE in cannabis users

Operative Complications

- Increased airway edema, bronchial endothelial damage
- Tachycardia due to adrenergic stimulation
- Questionable inconsistent effects on platelets

Medical Uses

Use	Dosages studied	Data (level of evidence)[a]
Pain	• THC: 5-20 mg • CBD: 1:0. 3-1 with THC • Nabilone: 1-2 mg	• Often used with opioids, may decrease opioid needs (3)[6-8] • 1:1 THC/CBD may decrease severe chronic pain, may decrease breakthrough pain (1)[7,9,10] • Nabilone was not effective (3)[11] • Impairs memory/cognition (1)[7-9]
Nausea	• THC: 30-45 mg • Nabilone: 0.5 mg	• THC more effective than prochlorperazine for chemotherapy-induced/cancer-related nausea (3)[12] • Nabilone did not decrease postoperative nausea/vomiting (1)[13]
Insomnia	• THC: 5-15 mg • CBD: 5-15 mg	• Associated with decreased severity of insomnia in patients (4)[14,15] • Does not change sleep quality or polysomnographic parameters in healthy participants (1)[16]
Weight gain	• THC: 5 mg • CBD: 2 mg • Nabilone: 0.5-1 mg	• Increases snacking/carbohydrate intake, but does not increase weight (1)[17,18] • Nabilone (synthetic THC) improved quality of life in lung cancer patients (2)[19]
Inflammation	• CBD: 5 mg-800 mg	• Dronabinol (synthetic THC) did not change IL-6 levels (1)[20] • CBD did not change cortisol levels (4)[21]
Cancer	NA	• Laboratory data for breast, colon, lung, prostate, lymphoma, leukemia, and malignant glioma (5)[22-27] • No high-quality data examining patient tumor response rates (4)[28]

Abbreviations: CBD, cannabidiol; IL-6, interleukin 6; NA, not applicable; THC, Δ9-tetrahydrocannabinol.

[a] Based on Oxford Centre for Evidence-Based Medicine Levels of Evidence.

Table 3. Perioperative/Surgical Cannabis Clinical Trials

Source	Study population, drug administration	Results
Buggy et al,[57] 2003	• Patients undergoing elective open abdominal hysterectomy (n = 40) • Single oral dose of 5-mg THC vs placebo after discontinuing PCA on POD2	• No difference in pain scores or time to rescue analgesia • "Increased awareness of surroundings" in THC group
Beaulieu et al,[11] 2006	• Patients undergoing major surgery with morphine PCA postoperatively (n = 41) • Oral nabilone, 1 or 2 mg, vs ketoprofen, 50 mg, vs placebo given 1 h preoperatively and every 8 × 24 h postoperatively	• Nabilone, 2-mg, group had higher pain scores • No difference in other measured variables • Study was closed early owing to poor accrual
Holdcroft et al,[8] 2006	• Patients undergoing surgery with morphine PCA postoperatively (n = 65) • Single oral dose of cannabis (THC to CBD, 1 to 0.3-0.5) with 5, 10, or 15 mg of THC after PCA was discontinued	• Fewer patients required rescue analgesia with increasing THC (25% with 15 mg, 50% with 10 mg, 100% with 5 mg) • Sedation increased with dose • More adverse events with 15 mg
Levin et al,[13] 2017	• Patients undergoing elective surgery with general anesthesia and at least 3 risk factors for PONV • Single oral dose 0.5-mg nabilone vs placebo given preoperatively (n = 340)	• No difference in nausea/vomiting • No difference in pain scores
Ibera et al,[56] 2018	• Patients undergoing orthopedic surgery (n = 27) • Single oromucosal dose of cannabis (THC to CBD ratio approximately 1:1); 21.6-mg THC vs 10.8-mg THC vs 1-mg midazolam/1-mg acetaminophen vs placebo	• High dose of cannabis was associated with higher bispectral index

Abbreviations: CBD, cannabidiol; PCA, patient-controlled analgesia; POD, postoperative day; PONV, postoperative nausea/vomiting; THC, δ-9-tetrahydrocannabinol.

Perioperative surgical clinical trials

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- Placebo controlled double blinded Randomized Trial
- Evaluating patients on pod 1,2,7, and 14
- 25 or 50mg of buccally absorbed CBD, q8 for 14 days
- All patients received percocet 5mg/325mg, 1-2 tabs q 4-6 hours
  - self weaning asap
- Surgical technique
  - POD 0: interscalene blocks, no catheters, allowed meds post
  - Open biceps tenodesis for all who needed it regardless of group
  - Sling for 2 weeks
  - Simple wrist, elbow, hand ROM exercises and codman and pendulum as tolerated

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- Outcome Measures
  - Primary Outcome measure: VAS
  - Secondary
    - post op patient satisfaction
    - opioid use
      - logged by patient on days 1-7, then ad needed from 8-14
    - potential complications (LFT elevation day 7 and 14, nausea)
    - Suicidality
  - Logged CBD for 14 days

TABLE 2
Patient Characteristics[a]

Variable	CBD (n = 52)	Control (n = 47)
Age, y	58.2 ± 8.8	57.1 ± 10.1
Female sex	21 (40.4)	17 (36.2)
Body mass index	29.1 ± 5.0	28.2 ± 7.1
Biceps tenodesis	13 (25.0)	10 (21.3)
Subacromial decompression	15 (28.8)	23 (48.9)
Both biceps tenodesis and subacromial decompression	17 (32.7)	13 (27.7)
No. of anchors used	3.0 ± 1.6	3.3 ± 1.4

[a]Data are shown as mean ± SD or n (%). CBD, cannabidiol.

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TABLE 3
Pain and Patient Satisfaction[a]

Variable	CBD	Control	*P* Value
Day 1			
VAS score	4.4 ± 3.1	5.7 ± 3.2	.04
Satisfaction	7.0 ± 3.0	5.6 ± 3.7	.04
Day 2			
VAS score	4.7 ± 2.8	5.3 ± 2.6	.32
Satisfaction	7.3 ± 2.5	6.0 ± 3.3	.03
Day 7			
VAS score	2.5 ± 1.9	3.2 ± 2.7	.15
Satisfaction	8.0 ± 2.6	7.9 ± 2.7	.78
Day 14			
VAS score	1.6 ± 1.4	2.3 ± 2.4	.11
Satisfaction	8.7 ± 2.3	8.5 ± 2.4	.71

[a]Data are shown as mean ± SD. CBD, cannabidiol; VAS, visual analog scale.

TABLE 4
Opioid Consumption and Nausea Levels[a]

Variable	CBD	Control	*P* Value
Opioid MME			
Day 1	15.2 ± 12.0	19.7 ± 13.6	.08
Day 2	10.3 ± 18.7	16.7 ± 36.6	.29
Day 7	59.3 ± 53.2	67.3 ± 55.2	.47
Day 14	8.0 ± 19.3	10.3 ± 22.7	.61
Nausea[b]			
Day 2	2.1 ± 2.6	2.5 ± 3.1	.51
Day 7	0.2 ± 1.1	0.6 ± 2.1	.23
Day 14	0.1 ± 0.4	0.5 ± 1.7	.15

[a]Data are shown as mean ± SD. CBD, cannabidiol; MME, morphine milligram equivalent.
[b]Rated on a scale from 0 (no nausea) to 10 (extreme nausea).

Buccally Absorbed CBD. Alaia et al 2022- Results

TABLE 5
Subgroup Analysis of Pain and Patient Satisfaction[a]

Variable	CBD 25 mg	CBD 50 mg	Control	*P* Value
Day 1				
VAS score	5.1 ± 2.9	3.9 ± 3.2	5.7 ± 3.2	.04
Satisfaction	5.7 ± 3.2	8.0 ± 2.5	5.6 ± 3.7	.005
Day 2				
VAS score	4.7 ± 2.7	4.7 ± 3.0	5.3 ± 2.6	.61
Satisfaction	6.5 ± 2.8	7.9 ± 2.1	6.0 ± 3.3	.02
Day 7				
VAS score	3.1 ± 2.1	2.1 ± 1.7	3.2 ± 2.7	.13
Satisfaction	7.4 ± 2.7	8.6 ± 2.4	7.9 ± 2.7	.34
Day 14				
VAS score	2.0 ± 1.4	1.1 ± 1.3	2.3 ± 2.4	.10
Satisfaction	8.3 ± 2.2	9.1 ± 2.4	8.5 ± 2.4	.58

[a]Data are shown as mean ± SD. CBD, cannabidiol; VAS, visual analog scale.

TABLE 6
Subgroup Analysis of Opioid Consumption and Nausea Levels[a]

Variable	CBD 25 mg	CBD 50 mg	Control	*P* Value
Opioid MME				
Day 1	15.4 ± 10.0	15.0 ± 13.6	19.7 ± 13.6	.23
Day 2	10.2 ± 14.1	10.3 ± 21.9	16.4 ± 36.6	.58
Day 7	51.4 ± 47.4	65.4 ± 57.5	67.3 ± 55.2	.53
Day 14	10.8 ± 25.6	5.5 ± 10.8	10.3 ± 22.7	.63
Nausea[b]				
Day 2	1.0 ± 1.6	2.9 ± 3.0	2.5 ± 3.1	.05
Day 7	0.1 ± 0.5	0.3 ± 1.4	0.6 ± 2.1	.46
Day 14	0.1 ± 0.5	0.1 ± 0.4	0.5 ± 1.7	.36

[a]Data are shown as mean ± SD. CBD, cannabidiol; MME, morphine milligram equivalent.
[b]Rated on a scale from 0 (no nausea) to 10 (extreme nausea).

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TABLE 7
Post Hoc Tukey Testing[a]

Variable	Adjusted *P* Value
VAS score on day 1	
CBD 50 mg–CBD 25 mg	.33
Control–CBD 25 mg	.71
Control–CBD 50 mg	.03
Satisfaction on day 1	
CBD 50 mg–CBD 25 mg	.03
Control–CBD 25 mg	.99
Control–CBD 50 mg	.006
Satisfaction on day 2	
CBD 50 mg–CBD 25 mg	.17
Control–CBD 25 mg	.78
Control–CBD 50 mg	.02
Nausea on day 2	
CBD 50 mg–CBD 25 mg	.04
Control–CBD 25 mg	.11
Control–CBD 50 mg	.78

[a]Post hoc testing was conducted on variables that demonstrated significant differences between subgroups on analysis of variance or the Kruskal-Wallis test. CBD, cannabidiol; VAS, visual analog scale.

References

Frost, et al. Topics in Pain Management . Current Concepts and treatment strategies. Lippincott Continuing Medical Education Institute. Volume 33, No. 8. March 2018.

Heath DM, Koslosky EJ, Bartush KC, Hogue GD. Marijuana in Orthopaedics: Effects on Bone Health, Wound-Healing, Surgical Complications, and Pain Management. JBJS Rev. 2022 Feb 21;10(2). doi: 10.2106/JBJS.RVW.21.00184. PMID: 35180183.

Stewart C, Fong Y. Perioperative Cannabis as a Potential Solution for Reducing Opioid and Benzodiazepine Dependence. JAMA Surg. 2021 Feb 1;156(2):181-190. doi: 10.1001/jamasurg.2020.5545. PMID: 33263719.

Alaia MJ, Hurley ET, Vasavada K, Markus DH, Britton B, Gonzalez-Lomas G, Rokito AS, Jazrawi LM, Kaplan K. Buccally Absorbed Cannabidiol Shows Significantly Superior Pain Control and Improved Satisfaction Immediately After Arthroscopic Rotator Cuff Repair: A Placebo-Controlled, Double-Blinded, Randomized Trial. Am J Sports Med. 2022 Sep;50(11):3056-3063. doi: 10.1177/03635465221109573. Epub 2022 Jul 29. PMID: 35905305.

Thank you.

Questions?