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The effect of an alternative medication (Dronabinol) on quality of life in patients with irritable bowel syndrome

1. Study Purpose and Rationale.

Irritable bowel syndrome is a very common functional gastrointestinal disorder characterized by chronic abdominal pain and altered bowel habits. It affects all ages and is the most common functional gastrointestinal disorder (FGID) in adults affecting up to 20% of individuals, and can be responsible for up to 40% of referrals to gastrointestinal clinics. Symptoms involve abdominal discomfort or pain along with changes in bowel habits, and it is often is associated with stress and depression.[2] The course of IBS is not as serious as inflammatory bowel disease, as it will never progress to cause bowel damage or cancer, but it has a large impact on quality of life, and causes higher levels of missed work and healthcare utilization.[1,2]

The diagnosis of irritable bowel syndrome may be made according to defined symptom criteria including the Rome criteria and absence of "red flags" (such as bloody stool, weight loss, fever, and pain awakening patient from sleep). The Rome III criteria defines IBS as recurrent abdominal pain or discomfort for at least 3 days/month in the last 6 months associated with two or more of the following: improvement with defecation, onset associated with a change in frequency of stool, onset associated with a change in form (appearance) of stool.[12] Once other GI syndromes have been ruled out, and because there are no physiological markers for IBS, it can be recognized only by its clinical features. Symptoms that also support the diagnosis of IBS include <3 bowel movements/week or >3/day, hard or watery stools, mucus in stool, urgency, feelings of incomplete evacuation, abdominal bloating.

There are various schools of thoughts to the pathophysiology of the disorder, but recently studies have suggested it may involve disordered bowel motility, altered brain-gut pathway, visceral pain hypersensitivity, stress, low grade inflammation causing immune activation, gut microflora alterations as well as genetic predispositions to disease pathology[5]. Because there is no single known etiology for IBS, therapy is aimed at symptom reduction and improving patient quality of life. Due to the wide range of symptomatology including bloating, pain, diarrhea, constipation, flatulence, unsatisfactory evacuation, treatment is usually geared towards the patient's most bothersome symptom.[5] Usually patient's disease is grouped as diarrhea or constipation predominant which often guides treatment. Previous attempts at treatment have included antidiarrheals, antispasmodics, anticholinergics, anxiolytics and antidepressants including tricyclics. Constipation predominant IBS (IBS-C) has had some success with treatment with lubiprostone and tegaserod. Diarrhea predominant IBS (IBS-D) has had some success with probiotic Bifidobacter infantis, the antibiotic rifaximin and alosetron.[5] These traditional medical therapies for IBS offer marginal efficacy with therapeutic gains over placebo of 7-15%.[5] Up to 25% of patients suffering from IBS have failed these conventional treatments and have sought their own relief through complementary and alternative medical therapy, and over 40% of patients report they would be willing to try alternative therapy if it may offer some relief. Such therapies include supplements such as fiber, probiotics, aloe vera, peppermint oil, and herbal remedies including cannabis as well as cognitive behavioral therapy, hypnosis, yoga,

acupuncture.[2,5] There are concerns with manufacturing standards, and lack of studies on efficacy and safety of these CAM modalities.

Many patients suffering from IBS will try anything to relieve their suffering and to improve their quality of life, and a growing number of patients have turned to complementary and alternative medicine once conventional techniques have failed them.[2,5] There have been various patient self-reports and observational studies on the effect of marijuana on symptoms of IBS. As far back as 3 BC, Chinese herbal traditions used cannabis in treatments for rheumatism. The effects of cannabis have been studied for chemotherapy related nausea, for reducing intraorbital pressure in glaucoma, alleviating tics in Tourette's syndrome and have even been linked in animal studies to preventing plaque formation in Alzheimer's disease. Currently there are no randomized controlled studies on the effects of Δ^9-tetrahydrocannabinol (THC) on IBS symptoms. Obviously, the psychoactive problems of the central receptors affected by cannabinoid molecules have overshadowed the therapeutic benefits, but there is still a vast amount of research to be completed. There has been a lot of momentum growing in the potential of the endocannabinoid system in modulating gastrointestinal inflammation, motility and limiting visceral sensitivity and pain.[15]

It has been known for decades now that the human body creates its own natural endocannabinoids (arachidonic acid ligands such as anandamide and 2-arachidonoyl glycerol) which bind to cannabinoid CB1 and CB2 receptors. These receptors are found in the brain, GI tract, bones, joints, blood vessels, and immune cells. The CB1 receptors are located in the enteric nervous system and sensory terminals of vagal and spinal neurons. These receptors are related to reduction of gastric and intestinal secretions, slowed motility and gastric emptying as well as gastro-protection.[10,15] Δ^9-THC is one of the most active components of cannabis, and now has been isolated and synthetically produced. Previously, the effect of Δ^9-THC has been believed to be anti-inflammatory, as well as having a role in immunology through cytokine cascades.[10,14,15] Dronabinol is a synthetic version of Δ^9-THC and is a nonselective cannabinoid receptor agonist. A RCT on the effect of dronabinol on colonic motor and sensory function showed that dronabinol relaxed the colon and reduced postprandial colonic motility and tone, as well as a centrally acting change in sensation to distention of the colon further suggests the potential for cannabinoid agonists in treating functional GI disorders.[7] Further study on the role of CB1 and CB2 receptors in the GI tract may offer some hope into new therapeutic targets for disorders including IBD, IBS and motility related disorders. [10,14,15]

Irritable bowel syndrome is a chronic condition whose treatment at this time is based on improving symptoms and quality of life rather than cure. This study's hypothesis is that a synthetic nonspecific cannabinoid receptor agonist, dronabinol, will improve quality of life compared to placebo in patients with moderate to severe irritable bowel syndrome.

2. Study Design and Statistical Procedures.

Study Design

The study will be a prospective, double-blind, placebo-controlled trial to study the effect of a cannabinoid medication on quality of life in patients with irritable bowel disease. Patients will be screened from the outpatient gastrointestinal clinic records from Columbia/New York Presbyterian and the Allen Pavilion. We will be searching for patients with the clinical diagnosis of irritable bowel disease. Written consent will be obtained from all participants prior to study enrollment. Study enrollment will likely take place over 2-3 months.

Once patients meet inclusion criteria, they will be given the commonly used irritable bowel quality of life survey the IBS-QOL.[8] This questionnaire studies patient's assessment of their emotional health, mental health, sleep, energy, physical functioning, diet, social role, and physical role. Those patients with an average IBS-QOL score over 50 indicating moderate to severe disease, with the mean being 63.2 will be included in the study. The blinded research assistants will randomly assign patients into two groups to either receive Δ^9-THC (dronabinol) or identical placebo. Patients will be treated over a period of 12 weeks. Starting at 2.5 mg per day, the dose will be increased by increments of 2.5 mg per day every 4 days to a target dose of 10.0 mg Δ^9-THC. The same dosing schedule was used to reduce medication at the end of the treatment period. If a subject is unable to tolerate the maximum dose, an adjustment will be made by decreasing study medication, until a tolerated dose is achieved. Patients will be instructed to take medication once a day in the morning together with breakfast. Patients will be given the IBS-QOL questionnaire at the start of the study, 6 weeks after starting the treatment phase, and at the conclusion at 12 weeks. During those visits they will also rate any new symptoms they may be experiencing including but not limited to headache, dizziness, confusion, somnolence, anxiety or depression, or physiological changes such as tachycardia or hypotension. Compliance with treatment was measured by pill counts at 6 weeks and 12 weeks during the study.

Patients will be free to withdraw from the study at any time, for any reason. Based on previous studies of patients with dronabinol, we do not expect significant adverse effects in the treatment group, but we will monitor patients closely in the intervention group for significant side effects that would prompt withdrawal from the study.[14] Subjects will be analyzed in an intention to treat analysis.

Statistical analysis

The primary outcome will be an improvement in the quality of life score on the IBS-QOL questionnaire. Prior studies have shown that the mean score on the IBS-QOL is 63.2 with a standard deviation of ±18.5. It was also suggested in prior analysis of this scale that a 33% improvement in QOL scores (an increase of 20.6 points) can be considered a clinically significant change.[9] We will study 100 patients, with 50 patients each assigned to placebo and treatment arms. Using a t-test with 80% power and an alpha-error rate of 0.05, we will have significant power to obtain an effect size of at least 10.6 point difference. Based on an estimated mean QOL score of 63.2 in the patients with IBS group with an SD of 18.5, it was estimated that approximately 100 patients would be needed to provide 80% power to detect a 16%(10.6 points) change in score between the two treatment groups (dronabinol and placebo).

n = 1 + 16(SD/effect)^2 50= 1+ 16 (18.5/effect size) ^2 , thus effect size is 10.6.

3. Study Procedures

Patients with a diagnosis of irritable bowel syndrome in outpatient GI clinics at Columbia/NY Presbyterian and Allen Pavilion will be screened for eligibility. As discussed in the study design section, the participants with be randomized to either the placebo arm or therapy arm. Those in the therapy arm will be started on 2.5mg dronabinol daily, increased by 2.5mg every four days until reaching the target dose of 10mg/day as long as it is tolerated well. The placebo arm will receive an equivalent dosage of sugar pills. They will have a similar downward titration at the end of the 12 week study period. The participants will complete the IBS-QOL questionnaire at the time of enrollment, 6 weeks into the treatment period and at the completion of the study/12

weeks. During the 12 weeks, their side effect profile will be monitored for the need to withdraw patients from the study.

4. Study Drugs or Devices

The study drug will be Δ9-THC/dronabinol/Marinol10mg PO/daily. It is an investigational drug for this purpose. Dronabinol is a nonselective cannabinoid receptor agonist which is metabolized by the liver, mainly excreted in bile/feces.
Previous dosing of the drug for chemo-related nausea used dosing of 5mg q2-4 hrs maxing out at 15 mg/m2 per dose. For AIDS associated anorexia/weight loss, it is started at 2.5mg PO BID, with a maximal dose of 20mg/day. We will titrate up to a conservative dose of 10mg/day.
There are no black box warnings.
Adverse reactions: dependency and abuse, withdrawal if high doses abruptly discontinued, seizures, depression, hallucinations. More common and less severe side effects may include dizziness, somnolence, paranoia, anxiety, confusion, euphoria, nausea/vomiting, tachycardia, hypotension, vasodilation.
Prior studies on effects of dronabinol on Tourettes syndrome showed no effect on cognition, neuropsychiatric performances or memory during a 6 week study period. Long term studies on adult humans who are regular marijuana users have not been able to show unequivocal long term toxicity. Some individual studies have reported problems with memory, but the results have been contradicted by other studies.[14]
The placebo will be a sugar pill that is similar in size and shape to dronabinol.

5. Study Questionnaires

IBS-QOL- Irritable Bowel Syndrome Quality of Life questionnaire
http://depts.washington.edu/yqol/docs/IBS-QOL_Info.pdf
This is a well know survey in which patient's rate their symptoms of IBS on their emotional health, mental health, sleep, energy, physical functioning, diet, social role, and physical role. The IBS-QOL consists of 34 items, each with a five-point response scale which is translated in a 0-100 scale with lower scores corresponding to lower QOL. The form takes an average of 10 minutes to complete. Patients with IBS symptoms averaged 63.2 ± 18.5 in a prior study, which also noted 33% improvement (20 points) as significant clinical response.[2,11]

6. Study Subjects.

Patients being follow by outpatient Gastroenterology clinics at Columbia/NY Presbyterian Hospital and the Allen Pavilion will be screened for eligibility.

Inclusion criteria:
-Male or female between ages 18-65 years
-Patients must have clinical diagnosis of IBS for over one year
-Patient must satisfy the Rome III Criteria for IBS:
Recurrent abdominal pain or discomfort (aka uncomfortable sensation) at least 3 days/month in the last 3 months associated with 2 or more of the following:

1. improves with defecation
2. onset associated with a change in frequency of stool

3. onset associated with a change in form (appearance) of stool

-Patients should currently be having symptoms
-Patients should have tried treatment before
-Patient has at least moderate to severe symptoms as determined by the initial score on the IBS-QOL questionnaire (a score ≥ the mean of 63.2)
-Female patients should have a negative pregnancy test and be using adequate contraception

Exclusion criteria
-Patients with significant GI tract disease, those who had previously undergone GI tract surgery
-Patients on drugs that alter GI motility
-Patients with prior history of drug or alcohol abuse
-Pregnancy

7. Recruitment

Patients receiving outpatient gastrointestinal care at Columbia/NY Presbyterian and the Allen hospital will be screened for eligibility by research assistants who then contacted the patients by phone and asked if they would like to participate. The faculty in the GI department will be notified of the study and asked their opinion on patients' suitability for the study. Participants were then mailed the respective questionnaires, information regarding the study, and consent forms, and asked to return them by prepaid mail.

8. Confidentiality of Study Data
All patient data will be de-identified and stored appropriately.

9. Potential Conflict of Interest
No potential conflicts of interest to disclose

10. Location of Study
This study will take place at Columbia/NY Presbyterian and the Allen Pavilion.

11. Potential Risks
The risks of this study are attributed to side effects of dronabinol which are listed under the section "study drugs".

12. Potential Benefits

An estimated 40% of patients suffering from IBS would be willing to try complimentary and alternative medication if it offered some hope in symptom relief. If dronabinol is able to improve the patient's quality of life, with minimal side effects, this would be a positive step in another avenue of therapy for this frustrating condition.

13. Alternative therapies

Patients with IBS are often stratified into diarrhea vs constipation predominant disease, and offered symptomatic treated based on their most bothersome complaints. Some conventional

treatments include fiber supplements, osmotic cathartics. Antispasmodics and anticholinergics may be used to treat painful contractions, but they show little success on diarrhea and may exacerbate constipation. Loperamide may be prescribed in diarrhea predominant disease but is only mildly successful. Tricyclic antidepressants suche as amitryptiline, desipramine, trimipramine may reduce visceral afferent signals to the CNS of perceived pain. Antidepressants Alternative therapies that have been studied without definitive success include aloe vera, probiotics, yoga, and biofeedback. In addition, patients may feely opt out of participating in this study and any further treatment. Eventually more selective cannabinoid receptor medications may limit the central nervous system side effects that may be worrisome.

14. Compensation to subjects:
None

15. Cost to subjects:
None

16. Minors as research subjects:
Not applicable

17. Radiation or radioactive substances:
Not applicable

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