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Original article

Dronabinol increases pain threshold in patients with functional chest pain: a pilot double-blind placebo-controlled trial

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SUMMARY. **Noncardiac chest pain is associated with poor quality of life and high care expenditure. The majority of noncardiac chest pain is either gastresophageal reflux disease related or due to esophageal motility disorders, and the rest are considered functional chest pain (FCP) due to central and peripheral hypersensitivity. Current treatment of FCP improves 40–50% of patients. Cannabinoid receptors 1 (CB_1) and 2 (CB_2) modulate release of neurotransmitters; CB_1 is located in the esophageal epithelium and reduces excitatory enteric transmission and potentially could reduce esophageal hypersensitivity. We performed a prospective study to evaluate its effects on pain threshold, frequency, and intensity in FCP. Subjects with FCP received dronabinol (5 mg, twice daily; $n = 7$; average age, 44 years; mean body mass index, 26.7) or placebo ($n = 6$; average age, 42 years; mean body mass index, 25.9) for 28 days (4 weeks). Chest pain, general health, and anxiety/depression questionnaires were assessed at baseline and at 4 weeks. Subjects underwent an esophageal balloon distention test prior to treatment and on last day of the study. Dronabinol increased pain thresholds significantly (3.0 vs. 1.0; $P = 0.03$) and reduced pain intensity and odynophagia compared to placebo (0.18 vs. 0.01 and 0.12 vs. 0.01, respectively, $P = 0.04$). Depression and anxiety scores did not differ between the groups at baseline or after treatment. No significant adverse effects were observed. In this novel study, dronabinol increased pain threshold and reduced frequency and intensity of pain in FCP. Further, large scale studies are needed to substantiate these findings.**

KEY WORDS: **cannabinoid receptors, dronabinol, functional chest pain.**

INTRODUCTION

Noncardiac chest pain (NCCP) is recurring angina-like substernal chest pain of noncardiac origin. The prevalence varies from 20 to 40%, with an estimated incidence of 200,000 new cases annually.[1,2] Approximately 60% of NCCP are gastresophageal reflux disease (GERD) related and the rest are nonGERD related due to esophageal motility disorders and hypersensitivity.[3] Rome III criteria for functional chest pain (FCP) include: burning retrosternal discomfort or pain, absence of GERD, and histopathology-based esophageal motility disorders for the past 3 months with symptom onset at least 6 months before diagnosis.[4]

Several hypersensitivity mechanisms include enhanced cerebral processing of visceral sensory input, abnormal mechano-physical properties, sustained longitudinal muscle contractions, altered autonomic activity, psychological abnormalities, and increased mucosal mast cells.[5]

Treatment of functional NCCP has focused on relieving visceral hypersensitivity through pain modulators, such as tricyclic antidepressants, and selective serotonin reuptake inhibitors (SSRI's).[6–9] In our clinic, the main TCA's used were Imipramine, and main SSRI's Serotonin-norepinephrine reuptake inhibitor (SNRI's) were Sertraline, and venlafaxine. In addition, theophylline inhibits adenosine-induced angina-like chest pain

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and adenosine-induced pain in other regions of the body, and increases pain thresholds in patients with FCP.[10] Our clinical experience with theophylline showed 70% immediate results that diminish with time in over 50% of patients. Currently, only 40–50% of patients respond to all treatment modalities and there is a large unmet therapeutic need.

The marijuana plant *Cannabis sativa* is one of the most commonly used illicit drugs today with over 16 million users in the United States.[11] The plant contains at least 80 different diverse chemical compounds that act on cannabinoid receptors located on cells that repress neurotransmitter release in the brain. Cannabinoid receptors are present throughout the GI tract, including in the esophagus, liver, pancreas, stomach, and the small and large intestines.[12–15] The Cannabinoid receptor 1 (CB_1) and Cannabinoid receptor 2 (CB_2) are found on macrophages, plasma cells, enteric neurons, nerve fibers, and terminals throughout the enteric nervous system.[14–19] CB_1 is also present on epithelial cells including in the esophagus and expressed mainly in the central and peripheral nervous system while CB_2 are present on immune cells.[13–15,18,20] Activation of CB_1 inhibits peristaltic reflex, slows down gastrointestinal and colonic transit and may play a role in symptom improvement in the GI tract.[21]

Visceral pain is a diffuse type of pain, which is often difficult to localize and usually accompanied by referred pain. It results from activation of nociceptors located in the thoracic, abdominal, or pelvic viscera. Cannabinoid receptor agonists inhibit gastric emptying and intestinal motility.[19] CB_1 is present in sites of neuronal circuitry involved in the transmission of visceral pain, which suggests that it plays a role in the control of GI perception.[22] Experimental data indicate a visceral antinociceptive action of cannabinoid receptor agonists.[23]

Several rat model studies have shown the relevance of CB_1 and CB_2 agonists in the modulation of pain and hypersensitivity.[15,24–26] Few clinical studies have been done in humans to evaluate the role of cannabinoids in visceral pain.

The delta-9-tetrahydrocannabinol (Δ9-THC) Dronabinol is a synthetic cannabinoid agonist of both CB_1 and CB_2, and currently marketed as an appetite stimulant and antiemetic. Use of cannabinoids has been limited due to its side effects. However, most of these side effects are seen with the higher doses of the drug (>40 mg/day).[27–32]

Thus far, the effect of dronabinol on esophageal sensation has not been described. The aim of this study was to evaluate the effects of dronabinol on pain threshold, frequency, and intensity in patients diagnosed with NCCP.

MATERIALS AND METHODS

Patients with unexplained NCCP referred to our tertiary care center were recruited to the study. Subjects were included if they fulfilled diagnostic criteria for FCP of presumed esophageal origin according to Rome III. All patients underwent cardiac evaluation that excluded a cardiac source for chest pain, and in many instances, after various empirical therapies including PPI's, TCA, and SSRI had proved to be ineffective for at least 3 months. Patients aged 18–75 years were included if they fulfilled diagnostic criteria of at least two weekly episodes of chest pain for the last 3 months, a normal cardiac evaluation (Stress test ± normal coronary angiogram), normal chest X-ray, upper GI endoscopy with normal esophageal biopsies, high resolution esophageal manometry, and a normal 24-hour pH impedance study (% fraction time of pH < 4.0 was <4.5). All patients had to have evidence of esophageal hypersensitivity with an abnormal esophageal balloon distention test (EBDT). Patients were excluded if they had: (i) history of requiring narcotics, other pain medications; (ii) substance abuse; (iii) Barrett's esophagus or peptic stricture; and (iv) significant physical or psychiatric comorbidity. All patients signed a written informed consent approved by the University of Iowa Human Subjects Institutional Review Board. All authors had access to the study data and reviewed and approved the final manuscript.

A total of 19 patients with FCP and esophageal hypersensitivity, as demonstrated by EBDT (described below), were invited to enroll. The study consisted of a baseline screening period, and a 4-week treatment period. During the baseline period, all patients were asked to maintain a daily chest pain diary for 2 weeks, in which they recorded the number of chest pain episodes, its severity (4-point Likert-like scale: 0 = absent, 1 = mild, 2 = moderate, and 3 = severe), and duration (minutes). On day 1, prior to randomization, patients completed Short Form-36 (SF-36), and Beck anxiety and depression inventories. Placebo capsules were matched accordingly to resemble dronabinol capsules. Subsequently, patients were randomized by the providing pharmacist based on 1:1 ratio to receive oral capsules of 5 mg dronabinol or placebo twice daily (Bid) for 4 weeks. Patients were contacted every 3 days by the research coordinators (ART, JAV) that verified medication compliance. In addition, patients were seen on day 14 in our clinic to return their empty bottle, get a refill and complete the Beck anxiety and depression inventories.

At day 28, patients underwent an EBDT, and completed questionnaires: (i) chest pain symptom questionnaire; (ii) Short Form-36 (SF-36); and (iii) Beck anxiety and depression inventories.[33–36]

Esophageal balloon distention test—Impedance planimetry

EBDT is a validated technique for examining sensory and biomechanical properties of the esophagus.[34,37]

The sensing system comprises of a flexible plastic probe, 6 mm in diameter, with four ring electrodes and a 4.5-cm long latex balloon that is attached to a leveling container. By raising or lowering the height of the leveling container, a dilute electrolyte solution (0.018% NaCl) is infused into the balloon to achieve its inflation or deflation. The probe also contains three water perfusion side holes for measuring intraluminal pressures. All subjects came for the study after an overnight fast. Oropharyngeal anesthesia was achieved with a local spray of tetracaine (pontocaine®, Hospira, Lake Forest, IL). The lubricated probe was passed through the mouth until the tip was located 55 cm from the teeth. The subject was asked to lie supine on a bed that is tilted, so that the head side was raised by 30°. The catheter was gradually withdrawn until the balloon lay across 10 cm above the lower esophageal sphincter and was adhered to that position. All measurements were performed at this level. After a rest period of 10 minutes, the balloon pressure was zeroed to the resting esophageal pressure. Next, by raising the leveling container in steps of 5 cm H_2O, the balloon pressure was increased up to 65 cm H_2O or maximum tolerable pressure. After a 3-minute rest period, each inflation was maintained for 3–5 minutes and subjects scored their sensory responses on a Likert scale: 0 = no sensation, 1 = first sensation of fullness or distension, 2 = mild discomfort (tolerable), 3 = pain, 4 = severe pain.[38,39] Baseline normal values were based on the classical previous studies.[34,39] All EBDT's were performed by a physician (SH) who was blinded to patient treatment.

Beck anxiety and depression inventories

The Beck Anxiety Inventory is a validated form of measuring anxiety separately from depression by assessing 21 somatic, affective, and cognitive symptoms that are associated with anxiety but not with depression. These symptoms are organized in a checklist and are given a rating, from 0 to 4, that corresponds with the amount the symptom bothered the patient. The sum of all the ratings is then calculated to find the class of anxiety. A score of 0–21 designates very low anxiety, 22–35 moderate anxiety, and a score greater than 36 indicates a potential cause for concern.

The Beck Depression Inventory is a validated form of measuring depression through the evaluation of 21 declarative statements linked to the indices of depression. The statements are numbered, with higher values representing a closer link to disturbances in mood related to depression. The sum of the values is calculated and then categorized as follows: 1–10 is consistent with normal ups and downs, 11–16 signifies mild mood disturbance, 17–20 borderline clinical depression, 21–30 moderate depression, 31–40 severe depression, and a score of over 40 indicates extreme depression.[35,36]

Chest pain symptom questionnaire

This validated questionnaire evaluates frequency of chest pain episodes, duration (1–3), intensity (1–3), and painful swallowing (1–3). It measures the overall changes in intensity and duration of the chest pain, abdominal pain, heartburn, and nausea through the study period.

Short Form-36 (SF-36)

A general health-related quality of life questionnaire that examines eight domains: Physical Functioning, Role Functioning Physical, Role Functioning Emotional, Mental Health, Vitality, Bodily Pain, General Health, and Social Functioning.

Statistics

Based on a previous study of theophylline for NCCP, we assumed a potential dropout rate of 20% and needed to enroll a total of 18 subjects for our study.[10] A sample size of $n = 7$ subjects per arm was used for this study. With this sample size, the comparison of Poisson rates for frequency of chest pain episodes was able to detect at the 0.05 significance level least a 35% reduction with dronabinol relative to control with 0.85 power. The data for age and biomechanical properties are expressed as mean ± SD. Esophageal sensory perception data are expressed as median. The differences in sensory data before and after dronabinol or placebo, and within groups, were analyzed and compared using the paired Student's *t*-test, Mann-Whitney *U*-test, and Wilcoxon signed-rank test when appropriate. The data for the mean number of days with chest pain and the number of chest pain episodes were compared between the two phases, dronabinol and placebo, using a negative binomial regression analysis. The Somer's D(R|C) Daily Trent Tests was used to analyze the daily chest pain score questionairres.[40]

RESULTS

Nineteen patients were enrolled in the study, and thirteen completed (11 female, 2 males mean age 43 years, range 29–63) (Table 1). Baseline BAI, BDI, daily chest pain scores, and SF 36 scores are described with no significant difference between placebo and dronabinol groups noted (Table 1). Ten patients received dronabinol 5 mg BID and nine received placebo BID (Fig. 1).

Pain intensity and odynophagia frequency were significantly decreased after 28 days of dronabinol treatment ($P = 0.04$) with a tendency for decreased frequency of chest pain episodes ($P = 0.06$) (Table 2).

On EBDT, patients treated with dronabinol showed a significantly lower pain perception at inflation levels of 15 and 20 CM/H_2O compared to baseline (1 vs. 3, 1.8 vs. 3, $P = 0.03$, 0.05, respectively) (Fig. 2) and compared to placebo (1 vs. 2.5, $P = 0.04$). In addition,

Table 1 Demographics and baseline questionnaires

	Dronabinol ($N = 7$)	Placebo ($N = 6$)
BMI (median)	26.74	25.92
Weight (median)	73.60	75.95
Age (median)	46.00	35.50
Heart rate (median)	67.00	74.50
Beck anxiety inventory	9.57	10.50
Beck depression inventory	9.14	8.50
SF 36 Physical function	84.29	55.83
SF 36 Role-physical	67.86	29.17
SF 36 Role-emotional	61.90	94.44
SF 36 Social function	76.79	62.50
SF 36 Bodily pain	50.29	45.33
SF 36 Mental health	69.14	90.00
SF 36 Vitality	49.29	48.33
SF 36 General health	62.86	54.67
Daily chest pain total score	10.83	9.80

*All *P*-values are nonsignificant.

patients treated with dronabinol had a significantly lower pain sensation compared to placebo at 20 and 30 CM/H_2O (1.8 vs. 2.8, 2.3 vs. 3.3, $P = 0.04$, respectively). Patients on placebo had no significant pain sensation changes between pretreatment and post-treatment (Fig. 3). There was a trend toward a higher balloon inflation average for initial sensation among patients in the dronabinol group from baseline to post-treatment (5–9.28, $P = 0.09$) but this was not seen in the placebo group (5–2.5, $P = 0.27$). No significant difference was seen when assessing maximum pain tolerance when comparing pretreatment to post-treatment in either group.

No significant differences were noted in the BAI, or the BDI when comparing pretreatment and post-treatment in either group as well as between the two groups. In addition, no significant difference on any of the eight domains was seen on the general quality of life questionnaire (SF 36) (Table 2). Pain intensity and odynophagia frequency were significantly decreased after 28 days of treatment ($P = 0.04$) with a tendency for decreased frequency of chest pain episodes ($P = 0.06$) (Table 3). Three patients in each group dropped out of the study due to noncompliance, and other issues. No major adverse events were reported, and minor adverse events were noted in both groups. None withdrew due to side effects of the drug. Two patients in the dronabinol group noted transient headache, fatigue, and one noted transient loose stools. In addition, two patients in the placebo group reported transient nausea and loose stools. All symptoms resolved while on treatment and did not necessitate stopping medication.

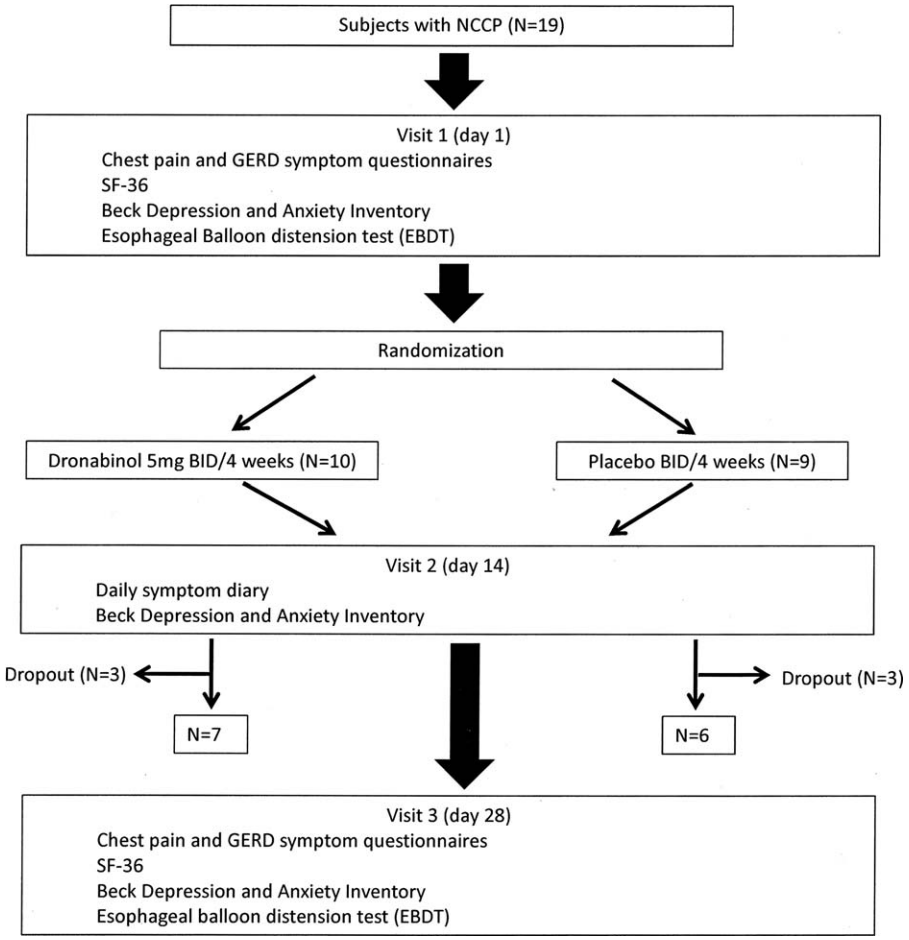

Fig. 1 Study flow chart.

Table 2 Beck and SF 36 questionnaires pre and day 28 of treatment

	Dronabinol			Placebo		
	Pretreatment	Post-treatment	*P*-value	Pretreatment	Post-treatment	*P*-value
Beck anxiety	9.57	7.43	0.42	10.50	5.83	0.21
Beck depression	9.14	7.43	0.44	8.50	3.00	0.06
SF 36 Physical function	84.29	87.50	0.50	55.83	61.67	0.25
SF 36 Role-physical	67.86	62.50	1.00	29.17	58.33	0.25
SF 36 Role-emotional	61.90	55.56	1.00	94.44	72.22	0.50
SF 36 Social function	76.79	70.83	1.00	62.50	85.42	0.38
SF 36 Bodily pain	50.29	62.50	0.25	45.33	44.50	1.00
SF 36 Mental health	69.14	69.33	0.88	90.00	85.33	0.63
SF 36 Vitality	49.29	52.50	0.75	48.33	48.33	1.00
SF 36 General health	62.86	54.33	0.63	54.67	54.67	1.00

DISCUSSION

Our study demonstrated that dronabinol decreased pain perception in patients with NCCP at different sequential balloon inflations. In addition, patients treated with dronabinol had an improvement in pain intensity and odynophagia frequency, as well as a trend toward improvement in chest pain episodes. However, there was no significant change in symptoms such as nausea and vomiting, regurgitation, or quality of life during the study period.

As CB_1 receptors are also present on epithelial cells including esophagus, these findings are in direct corroboration with experimental data indicating a visceral antinociceptive action of cannabinoid receptor agonists.[23] In addition, CB_1 receptors have been located in brain areas involved in the triggering of TLESRs as well as in the nodose ganglion from which vagal afferents emanate.[41]

Beaumont *et al*. reported that 10 and 20 mg of Δ9-THC given to healthy volunteers on three occasions a week apart, significantly reduced the number of transient lower esophageal sphincter relaxations with a nonsignificant reduction of acid reflux episodes in the first postprandial hour and normalization after 3 hours.[42] In addition, Basal LES pressure decreased after 45 minutes and normalized after 100 minutes.[42] The authors hypothesized that the fading effect could be due to insufficient serum levels of Δ9-THC in the second and third postprandial hours. Significant side effects were observed with 20 mg dosage.[42] While our study did not focus on the effect of dronabinol on esophageal motility, we think it is important to acknowledge the current trend in the literature.

Thus far, there are no other studies evaluating the effect of Δ9-THC on esophageal motility and impedance planimetry. The aforementioned study was a conceptual single dose given on three occasions a week apart.[42] In our 28 continuous day study, both groups did not report any significant change in symptoms such as nausea and vomiting or regurgitation during or after the study. It is our assumption that dronabinol did not affect esophageal motility. However, further studies are clearly required.

There is limited and conflicting data regarding the effects of the cannabinoid on GI motility in healthy human subjects. McCallum *et al*. showed that Δ9-THC (10 mg) administered 1 hour before a meal, delayed gastric emptying of a radiolabeled solid meal in nine male and four female healthy subjects, who were experienced cannabis users.[43]

In contrast, Bateman found that gastric emptying of liquid, measured by real time ultrasound, was unaffected by Δ9-THC (0.5 and 1 mg i.v.) in seven fasted cannabis-naive male volunteers.[44]

Esfandyari *et al*. reported an overall retardation of gastric emptying with dronabinol that was more

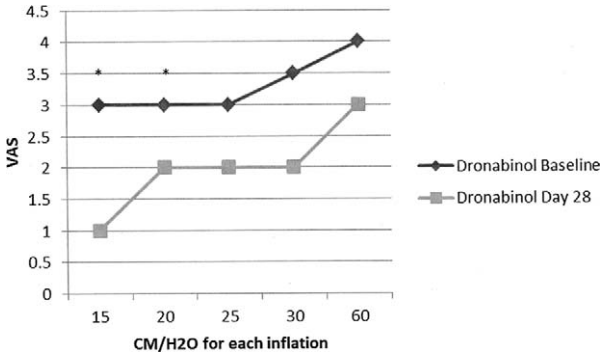

Fig. 2 Pain perception pre and day 28 of dronabinol treatment (*$P < 0.05$).

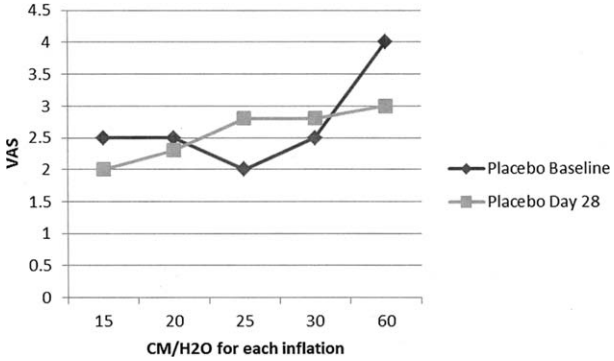

Fig. 3 Pain perception pre and day 28 of placebo treatment.

Table 3 Daily chest pain variables of patients treated with dronabinol pre and day 28

Chest pain variables ($N = 7$)	Somer's D(R|C) test value	Somer's D(R|C) SE	Upper 95% Boundary for Somer's D(R|C)	Lower 95% Boundary for Somer's D(R|C)	*P*-value for Somer's D(R|C)
Odynophagia total	−0.0613	0.0310	−0.1221	−0.0004	0.0484*
Chest pain intensity	−0.0924	0.0467	−0.1840	−0.0007	0.0481*
Chest pain duration	−0.0553	0.0482	−0.1498	0.0391	0.2507
Chest pain total	−0.0853	0.0468	−0.1771	0.0065	0.0686

* indicates the significant *P*-values.

pronounced in females than in males with an increase in fasting gastric volumes among the later. No significant treatment differences were detected for gastric volumes, small bowel, and colonic transit.[45]

Klooker *et al*. examined the effects of dronabinol at doses of 5 and 10 mg compared to placebo on rectal sensitivity in 10 IBS patients and 12 healthy volunteers, and did not find altered rectal perception to distension compared to placebo. In addition, dronabinol increased awareness of the surrounding, lightheadedness and sleepiness with the highest dose of 10 mg, whereas no side effects where reported on placebo. The authors concluded that although Δ9-THC was not beneficial for the treatment of visceral rectal perception, the results might be hampered due to the higher anxiety levels (heart rate) in the dronabinol group compared to placebo group.[46]

In another study, a single dose of dronabinol (2.5 and 5 mg) decreased fasting colonic motility and increased colonic compliance compared to placebo selectively in patients with IBS-D or IBS-A. The single dose (2.5 and 5 mg) did not affect colorectal distention pain scores, nor cause significant central effects.[42]

Esfandyari *et al*. demonstrated that a single dose of dronabinol 7.5 mg relaxes the colon and reduces postprandial colonic motility and tone. The authors concluded that increase in sensation ratings to distension in the presence of relaxation of the colon suggests central modulation of perception.[47] However, it had no effect on intestinal or colonic transit, and the authors hypothesized that this is possibly due to rapid metabolism.

Cannabinoids are distributed throughout the body and are highly lipid-soluble and accumulate in fatty tissue. The release of cannabinoids from fatty tissue is responsible for the prolonged terminal elimination half-life of up to 36 hours.[48] Hence, the effect of the dronabinol may have been different in the previous studies if given for a longer period of time, as was done in our study. Undoubtedly, this area needs to be further explored in large scale studies.

Dronabinol decreased odynophagia frequency in our cohort. Habitual rapid food intake that may lead to ineffective esophageal motility disorder has been implicated as a cause of odynophagia.[49] Interestingly, our cohort did not demonstrate ineffective peristalsis, nor report any habitual change during the study.

Based on symptom diary analysis, dronabinol significantly shortened the duration of pain as well as induce a trend toward a decrease in the pain frequency. However, no significant effect on quality of life was observed. We believe that the duration of the study (28 days) was insufficient to evaluate a substantial effect on quality of life, and based on safety data of previous studies that reported significant side effects with dosage of ≥20 mg, we decided to limit our daily dosage to 10 mg/day.[42]

Previous epidemiological studies have found that the life time probability of developing cannabis dependence was 8% for those on a daily use.[50] Although our study protocol was 5 mg twice a day, it is our belief that due to the biphasic half-life elimination it would be feasible to initiate a twice to three times a week protocol that will decrease the addiction potential of the drug and we are currently evaluating a triweekly (three times a week) protocol.

We believe that the safety demonstrated with 10 mg Δ9-THC daily should encourage further exploring this treatment.

Our study is not without limitations. Due to our strict inclusion criteria, our cohort was small, in addition to the fact that the PI relocated to another institute. However, due to the statistical significance seen in this small cohort, we believe that the study would serve as a basic reference for future large scale studies (as we are doing now). It is our belief that due to under power type II statistical error, only a tendency for decreased frequency of chest pain episodes ($P = 0.06$) (Table 3) was seen, and the frequency would be significantly lower in a larger study cohort. In addition, due to the novelty of this treatment for nonGERD related NCCP, we did not compare dronabinol to any of the current treatments, and believe that such future studies are warranted.

In summary, our pilot study demonstrates that dronabinol improves initial esophageal pain sensation, esophageal pain sensation, improves odynophagia frequency, and decreases intensity of chest pain episodes in non-GERD related NCCP. In addition, there is also a trend toward decreasing frequency of chest pain episodes. Thus far, it is unclear which subtype of NCCP will benefit the most form dronabinol. It is postulated that Δ9-THC will be effective among all types of NCCP with decreased pain threshold including GERD, and in particular PPI resistant GERD

symptoms that are likely due to proximal reflux in a hypersensitive esophagus.

We think it should be evaluated as an additional therapy to the current GERD treatment armamentarium. Additional large scale studies are needed to further classify its role in the treatment of NCCP and to evaluate its side effects when compared to marijuana.

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