ROLE OF CANNABIS FOR CANCER PATIENTS: WHAT IS THE DATA?

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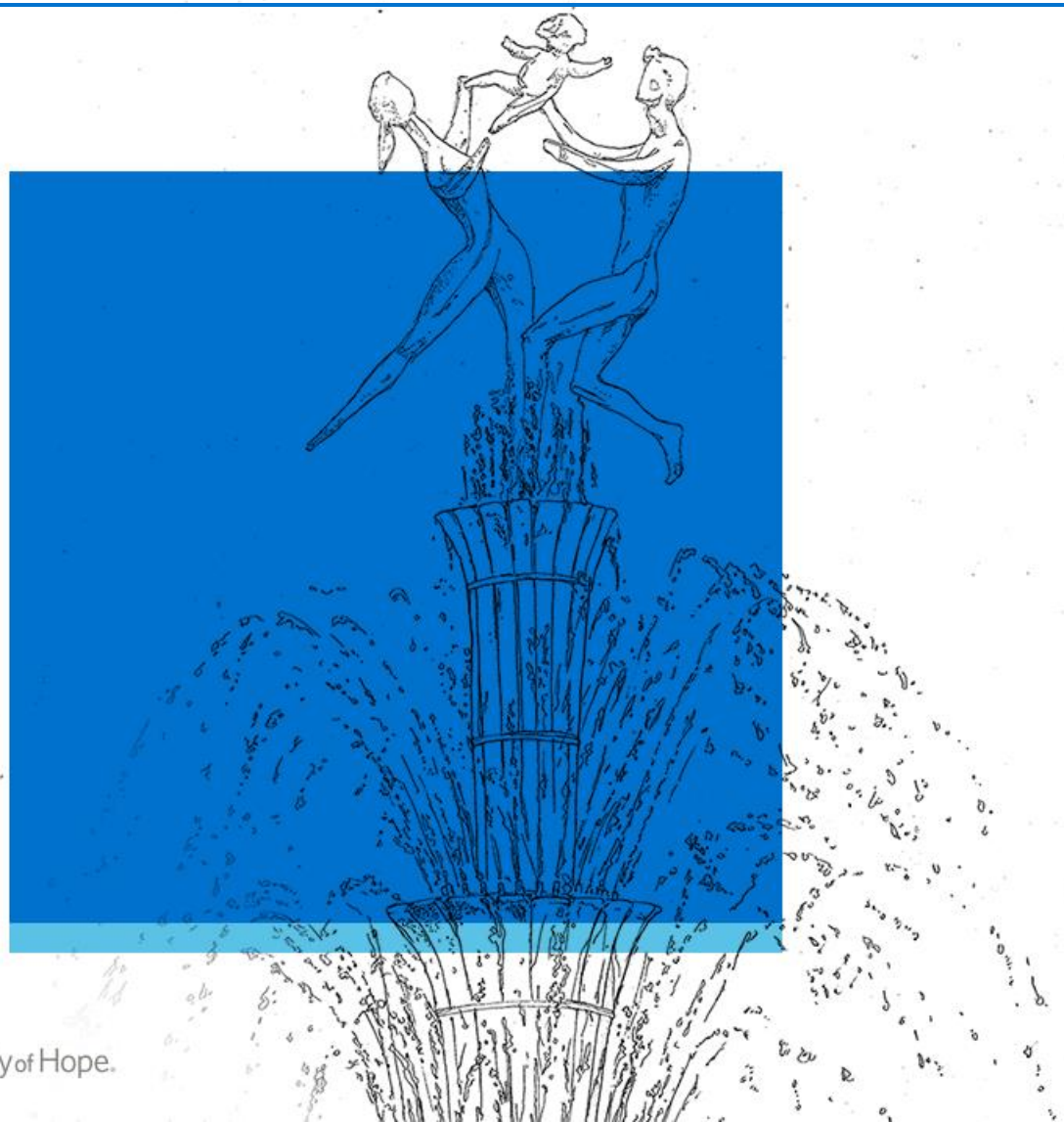
Disclosures

- I have nothing to disclose.

Objectives



- Terminology and Definitions
- Nabiximols
- Cannabis and Cytochrome CYP450
- Cannabis and Immunotherapy
- Cannabis and Chemotherapy
- Cannabis promises in oncology

Terminology and Definitions – Cannabis

- ***Cannabis*** **and** ***marijuana*** **frequently used interchangeably**

- **Cannabis = a generic term that includes: cannabinoids**
  marijuana
  hemp derived from the plant
  Cannabis sativa

- **Cannabis = any of the aerial parts [exposed to air] of a plant in the genus Cannabis and does not mean hemp**

- **Hemp = any part of a plant in the genus Cannabis, whether growing or not, with a THC concentration of less than 0.3 (three-tenths) percent on a dry weight basis**

American Herbal Products Association

Jett J, Stone E, Warren G, Cummings KM. Cannabis Use, Lung Cancer, and Related Issues. J Thorac Oncol. 2018 Apr;13(4):480-487. doi: 10.1016/j.jtho.2017.12.013. Epub 2018 Jan 31. PMID: 29374567
Birdsall SM, Birdsall TC, Tims LA. The Use of Medical Marijuana in Cancer. Curr Oncol Rep. 2016 Jul;18(7):40. doi: 10.1007/s11912-016-0530-0. PMID: 27215434

Terminology and Definitions - Cannabinoid

- **Cannabinoid = a chemical compound that influences cannabinoid receptors in cells to affect neurotransmitter release**

Endocannabinoids

- **Produced by and found in the nervous systems and in the immune systems of humans and animals**
- **Two most well understood: anandamide(AEA) and 2-arachidonoylglycerol(2-AG**

Synthetic cannabinoids

- **Isolated and reproduced in a laboratory**
- **Prescription drug: Dronabinol Nabilone, Nabiximols**

Phytocannabinoids

- **Found in plants**
- **Cannabis flowers secrete resin that contains over 100 phytocannabinoids, not all active or understood**
- **Two of the best-known and well-studied: THC and CBD**

Byars T, Theisen E, Bolton DL. Using Cannabis to Treat Cancer-Related Pain. Semin Oncol Nurs. 2019 Jun;35(3):300-309. doi: 10.1016/j.soncn.2019.04.012. Epub 2019 Apr 30. PMID: 31053395.

NCCN Guidelines for Adult Cancer Pain - Cannabinoids

- **FDA has approved:**

1. **Dronabinol: refractory nausea and vomiting associated with cancer treatment & anorexia and weight loss related to AIDS**

2. **Nabilone: refractory nausea and vomiting associated with cancer treatment**

3. **Cannabidiol: seizures associated with rare forms of severe epilepsy**

Swarm RA, Paice JA, Anghelescu DL, Are M, Bruce JY, Buga S, Chwistek M, Cleeland C, Craig D, Gafford E, Greenlee H, Hansen E, Kamal AH, Kamdar MM, LeGrand S, Mackey S, McDowell MR, Moryl N, Nabell LM, Nesbit S; BCPS, O'Connor N, Rabow MW, Rickerson E, Shatsky R, Sindt J, Urba SG, Youngwerth JM, Hammond LJ, Gurski LA. Adult Cancer Pain, Version 3.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2019 Aug 1;17(8):977-1007. doi: 10.6004/jnccn.2019.0038. PMID: 31390582

Nabiximols (SATIVEX®) - Indications

- **Approved in Canada under the Notice of Compliance with Conditions (NOC/c) as:**

1. **adjunctive tx for symptomatic relief of spasticity in adult patients with multiple sclerosis (MS) who have not responded adequately to other therapy and who demonstrate meaningful improvement during an initial trial of therapy**

2. **adjunctive tx for the symptomatic relief of neuropathic pain in adult patients with multiple sclerosis**

3. **adjunctive analgesic tx in adult patients with advanced cancer who experience moderate to severe pain during the highest tolerated dose of strong opioid therapy for persistent background pain**

- **Not approved in the US**

https://www.gwpharm.com › healthcare-professionals

Nabiximols (SATIVEX®) – Product

- Buccal spray
- Combination of: 27mg/ml delta-9-tetrahydrocannabinol + 25mg/ml cannabidiol (Cannabis sativa L. extracts)
- Pack Sizes: 5.5 ml (48 metered sprays) or 10 ml (up to 90 metered sprays)
- Each dose contains up to 0.04 g of ethanol
- Elimination: urine + feces

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Nabiximols (SATIVEX®) - Presentation

Nabiximols (SATIVEX®) - Contraindications

- known or suspected allergy to cannabinoids, propylene glycol, ethanol or peppermint oil
- history of serious cardiovascular disease
- history of schizophrenia or any other psychotic disorder
- children under 18 years of age
- women of child-bearing potential not on a reliable contraceptive or men intending to start a family
- pregnant or nursing women
- caution with sedatives, opioids, alcohol

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Nabiximols (SATIVEX®) - Treatment initiation and stabilization

- Day 1: one spray in AM and one spray PM
- Day 1+: gradually increase the total number of sprays, by one spray each day, as needed and tolerated; at least a 15-minute gap between sprays
- Dose titrated to a tolerated regimen that gives acceptable pain relief
- Usual dose range: 4 – 8 sprays daily
- Most patients require 12 sprays or less
- Limited experience with doses higher than 12 sprays per day

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Nabiximols (SATIVEX®) – Important to know

- **Immune System: NO clinically significant abnormalities of immune function observed in clinical trials**

- **Metabolism. Via Cytochrome P_{450} enzyme system such as CYP_3A_4, CYP_2D_6, CYP_2C_{19}, CYP_1A_2, CYP_2C_9 → drug – drug interactions**

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Nabiximols (SATIVEX®) – NCCN statement

- **Nabiximols** :

  a) 2 randomized controlled placebo-controlled trials: significantly reduced cancer pain compared to placebo in patients on opioids

  b) 1 study: no benefit in controlling chemotherapy related neuropathic pain compared to placebo

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Adult Cancer Pain Version 2.2021, NCCN.org

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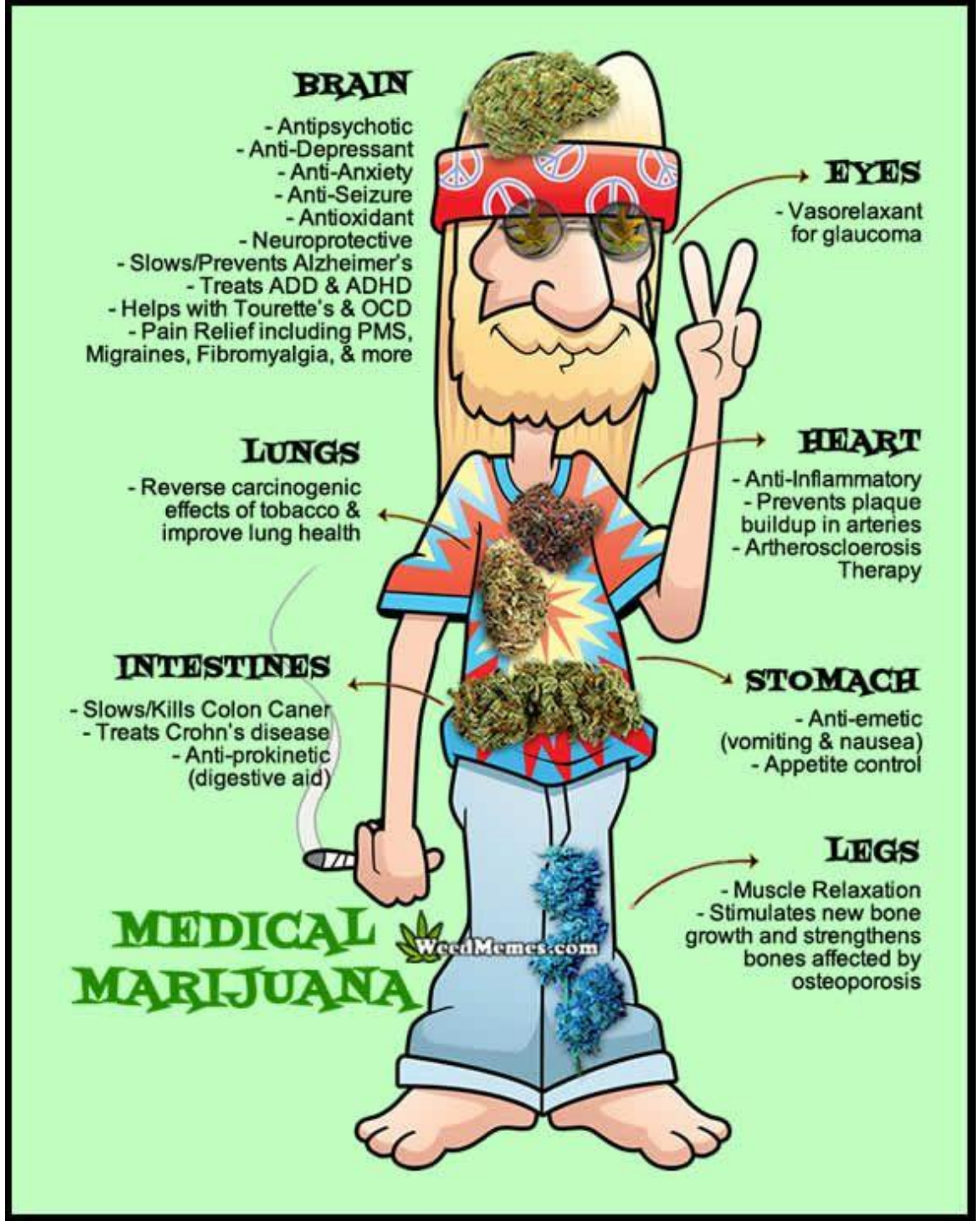
- **Two of the best-known and well-studied: THC and CBD**
- ***Highest concentration in female flowers of the plant***

Byars T, Theisen E, Bolton DL. Using Cannabis to Treat Cancer-Related Pain. Semin Oncol Nurs. 2019 Jun;35(3):300-309. doi: 10.1016/j.soncn.2019.04.012. Epub 2019 Apr 30. PMID: 31053395.



https://trenzpruca.wordpress.com

Cannabis – Observational Study

- 279 out of 17,000 adult Israeli advanced cancer patients authorized to use cannabis for medical purposes
- Route of administration: > 90% smoking
- Median age: 60 years
  Diagnoses: lung (18%), ovarian (12%), breast (10%), colon (9%), pancreatic (7.5%)
  Metastatic disease: 84%
- Active palliative 71%, supportive 13%, curative 6%
- Indications: pain 76%
  anorexia 56%
  generalized weakness 52%
  nausea 41%

Government of Canada - Information for health care professionals - Cannabis (marihuana, marijuana) and the cannabinoids - ISBN: 978-0-660-27828-5, Pub.: 180312

Cannabis – Observational Study

- **Outcomes:**
  - 70% improvement in pain control and general well-being
  - 60% improvement in appetite
  - 50% reduced nausea and vomiting
  - 44% reduced anxiety
  - 83% rated the overall efficacy of cannabis as being high

- **Adverse effects:**
  - 62% no adverse effects
  - 20.3% fatigue
  - 18.8% dizziness
  - 6%) delusions
  - 4.4% mood change

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Cannabis – Why should we know about it

- Legalized in many states
- FDA has not approved marijuana for any indication although both isolated THC and CBD pharmaceuticals are licensed and approved
- DEA considers it a Schedule I substance
- Common among patients with cancer; 24% to 40% of patients with cancer in the US use marijuana → clinicians need to assess for use & provide education on state and federal regulations
- Patients and caregivers inquire about potential benefit of medical marijuana at some point during their cancer care

Swarm RA, Paice JA, Anghelescu DL, Are M, Bruce JY, Buga S, Chwistek M, Cleeland C, Craig D, Gafford E, Greenlee H, Hansen E, Kamal AH, Kamdar MM, LeGrand S, Mackey S, McDowell MR, Moryl N, Nabell LM, Nesbit S; BCPS, O'Connor N, Rabow MW, Rickerson E, Shatsky R, Sindt J, Urba SG, Youngwerth JM, Hammond LJ, Gurski LA. Adult Cancer Pain, Version 3.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2019 Aug 1;17(8):977-1007. doi: 10.6004/jnccn.2019.0038. PMID: 31390582

Cannabis – What we should know about it

- Patients with no prior experience with cannabis : begin at the very lowest dose
  stop if side effects occur

- Consumption of smoked/inhaled or oral cannabis proceed slowly:
  wait minimum of 10 – 20 minutes between puffs or inhalations
  wait minimum of 30 minutes, but preferably 3 h, between bites of oral products

- Edible cannabis products accounted for only 0.32% of sales between 2014 and 2016 but for 10.7% of emergency department visits during that time period

- Dose escalation be done slowly

- Tapering guidelines have not been published, but should be done slowly

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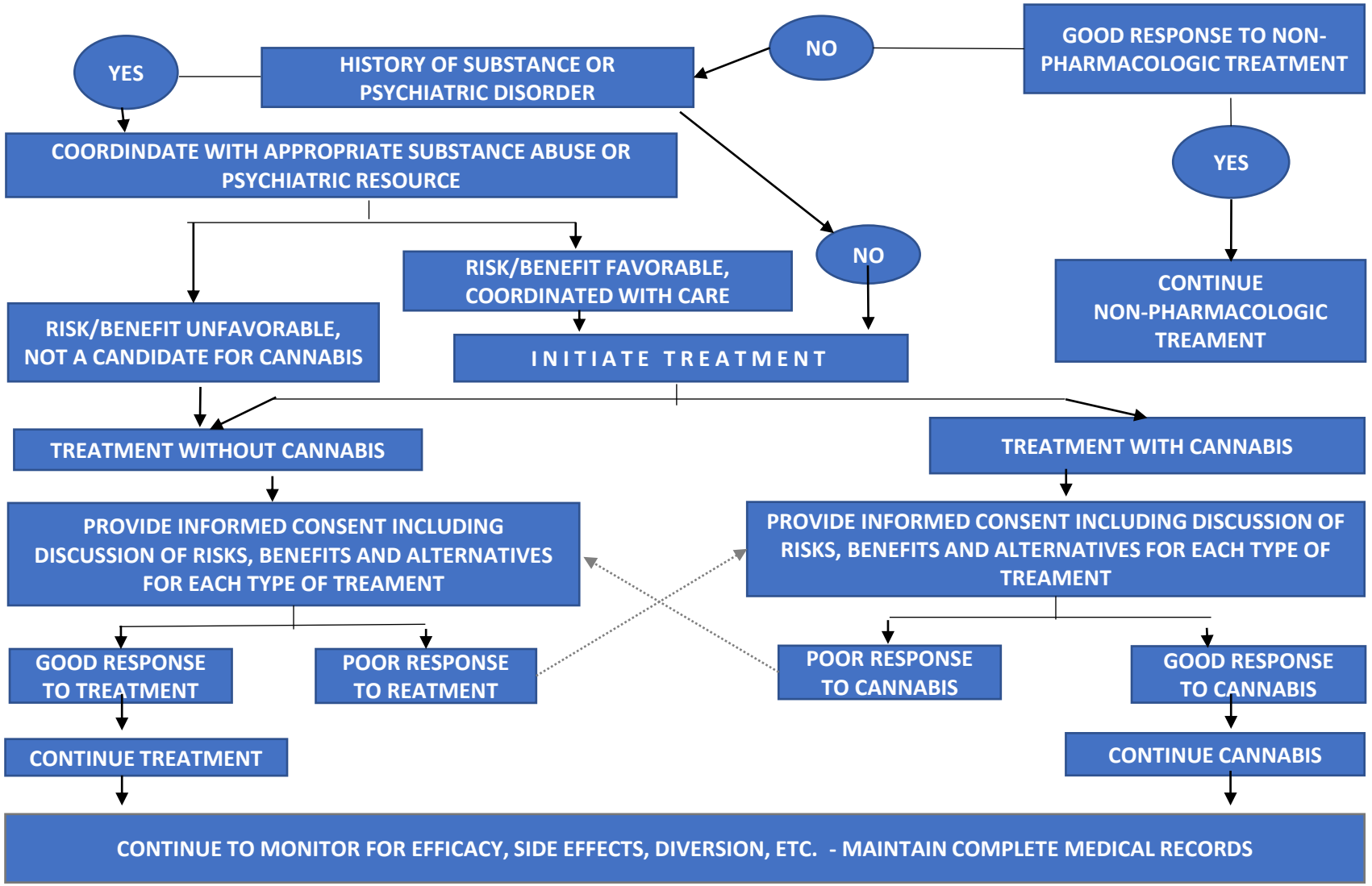
Medical Board of California – Guidelines for the Recommendation of Cannabis for Medical Purposes



Recommendations for Evaluation and Management of Patients

(1) **Take** a medical history and **perform** a physical examination
(2) **Assess** symptoms to be treated, **identify** any active diagnoses, and **ensure** patients are under optimal management
(3) **Assess** psychological contributors and risk of addiction or substance abuse
(4) **Document** any history or current use of illicit or non-prescribed drugs, including cannabis and synthetic cannabinoids
(5) **Determine** the effect of previous use of cannabinoids for medical purposes
(6) **Consider** a urinary drug screening to assess current use of prescribed and non-prescribed medications
(7) **Set** goals for treatment with cannabis – e.g., pain reduction, increased functional abilities, improved sleep quality, increased quality of life, reduced use of other medications
(8) **Develop** a treatment plan incorporating these goals
(9) **Discuss** likely and possible side effects that might be experienced with cannabis/cannabinoid use
(10) **Discuss** the risks of addiction
(11) **Develop** a follow-up schedule to monitor the patient
(12) **Determine** whether the goals of treatment are being achieved and the appropriateness of the response
(13) **Monitor** for potential misuse or abuse (being aware of clinical features of cannabis dependence)
(14) **Develop** a treatment strategy, particularly for patients at risk
(15) **Maintain** an ongoing relationship with the patient

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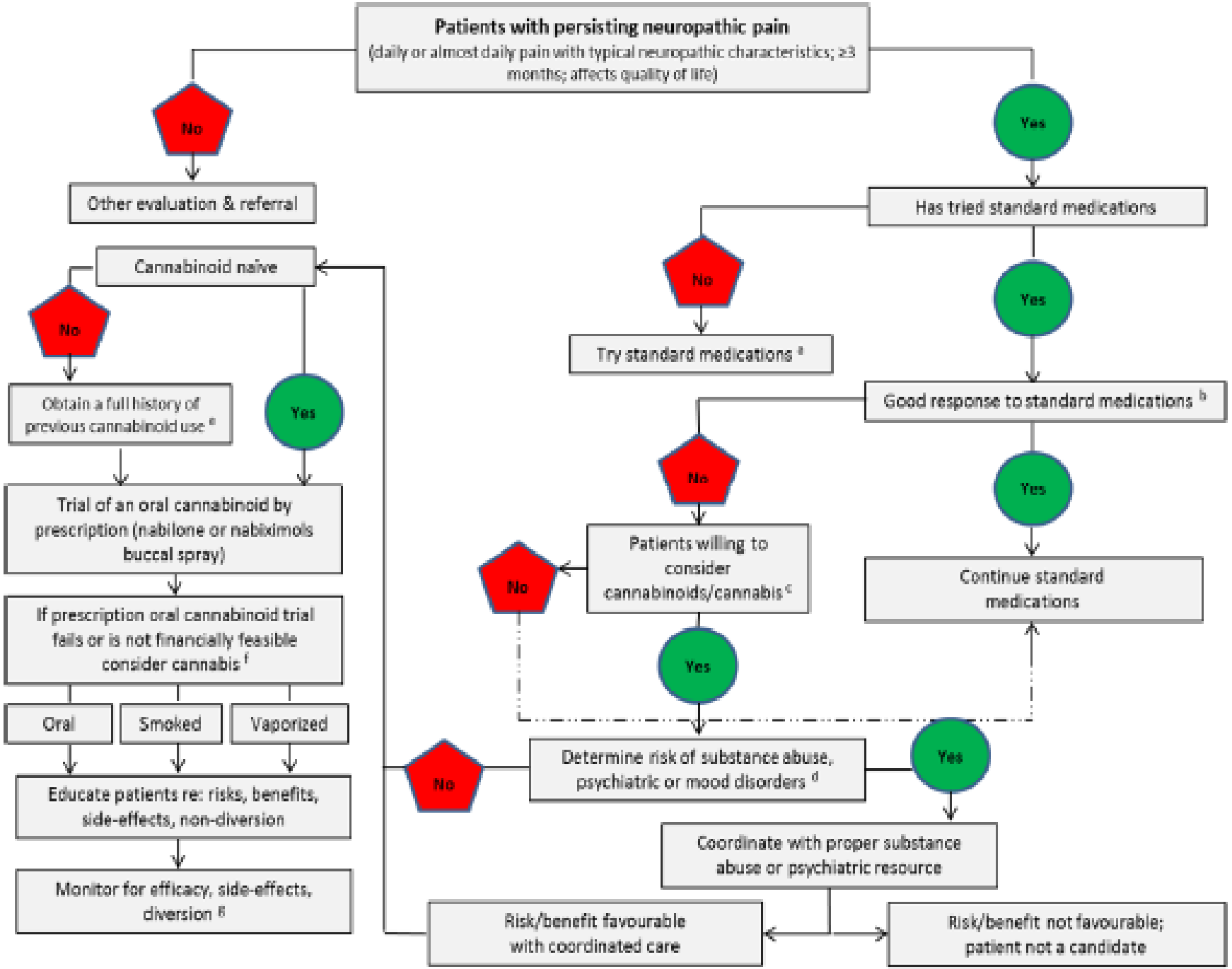

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Cannabis and CYP450 – What we should know about

- **Δ9-THC: - metabolized via CYP 2C9, 2C19, 2D6, and 3A4**
  - inhibits CYP isozymes 3A4, 3A5, 2C9, 2C19, 1A1, 1A2, 1B1, 2A6

- **CBD: - metabolized by CYP 2C19 and 3A4**
  - potential substrate for CYP 1A1, 1A2, 2C9, 2D6, 2E1, 3A5
  - potential to inhibit CYP 2C19, 3A4, and 3A5, 1A1, 1A2, 1B1, 2A6

- **CBN: - metabolized by CYP 2C9 and 3A4**
  - potential substrate for CYP 2C19
  - potential to inhibit CYP isozymes 1A1, 1A2, 1B1 and 2A6

Abrams DI, Guzman M. Cannabis in cancer care. Clin Pharmacol Ther. 2015 Jun;97(6):575-86. doi: 10.1002/cpt.108. Epub 2015 Apr 17. PMID: 25777363.
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https://www.gwpharm.com › healthcare-professionals

Cannabis & Immunotherapy – What we should know about

- **CB_2 receptors associated with anti-inflammatory and immunomodulatory effects → can potentially interfere with immunotherapy**

Kovalchuk O, Kovalchuk I. Cannabinoids as anticancer therapeutic agents. Cell Cycle. 2020 May;19(9):961-989. doi: 10.1080/15384101.2020.1742952. Epub 2020 Apr 5. PMID: 32249682; PMCID: PMC7217364.

- **Phytocannabinoids: potential to modulate the activation and balance of human T-helper 1 (Th_1)/T-helper 2 (Th_2) cells, lymphocytes, and killer cells**

- **Δ^9-THC: - differentially suppress CD_8 T-cells and cytotoxic T lymphocytes (CTLs) and reduce their cytolytic activity or may trigger T cell exhaustion**
  - inhibits both the proliferation of lymphocytes responding to an allogeneic stimulus and the maturation of these lymphocytes to mature CTLs

Bar-Sela G, Cohen I, Campisi-Pinto S, et al. Cannabis Consumption Used by Cancer Patients during Immunotherapy Correlates with Poor Clinical Outcome. *Cancers (Basel)*. 2020;12(9):2447. Published 2020 Aug 28. doi:10.3390/cancers12092447

Cannabis & Immunotherapy – What we should know about

- **Retrospective, observational study 2015-2016:**
  - **Division of Oncology at Rambam Health Care Campus, Haifa, Israel**
  - **140 patients (89 nivolumab alone, 51 nivolumab plus cannabis)**
  - **Diagnosis: advanced melanoma, NSCLC, RCC**
  - **Results: Cannabis was the only factor that reduced RR to immunotherapy (37.5% RR in nivolumab alone compared with 15.9% in the nivolumab-cannabis group (*p* = .016, odds ratio = 3.13, 95% confidence interval 1.24–8.1**

Cannabis use was not a significant factor for PFS or OS

- **Conclusions:** ***Use of cannabis during immunotherapy treatment decreased RR; caution about use required when starting immunotherapy***

City of Hope

Taha T, Meiri D, Talhamy S, Wollner M, Peer A, Bar-Sela G. Cannabis Impacts Tumor Response Rate to Nivolumab in Patients with Advanced Malignancies. Oncologist. 2019 Apr;24(4):549-554. doi: 10.1634/theoncologist.2018-0383. Epub 2019 Jan 22. PMID: 30670598; PMCID: PMC6459234.

Cannabis & Immunotherapy – What we should know about

- **Prospective observatory study 2016 – 2018:**
  - 102 patients: 68 immunotherapy and 34 immunotherapy plus cannabis
  - All cannabis users used less than 40 g of cannabis monthly ; 8 used only cannabis oil, 6 used combined oil and flowers
  - Use of cannabis had been started nine months to two weeks before the first immunotherapy treatment
  - Metastatic malignancies (stage IV disease) ; > 50% NSCLC
  -Results: Cannabis-users showed a significantly lower percentage of clinical benefit (CR + PR + SD) outcomes: 39% vs. 59% over nonusers ($p = 0.035$)
  Cannabis users were more likely to show symptoms of progressive disease, namely: $n = 29$ out of $n = 34$ (61%) patients in the IC-G group compared to $n = 27$ patients out of $n = 68$ (41%) in the I-G experienced progressive disease ($p = 0.035$)

- ***Conclusions: Cannabis consumption needs to be carefully considered due to its potential effects on the immune system, especially during treatment with immunotherapy***

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Cannabis & Immunotherapy – What we should know about

- **Retrospective study 2014 - 2018:**
  -104 patients with advanced-stage malignancy received at least 2 months of immune checkpoint inhibitors
  - 66.8% received Nivolumab, and 26% received Pembrolizumab
  - Diagnosis: 41.3% lung adenoCA, 20.3% SCC lung, 11.5% SCC head and neck, 26.9% other tumor types; 19.2% had brain metastasis and 22.1% bone metastasis
  - 28 patients cannabis + immunotherapy, 23 were prescribed dronabinol and 5 used cannabis recreationally
  - Results: Non-cannabis users had significantly longer overall survival (OS) compared to cannabis users (40 months vs 16 months, p = 0.004)

- ***Conclusions: This study shows significant association between the use of cannabis during immunotherapy treatment and worse OS***

City of Hope

Biedny, A. , Szpunar, S. , Abdalla, A. , Kafri, Z. & Hadid, T. (2020). *Journal of Clinical Oncology, 38* (15), e15064. doi: 10.1200/JCO.2020.38.15_suppl.e15064.

Cannabis & Chemotherapy – What we should know about

- **CBD: increased $TRPV_2$ activation and uptake of cytotoxic drugs leading to apoptosis of glioma cells → coadministration of CBD with cytotoxic agents may increase drug uptake and potentiate cell death in human glioma cells**
- **CBD + THC: may enhance the antitumor activity of temozolomide in mouse models of cancer**
- **Δ_9- THC + cisplatin or doxorubicin: reduced viability of an astrocytoma cell line in a synergistic manner**
- **Δ_9-THC (15 mg/kg/day) and temozolomide (5 mg/kg/day): reduced growth of glioma tumor in mice in a synergistic manner**
- ***Conclusions: Cannabinoids might sensitize certain tumors to the anti-neoplastic action of conventional chemotherapeutic drugs***

https://www.cancer.gov/about-cancer/treatment/cam/hp/cannabis-pdq

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Cannabis and Oncology - Promises

- CB_1 receptor - upregulated in cellular hepatocarcinoma, Hodgkin lymphoma cells
  - its expression correlates with the severity of the disease in human ovarian cancer
- CB_2 receptor - overexpressed in human breast adenocarcinomas associated with HER2+ and in glioma
- CB_1 and CB_2 expression - proposed to be a factor of bad prognosis following surgery in stage IV of colorectal cancer

Pellati F, Borgonetti V, Brighenti V, Biagi M, Benvenuti S, Corsi L. *Cannabis sativa* L. and Nonpsychoactive Cannabinoids: Their Chemistry and Role against Oxidative Stress, Inflammation, and Cancer. Biomed Res Int. 2018 Dec 4;2018:1691428. doi: 10.1155/2018/1691428. PMID: 30627539; PMCID: PMC6304621.

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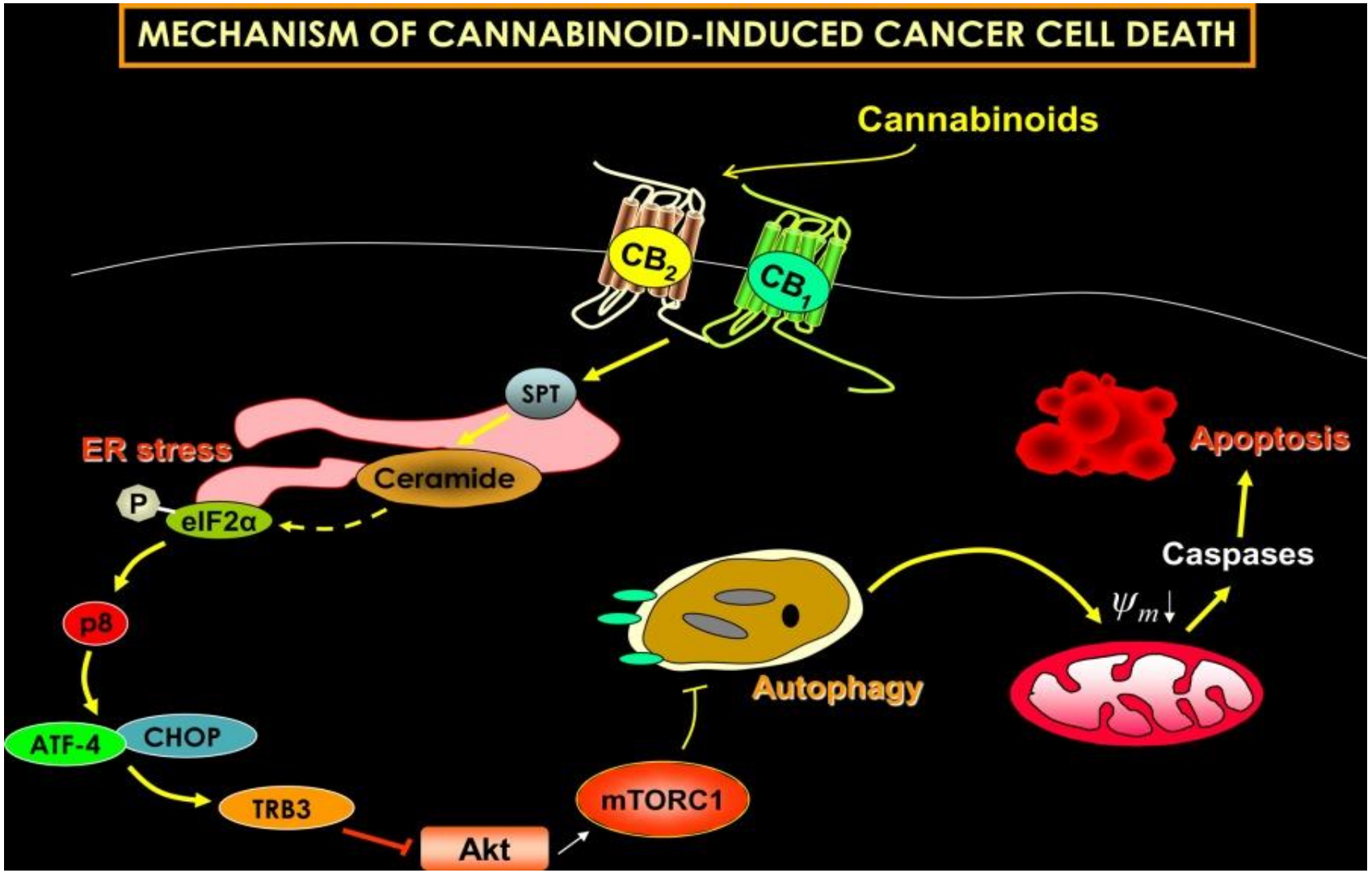

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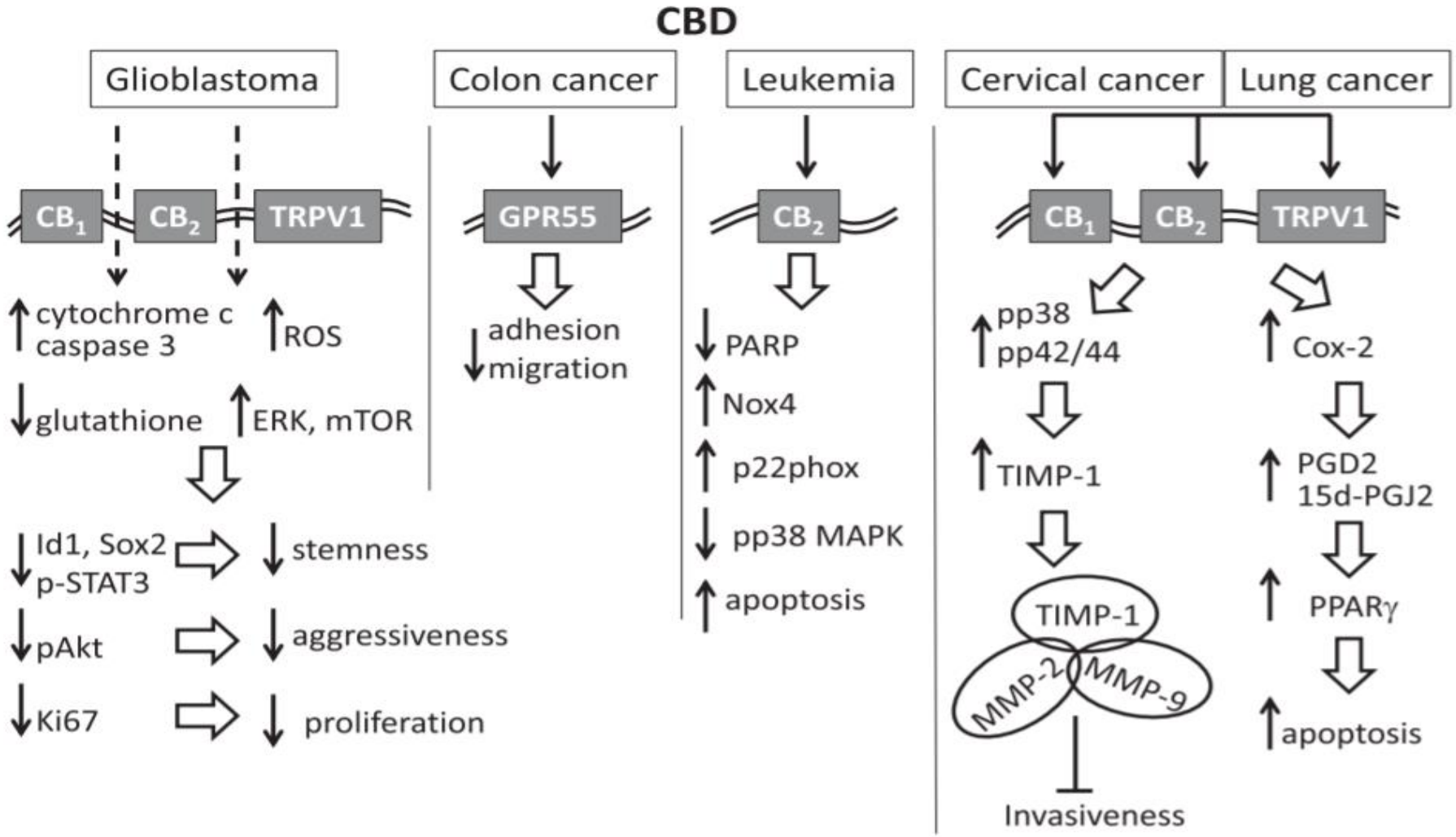

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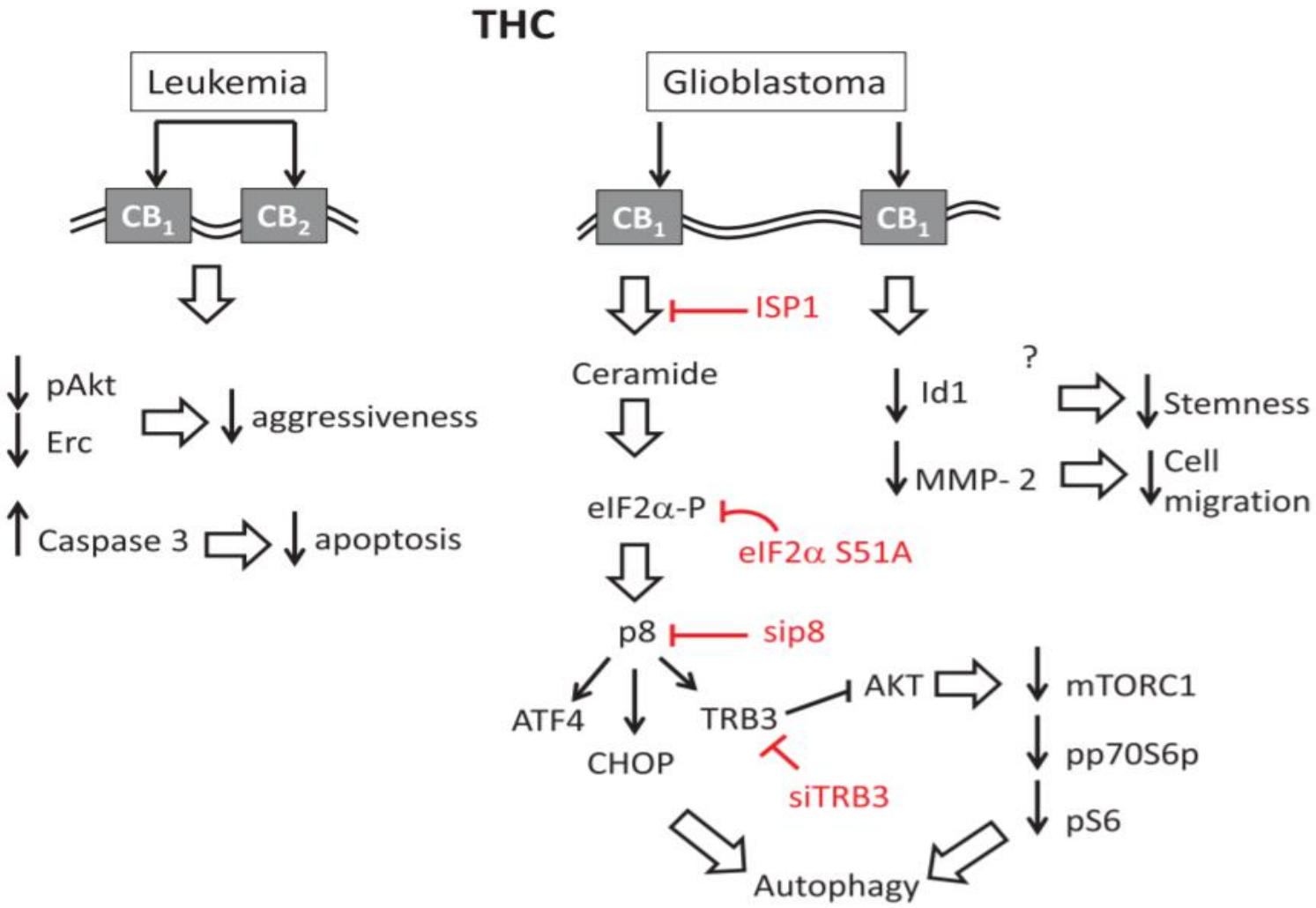

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Questions?

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