



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 percent on a dry weight basis**

American Herbal Products Association

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,**

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**
- ***Highest concentration in female flowers of the plant***
- **Nabiximols**

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**

Nabiximols (SATIVEX®) – Product



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

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**

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**

Nabiximols (SATIVEX®) – Important to know



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

- **Metabolism. Via Cytochrome P₄₅₀ enzyme system such as CYP_{3A4}, CYP_{2D6}, CYP_{2C19}, CYP_{1A2}, CYP_{2C9} → drug – drug interactions**

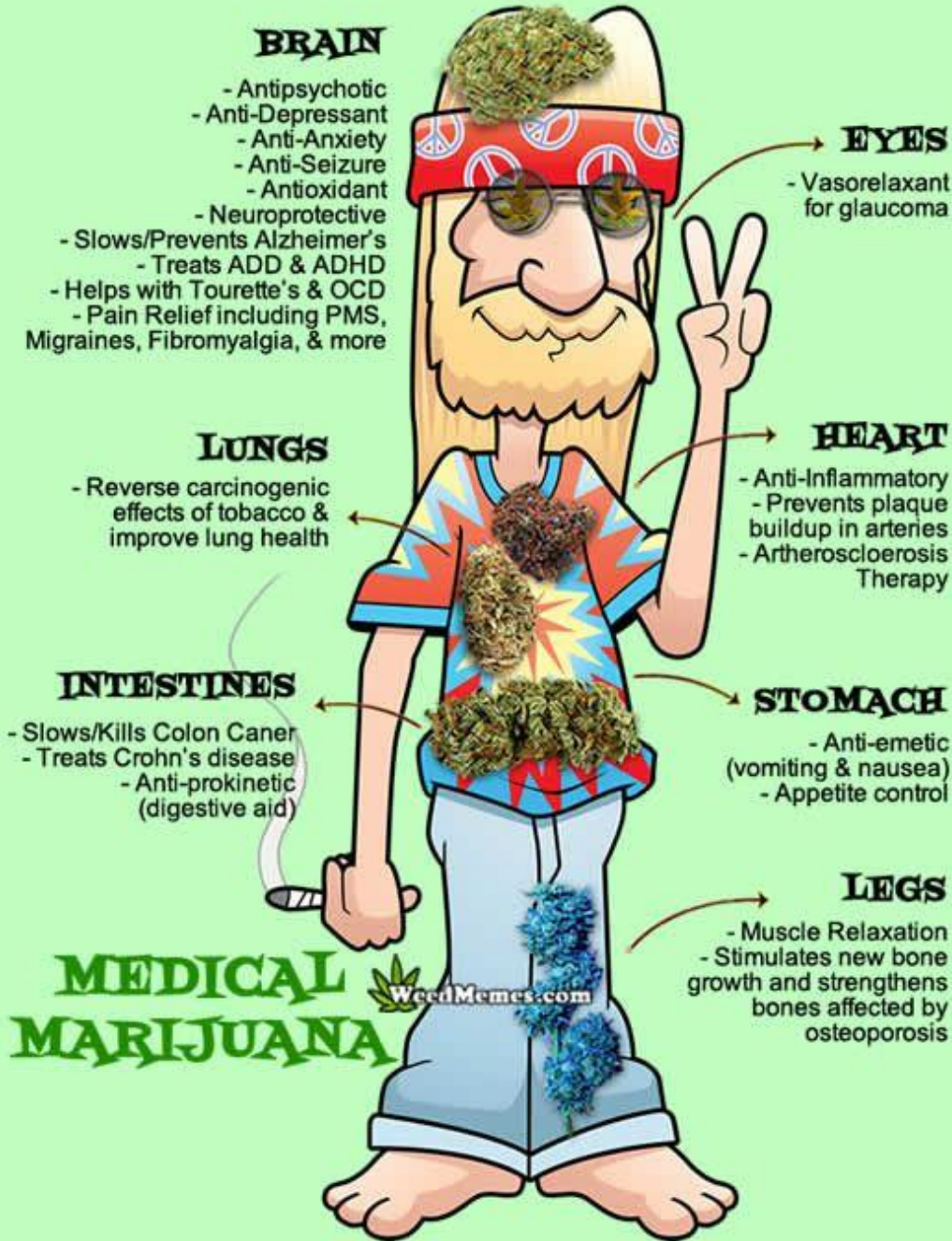
Nabiximols (SATIVEX®) – NCCN statement



- **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**



BRAIN

- Antipsychotic
- Anti-Depressant
- Anti-Anxiety
- Anti-Seizure
- Antioxidant
- Neuroprotective
- Slows/Prevents Alzheimer's
- Treats ADD & ADHD
- Helps with Tourette's & OCD
- Pain Relief including PMS, Migraines, Fibromyalgia, & more

EYES

- Vasorelaxant for glaucoma

LUNGS

- Reverse carcinogenic effects of tobacco & improve lung health

HEART

- Anti-Inflammatory
- Prevents plaque buildup in arteries
- Artherosclerosis Therapy

INTESTINES

- Slows/Kills Colon Cancer
- Treats Crohn's disease
- Anti-prokinetic (digestive aid)

STOMACH

- Anti-emetic (vomiting & nausea)
- Appetite control

LEGS

- Muscle Relaxation
- Stimulates new bone growth and strengthens bones affected by osteoporosis

MEDICAL MARIJUANA

WeedMemes.com

Cannabis – Observational Study



- **279 out of 17,000 adult Israelis w/ advanced cancer 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%

Cannabis – Observational Study



- **Outcomes:**

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

- **Adverse effects:**

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

Cannabis – Why should we know about it



- **Legalized in many states**
- **FDA has not approved marijuana for any indication**
- **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

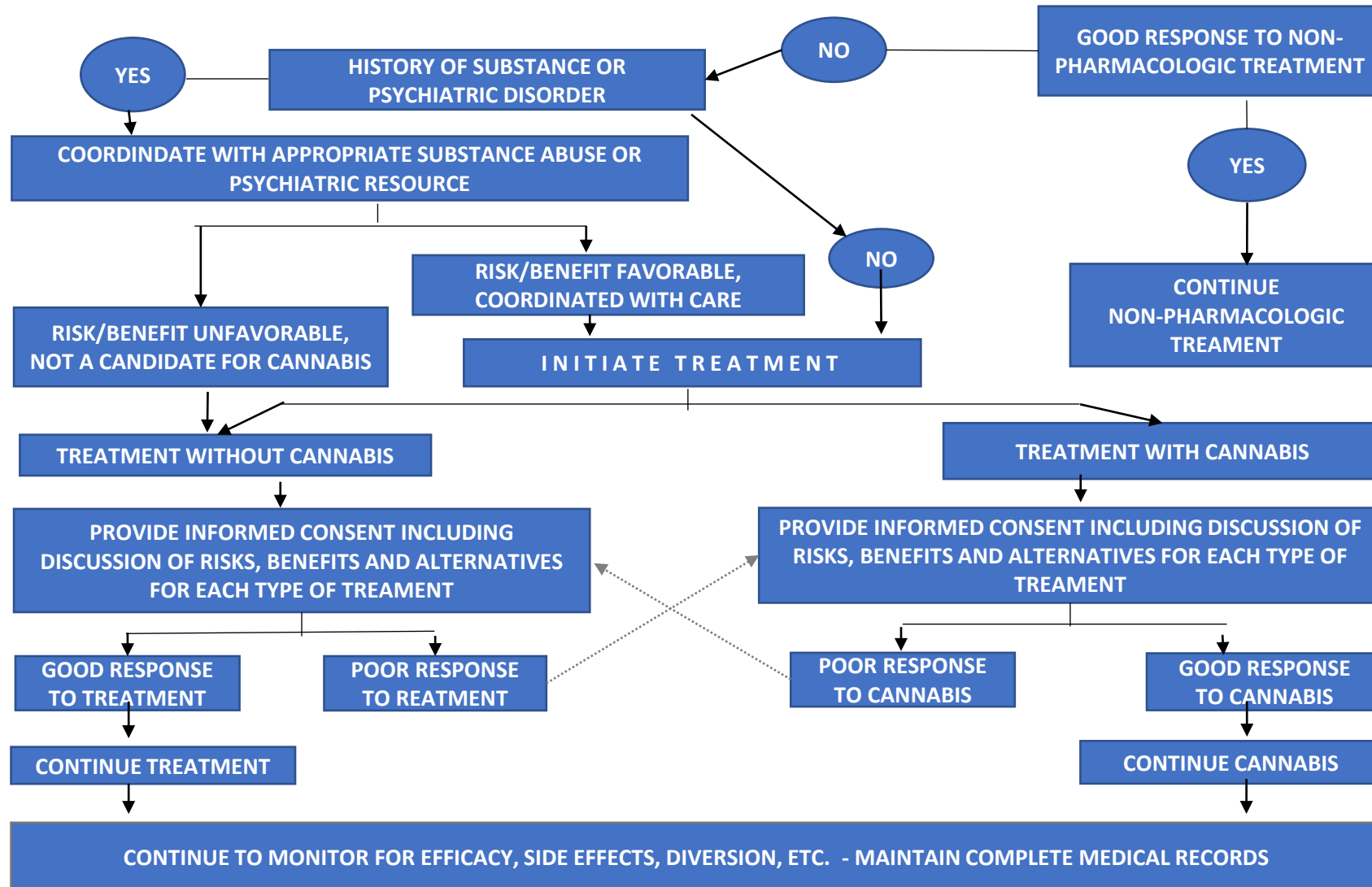


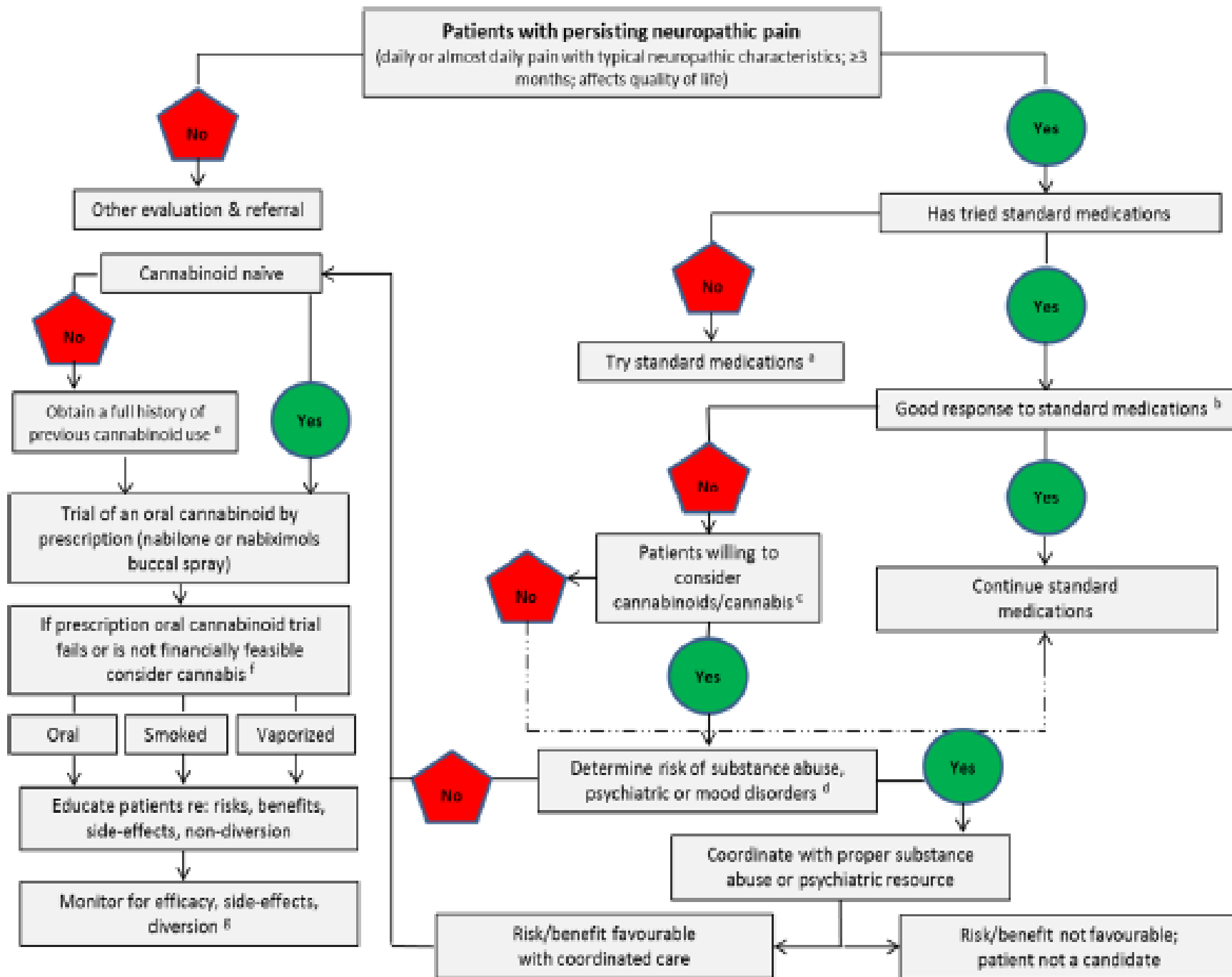
- **Patients with no prior experience with cannabis : begin at the very lowest dose
stop if side effects occur**
- **Consumption of smoked/inhaled or oral cannabis proceed slowly:
wait minimum of 10 – 20 minutes between puffs or inhalations
wait minimum of 30 minutes, but preferably 3 h, between bites 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**

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

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

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





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<https://www.canada.ca/content/dam/hc-sc/documents/services/drugs-medication/cannabis/information-medical-practitioners/information-health-care-professionals-cannabis-cannabinoids-eng.pdf>

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

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.
Government of Canada - Information for health care professionals - Cannabis (marihuana, marijuana) and the cannabinoids - ISBN: 978-0-660-27828-5,
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Cannabis & Immunotherapy – What we should know about



- **CB₂ 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 (Th₁)/T-helper 2 (Th₂) cells and killer cells**
- **Δ⁹-THC: - differentially suppress CD8 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***
- ***RR = response rate; PFS = progression free survival; OS = overall survival***

Cannabis & Immunotherapy – What we should know about



- **Prospective observatory study 2016 – 2018:**
 - 102 patients: 68 immunotherapy (IG) and 34 immunotherapy plus cannabis (IC-G)
 - 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 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***
- ***Immunotherapy: Pembrolizumab, Nivolumab, Durvalumab, Atezolizumab, Ipilimumab***

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 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***
- **OS = overall survival**

Cannabis & Chemotherapy – What we should know about



- **CBD: increased TRPV₂ 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**
- **Δ⁹- THC + cisplatin or doxorubicin: reduced viability of an astrocytoma cell line in a synergistic manner**
- **Δ⁹-THC (15 mg/kg/day) and temozolomide (5 mg/kg/day): reduced growth of glioma tumor in mice in a synergistic manner**
- **CBD + THC: may enhance the antitumor activity of temozolomide in mouse models of cancer**
- ***Conclusions: Cannabinoids might sensitize certain tumors to the anti-neoplastic action of conventional chemotherapeutic drugs***
- *TRPV = Transient receptor potential cation channel vanilloid*

Cannabis and Oncology - Promises



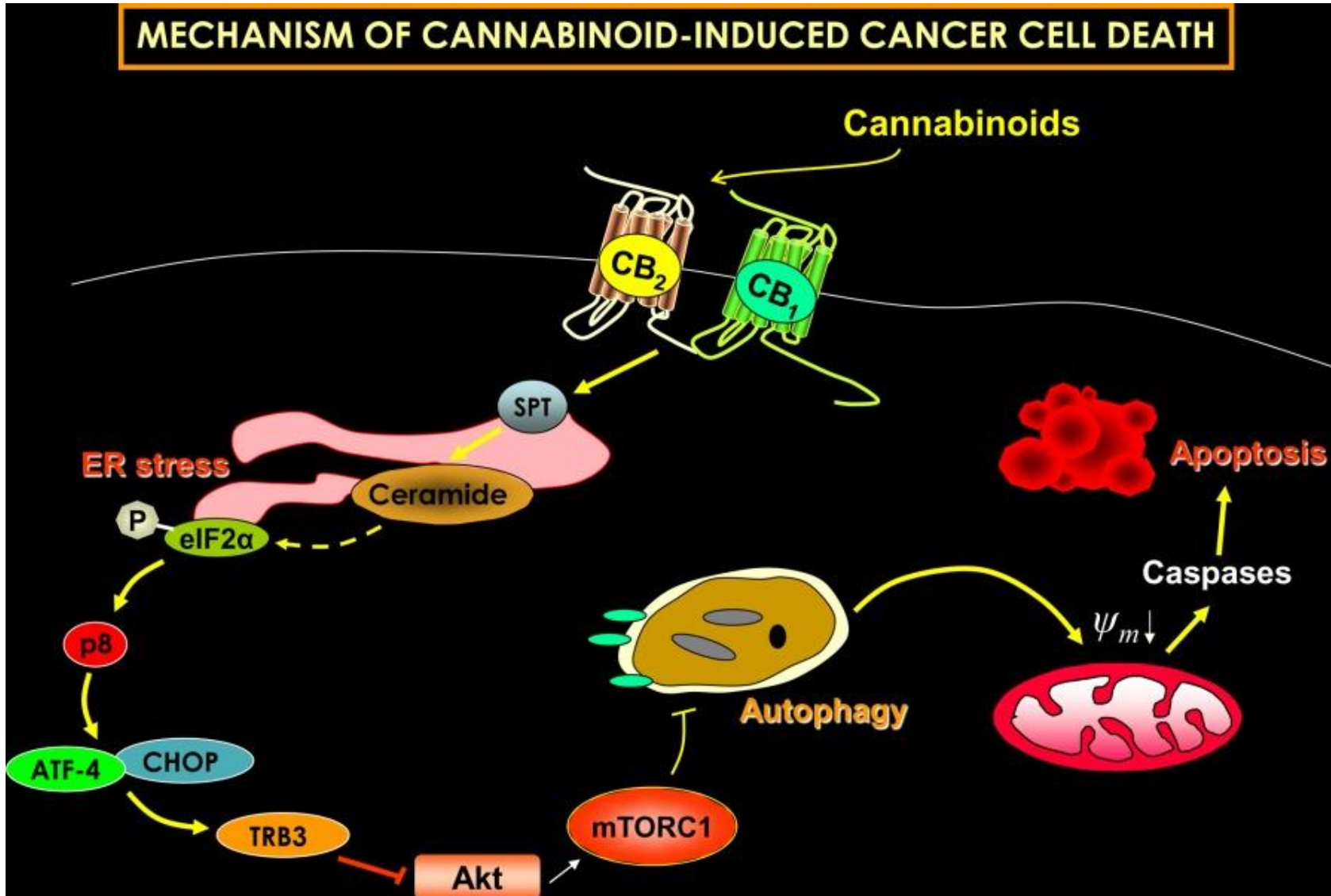
- **CB₁ receptor - upregulated in HCC, Hodgkin lymphoma cells**
 - its expression correlates with the severity of the disease in human ovarian cancer
- **CB₂ receptor - overexpressed in human breast adenocarcinomas associated with HER2+ and in glioma**
- **CB₁ and CB₂ expression - proposed to be a factor 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.

Cannabis and Oncology - Promises



MECHANISM OF CANNABINOID-INDUCED CANCER CELL DEATH



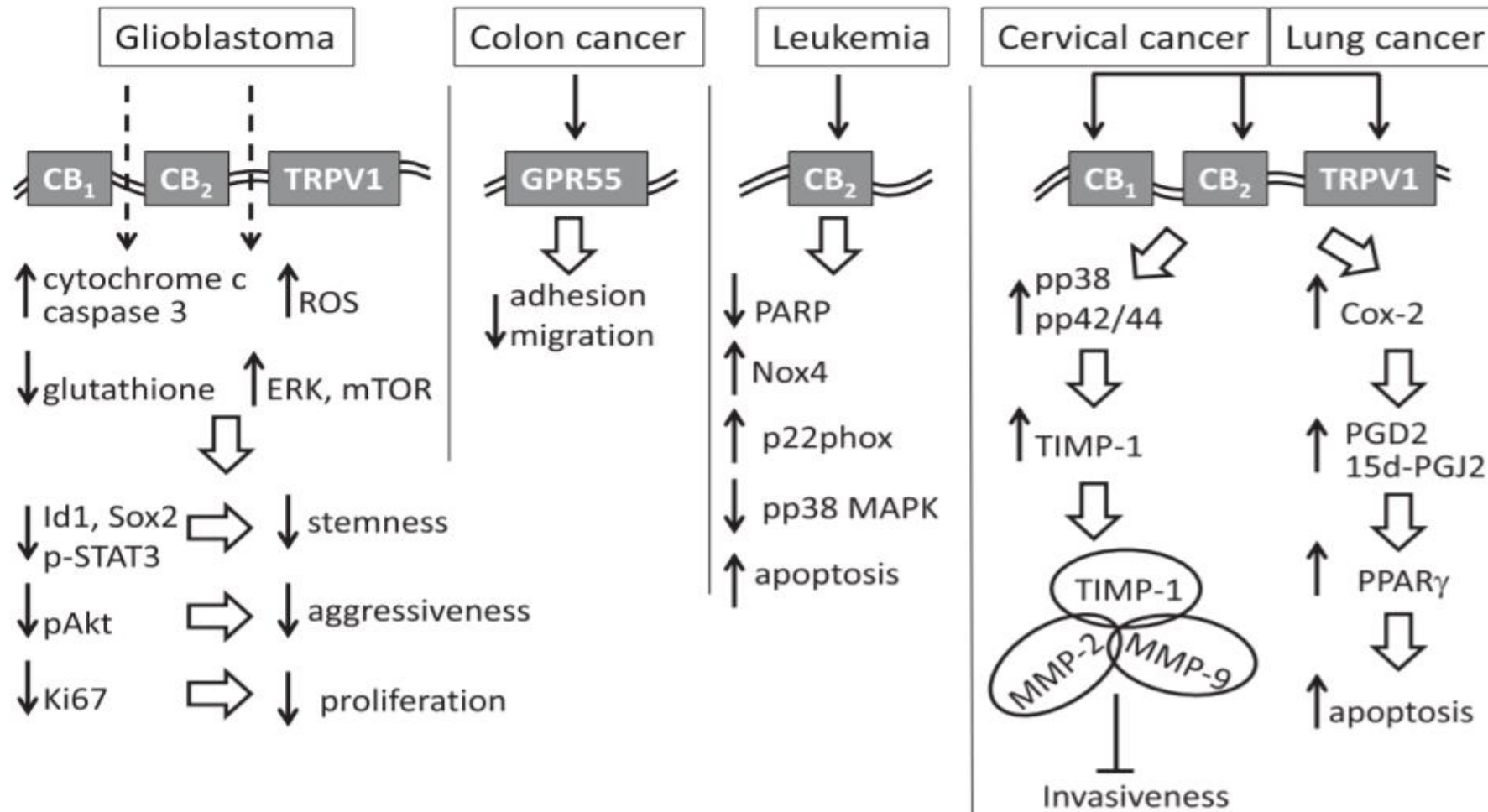
SPT= serine palmitoyl transferase
ER = endoplasmic reticulum
P8, ATF4, CHOP = transcription factors
TRB3 = pseudokinase

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Cannabis and Oncology - Promises



CBD

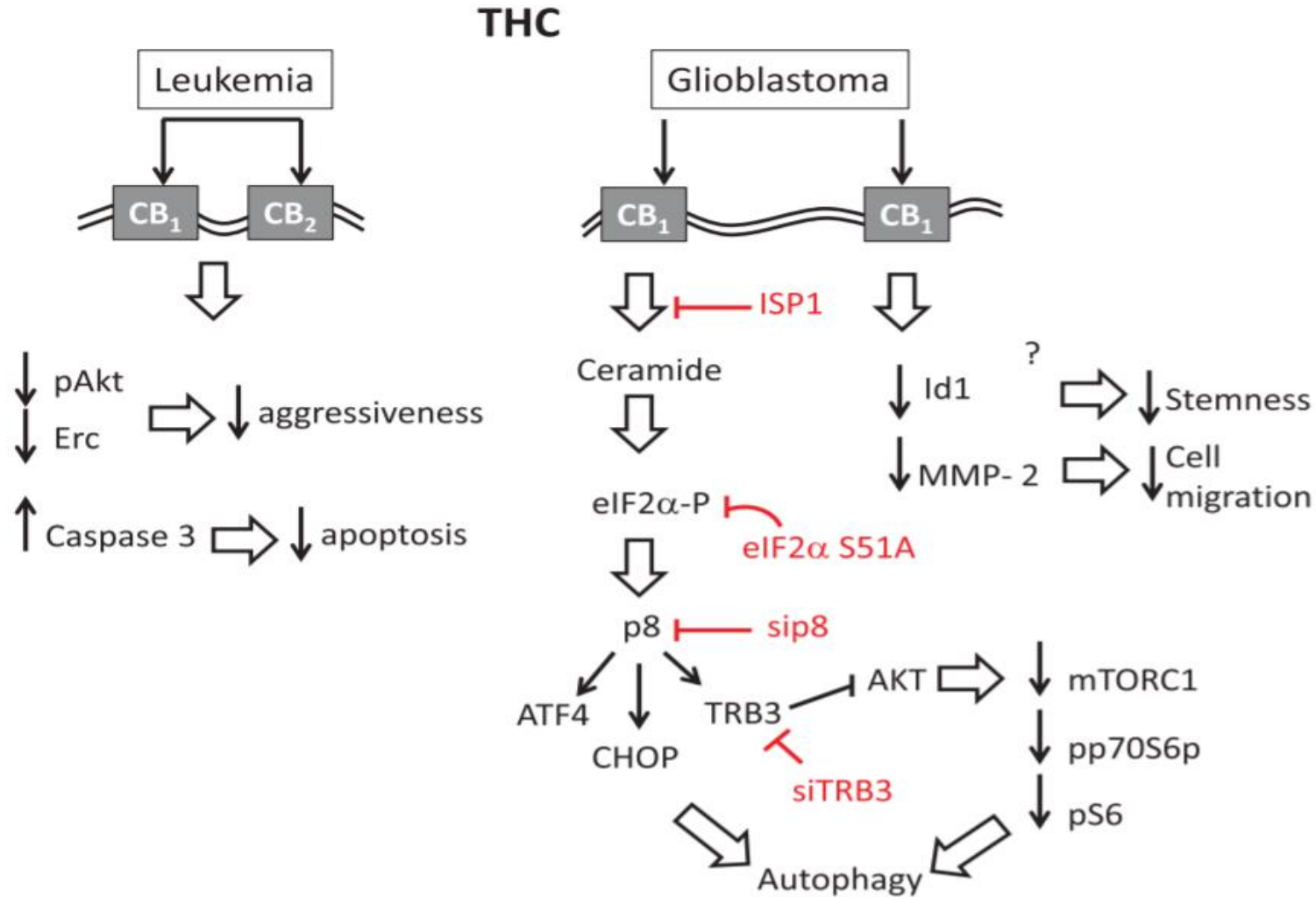


TRPV = Transient receptor potential cation channel vanilloid

GPR = G protein coupled receptor

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Questions?

