MEDICAL CANNABIS AND CANCER PAIN

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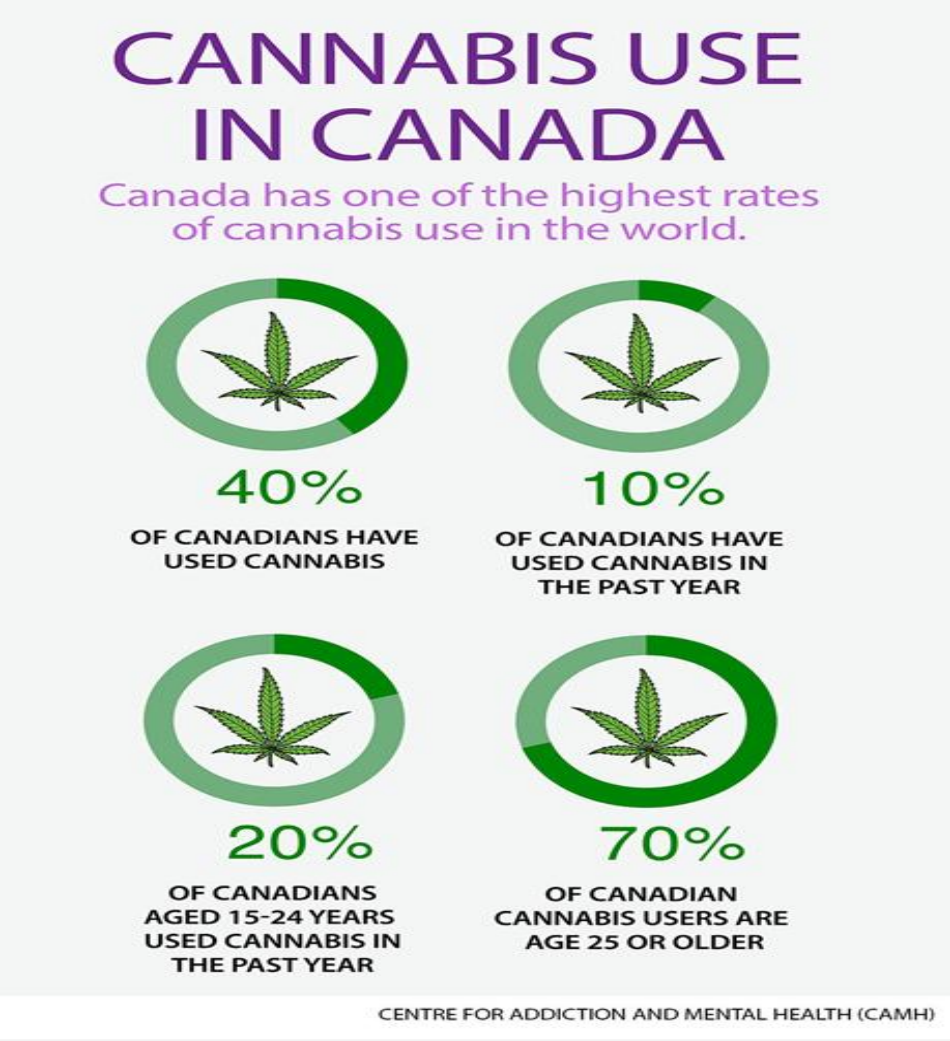
OBJECTIVES

- Who among cancer patients is using medical cannabis
- Why are they using it
- What other options are there
- How effective is it
- How safe is it – side effects and toxicity
- What next

STATS



- 2014 WebMD poll
- 84% of oncologists believe patients should have access to marijuana
- Highest among medical subspecialists in their support

DEMOGRAPHICS

- Data from first year (2014-2015) after ruling changes in Canada
- Data from outpatient palliative care clinic in Hamilton
- cancer patients prescribed medicinal cannabis for any indication
- 43 palliative patients with prognosis <12 months
- 30% GI malignancy
- 21% lung cancer
- 5% breast

DEMOGRAPHICS

- age 31-50 21%
- Age 51-75 79%
- male 63%
- Married 58%

OTHER DEMOGRAPHICS

THE USE OF MEDICAL CANNABIS IN CANCER PATIENTS (JOURNAL OF PAIN MANAGEMENT 02-2017)

- Surveys conducted at time of prescription, 4 months and 10 months
- Survey data for 164 people who self identified as having cancer

- Study ran from Jan 2015- Oct 2016
- One LLP

DEMOGRAPHIC INFO

Demographic	n (%)
Gender (Total n=164)	
Male	92 (56.1%)
Female	72 (43.9%)
Age (Total n=164) in years	
≤18	2 (1.2%)
19-29	4 (2.4%)
30-39	20 (12.2%)
40-49	22 (13.4%)
50-59	46 (28.0%)
60-69	45 (27.4%)
≥70	25 (15.2%)
Ethnicity (Total n=162)	
Caucasian	134 (82.7%)
Spanish/Hispanic/Latino	2 (1.2%)
Native Canadian	11 (6.8%)
Black/African American	1 (0.6%)
Asian	2 (1.2%)
Prefer not to answer	6 (3.7%)
Other	6 (3.7%)
Other conditions (Total n=142)	
Arthritis	29 (20.4%)
Depression	23 (16.2%)
Anxiety	19 (13.4%)
PTSD	13 (9.2%)
Sleep disorder	10 (7.0%)
Previous cannabis use (Total n=144)	
Yes	81 (56.3%)
No	55 (38.2%)

Primary cancer (Total n=164)	
Breast	22 (13.4%)
Prostate	12 (7.3%)
Lung	12 (7.3%)
Gastrointestinal	29 (17.7%)
Gynecologic	15 (9.2%)
Skin	5 (3.1%)
Osteosarcoma	3 (1.8%)
Urothelial	5 (3.1%)
Brain	7 (4.3%)

February 12, 2017

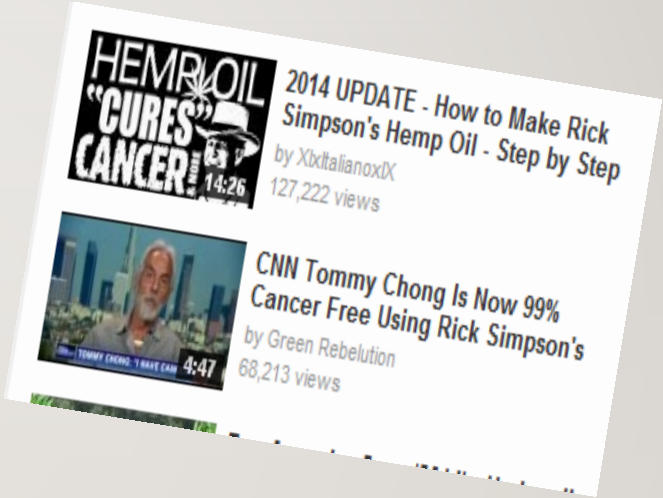
Leukemia and lymphoma	22 (13.4%)
Hepatocellular	3 (1.8%)
Male reproductive cancers	2 (1.2%)
Thyroid	5 (3.1%)
Other	22 (13.4%)

WHY ARE CANCER PATIENTS USING CANNABIS?

- Pain
- Nausea/vomiting
- Appetite stimulation
- Mood disorder (anxiety/depression)
- sleep

WHAT ARE YOUR PATIENTS LEARNING ABOUT MEDICAL MARIJUANA

How Cannabis Oil Works to Kill Cancer Cells



Grandfather, 63, claims he cured his cancer with 'Breaking Bad' style homemade CANNABIS OIL

Can you use medical marijuana for cancer treatment?

NATIONAL CANCER INSTITUTE

- **Antitumor activity**
  - Studies in mice and rats have shown that cannabinoids may inhibit tumor growth by causing cell death, blocking cell growth, and blocking the development of blood vessels needed by tumors to grow. Laboratory and animal studies have shown that cannabinoids may be able to kill cancer cells while protecting normal cells.
  - A study in mice showed that cannabinoids may protect against inflammation of the colon and may have potential in reducing the risk of colon cancer, and possibly in its treatment.
  - A laboratory study of delta-9-THC in hepatocellular carcinoma (liver cancer) cells showed that it damaged or killed the cancer cells. The same study of delta-9-THC in mouse models of liver cancer showed that it had antitumor effects. Delta-9-THC has been shown to cause these effects by acting on molecules that may also be found in non-small cell lung cancer cells and breast cancer cells.
  - A laboratory study of cannabidiol in estrogen receptor positive and estrogen receptor negative breast cancer cells showed that it caused cancer cell death while having little effect on normal breast cells.
  - A laboratory study of cannabidiol in human glioma cells showed that when given along with chemotherapy, cannabidiol may make chemotherapy more effective and increase cancer cell death without harming normal cells.

http://www.cancer.gov/cancertopics/pdq/cam/cannabis/patient/page2

AMERICAN CANCER SOCIETY

- More recently, scientists reported that THC and other cannabinoids such as CBD slow growth and/or cause death in certain types of cancer cells growing in laboratory dishes. Some animal studies also suggest certain cannabinoids may slow growth and reduce spread of some forms of cancer. There have been some early clinical trials of cannabinoids in treating cancer in humans and more studies are planned. While the studies so far have shown that cannabinoids can be safe in treating cancer, they do not show that they help control or cure the disease.
- Cannabinoid levels in marijuana are unpredictable and lower than doses used in most animal studies, so any benefit from this compound would require use of a purified and concentrated form. This is also true of marijuana oil or hemp oil, since purified oils contain roughly the same ratios of compounds as the plants from which they are made. Even though some proponents of marijuana oil recommend using *Cannabis indica* (rather than *C. sativa*) for its higher cannabidiol levels and lower THC levels, the levels cannot be considered consistent or predictable

http://www.cancer.org/treatment/treatmentsandsideeffects/complementaryandalternativemedicine/herbsvitaminsandminerals/marijuana

ALTERNATIVES TO MEDICINAL CANNABANOIDS

SYNTHETIC CANNABINOIDS: NABILONE AND (DRONABINOL)

- Nabilone (Cesamet) covered by
  - ODB (no LU code needed)
  - private insurance plans
  - Approved for treatment of CINV, AIDS anorexia
- Dose range: 0.25mg/day to 6 mg/day
- Usually dosed 2-3 times per day with larger doses
- Recommend starting at night and then adding daytime dose
- Starting dose based on recent cannabis usage, age

SYNTHETIC CANNABINOIDS

Sativex:

- Sublingual spray contains Delta-9-THC and cannabinadiol
- Approved for MS patients and palliative cancer pain
- Not covered by ODB
- Covered by some private insurance plans
- $300/month

EFFICACY OF CANNABIS FOR CANCER PAIN

THE USE OF MEDICAL CANNABIS IN CANCER PATIENTS (JOURNAL OF PAIN MANAGEMENT 02-2017) -RESULTS

- At baseline pain was present in 75.0% (n=140) of 164 cancer patients who responded to the question.
- Of the patients who reported on their pain at both baseline and 4-month FU (n=24), the proportion of those experiencing severe pain was reduced from 45.8% (n=11) to 16.7% (n=4), however the differences were not statistically significant (p=0.06).
- Since very few patients answered this question at baseline and 10-month FU, the results from 10-month FU were not included.

RESULTS

Table 2. Changes in pain severity and the ability to cope with pain at baseline and 4-month FU

	Baseline n (%)	**4-month FU n (%)**	**P-value***
Pain severity (Total n=24)			
Mild	6 (25.0%)	13 (54.2%)	0.06
Moderate	7 (29.2%)	7 (29.2%)	
Severe	11 (45.8%)	4 (16.7%)	
Ability to cope (Total n =12)			
Very easy	1 (8.3%)	5 (41.7%)	**<0.0001**
Somewhat easy	2 (16.7%)	4 (33.3%)	
Somewhat difficult	2 (16.7%)	3 (25.0%)	
Very difficult	7 (58.3%)	0 (0.0%)	

*Bolded values represent statistical significance ($p<0.05$)

STUDY LIMITATIONS

- compliance rate was low, especially at FU intervals.
- small sample size limited the power of the statistical analysis.
- It is also possible that there was a higher incidence of responses with patients experiencing more positive outcomes, resulting in a positive skew in the data.
- The survey also did not include validated questionnaires specific to cancer.
- FU surveys were not consistently completed at exactly 4 and 10 months from baseline by all patients.

Current cannabis use (Total n=62)	
Yes	62 (73.8%)
No	22 (26.2%)

PAIN

- JAMA 2015 systematic review and meta-analysis
- 28 studies, 2454 pts
- Included different cannabanoids formulations
- Generally showed improvement in pain measures OR 1.4 vs placebo
- Included cancer pain (3 studies) and neuropathic pain

CANCER PAIN

- 2 randomized double blind controlled studies

1. 10 cancer patients (Noyes et al, 1975)
   - Dose range of 5, 10, 15, and 20 mg delta-9-THC
   - 15 and 20 mg doses associated with significant pain relief
2. 36 cancer patients (Noyes et al, 1975)
   - Compared 10 and 20 mg of delta-9-THC with 60 and 120 mg of codeine
   - Lower and higher doses were equianalgesic to the codeine and only the higher doses of either drug produced statistically significant reductions in pain

- Limiting factor: higher doses of delta-9-THC associated with somnolence, dizziness, ataxia and blurred vision

JOHNSON STUDY –
JOURNAL OF PAIN AND SYMPTOM MANAGEMENT 2009

Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study of the Efficacy, Safety, and Tolerability of THC:CBD Extract and THC Extract in Patients with Intractable Cancer-Related Pain-

- 177 Terminal cancer related pain refractory to strong opioids (270 MME avg)
- 2 week trial comparing:
  - THC:CBD (60 pts)
  - THC (58 pts)
  - Placebo (59 pts)
  - Allowed for dose titration by patients within a range of 22-32 mg THC and 20-30mg CBD (8-12 sprays)

JOHNSON -

- Mean number of sprays was between 8-9 per day (approx. 21 mg each CBD and or THC)
- THC:CBD
  - produced statistically significant reduction in pain compared to placebo (-1.37 vs. -0.69 p=0.024)
  - Twice as many patients achieved a 30% reduction in pain over placebo (n=23 42% versus n=12 21%)
- No statistically significant difference between THC and placebo groups in either of the above measures
- No change in MME used in any group which was a second primary endpoint
- 13% of patients in each group died of their disease during the two week study

PORTENOY STUDY

JOURNAL OF PAIN 2012

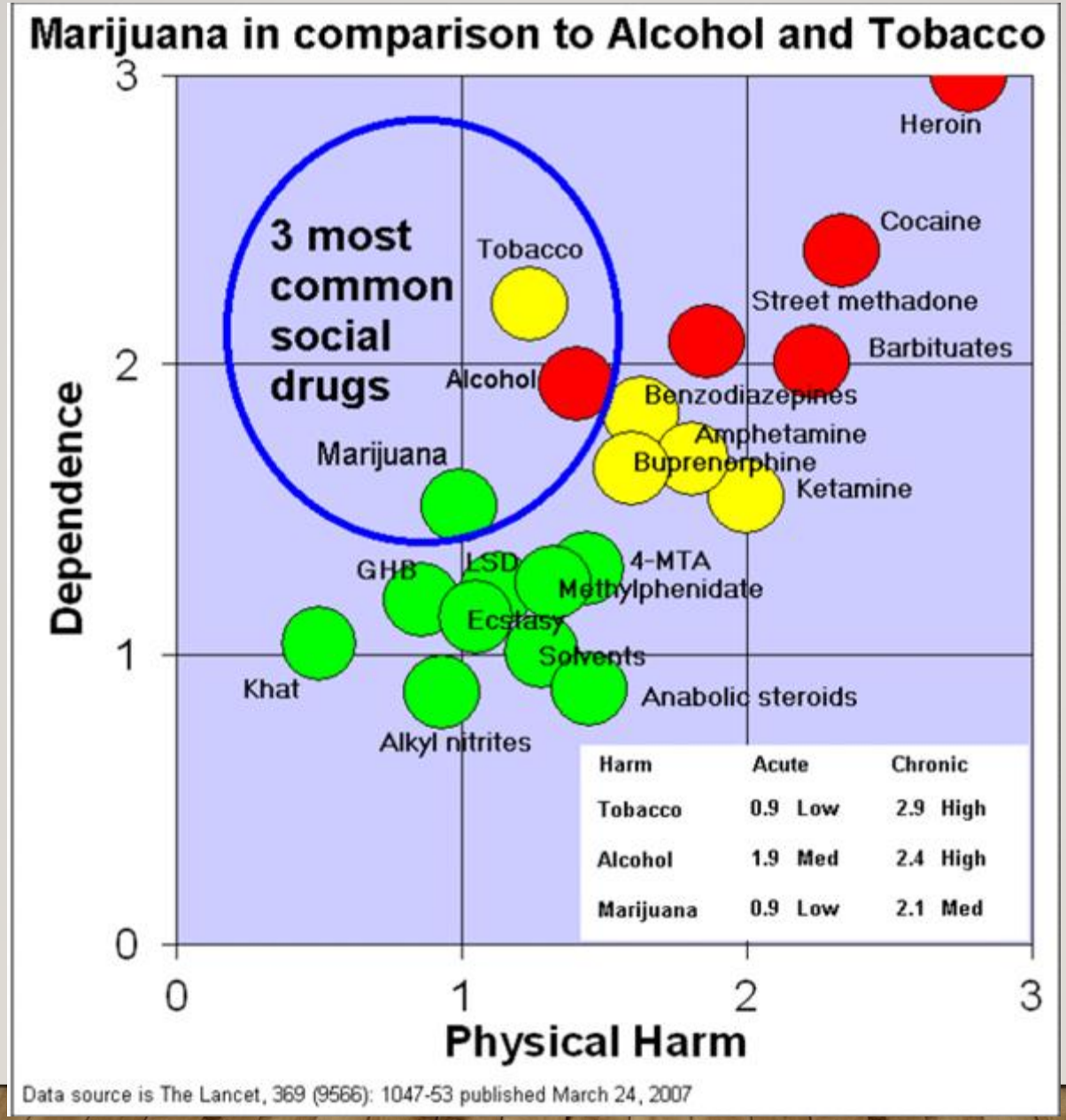
- Multicenter randomized double-blind placebo controlled graded dose sativex study in advanced cancer patients
- Avg daily pain between 4 and 8 for at least 3 days during run in period on max tolerated opioid dose
- Randomized to one of three groups 1-4 sprays per day or 6-10 or 11-16 and could be either placebo or sativex
- Dosing was bid
- One week to titrate in then 4 weeks on trial dose
- Stable opioids but allowed BT dosing

PORTENOY STUDY

- 263 patients completed study
- In the high dose group only 64% were able to take the scheduled doses compared to 85 and 90% in the other groups
- Primary endpoint of 30% reduction in pain was not statistically significant
- Secondary endpoint of continuous responder rate was statistically significant in two lower dose groups as was mean average pain score and worst pain scores
- Low dose group showed a 26% change in pain score
- Sleep disturbance scores and opioid use show non-stat significant improvement in the low dose group
- Approx 20% of patients on study died from their disease while on study

SAFETY, SIDE EFFECTS, TOXICITY

- Consider the alternatives medications
- Consider the alternative ‘perscribers’
- Consider the community


Marijuana in comparison to Alcohol and Tobacco
3 most common social drugs
Heroin
Cocaine
Tobacco
Street methadone
Barbituates
Alcohol
Benzodiazepines
Amphetamine
Buprenorphine
Ketamine
Marijuana
GHB
LSD
4-MTA
Methylphenidate
Ecstasy
Solvents
Khat
Anabolic steroids
Alkyl nitrites
Dependence
Physical Harm
0
1
2
3
Harm | Acute | Chronic
Tobacco | 0.9 Low | 2.9 High
Alcohol | 1.9 Med | 2.4 High
Marijuana | 0.9 Low | 2.1 Med
Data source is The Lancet, 369 (9566): 1047-53 published March 24, 2007

Comparison of Risk for Physical Harm, Dependence and Social Harm of 20 Substances

	Physical harm				Dependence				Social harm			
	Mean	Acute	Chronic	Intravenous	Mean	Pleasure	Psychological dependence	Physical dependence	Mean	Intoxication	Social harm	Health-care costs
Heroin	2·78	2·8	2·5	3·0	3·00	3·0	3·0	3·0	2·54	1·6	3·0	3·0
Cocaine	2·33	2·0	2·0	3·0	2·39	3·0	2·8	1·3	2·17	1·8	2·5	2·3
Barbiturates	2·23	2·3	1·9	2·5	2·01	2·0	2·2	1·8	2·00	2·4	1·9	1·7
Street methadone	1·86	2·5	1·7	1·4	2·08	1·8	2·3	2·3	1·87	1·6	1·9	2·0
Alcohol	1·40	1·9	2·4	NA	1·93	2·3	1·9	1·6	2·21	2·2	2·4	2·1
Ketamine	2·00	2·1	1·7	2·1	1·54	1·9	1·7	1·0	1·69	2·0	1·5	1·5
Benzodiazepines	1·63	1·5	1·7	1·8	1·83	1·7	2·1	1·8	1·65	2·0	1·5	1·5
Amphetamine	1·81	1·3	1·8	2·4	1·67	2·0	1·9	1·1	1·50	1·4	1·5	1·6
Tobacco	1·24	0·9	2·9	0	2·21	2·3	2·6	1·8	1·42	0·8	1·1	2·4
Buprenorphine	1·60	1·2	1·3	2·3	1·64	2·0	1·5	1·5	1·49	1·6	1·5	1·4
Cannabis	0·99	0·9	2·1	0	1·51	1·9	1·7	0·8	1·50	1·7	1·3	1·5
Solvents	1·28	2·1	1·7	0	1·01	1·7	1·2	0·1	1·52	1·9	1·5	1·2
4-MTA	1·44	2·2	2·1	0	1·30	1·0	1·7	0·8	1·06	1·2	1·0	1·0
LSD	1·13	1·7	1·4	0·3	1·23	2·2	1·1	0·3	1·32	1·6	1·3	1·1
Methylphenidate	1·32	1·2	1·3	1·6	1·25	1·4	1·3	1·0	0·97	1·1	0·8	1·1
Anabolic steroids	1·45	0·8	2·0	1·7	0·88	1·1	0·8	0·8	1·13	1·3	0·8	1·3
GHB	0·86	1·4	1·2	0	1·19	1·4	1·1	1·1	1·30	1·4	1·3	1·2
Ecstasy	1·05	1·6	1·6	0	1·13	1·5	1·2	0·7	1·09	1·2	1·0	1·1
Alkyl nitrites	0·93	1·6	0·9	0·3	0·87	1·6	0·7	0·3	0·97	0·8	0·7	1·4
Khat	0·50	0·3	1·2	0	1·04	1·6	1·2	0·3	0·85	0·7	1·1	0·8

Table 3: Mean independent group scores in each of the three categories of harm, for 20 substances, ranked by their overall score, and mean scores for each of the three subscales

SURVEY DATA ON SIDE EFFECTS

Table 8. Side effects at follow-up

Side effect	Time point	
	4 months (Total n=9) n (%)	10 months (Total n=3) n (%)
Dry mouth	4 (44.4%)	2 (66.7%)
Psychoactive effects	4 (44.4%)	1 (33.3%)
Decreased memory	4 (44.4%)	1 (33.3%)
Decreased concentration	2 (22.2%)	2 (66.7%)
Sleepiness	3 (33.3%)	1 (33.3%)

Table 6. Most Common Treatment-Emergent Adverse Events (Reported by ≥5% of Patients)

	Number (Percentage) of Patients				
Description of Event	Nabiximols 1–4 Sprays (N = 91)	Nabiximols 6–10 Sprays (N = 87)	Nabiximols 11–16 Sprays (N = 90)	All Nabiximols (N = 268)	Placebo (N = 91)
Neoplasm progression	24 (26.4%)	11 (12.6%)	12 (13.3%)	47 (17.5%)	13 (14.3%)
Nausea	16 (17.6%)	18 (20.7%)	25 (27.8%)	59 (22.0%)	12 (13.2%)
Dizziness	10 (11%)	21 (24.1%)	20 (22.2%)	51 (19%)	12 (13.2%)
Vomiting	9 (9.9%)	14 (16.1%)	19 (21.1%)	42 (15.7%)	7 (7.7%)
Somnolence	8 (8.8%)	16 (18.4%)	15 (16.7%)	39 (14.6%)	4 (4.4%)
Disorientation	5 (5.5%)	5 (5.7%)	8 (8.9%)	18 (16.7%)	1 (1.1%)
Anorexia	6 (6.6%)	5 (5.7%)	11 (12.2%)	22 (8.2%)	10 (11.0%)
Constipation	4 (4.4%)	10 (11.5%)	6 (6.7%)	20 (7.5%)	7 (7.7%)
Dry mouth	7 (7.7%)	8 (9.2%)	7 (7.8%)	22 (8.2%)	7 (7.7%)
Anemia	6 (6.6%)	5 (5.7%)	8 (8.9%)	19 (7.1%)	4 (4.4%)
Diarrhea	5 (5.5%)	4 (4.6%)	8 (8.9%)	17 (6.3%)	4 (4.4%)
Dysgeusia	1 (1.1%)	7 (8.0%)	3 (3.3%)	11 (4.1%)	2 (2.2%)
Headache	5 (5.5%)	6 (6.9%)	4 (4.4%)	15 (5.6%)	1 (1.%)
Asthenia	6 (6.6%)	7 (8%)	5 (5.6%)	18 (6.7%)	6 (6.6%)
Hallucination	1 (1.1%)	1 (1.1%)	6 (6.7%)	8 (3.0%)	5 (5.5%)
Decreased appetite	4 (4.4%)	5 (5.7%)	2 (2.2%)	11 (4.1%)	2 (2.2%)
Fatigue	4 (4.4%)	4 (4.6%)	5 (5.6%)	13 (4.9%)	4 (4.4%)
Pain	4 (4.4%)	2 (2.3%)	5 (5.6%)	11 (4.1%)	2 (2.2%)
Insomnia	2 (2.2%)	2 (2.3%)	4 (4.4%)	8 (3.0%)	5 (5.%)
Stomatitis	5 (5.5%)	2 (2.3%)	3 (3.3%)	10 (3.7%)	0
Weight decreased	5 (5.5%)	1 (1.1%)	2 (2.2%)	8 (3.0%)	2 (2.2%)

CANNABIS WITHDRAWAL

- Mild and short lived (1 - 14 days)
  - 2-6 days average
- Restlessness, irritability, mild agitation, insomnia, sleep disturbance, nausea and cramping, craving, decreased appetite, chills, shakiness, and stomach pain

WHAT NEXT?

HIGH PRIORITIES FOR THE NEXT FIVE YEARS

- Ability to measure peak and trough levels for both THC and CBD and build knowledge base around this for various methods of cannabinoid delivery
- Enhance trial methodology for dose titration studies
- Identify a therapeutic range for both THC and CBD for cancer patients with both general pain and neuropathic pain
- Examine potential opioid sparing effects of cannabinoids in cancer pain population