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Marijuana in Combination with Opioids in Palliative and Hospice Patients.

NCT#03233633

Study Protocol Title

Marijuana in combination with opioids for pain and symptom control in hospice patients.

Principal Investigator, Research Team, and Study Site

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1.0 Research Synopsis

Study Title: Marijuana in combination with opioids for pain and symptom control in hospice patients.

Clinical Phase:	Exploratory/Pilot (Phase I)
IND Sponsor	N/A

2.0 Background and Significance

The Connecticut Hospice, Inc., the first Hospice who served for four decades in the United States, recently received The Joint Commission 's first advanced palliative hospital certification without recommendations for improvement, embarks on a new study.

Hospice care (Johnson-Hurzeler 1998) involves managing symptoms and quality of life for patients whose life expectancy is less than six months. (Kruse 2013) A study involving 100 hospice inpatients revealed high incidence of many symptoms, including chronic pain (62% of patients), anorexia (58%), constipation (52%), nausea (37%), vomiting (24%), sleep issues (22%), and anxiety (19%). (Potter 2003) The majority of hospice patients are prescribed opioids for pain control. The typical process involves administering a certain dosage of opioids and, depending upon pain relief and side effects, the dosage (in mgs) may be adjusted accordingly in increments of 25%. Common side effects of opioid medications include constipation, nausea, sedation, respiratory depression, dependence, and death. (Bruehl 2014)

In studies to date, marijuana has shown promise as an adjunctive medication for patients who require opioids for pain management. (Karst 2009) An Australian study—POINT (Pain and Opioids in Treatment)—collected reports from I ,514 patients on the efficacy of marijuana in combination with opioids for management of pain from a diverse range of causes. (Degenhardt 2015) In general, patients reported that the combination of marijuana and opioids was more effective for pain relief than opioids alone. (Degenhardt 2015) Another study, which included 21 patients suffering from chronic pain, found increased efficacy in pain control with the addition of marijuana to opioid regimens; investigators concluded that addition of marijuana to opioid regimens may result in a lowered effective dose of opioids. (Abrams 2011) In the same study, investigators reasoned that marijuana facilitates the activities of opioids either by slowing opioid

metabolism or by increasing plasma opioid levels. (Abrams 2011) Marijuana may also facilitate the pain-relieving effects of opioid medications by acting upon opioid receptors. (Cichewicz 2004; Abrams 2011) Animal studies have shown the possibility of direct interaction between cannabinoid and opioid receptors. (Bushlin 2010) In studies, marijuana has been shown to reduce pain associated with multiple sclerosis, HIV, chronic neuropathic pain, rheumatoid arthritis, and acute pancreatitis. (Fine 2013) Surveys of medical marijuana have shown that the drug can improve pain and control insomnia with minimal side effects in some patients. (Wilsey 2008) Marijuana is also known to help mitigate nausea and vomiting. (Sharkey 2014) Dronabinol, a pill which is chemically identical to THC, was approved in 1992 by the FDA as an appetite stimulant in AIDS patients. (Grant 2005) The latter may indicate the use of marijuana for hospice patients experiencing anorexia.

Most studies of the medical benefits of marijuana so far have included fewer than 200 patients. Federal restrictions make it difficult for the research to advance. Marijuana is currently characterized by the Federal Government as a Schedule-I controlled substance, meaning that according to federal law, "(A) The drug or other substance has a high potential for abuse. (B) The drug or other substance has no currently accepted medical use in treatment in the United States. (C) There is a lack of accepted safety for use of the drug or other substance under medical supervision." (21 U.S. Code *812) The DEA and FDA have yet to grant their approval for largescale studies of the medical applications of marijuana; however, in 2014, the FDA vowed to reexamine the scheduling of marijuana so that more large-scale research could perhaps be conducted. (Ferner 2014)

In 2012, Connecticut lawmakers passed a law allowing for the palliative use of marijuana. The law enables doctors to prescribe marijuana (i.e. dried leaves) and its derivatives (i.e. oils, waxes, edibles, transdennal, and sublingual preparations) to patients suffering from specific conditions.

Under Connecticut state law "Debilitating Medical Condition" includes Cancer or terminal illness requiring end-of-life care. This study specifically will enroll cancer and non-cancer patients as a primary diagnosis suffering from pain and having a terminal illness (defined as having less than 6 months to live) requiring end of life care. Table-I .(pg. 8) Originally published in Cancer Therapeutics in 1998, and revised in 2016, includes the specific inclusion diagnoses for this study). Under the international classification of disease (ICD-10), these diagnoses are categorized in The Connecticut Hospice-Hospital database for fiscal year 2016, representing patients that have been referred and admitted.

Table 1. The Connecticut Hospice, Inc.

SUMMARY GUIDELINES FOR INITIATION OF ADVANCED CARE

(OVER FOR REFERRAL INFORMATION)

Authored by: Robert U. Massey, M.D.
Rosemary Johnson-Hurzeler, RN, MPH, HA

Limited response to additional therapy expected and not durable.

First-line salvage therapies have failed. Less than 30% response to second-line or other therapy expected and not durable.

Dementia beyond State 7 of the Functional Assessment Staging Scale for Alzheimer's Disease or multi-symptoms present and declining functional status (Karnofsky and when there is partial or total dependence in ADLs.)

Progressive nerve degeneration with resultant partial/total paresis or paralysis of extremities and muscles of respiration. Optimal therapy reached. (i.e. no further response to therapies expected). With major symptoms present and declining functional status (Kamofsky 50% and when there is partial or total dependence in ADLs).

Massive CVA with no rehabilitation potential; patient unable to eat. Optimal therapy reached (i.e. no further response to therapies expected, with major symptoms present and declining functional status (Karanofsky and when there is partial or total depended in ADCs).

Congenital defects. complication of infections, or trauma based upon individual case review.

Long-standing history of congestive heart failure or multiple MI. Class IV NY Heart Association Symptoms and ejection fraction No further responses expected to medical therapy and no options for CABG, grafting, angioplasty, pacemaker, or transplant. Any one of the following dyspnea, angina, othopnea, edema. Any two of the following: Kamofsky <50%, minimal activity tolerance, dependence on 20 or more ADLs.

Degradation of PFTs: FEVI after bonchodialator <30 % of predicted, decrease in FEVI on yearly serial testing of >40ml/year. Cor pulmonade, Hypoxemia, significant C02 retention as measured by ABGs. Optimal therapy reached with multiple bronchodialators and steroid dependence with dyspnea (of any kind) and 02 dependence. Declining functional status including Karnofsky <50%, chair-bound, minimal activity tolerance, and dependence on 2 or more ADLs.

Worsening LFTs and documented evidence of disease (utilizing abdominal ultrasound, CT, HIDA Scan, Cholangiography. ERCP or any appropriate diagnostic imaging demonstrating biliary obstruction, hepatic vein occlusion, hepatic artery thrombosis, hepatocellular dysfunction. No expectation of success from medical management and/or surgical intervention. Presence of any one major symptom and declining function status (Karnofsky <50% and dependence in 2 or more ADLs).

10. Decision made to stop dialysis with one of the following conditions: chronic dialysis necessary to sustain life, disease progression despite interventions, intolerable associated medical complications of non-renal disease. In addition. at least one of the following: peripheral vascular disease degradation, hypotension, dementia, depression, resistance to dialysis Rx; and. declining functional status.

11. CD4<50 with concurrent ongoing major infections, and the presence of at least one of the following: lymphoma, Kaposi's Sarcoma, PMH, HIV encephalopathy, HIV wasting syndrome. Progression of disease on antiretroviral therapy and the presence of major symptoms with declining function status.

Important Note on these Guidelines: The footnotes above are an integral part of these guidelines. They must be used in conjunction with the matrix at the left. Cancer Therapeutics: May/June 1998*Vol 1, No.2

Disease Category	Refer to Advanced Care Upon			
Cancer	**Initial Diagnosis**	**Recurrence**	**Progression**	**Critical Clinical Decision**
Brain/CNS Tumor				
Breast				
Colorectal				
Esophagus				
Gall Bladder				
Head & Neck				
Leukemia				
Liver				
Lung				
Lung – inoperable				
Melanoma				
Ovarian - inoperable				
Ovarian/GYN				
Pancreatic				
Prostate/GU				
Renal				
Sarcoma				
Stomach Non-Hodgkin's Lymphoma				
End-Stage Diseases				
Neurological: Alzheimers Disease				
ALS			4	
CVA				5
MS				4
Congenital, Infectious, or Traumatic Disability				
Heart Failure			7	
Lung-COPD			8	
Liver Failure/ Cirrhosis			9	
Kidney Failure				10
AIDS			11	

Initial Diagnosis: The first diagnosis of disease by a physician.

Recurrence: Subsequent diagnosis of same disease resulting from limited response to additional therapy expected and not durable.

Progression: Continuation of disease process.

Critical Clinical Decision: Consensus decision made by physician, patient, and family that want to forego any continuing curative or rehabilitative treatment.

Footnotes

All patients participating in this study will be registered as medical marijuana patients in accordance with state law. This study will provide a basis for expanding the indications for which marijuana can legally be prescribed in the state of Connecticut, thereby benefiting additional patients.

The constituents of marijuana that have been most extensively studied for therapeutic purposes so far are A9-tetrahydrocannabinol (A9-THC) and cannabidiol (CBD). (Fine 2013) A9-THC acts primarily on Cannabinoid-l receptors (CB I), which are most densely concentrated in central nervous tissue (brain and spinal tissue); CBD acts primarily on Cannabinoid-2 receptors (CB2), which exist mostly in peripheral tissues (all other tissues). (Fine 2013) Activation and inhibition of cannabinoid receptors affects pain perception, cognition and memory, locomotor activity, endocrine functions, temperature control and heart rate, nausea and vomiting, intraocular pressure, inflammation, and immune recognition and antitumor activity. (Fine 2013) Both CB- 1 and CB-2 receptors are involved in regulating inflammatory pain. (Elikottil 2009) Relevantly for this study, A9-THC and CBD's actions upon cannabinoid receptors may reduce inflammation and pain. (Fine 2013) Furthermore, A9-THC has been shown to reduce nausea and vomiting. (Fine 2013) Whereas higher doses of A9-THC have been associated with adverse psychological effects—e.g. psychosis-like symptoms and motor and cognitive impairment—CBD seems to block, to a certain extent, those adverse psychological and cognitive effects of A9-THC. (Solowij 2014) Evidence of a physiological basis for the opposing effects of A9-THC and CBD emerged through an fMRI study in which researchers cross-referenced the behavioral effects of these substances with their respective fMRI images. (Bhattacharyya 2010)

The research summarized above demonstrates the potential role of marijuana and its derivatives in the treatment of chronic pain—whether inflammatory or neuropathic—nausea, vomiting, sleep disorders, and wasting syndrome. Identification of a combination therapy that is safer and/or more effective than current approaches is a desirable prospect. Clinical trials utilizing Sativex an oral mucosal spray containing THC and CBD, approved in Canada for the spasticity associated with MS, and Marinol a synthetic oral THC product FDA approved in the United States provide evidence for efficacy and safety of oral THC containing treatments. The protocol is justified by the potential benefits of marijuana, the risks of opioid monotherapy, and the lack of research regarding opioid-marijuana combination therapy for improved pain control in hospice patients.

The primary goal of this study is to further substantiate marijuana's role in pain management, specifically for the hospice patient. The drug preparations used in the study will be administered orally. The dosage will be marijuana containing a 30:1 CBD:THC ratio. Either 40 mg/1 .5 mg or 80 mg/3 mg. Safety and efficacy data on THC and CBD can be cited in various clinical studies. The product to be utilized is based on current clinical published research (Partial references 21 , 26, 37) utilizing CBD and THC as the main cannabinoids. The study drug will be provided by NIDA (The National Institute for Drug Safety).

3.0 Objectives

Primary

1. Improve pain management as identified by decreased overall numeric pain scores
2. Reduce opioid dosage increases
3. Reduce overall opioid utilization

Secondary

Evaluate changes in patient weight, appetite, nausea and vomiting, 02 saturation, feelings of well-being, anxiety, and depression.

4.0 Study Design and Methodology

Design

This will be an open-label study. Patients will choose to participate in a Marijuana adjuvant treatment group, receiving marijuana in combination with standard opioid therapy.

The goal is to enroll at least 66 Hospice patients in the study.

Methodology

Patients will be notified of the study's existence through communication with the study's investigation team at time of admission. Patients will be screened for study eligibility—see section 6.0 for study eligibility factors— and if the patient is both eligible and interested in participating, the sub-investigator will discuss and review the informed consent form with the patient and obtain their signature; the patient will then have a consultation with a prescribing physician; and, if the physician has determined that medical marijuana is a viable option for that patient, registration with the Connecticut Medical Marijuana program will begin. For patients who have already been prescribed both marijuana and opioid medication upon admission to Hospice, signing the consent form will complete study enrollment.

Patients' initial opioid dose, dosing schedule and numeric pain score will be recorded. For the duration of the study (at least five days) changes in opioid doses and numeric pain scores will be tracked daily.

Marijuana will be administered to the patient via oral route three times daily for at least five days. Patients will receive CBD:THC product provided by NIDA.

On admission to the study, a modified Edmonton Symptom assessment scale to quantify baseline appetite, depression, nausea, vomiting, overall well-being, and anxiety.

Data Tracking: Primary objective tracking will include average numeric pain scores and number of opioid dosage increases and average daily opioid amount (mg equivalents of morphine). Secondary objectives include Weight, Appetite, N/V, 02 Saturation, Self-reported data points from the modified Edmonton Assessment Scale.

Data Tracking Intervals: Primary objective tracking of pain will be daily every 4 hours (twice per shift). Secondary objective tracking as follows: Weight daily, Appetite every 8 hours (every shift), N/V, 02 saturation as reported by clinician documentation, Edmonton scale results three times weekly.

Analysis

Following the data collection phase, investigators will calculate average numeric pain scores, average number of increases in opioid dosage and average daily opioid amount (mg equivalents of morphine). Analysis will examine whether the addition of CBD/THC with opioid therapy had

a stabilizing effect or improvement in pain management (lower average numeric pain scores, few dosage increases, lower opioid doses and subsequently less opioid therapy needed)

Additionally calculations will include results of changes in weight, calculation of average changes in 02 saturation, and average changes in Edmonton-Scale scores for secondary data collection points.

Patient Selection to Ensure Validity

The study will enroll patients with a primary diagnosis (Table 1) of cancer and non-cancer with associated pain considered to have a terminal illness requiring end of life care, utilizing routine or as needed opioid therapy for pain.

5.0 Study Population

Adult (218 years of age), non-pregnant, alert and oriented hospice inpatients. Subjects must take opioids for pain management either routinely scheduled or on an as needed basis to qualify.

Inclusion / Exclusion Criteria

Included: alert adults (age 18+) requiring opioids for pain management (routine or as needed) with a cancer diagnosis or non-cancer diagnosis as their terminal illness as defined in Table l .

Excluded: pregnant women, children (patients < 18 years of age), minimally or unresponsive patients unable to take oral medications, and agitated combative patients.

Sample Size

66 patients is the target.

The average length of stay at The Connecticut Hospice, Inc. is twelve days. At the end of each nine day cycle (i.e. the time by which the average patient has three days to live), we can expect roughly thirty-five out of thirty-nine inpatients to take opioid medication(s) to manage pain. Since the study will happen over about 180 days, this means the population size for the length of the study should be about 700 patients.

Therefore, assuming a 95% confidence interval, a 5% error margin, and a statistical significance level of .05, we have calculated a target sample size of 66 patients.

6.0 Study Agent and Intervention Description

Options

Capsules: 40 mg/l .5 mg or 80 mg/3 mg CBD:THC per capsule (Gelatin capsules: Apothecon).

Interventions

All patients and marijuana naive (no marijuana use within the last 30 days) will receive 40/1.5 mg CBD:THC three times daily. Marijuana tolerant patients (Marijuana use currently or within the last 30 days) will receive 80 mg/3 mg CBD: THC three times daily.

Patients who experience three scheduled opioid dosage increases while receiving the 40 mg/l .5 mg regimen will have an increase to the 80 mg/3 mg dosage three times daily for the remainder of the study.

Security/Records

All study drugs will be secured abiding by federal and state regulations for storage of Scheduled substances.

Running inventory will be maintained for all study product. The pharmacy staff will record receipt and dispensing of study product, and maintain adequate supply and availability for the study population in accordance with all federal narcotic regulations.

Storage of Scheduled study product will be accessible to pharmacy personnel and clinical staff caring for the patient, in accordance with the hospital's policies and procedures and in accordance with both state and federal storage requirements.

7.0 Study Schedule:

Patients must have, at minimum, a 3-day life expectancy

SCREENING

ENROLLMENT

DOSING -5 Ongoing Assessment of Patient Progress and Safety

DATA COLLECTION

DATA ANALYSIS

Adverse/Serious Adverse Events: dysphoria, extreme anxiety/panic attack, paranoia, psychosis, ataxia, impaired motor coordination, any condition that would typically not be associated with the patients admitting diagnosis or normal course of illness.

Adverse reactions will be immediately documented on the Connecticut Hospice Adverse Drug Reaction Form and evaluated by the PI and clinical investigation team. The research team will

determine whether changes to the study protocol, including discontinuation of the study, are warranted.

10.0 Statistical Analysis Plan

The calculation of the average daily numeric pain scores, the average number of opioid dosage increases, and average daily opioid amounts (mg of morphine equivalents) will be evaluated. In addition, the secondary measures of, oxygen saturation, heart rate and body weight, findings from the Edmonton numeric assessment scale: nausea/vomiting, appetite, depression, anxiety and overall well-being will be examined.

There will be a database for tracking all primary and secondary data.

Sample size determination

See sample-size calculation and justification under "Study Population" (section 6.0).

Missing, unused, and spurious data

Missing, unused, and spurious data will be documented ongoing and noted in the final study results.

11.0 Informed Consent Process

See attached Informed Consent waiver.

All patients will be given, in addition to the written consent form, a simple verbal explanation of the study's goals and methods to ensure full consent. (Translated as applicable)

Privacy and confidentiality

Human subject's names will be kept on a password protected database, and will be linked only with a study identification number for this research. There are no patient identifiers. All data will be entered into a computer that is password protected. Data will be stored in a locked office of the investigators and usually maintained for a minimum of three years after the completion of the study.

12.0 Risk/Benefit to Participants

Risks to Participants

See potential adverse effects, above.

Benefits to Participants

Patients may experience increased effectiveness in pain management and overall well-being.

This study has the potential to yield insight on the medical benefits of marijuana for terminally ill patients who require opioids for pain management and reduce overall opioid utilization.

13.0 Study Timeline:

Target timeline: Anticipated October 2016-0ctober 2017

All stages—i.e. screening and enrollment, treatment, and data collection and analysis—will be ongoing given the terminally-ill nature of the hospice population.

Stage 1 : Screening and enrollment

Stage 2: Treatment

Stage 3: Data collection and analysis

Data Safety Monitoring:

Monitoring will be an ongoing review of the study throughout its duration.

Any action resulting in a temporary or permanent suspension or delay of the study will be reported to the IRB and to the Office of Clinical Research. The PI will report any reasons for delay in study progression outside the planned study design, including but not limited to noncompliance with the protocol or any delay in the initiation of the study due to administrative reasons.

Once patients are enrolled, data will be collected ongoing and protocol compliance will be recorded. Nurses will be present during drug administration.

Conflict of Interest: N/A

Publication and Presentation Plans:

Not defined at present.

14.0 References:

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