Assessing the prevalence and current trends in the use of cannabidiol (CBD) products in patient with active malignancy

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Baylor College of Medicine
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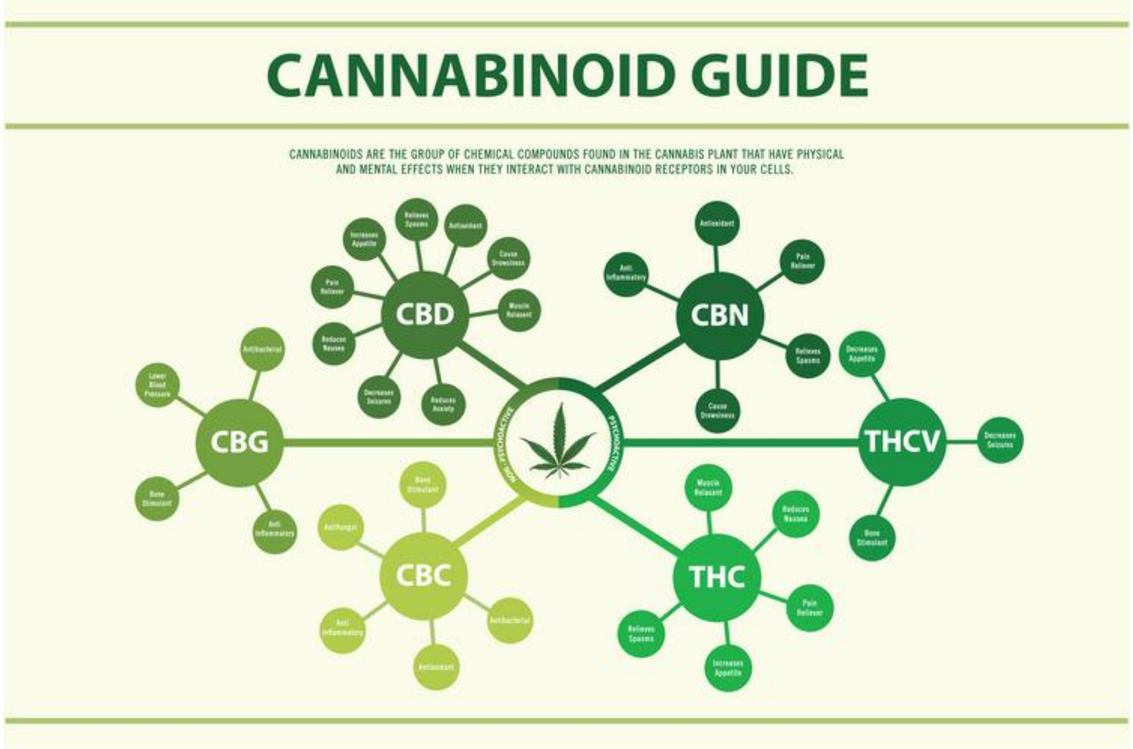
Overview

- Background on CBD products
- Project design
- Preliminary results
- Future directions

Cannabis

- Products derived from *Cannabis sativa*
- Cannabinoids
  - Delta-9-tetrahydrocannabidol (THC)
    - Primary psychoactive cannabinoid
  - Cannabidiol (CBD)
- Cannabinoid products are commonly used as an adjunct for management of symptoms such as pain, anorexia, nausea, insomnia, and anxiety



https://www.seedcannabisco.com/cannabinoids/

https://www.nccih.nih.gov/health/cannabis-marijuana-and-cannabinoids-what-you-need-to-know

Cannabinoid Derived Products

- THC dominant (THC/CBD >5:1)
  - Prescription product(s): Dronabinol, Nabilone
- Balanced (THC/CBD 1:1)
  - Prescription product(s): Nabiximols*
- CBD dominant (THC/CBD 1:10+)
  - Prescription product(s): Epidiolex (purified CBD solution used to treat pediatric epilepsy syndromes)

Steele G, Arneson T, Zylla D. A Comprehensive Review of Cannabis in Patients with Cancer: Availability in the USA, General Efficacy, and Safety. Curr Oncol Rep. Feb 1 2019;21(1):10. doi:10.1007/s11912-019-0757-7

CBD Products

- Formulations: oral pills, oral solutions, oils, inhaled vaporized oil, topical creams/gels

- Not reported to have significant psychoactive effects
  - CBD has biologic activity on the G protein-coupled cannabinoid receptors (CB_1 and CB_2) at a lower affinity than THC

- Metabolized extensively through the CYP450 isoenzyme family (especially CYP3A4 and CYP2C19)

- Products may inadvertently contain some THC

Devinsky O, Cilio MR, Cross H, et al. Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. Epilepsia. 2014;55(6):791-802.
Devinsky O, Cross JH, Laux L, Marsh E, Miller I, Nabbout R, Scheffer IE, Thiele EA, Wright S; Cannabidiol in Dravet Syndrome Study Group. Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. N Engl J Med. 2017 May 25;376(21):2011-2020. doi: 10.1056/NEJMoa1611618. PMID: 28538134
VanDolah HJ, Bauer BA, Mauck KF. Clinicians' Guide to Cannabidiol and Hemp Oils. Mayo Clin Proc. 2019 Sep;94(9):1840-1851. doi: 10.1016/j.mayocp.2019.01.003. Epub 2019 Aug 22. PMID: 31447137.
Balachandran P, Elsohly M, Hill KP. Cannabidiol Interactions with Medications, Illicit Substances, and Alcohol: a Comprehensive Review. J Gen Intern Med. 2021 Jul;36(7):2074-2084. doi: 10.1007/s11606-020-06504-8. Epub 2021 Jan 29. PMID: 33515191; PMCID: PMC8298645..

Agriculture Improvement Act of 2018

- Cannabis plant and its derivatives with <0.3% delta-9-tetrahydrocannabidiol (THC) by dry weight were no longer considered controlled substances


irwin naturals
CBD Oil
1000 mg CBD*
Full-Spectrum Hemp Extract
UNFLAVORED
DIETARY SUPPLEMENT • 1 FL OZ (29.5 mL)


ASPEN GREEN
EXTRA
CBD
FOCL


SUNDAY SCARIES
GUMMIES FOR CHILLIN'
20 CBD GUMMIES

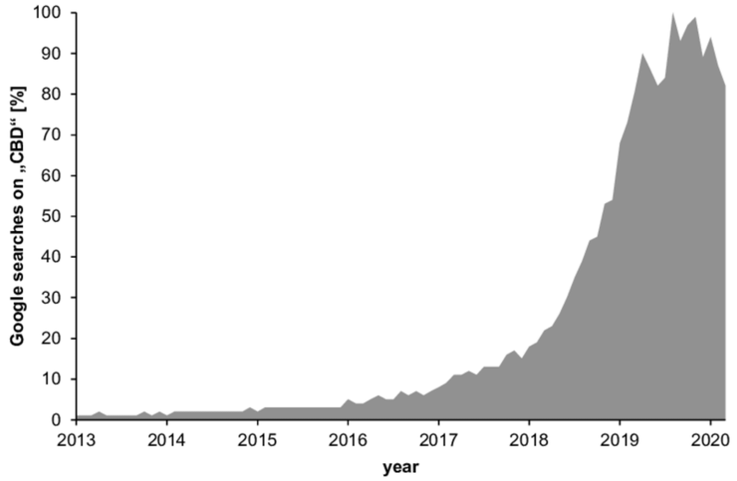

THE BODY SHOP
CBD


3CHI
SLEEP
3CHI
CALM


CORN
BREAD
FULL SPECTRUM
CBD CAPSULES
25MG CBD
1MG THC
750MG
30 CAPSULES
PER CAPSULE
HERBAL SUPPLEMENT

A 2019 Gallup study showed 14% polled Americans used CBD-products.

Multiple studies evaluating Google trends showed public interest in CBD oil demonstrated an upward trend in internet searches for “CBD” in recent years.



Brenan, Megan. “14% Of Americans Say They Use CBD Products.” *Gallup.com*, Gallup, 20 Nov. 2021, https://news.gallup.com/poll/263147/americans-say-cbd-products.aspx.
Leas EC, Nobles AL, Caputi TL, Dredze M, Smith DM, Ayers JW. Trends in Internet Searches for Cannabidiol (CBD) in the United States. JAMA Netw Open. 2019 Oct 2;2(10):e1913853. doi: 10.1001/jamanetworkopen.2019.13853. PMID: 31642924; PMCID: PMC6820034.
Narayanan S, Lazar Neto F, Tanco K, Lopez G, Liu W, Bruera E, Subbiah V. Cannabidiol (CBD) Oil, Cancer, and Symptom Management: A Google Trends Analysis of Public Interest. J Altern Complement Med. 2020 Apr;26(4):346-348. doi: 10.1089/acm.2019.0428. Epub 2020 Jan 22. PMID: 31971821; PMCID: PMC7153638.
Golombek P, Müller M, Barthlott I, Sproll C, Lachenmeier DW. Conversion of Cannabidiol (CBD) into Psychotropic Cannabinoids Including Tetrahydrocannabinol (THC): A Controversy in the Scientific Literature. *Toxics*. 2020;8(2):41. Published 2020 Jun 3. doi:10.3390/toxics8020041

Challenges with CBD Product Use

- There are documented discrepancies between marketed concentrations of CBD in available products and the actual concentration of CBD

- In vitro studies of drug interactions with CBD and common chemotherapeutics have been done but there is limited in vivo data

Bonn-Miller MO, Loflin MJE, Thomas BF, Marcu JP, Hyke T, Vandrey R. Labeling Accuracy of Cannabidiol Extracts Sold Online. JAMA. 2017 Nov 7;318(17):1708-1709. doi: 10.1001/jama.2017.11909. PMID: 29114823; PMCID: PMC5818782.
Opitz BJ, Ostroff ML, Whitman AC. The Potential Clinical Implications and Importance of Drug Interactions Between Anticancer Agents and Cannabidiol in Patients With Cancer. J Pharm Pract. 2020 Aug;33(4):506-512. doi: 10.1177/0897190019828920. Epub 2019 Feb 18. PMID: 30776990

Highlights of Currently Published Research of Cannabinoid Use in an Oncologic Population

Reported outcomes of global symptom management

Year	Author	n	Product?	Conclusion
2006	Strasser	243	THC/CBD, THC (capsule)	Neither THC/CBD nor THC improve quality of life.
2016	Cote	56	THC (Nabilone)	THC does not improve overall quality of life compared to placebo.
2023	Hardy	142	CBD (oil)	CBD does not change total symptom burden.

Strasser F, Luftner D, Possinger K, et al. Comparison of orally administered cannabis extract and delta-9-tetrahydrocannabinol in treating patients with cancer-related anorexia-cachexia syndrome: a multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial from the Cannabis-In-Cachexia-Study-Group. *J Clin Oncol*. Jul 20 2006;24(21):3394-400. doi:10.1200/jco.2005.05.1847
Côté M, Trudel M, Wang C, Fortin A. Improving Quality of Life With Nabilone During Radiotherapy Treatments for Head and Neck Cancers: A Randomized Double-Blind Placebo-Controlled Trial. *Ann Otol Rhinol Laryngol*. Apr 2016;125(4):317-24. doi:10.1177/0003489415612801
Hardy J, Greer R, Huggett G, Kearney A, Gurgenci T, Good P. Phase IIb Randomized, Placebo-Controlled, Dose-Escalating, Double-Blind Study of Cannabidiol Oil for the Relief of Symptoms in Advanced Cancer (MedCan1-CBD). *J Clin Oncol*. Mar 1 2023;41(7):1444-1452. doi:10.1200/jco.22.01632

Highlights of Currently Published Research of Cannabinoid Use in an Oncologic Population

Reported outcomes in management of cancer related pain

Year	Author	n	Product?	Conclusion
2010	Johnson	177	THC/CBD, THC (oromucosal spray)	THC/CBD lowers pain score, THC alone does not.
2012	Portenoy	360	THC/CBD (Nabiximols)	THC/CBD does not lower pain response rate.
2016	Cote	56	THC (Nabilone)	THC does not improve pain over placebo.
2017	Fallon (Study 1)	399	THC/CBD (Nabiximols)	THC/CBD does not change pain score.
2017	Fallon (Study 2)	206	THC/CBD (Nabiximols)	THC/CBD does not change severity of pain score.
2018	Lichtman	397	THC/CBD (Nabiximols)	THC/CBD does not improve pain score more than placebo.
2023	Hardy	142	CBD (oil)	CBD does not improve pain over placebo.

Côté M, Trudel M, Wang C, Fortin A. Improving Quality of Life With Nabilone During Radiotherapy Treatments for Head and Neck Cancers: A Randomized Double-Blind Placebo-Controlled Trial. *Ann Otol Rhinol Laryngol*. Apr 2016;125(4):317-24. doi:10.1177/0003489415612801

Hardy J, Greer R, Huggett G, Kearney A, Gurgenci T, Good P. Phase IIb Randomized, Placebo-Controlled, Dose-Escalating, Double-Blind Study of Cannabidiol Oil for the Relief of Symptoms in Advanced Cancer (MedCan1-CBD). *J Clin Oncol*. Mar 1 2023;41(7):1444-1452. doi:10.1200/jco.22.01632

Johnson JR, Burnell-Nugent M, Lossignol D, Ganae-Motan ED, Potts R, Fallon MT. 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. *J Pain Symptom Manage*. Feb 2010;39(2):167-79. doi:10.1016/j.jpainsymman.2009.06.008

Portenoy RK, Ganae-Motan ED, Allende S, et al. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. *J Pain*. May 2012;13(5):438-49. doi:10.1016/j.jpain.2012.01.003

Fallon MT, Albert Lux E, McQuade R, et al. Sativex oromucosal spray as adjunctive therapy in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy: two double-blind, randomized, placebo-controlled phase 3 studies. *Br J Pain*. Aug 2017;11(3):119-133. doi:10.1177/2049463717710042

Lichtman AH, Lux EA, McQuade R, et al. Results of a Double-Blind, Randomized, Placebo-Controlled Study of Nabiximols Oromucosal Spray as an Adjunctive Therapy in Advanced Cancer Patients with Chronic Uncontrolled Pain. *J Pain Symptom Manage*. Feb 2018;55(2):179-188.e1. doi:10.1016/j.jpainsymman.2017.09.001

Highlights of Currently Published Research of Cannabinoid Use in an Oncologic Population

Reported outcomes in management of chemotherapy-induced nausea & vomiting (CINV)

Year	Author	n	Product?	Primary Outcome Conclusion
1979	Frytak	116	THC (capsule)	THC provides a benefit over placebo, but no benefit over prochlorperazine.
1979	Herman	113	THC (Nabilone)	THC is superior to prochlorperazine, and patients prefer THC.
1980	Sallan	84	THC (capsule)	Compared to prochlorperazine, THC is preferred among patients and more likely to achieve a response.
1980	Orr	55	THC (capsule)	THC is superior to prochlorperazine.
1981	Einhorn	80	THC (Nabilone)	THC reduces nausea and is preferred by patients, compared to prochlorperazine.
1982	Ungerleide	214	THC (oral)	THC and prochlorperazine are equally effective.
1982	Wada	114	THC (Nabilone)	THC reduces nausea and vomiting over placebo.
1991	Lane	62	THC (Dronabinol)	Combination THC and prochlorperazine is more effective than either agent alone.
2007	Meiri	64	THC (Dronabinol)	THC, ondansetron, and combination therapy are similarly effective in treating nausea over placebo.
2016	Cote	56	THC (Nabilone)	THC does not improve nausea or antiemetic consumption compared to placebo.
2020	Grimison	81	THC/CBD (oral extract)	THC/CBD added to standard antiemetics is associated with less nausea/vomiting.
2023	Hardy	142	CBD (oil)	CBD does not change nausea or vomiting over placebo.

Côté M, Trudel M, Wang C, Fortin A. Improving Quality of Life With Nabilone During Radiotherapy Treatments for Head and Neck Cancers: A Randomized Double-Blind Placebo-Controlled Trial. *Ann Otol Rhinol Laryngol*. Apr 2016;125(4):317-24. doi:10.1177/0003489415612801

Hardy J, Greer R, Huggett G, Kearney A, Gurgenci T, Good P. Phase IIb Randomized, Placebo-Controlled, Dose-Escalating, Double-Blind Study of Cannabidiol Oil for the Relief of Symptoms in Advanced Cancer (MedCan1-CBD). *J Clin Oncol*. Mar 1 2023;41(7):1444-1452. doi:10.1200/jco.22.01632

Frytak S, Moertel CG, O'Fallon JR, et al. Delta-9-tetrahydrocannabinol as an antiemetic for patients receiving cancer chemotherapy. A comparison with prochlorperazine and a placebo. *Ann Intern Med*. Dec 1979;91(6):825-30. doi:10.7326/0003-4819-91-6-825

Herman TS, Einhorn LH, Jones SE, et al. Superiority of nabilone over prochlorperazine as an antiemetic in patients receiving cancer chemotherapy. *N Engl J Med*. Jun 7 1979;300(23):1295-7. doi:10.1056/nejm197906073002302

Sallan SE, Cronin C, Zelen M, Zinberg NE. Antiemetics in patients receiving chemotherapy for cancer: a randomized comparison of delta-9-tetrahydrocannabinol and prochlorperazine. *N Engl J Med*. Jan 17 1980;302(3):135-8. doi:10.1056/nejm198001173020302

Orr LE, McKernan JF, Bloome B. Antiemetic effect of tetrahydrocannabinol. Compared with placebo and prochlorperazine in chemotherapy-associated nausea and emesis. *Arch Intern Med*. Nov 1980;140(11):1431-3. doi:10.1001/archinte.140.11.1431

Einhorn LH, Nagy C, Furnas B, Williams SD. Nabilone: an effective antiemetic in patients receiving cancer chemotherapy. *J Clin Pharmacol*. Aug-Sep 1981;21(S1):64s-69s. doi:10.1002/j.1552-4604.1981.tb02576.x

Ungerleider JT, Andrysiak T, Fairbanks L, Goodnight J, Sarna G, Jamison K. Cannabis and cancer chemotherapy: a comparison of oral delta-9-THC and prochlorperazine. *Cancer*. Aug 15 1982;50(4):636-45. doi:10.1002/1097-0142(19820815)50:4<636::aid-cncr2820500404>3.0.co;2-4

Wada JK, Bogdon DL, Gunnell JC, Hum GJ, Gota CH, Rieth TE. Double-blind, randomized, crossover trial of nabilone vs. placebo in cancer chemotherapy. *Cancer Treat Rev*. Dec 1982;9 Suppl B:39-44. doi:10.1016/s0305-7372(82)80034-0

Lane M, Vogel CL, Ferguson J, et al. Dronabinol and prochlorperazine in combination for treatment of cancer chemotherapy-induced nausea and vomiting. *J Pain Symptom Manage*. Aug 1991;6(6):352-9. doi:10.1016/0885-3924(91)90026-z

Meiri E, Jhangiani H, Vredenburgh JJ, et al. Efficacy of dronabinol alone and in combination with ondansetron versus ondansetron alone for delayed chemotherapy-induced nausea and vomiting. *Curr Med Res Opin*. Mar 2007;23(3):533-43. doi:10.1185/030079907x167525

Grimison P, Mersiades A, Kirby A, et al. Oral THC:CBD cannabis extract for refractory chemotherapy-induced nausea and vomiting: a randomised, placebo-controlled, phase II crossover trial. *Ann Oncol*. Nov 2020;31(11):1553-1560. doi:10.1016/j.annonc.2020.07.020

Our Project

Study Objective

To complete a descriptive analysis of the current familiarity and usage patterns of CBD products in an oncologic population through a voluntary survey to allow us to understand patterns of CBD product selection while also understanding what symptoms patients hope to palliate with alternative therapies

Project Design

1

Collect voluntary, anonymous patient surveys at the Baylor Scott and White Temple Vasicek Cancer Center

Cannabidiol (CBD) Survey

Thank you for participating in this voluntary and completely anonymous survey regarding CBD oil and related products. With the growing availability of CBD products in our state, the objective of our research study is to understand the role these products have in your overall cancer care.

The survey is a total of 4 pages.

By completing this questionnaire, you are giving your consent to participate in this study and for your data to be used as descriptive data. Please confirm your consent:

☐ I consent to participate ☐ I do not consent

Section 1: Basic Information

1. What is your age?

   _____

2. What is your gender?

   ☐ Female ☐ Male ☐ Prefer not to specify

3. What is the primary site of the cancer you have been diagnosed with?

   ☐ Breast

   ☐ Gastrointestinal (esophageal, gastric, gallbladder, pancreas, small or large bowel)

   ☐ Gynecologic (ovarian, uterine, vaginal) ☐ Head & Neck

   ☐ Hematologic (leukemia, lymphoma, myeloma)

   ☐ Lung ☐ Prostate ☐ Skin & Soft Tissue

   ☐ Urinary (bladder, renal) ☐ Other: _____

4. What stage is your cancer?

   ☐ Stage I ☐ Stage II ☐ Stage III ☐ Stage IV (Metastatic)

   ☐ I am not sure

5. When were you diagnosed with cancer?

   ☐ Less than 6 months ago ☐ 6 – 12 months ago

   ☐ 1 –3 years ago ☐ Greater than 3 years ago

6. Are you currently on active cancer treatment (chemotherapy, immunotherapy, hormonal therapy, etc.)?

   ☐ Yes ☐ No

7. Are you currently, or have you previously, been prescribed medicinal marijuana by a health care provider?

   ☐ Yes ☐ No

Section 2: CBD-Related Information

1. Have you ever used CBD products (oil, gummies, capsules, topical, etc)?

   ☐ Yes ☐ No

2. **If you answered "yes" to question 1**, please answer the following questions:

   a. Did you start using CBD products before or after a diagnosis of cancer?

      ☐ Before cancer diagnosis ☐ After cancer diagnosis

   b. Which product did you use? If you used multiple products, you can mark any applicable items.

      ☐ CBD oil ☐ CBD gummies ☐ CBD capsules

      ☐ Topical CBD (cream, lotion) ☐ CBD vapes

      ☐ Other: _____

   c. Did you discuss the use of CBD product with a health care provider before starting?

      ☐ Yes ☐ No

   d. How long have you used CBD products?

      ☐ 0 – 3 months ☐ 4 – 6 months ☐ 7 – 12 months ☐ Over a year

   e. How did you decide which product to use?

      ☐ Cost ☐ Appearance of packaging

      ☐ Recommendation by friend or family member

      ☐ Recommendation by store employee

      ☐ Other: _____

      _____

   f. How often do/did you use CBD products?

      ☐ Multiple times daily ☐ Daily ☐ Weekly ☐ Monthly ☐ As needed

   g. Did you experience any side effects while on CBD products?

      ☐ No

      ☐ Yes, please specify: _____

3. **If you answered "no" to question 1**, please answer the following questions:
   a. Have you ever considered using CBD products?

   ☐ Yes ☐ No

   b. What are your concerns regarding use of CBD products? If you have multiple concerns, you can mark any applicable items.

   ☐ Interaction with other medications ☐ Cost

   ☐ Unsure of which product/brand to use ☐ Personal/ethical concerns

   ☐ Other: _____

   _____

Section 3: Symptom-Related Information

This section is to be completed by those who have tried/are using CBD products.

1. What symptom(s) did you hope to address with use of CBD products? If you have more than one reason for starting, you can mark all applicable items.

   ☐ Anxiety ☐ Increase appetite

   ☐ Cancer-related pain ☐ Depression

   ☐ Insomnia ☐ Nausea/Vomiting

   ☐ Shortness of Breath

   ☐ Other: _____

   _____

2. How well controlled were your symptoms with prescription medications before starting CBD therapy?

   ☐ Poorly controlled ☐ Moderately controlled ☐ Well controlled

3. How well controlled were your symptoms after starting CBD therapy?

   ☐ Poorly controlled ☐ Moderately controlled ☐ Well controlled

4. If you stopped using CBD products, what was the reason why? If you have more than one reason for stopping, you can mark all applicable items.

   ☐ Cost ☐ Felt it was ineffective

   ☐ Change to medical marijuana product

   ☐ Other: _____

   _____

5. Would you recommend the use of CBD products to other patients?

   ☐ Yes ☐ No

Project Design

1. Collect voluntary, anonymous patient surveys at the Baylor Scott and White Temple Vasicek Cancer Center

2. Paper surveys to be manually entered into a secure data base for analysis. Physical surveys were stored in a secure location

Project Design

1. Collect voluntary, anonymous patient surveys at the Baylor Scott and White Temple Vasicek Cancer Center

2. Paper surveys to be manually entered into a secure data base for analysis. Physical surveys were stored in a secure location

3. Descriptive statistical analysis of survey results

Project has been reviewed and approved by the Baylor Scott & White Temple Institutional Review Board (IRB)

Patient Criteria

Inclusion Criteria

1. Adults aged 18 years and older
2. Patients undergoing active systemic therapy with chemotherapy, targeted therapy, and immunotherapy for cancer

Exclusion Criteria

1. Patients who are prescribed medical marijuana therapy
2. Patients unable to independently complete the survey in English
3. Pregnant patients as there is limited data regarding safety of CBD containing products in this population

Preliminary Results

Patient Population

- 54 surveys were collected and processed into the database as of June 30, 2023
  - 2 patients who completed surveys were prescribed medical marijuana

Patient Characteristics Highlights	
Mean Age	62 years old
Male	54%
Female	46%
Gastrointestinal Cancer	94%
Stage III cancer	26%
Stage IV cancer	31%
Unsure of cancer stage	30%

Patients Who Did Not Use/Try CBD Products

- 76% (n=41) patients reported never using CBD products
- 26% of these patients considered CBD product use
- Top 3 areas of concern
  - Potential drug interactions
  - Brand/product selection
  - Personal/ethical concerns

CBD Product Use

- 24% of surveyed patients (n=13) had used CBD-products
  - Only 15% of these patients discussed use with a medical provider
- A majority of patients used CBD oil (46%) or gummies (46%)
- Most common reasons for CBD use reported:
  - Pain (31%)
  - Anxiety (23%)
  - Nausea/Vomiting (23%)
  - Appetite Stimulation (23%)

CBD Product Use

- 33% (3/9) reported that symptoms were well controlled before CBD use, compared to 78% (7/9) after CBD us
- 73% (8/9) patients who used CBD products would recommend it to a friend/family member/colleague
- 23% (3/9) patients stopped CBD product used and started medical marijuana

Study Strengths

- Real-world data
- Surveying both patients who have used/are using CBD-products and those who have not used products
- Evaluates what patients factor into specific CBD-product selection

Study Limitations

- All outcomes are self reported
- Some surveys were only partially completed
- Survey population is predominantly composed of patients with gastrointestinal malignancy thus far
- Data is not further stratified by specific systemic therapy (chemotherapy, immunotherapy, targeted therapy, etc)
- Details about specific product (ie product name, formulation, etc) are not obtained or uniform amongst patients

Future Directions

Immediate Next Steps

- Plan to obtain an additional ~150 patient surveys between July 2023 and December 2023
  - Goal: total of 150-200 patient surveys
  - Hope to capture a variety of hematologic malignancies and solid tumors

- Perform descriptive analysis of final surveyed patients
  - Review type(s) of CBD products used by patients and factors that impacted selection of product
  - Evaluate for differences is self-reported outcomes by cancer type, cancer stage, and/or chemotherapy regimen

Further Areas of Study

- Survey physicians and providers to determine their familiarity with CBD products
- Develop clinician focused resources for counseling patients on CBD product use
- Conduct large double-blind randomized controlled trial with CBD-only, THC, or combination products compared to placebo in a pre-specified oncologic population evaluating palliative care-based outcomes, drug-drug interactions, and adverse events

Thank you!

Any questions or comments?