Original Research
Effects of Dronabinol on Dyspnea and Quality of Life in Patients with COPD

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Running Head: **Dronabinol for Dyspnea and Quality of Life in COPD**

*Keywords***:** COPD; cannabinoids; dyspnea; exercise tolerance; quality of life;

Abbreviations:
COPD: Chronic obstructive pulmonary disease.

QoL: Quality of life.

THC: Tetrahydrocannabinol.

HIV: Human immunodeficiency virus.

CB1: Cannabinoid type 1.

ATS: American thoracic society.

ERS: European respiratory society.

ISRCTN: International Standard Randomised Controlled Trial Number.

PaCO2: Arterial partial pressure of carbon dioxide.

ABG: Arterial blood gas.

PSFDQ: Pulmonary function status and dyspnea questionnaire.

SGRQ: St. Georges respiratory questionnaire.

ISWT: Incremental shuttle walk.

GDS: Geriatric depression scale.

SD: Standard deviation.

FEV1: Forced expiratory volume in the first second.

AE: Adverse event.

SAE: Severe adverse event.

SSRI: Selective serotonin reuptake inhibitor.

This article has an online supplement.

ABSTRACT

Background: Dyspnea is frequently a debilitating symptom in chronic obstructive pulmonary disease (COPD). Cannabinoid receptor agonists have potential to alter dyspnea in these patients.

Objective: To determine if dronabinol, a pure cannabinoid, improves dyspnea and exercise tolerance in COPD.

Methods: In this double-blind randomized, cross-over pilot study, COPD patients received up to 20mg oral dronabinol or placebo daily for six weeks with an intervening washout period. Dyspnea and fatigue were assessed using Borg scale at rest and after an incremental shuttle walk. Functional status, mood, and depression were measured using St. George's Respiratory Questionnaire (SGRQ), Pulmonary Functional Status and Dyspnea Questionnaire (PFSDQ) and Geriatric Depression Scale (GDS).

Results: Eleven subjects (with mean FEV_1 50.8 ± 24.8%) completed the study with no improvement in dyspnea at rest or post exercise taking dronabinol vs. placebo (Borg scale 0.27, 95% CI -0.59 to 1.14 vs. 0.23 points, 95% CI -0.71 to 1.07 at rest and 0.82, 95% CI -0.59 to 2.22 vs. 0.36 points, 95% CI 0.13 to 2.78 post-exercise; p=0.94 and p=0.69 respectively). Dronabinol compared with placebo showed no significant change in PSFDQ dyspnea scores (0.64, 95% CI -3.92 to 5.20 vs. 5.0, 95% CI -6.29 to 16.29; p=0.43) or shuttle walk distances (20.7 m, 95% CI -21.5 to 62.8 vs. 13.7 m, 95% CI -24.8 to 52.2; p=0.69). There were no significant differences in fatigue at rest and post-exercise, SGRQ scores or GDS scores.

Conclusion: In this pilot study, dronabinol did not significantly improve dyspnea or exercise capacity compared with placebo.

BACKGROUND

Dyspnea is the most common and frequently a debilitating symptom in patients with chronic obstructive pulmonary disease (COPD).[1] Despite decades of research, the pathophysiology of exertional dyspnea in COPD is yet to be fully understood.[2] Several cortical and subcortical central neural pathways play a role in exacerbating dyspnea in COPD patients.[3] Exertion appears to result in an imbalance between rising central neural drive and impaired thoracic volume displacement. This imbalance intensifies the sensation of dyspnea on exertion.[1] The mismatch between medullary respiratory motor discharge and peripheral mechano-sensor afferent feedback results in a distressing urge to breathe independent of muscular effort.[1]

Most current therapies aim to improve ventilatory mechanics, however despite maximal conventional therapy, a significant proportion of patients remain symptomatic. Furthermore, as the disease progresses, these patients experience a downward spiral of physical deconditioning and reduced exercise capacity, compounding the impact of COPD on quality of life.[4] This contributes to a high prevalence of depressive disorders in these patients.[5] Modulation of the neuronal component of COPD related dyspnea perception and "air hunger" has the potential to decrease the perception of dyspnea, improve quality of life (QoL) and exercise capacity. Such therapies targeting the central neural signaling of dyspnea are limited at present.[6-9]

 In the USA, tetrahydrocannabinol (Δ9-THC) is manufactured as dronabinol in sesame oil based soft gel capsules (Marinolâ (dronabinol), US Food and Drug Administration. Rev Sep 2004. Retrieved 7 Aug 2023 at https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/018651s021lbl.pdf). It is currently FDA approved for use in HIV-associated cachexia to stimulate appetite, and in treatment of chemotherapy induced nausea and vomiting. It is generally well tolerated in these populations

and has been used off-label in palliative care medicine for relief of "air-hunger".[10] There are currently no large, prospective trials exploring the role of cannabinoids in COPD related dyspnea. One pilot study suggests a possible overlap between cannabinoid (CB1) receptors and cortical centers responsible for dyspnea perception and demonstrated a reduction in the perception of "air hunger" in COPD patients following administration of dronabinol.[10]

While another study involving vaporized cannabis in COPD did not show improvement in dyspnea and exercise endurance.[11] , Our randomized, controlled pilot study tested the hypothesis that dronabinol would improve dyspnea intensity and thereby exercise tolerance in patients with COPD.

METHODS

Study sites and participants.

Our study was a prospective, randomized, double-blind, placebo-controlled, crossover pilot study conducted at VA Loma Linda Healthcare System, Loma Linda, California. Potential participants were referred by the pulmonary rehabilitation staff to the study investigators and were screened for eligibility. Eligible participants had a diagnosis of COPD as defined by the American Thoracic Society (ATS) and European Respiratory Society (ERS).[12] and remained dyspneic despite maximal medical therapy indicated for their level of disease. Subjects with COPD were identified using the 1981 Crapo et al. spirometry reference equations as the normal value data set, as this was the standard used in the Pulmonary Function laboratory at the VA Loma Linda Healthcare System at the time the study was conducted. [13] All subjects had also completed a

pulmonary rehabilitation program (including reconditioning exercise, education, and support group meetings) prior to study enrollment.

Participants were excluded if their pre-enrollment urine drug screen was positive for THC, if they had chronic hypercapnia ($paCO_2$ >45mmHg) or were anemic (hemoglobin < 7g/dL). Subjects who were pregnant or subjects with known allergy to sesame seeds, sesame oil or dronabinol, and those with uncompensated acute heart failure or a history of neuromuscular disease were also excluded from the study. Additional clinical characteristics of the study subjects are available in the supplemental file, table S4.

The study was approved by the Institutional Review Board (IRB) at the VA Loma Linda Healthcare System and all subjects gave written informed consent prior to any study procedures. The study conformed to the amended Declaration of Helsinki, apart from registration in a database. A letter of exemption from an investigational new drug application (IND) from the US Food and Drug Administration (FDA) was obtained before the study was started.

Study design and interventions

After obtaining informed consent, the enrolled subjects underwent an arterial blood gas (ABG), a urine drug screen, and a focused history and physical examination were performed. This was followed by randomization. Screening and enrollment are depicted in Figure 1.

This was a randomized double-blind, placebo-controlled pilot study. A computer-generated random number sequence was used for randomization to drug vs. placebo. All study personnel including outcome assessors as well as study participants were blinded to study medication allocation. Only the research pharmacist involved in this study had access to study medication allocation and randomization and the study was "unblinded" only after all study procedures and

outcomes had been assessed. The pharmacist was not involved in making outcome assessments on the study participants.

Participants were randomized in a 1:1 fashion to either the study drug or the placebo arm for Phase I and crossed over to the other arm during Phase II. A random number table was used to generate a list of random numbers, with the odd/even numbers determining the order of administering either the study drug or the placebo enclosed within individual envelopes. These were given to the research pharmacist who opened an envelope each time a new participant was enrolled. The research pharmacist was blinded to all other study procedures and the investigators remained blinded to the randomization until all study procedures were completed. Each study phase consisted of a 2-week run in period followed by a 4-week treatment period. Dronabinol capsules were over-encapsulated in a gelatin capsule filled with corn starch. A matching gel placebo corn starch capsule with similar color, consistency and weight was prepared by the research pharmacist at the Loma Linda VA Medical Center. The study medication (dronabinol or placebo) was dispensed by the research pharmacist, labeled as "investigational drug".

Depending on the arm of the study they were in, subjects were started on either placebo or dronabinol 5mg capsules orally. During the run-in period, study participants were asked to start taking the study drug (or matching placebo) 5 mg once daily in the morning for 3 days. If well tolerated, participants gradually increased the frequency to up to 5 mg four times daily by day 9. They continued 5 mg four times daily for the remainder of the run-in period and the four-week study period before the drug washout time. At any point during the run-in phase, if the participants reported side effects, they were given the option to reduce the dosing frequency to the previously well-tolerated dosage and to remain at the same frequency for the rest of the run-

in and study periods. On completion of the first phase, each patient underwent an eight to twelve-week washout. This was followed by crossover to a similarly structured Phase II (Figure 2).

We evaluated dyspnea and fatigue, both at rest and post exercise, using the modified Borg scale.[14] To evaluate quality of life before and after each phase, we employed the St. George's Respiratory Questionnaire (SGRQ).[15] To study changes in functional status before and after the two phases, we employed the modified Pulmonary Functional Status and Dyspnea Questionnaire (PFSDQ).[16] To further assess exercise capacity and exercise induced dyspnea and fatigue, we used the incremental shuttle walk (ISWT).[17] To determine effects on mood and symptoms of depression, we used the shortened Geriatric Depression Scale (GDS).[18] The blinding of treatment order was maintained until all subjects had completed the trial.

Study Outcomes

The primary outcomes of this study were change in Borg dyspnea scale at rest and post exercise, shuttle walk distances before and after Phase I and II of the study, and the PSFDQ scores before and after Phase I and II of the study. The secondary outcomes were changes in Borg fatigue score at rest and post exercise, the SGRQ scores and GDS scores before and after Phase I and II. Safety outcomes were the number of adverse events during the study.

Statistical Analysis

Participants who completed both phases of the study were included in per protocol analysis for primary and secondary outcomes. All participants who received at least a single dose of study drug or placebo were included in safety outcomes. Outcome measures were assessed for normality using the Shapiro-Wilk test. For normally distributed variables, the values on the

dronabinol phase were compared to those on placebo using the paired t-test. Non-normally distributed data was analyzed with the Wilcoxon signed rank test. All statistical procedures were carried out using Stata, version 15. Values are listed as means ± standard deviation (SD). A p value of less than 0.05 was considered statistically significant.

RESULTS

A total of twenty-four subjects were enrolled in the study. Of those, only 11 subjects completed both phases of the study ("completers"). Subjects were predominantly male and white. Thirteen subjects dropped out of the study before completion ("dropouts") after at least one dose of study medication. The demographics and clinical characteristics of the subjects at baseline are listed in Table 1. Comorbidities and treatment of medical conditions including COPD are summarized in in the supplemental table S2.

Notably, subjects who dropped out had numerically higher mean predicted percentage of forced expiratory volume in first second (%FEV1) but also had a higher prevalence of diabetes, osteoarthritis, and anxiety. Among the 11 subjects who completed the study, 4 had an FEV1 <50% of predicted (COPD GOLD stages 3 and 4) while 7 had an FEV1 >50% of predicted (COPD GOLD stages 1 and 2).

Two subjects were withdrawn before administration of the study medications on meeting exclusion criteria after enrollment. One had hypercapnia ($PaCO_2$ greater than 45) and the other had an uncontrolled psychiatric illness. A total of 22 patients (study dropouts and completers) were included in safety outcomes. Among 11 completers, 6 had placebo and 5 had active drug as the lead treatment. Among 11 dropouts (who received at least one treatment), 6 had placebo

and 5 had active drug as the lead treatment. Baseline characteristics of subjects who completed the study compared to subjects who dropped out were not significantly different.

Primary outcomes are displayed in Figure 3. Dronabinol did not improve dyspnea measured by Borg dyspnea score at rest or after exercise. The change in Borg dyspnea scale at rest was 0.27 (95% CI, -0.6 to 1.1) points following treatment with dronabinol compared to 0.23 (95% CI -0.7 to 1.1) points following placebo (mean difference -0.04, 95% CI -1.4 to 1.2, p=0.94). Following ISWT, the Borg dyspnea scale changed by 0.8 (-.06 to 2.2) points on dronabinol compared to 0.4 (0.1 to 2.8) on placebo (mean difference -0.4, 95% CI -3.7 to 0.6, p=0.69). Similarly, PSFDQ dyspnea score marginally improved on both dronabinol (0.6 points, 95% CI -3.9 to 5.2) and placebo (5.0 points, 95% CI -6.3 to 16.3). Overall, dyspnea measured by PFSDQ did not improve on dronabinol as compared to placebo (mean difference -4.4 points, 95% CI -14.0 to 5.2).

The mean improvement in shuttle walk distance was 20.7 m (95% CI -21.5 to 62.9) on dronabinol compared with 13.7 m following placebo (mean improvement 7.0 m, 95% CI -31.3 to 45.3, p=0.69). We examined changes in shuttle walk distance among subjects with severe to very severe COPD (GOLD stages 3 and 4) as compared to mild to moderate COPD (GOLD stages 1 and 2) while taking either placebo or dronabinol. There was no significant difference in the change in shuttle walk distance following either placebo or study drug based on COPD severity (Wilcoxon rank-sum test, p=1.0 and p=0.09 respectively). Additionally, there was no significant difference between shuttle walk distance before and after placebo or before and after study drug based on COPD severity (Wilcoxon signed-rank test, p=0.58 and p=0.55 respectively).

The effect of dronabinol on fatigue and SGRQ scores is summarized in table 2. Overall, dronabinol did not improve fatigue or respiratory symptoms. The total treatment effect of dronabinol on fatigue before and after ISWT was -0.9 (95% CI -2.6 to 0.7, p=0.22) and 1.7 (95% CI -2.0 to 5.4, p=0.30). The effect on PSFDQ fatigue score was 6.2 (95% CI -1.8 to 14.1, p=011) indicating a non-significant worsening in functional status and symptom-control. Changes in SGRQ scores following dronabinol compared with placebo suggested no improvement in quality of life (table 2). The total treatment effect of dronabinol on GDS scale was 0.4 points (95% CI -1.7 to 0.9, p=0.56) indicating no improvement in depressive symptoms.

There were 12 adverse events (AEs) and 1 serious adverse event (SAE). There was profound reluctance on the part of patients who experienced an AE to continue study drug. Eight participants had at least one AE (including 1 SAE) and seven of these eight participants dropped out of the study before completion of both arms of the protocol. Only one of the patients who experienced an adverse event was able to continue taking study drug at a lower dose. Overall adverse events were similar between the dronabinol arm and the placebo arm. Investigators attributed 4 adverse reactions to the study drug.

All four AEs deemed possibly related to or likely related to study medication occurred in subjects who were on dronabinol at the time of the AE. Seven AEs and the one SAE (mechanical fall) were deemed unlikely to be related to the study drug. Dizziness and lightheadedness were the most common AEs and were likely related to the study drug. Majority of adverse events were moderate in intensity and all AEs in subjects who dropped out resolved after study drug was discontinued. A breakdown of all adverse events is shown in tables 3 and supplemental table S3.

DISCUSSION

Contrary to our hypothesis, in this randomized, double-blind, placebo-controlled, cross-over pilot study dronabinol, when compared to placebo, did not improve dyspnea as measured by the Borg scale at rest or after the shuttle walk. Dronabinol compared to placebo did not improve functional status or activity associated dyspnea as measured by the PFSDQ questionnaire in subjects with COPD.

Some of the earliest references to the use of *Cannabis sativa* plant date back as far as 4,000 B.C. in China.[19] Over the millennia, the plant has been consumed in various forms for recreational and, less commonly, for medicinal purposes.[20] In 1974, the most active and clinically relevant component, Δ9-tetrahydrocannabinol (THC) in *C. sativa* extracts was identified.[21] Subsequent discovery and cloning of the two cannabinoid receptors, CB1and CB2, have led to expanded pharmacological research.[22-24] Of particular interest for the perception of and response to dyspnea, is the presence of CB1 receptors in the frontal cortex, hypothalamus, and the brainstem – areas involved in regulating dyspnea.[2, 25-27] Although initially showing some promise,[6-9] other psychoactive agents such as opioids, benzodiazepines and SSRIs have not been shown to alleviate dyspnea in COPD in larger, randomized trials.[28-30] We hypothesized that by acting on the central CB1 receptors, dronabinol would improve exercise capacity and dyspnea scores. However, our randomized pilot study did not support this hypothesis.

The cross-over design of this study yielded an efficient comparison of treatment to placebo while eliminating the effects of confounding co-variates. Our study evaluated patient centered outcomes in COPD such as degree of dyspnea, exercise capacity, overall quality of life and mental well-being. Eligibility criteria were stringent and further minimized the influence of other

factors such as anemia, hypercapnia, musculoskeletal disease or uncontrolled cardiac disease on dyspnea and exercise tolerance.

Our study has several limitations. This was single center study comprising of mostly white, male patients within the veteran population. Our sample size was small. The confidence limits around the improvement in shuttle walk distances in our study included the "minimum important difference" of the test in COPD patients. [31] However, given the small sample size, a clinically significant treatment effect on shuttle walk distances could not be ruled out. Additionally, we did not measure physiological parameters such as lung volumes, flow rates or minute ventilation changes during exercise in response to the intervention. These measures could have provided valuable mechanistic insights into the effect of study medication on dyspnea in COPD patients. Furthermore, assessments were made after subjects had exercised to the point of symptomatic limitation likely blunting the determination of study drug efficacy. Isotime symptom score responses recorded at specific time intervals during fixed-intensity exercise testing may be better suited for this purpose.[32]

The stringent eligibility criteria, arguably a strength of the study, also resulted in exclusion of most patients screened. This may have also resulted in a disproportionate recruitment of subjects with milder COPD (see table 1). Inclusion of more severe COPD patients may have altered our outcomes. In addition, we experienced a higher than anticipated dropout rate. Thirteen of the 24 enrolled participants dropped out of the study before completion. All patients who had AEs possibly related to or likely related to study medication were on dronabinol at the time of the AE.

Another potential limitation was the long (8-12 weeks) wash-out period. This was done to ensure complete elimination of the study drug as determined by a urine drug screen. This may have led to a higher rate of attrition from the study. Dronabinol is a synthetic THC compound and is

known to have certain psychoactive side effects such as dizziness, drowsiness, and cognitive impairment. Unfortunately, our study did not systematically assess or track these effects of the study drugs. Hence, we could not determine if there was any blinded treatment preference amongst the subjects.

Serial measurements of circulating cannabinoid concentrations would have determined if a steady state blood level had been achieved over the 4-week intervention period. Unfortunately, we did not have the laboratory capabilities to carry out such measurements. Finally, although the study subjects' weight and body mass index were collected at the time of enrollment in the study, we did not assess the effects of the drug on body mass at other points during the study. A change in body mass could have influenced the subjects' exercise performance.

CONCLUSION

In our small clinical pilot study involving subjects with COPD and dyspnea on exertion, dronabinol did not show significant improvement in dyspnea, fatigue, shuttle walk distance, quality of life, and depression when compared to placebo. Larger randomized trials are needed to definitively assess the impact of dronabinol and related THC compounds in COPD.

Author roles:

Abdul H. Zaid: Was involved in designing the study, analysis, and interpretation of data for the work; drafting the work.

Suman Thapamagar: Was involved in designing the study, analysis, and interpretation of data for the work; drafting the work.

James D. Anholm: Was involved in designing the study, analysis, and interpretation of data for the work; drafting the work.

Laura Weaver-Carnahan: Was involved in designing the study, analysis, and interpretation of data for the work; drafting the work.

Lien M. Duong: Was involved in designing the study, analysis, and interpretation of data for the work; drafting the work.

Lennard Specht: Was involved in designing the study, analysis, and interpretation of data for the work; drafting the work.

All authors have given final approval of the version to be published and have agreed to be accountable for all aspects of the work.

Declaration of interest:
All authors have no conflicts of interest to disclose.

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Table 1: Baseline characteristics*

Characteristics	Completers (N=11)	Dropouts (N=13)
Age, years, mean ± SD	72.0 ± 9.7	71.3 ± 5.1
Sex, Male n (%)	11 (100%)	12 (92.3%)
BMI, Kg/m^2, mean ± SD	29.2 ± 11.7	28.7 ± 6.1
SpO$_2$, %, mean ± SD	96.0 ± 4.0	95.3 ± 4.1
COPD related variables		
FVC, % mean ± SD	73.1± 19.9	
FEV$_1$, %, mean ± SD	50.8 ± 24.8	43.3 ± 14.2
FEV1/FVC	47.3±15.4	
PCO$_2$, mmHg, mean ± SD	38.9 ± 4.5	39.7± 4.3
HCO$_3^-$, mmol/l	23.8 ± 1.8	25.1 ± 2.1
Measurements of dyspnea, fatigue, and impact of COPD		
Borg Dyspnea score, mean ± SD		
Before Shuttle test	1.5 ± 0.9	1.2 ± 1.3
After shuttle test	6.5 ± 1.9	4.2 ± 1.9
Borg Fatigue score, mean ± SD		
Before Shuttle test	1.6 ± 1.6	0.3 ± 0.4
After shuttle test	5.1 ± 2.8	4.9 ± 0.6
PSFDQ Dyspnea score, mean ± SD	43.8 ± 20.0	35.1 ± 18.9
PSFDQ Activity score, mean ± SD	36.8 ± 20.1	36.1 ± 18.4
SGRQ Scores, mean ± SD		
Symptoms score	60.1 ± 13.1	62.7 ± 24.4
Activity score	80.9 ± 11.0	72.9 ± 19.1
Impact score	44.3 ± 13.1	45.8 ± 22.8
Total score	58.0 ± 10.3	56.8 ± 19.2
GDS score, mean ± SD	4.5 ± 1.8	3.5 ± 3.5
Incremental Shuttle Walk Test (ISWT) Walk distance, meters, mean ± SD	301.9 ± 94.6	290.5 ± 79.8

Abbreviations: BMI: body mass index; SpO$_2$: oxygen saturation by pulse oximetry; FEV$_1$: forced expiratory volume in 1 second; PCO$_2$: arterial partial pressure of CO$_2$; HCO$_3^-$: plasma bicarbonate; PSFDQ: Pulmonary Functional Status and Dyspnea Questionnaire; SGRQ: St. George Respiratory Questionnaire; GDS: geriatric depression scale.

* All baseline measurements were made before randomization (before phase I)

Table 2: Secondary outcomes

Variables	Dronabinol group	Placebo group	Total Treatment effect[a]	Significance (paired t-test)
Borg fatigue score, at rest, n=7				
Before Intervention, mean ± SD	1.7 ± 1.2	1.1 ± 1.3		
After Intervention, mean ± SD	1.2 ± 1.1	1.6 ± 1.3		
Treatment effect, mean difference (95% CI)	0.5 (-1.5 to 2.5)	-0.4 (-1.4 to 0.6)	-0.9 (-2.6 to 0.7)	p=0.22
Borg fatigue score, after exercise, n=7				
Before Intervention, mean ± SD	5.3 ± 1.9	5.1 ± 2.7		
After Intervention, mean ± SD	3.6 ± 1.9	4.9 ± 2.5		
Treatment effect, mean difference (95% CI)	1.7 (-0.7 to 4.1)	0 (-2.3 to 2.3)	1.7 (-2.0 to 5.4)	p=0.30
PSFDQ Fatigue score, n=11				
Before Intervention, mean (±SD)	34.3 ± 23.7	38.1 ± 21.4		
After Intervention, mean (±SD)	34.3 ± 22.5	31.9 ± 17.8		
Treatment effect, mean difference (95% CI)	0 (-5.1 to 5.2)	6.2 -1.3 to 13.7)	6.2 (-1.8 to 14.1)	p=0.11
SGRQ total score, n=11				
Before Intervention, mean ± SD	55.3 ± 10.5	55.9 ± 11.6		
After Intervention, mean ± SD	54.1 ± 13.8	53.3 ± 10.5		
Treatment effect, mean difference (95% CI)	1.2 (-3.5 to 5.9)	2.6 (-1.1 to 6.4)	-1.4 (-7.2 to 4.3)	p=0.59
SGRQ symptoms score, n =11				
Before Intervention, mean ± SD	61.3 ± 15.3	62.8 ± 14.6		
After Intervention, mean ± SD	58.3 ± 13.8	57.9 ± 19.1		
Treatment effect, mean difference (95% CI)	3.1 (-2.9 to 9.0)	4.9 (-1.4 to 11.2)	-1.8 (-11.9 to 8.3)	p=0.70
SGRQ Activity score, n =11				
Before Intervention, mean ± SD	76.7 ± 12.6	81.0 ± 13.9		
After Intervention, mean ± SD	73.2 ± 14.7	77.9 ± 14.8		
Treatment effect, mean difference (95% CI)	3.5 (-3.6 to 10.7)	3.1 (-4.8 to 11.1)	0.4 (-10.2 to 11.0)	p=0.93
SGRQ Impact score, n =11				
Before Intervention, mean ± SD	41.3 ± 12.1	40.53 ± 14.9		
After Intervention, mean ± SD	42.0 ± 16.0	37.8 ± 12.7		
Treatment effect, mean difference (95% CI)	-0.7 (-7.5 to 6.1)	2.8 (3.7 to 9.2)	-3.5 (-10.9 to 4.0)	p=0.33
Geriatric Depression Scale, n =11				
Before Intervention, mean ± SD	4.4 ± 2.3	4.4 ± 0.8		

After Intervention, mean ± SD	4.4 ± 1.9	3.7 ± 1.6		
Treatment effect, mean difference (95% CI)	0.4 (-0.5 to 1.3)	0.7 (-0.3 to 1.7)	0.4 (-1.7 to 0.9)	p=0.56

Abbreviations: SD, Standard deviation; 95% CI, 95% Confidence interval; SGRQ, St Georges' Respiratory Questionnaire; a Total treatment effect is the difference of mean difference between Dronabinol group and Placebo group.

Table 3: Adverse events

Events	AE while on placebo	AE while on study drug	Total (N=11)
Adverse events (AEs)			
Bradycardia	1	0	1
COPD exacerbation	2	1	3
Dizziness/ lightheadedness	1	3	4
Hypotension	0	1	1
Otitis media	1	0	1
Rhinitis, unspecified	1	0	1
Urinary retention	0	1	1
Total AEs	6	6	12
Serious adverse Events (SAEs)			
Mechanical fall and femur fracture	1	0	1
Total AE and SAEs	7	6	13
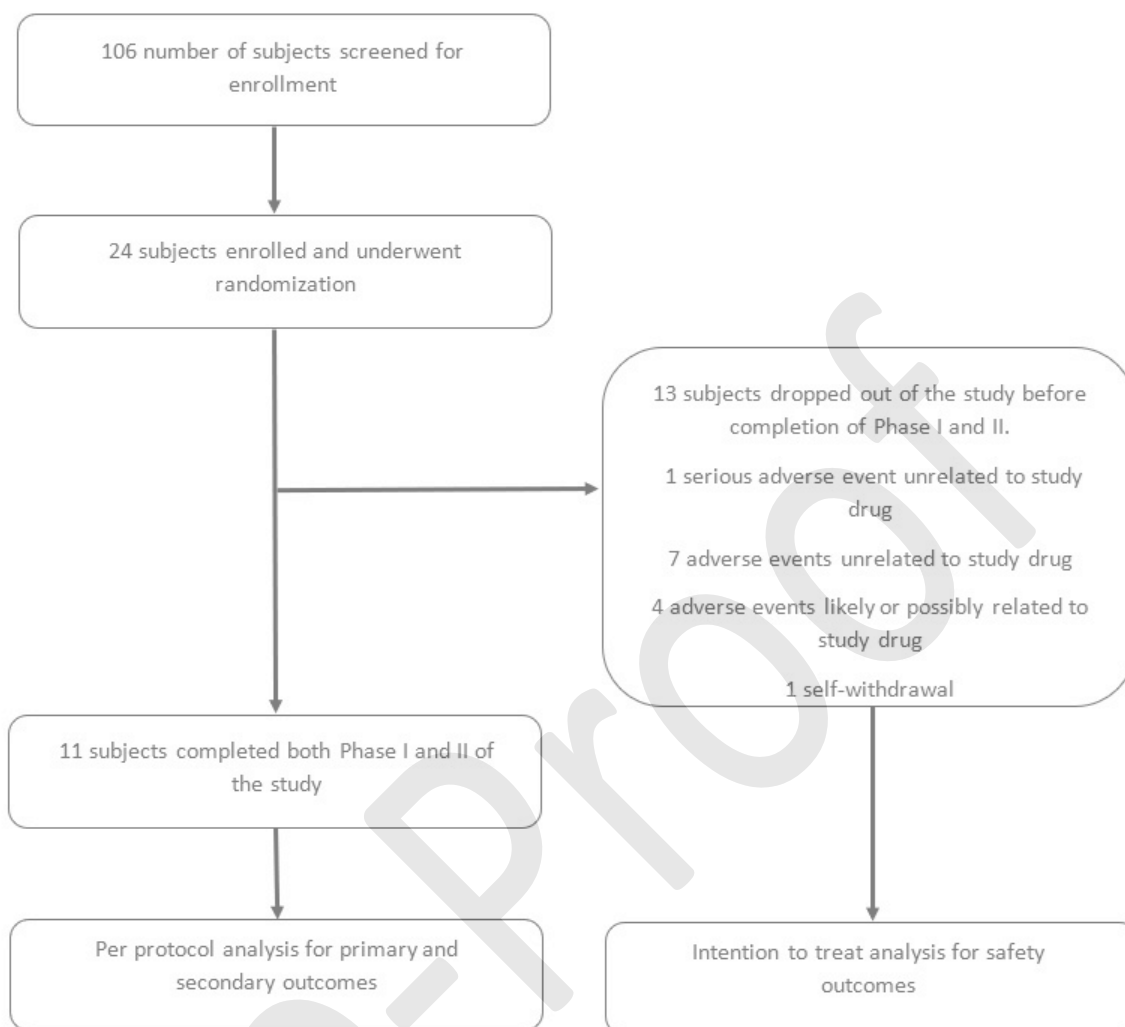
Figure 1. Screening, enrollment, and types of analyses performed for outcomes.
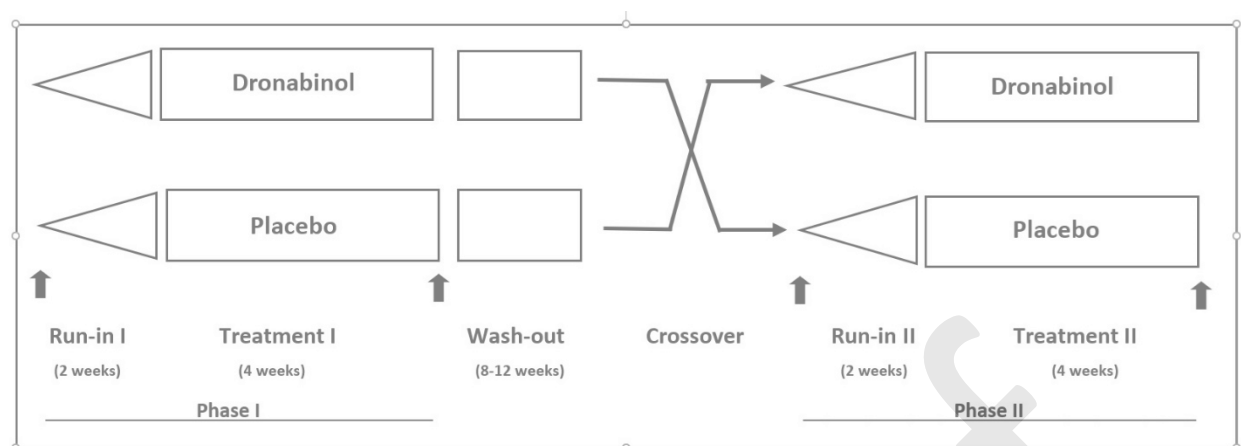
Figure 2. Graphical display of study protocol – Two phase design with cross-over.

(Note: ⬆ indicates the timing of the assessments during the study).

Figure 3: Primary outcomes: A. Change in dyspnea before shuttle walk test, B. Change in dyspnea after shuttle walk, C. Change in PSFDQ score following placebo and dronabinol, D. Change in shuttle walk distance following placebo and dronabinol.

Online Supplements

Table S1: Comorbidities and concomitant medications

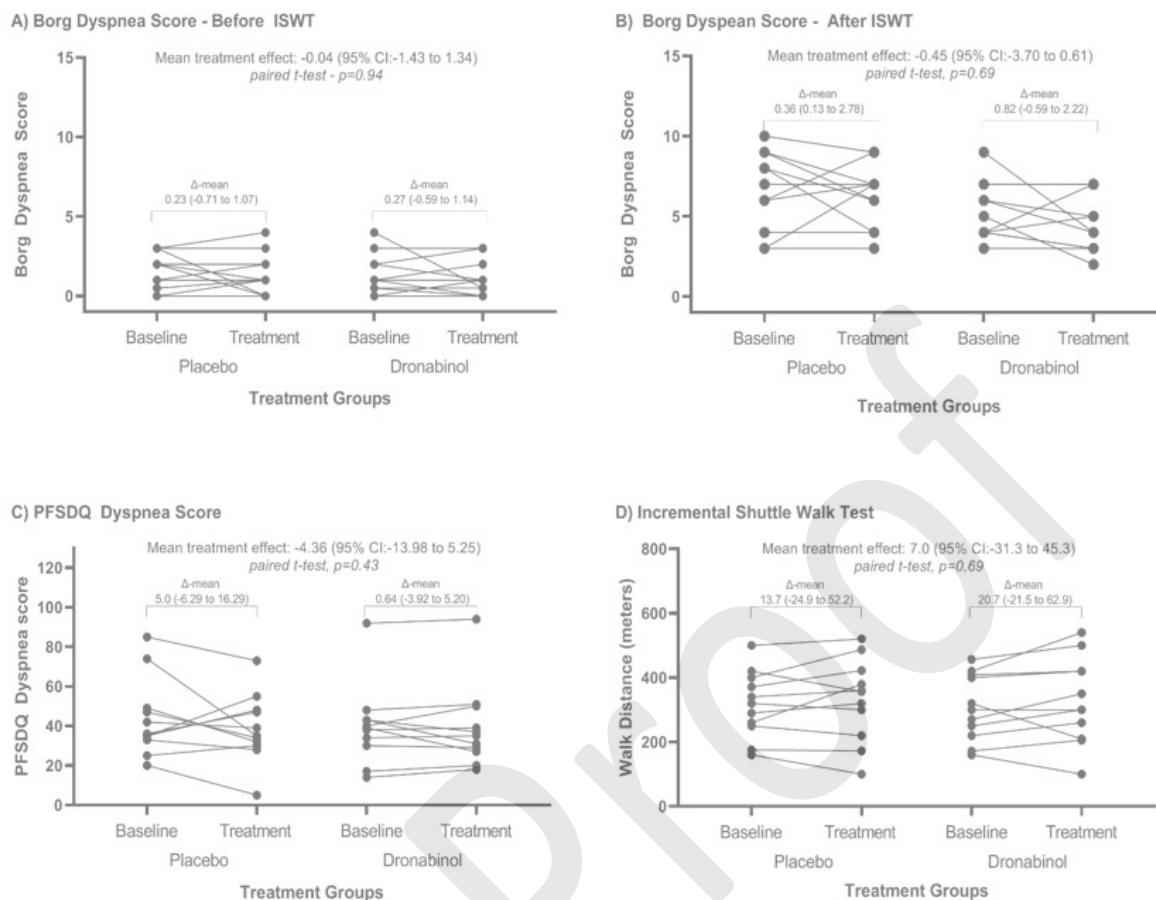| Characteristics	Completers (N=11)	Dropouts (N=13)
Comorbidities		
Hypertension	11 (100%)	9 (81.8%)
Diabetes	0 (0%)	6 (54.5%)
Gastroesophageal Reflux Disease	4 (36.3%)	5 (45.4%)
Coronary Artery Disease	4 (36.3%)	3 (27.2%)
Depression	2 (18.1%)	3 (27.2%)
Osteoarthritis	2 (18.1%)	5 (45.4%)
Hyperlipidemia	2 (18.1%)	1 (9.1%)
Chronic Kidney Disease	1 (9.1%)	1 (9.1%)
Atrial Fibrillation	1 (9.1%)	3 (27.2%)
Congestive Heart Failure	1 (9.1%)	0 (0%)
Obstructive Sleep Apnea	1 (9.1%)	3 (27.2%)
Anxiety	1 (9.1%)	3 (27.2%)
Spinal Stenosis	1 (9.1%)	0 (0%)
Obesity	1 (9.1%)	2 (18.1%)
Migraine	0 (0%)	1 (9.1%)
Concomitant medications		
Calcium channel blocker	7 (63.6%)	5 (45.4%)
Statin	6 (54.5%)	3 (27.2%)
Antiplatelets	5 (45.4%)	5 (45.4%)
Betablocker	4 (36.3%)	1 (9.1%)
Diuretics	4 (36.3%)	3 (27.2%)
ACE inhibitor	3 (27.2%)	3 (27.2%)
SSRI	2 (18.1%)	1 (9.1%)
Nitrates	1 (9.1%)	1 (9.1%)
Sildenafil	1 (9.1%)	0 (0%)
Hydrocodone	1 (9.1%)	0 (0%)
Benzodiazepine	0 (0%)	1 (9.1%)
Gabapentin	0 (0%)	1 (9.1%)
Glipizide	0 (0%)	2 (18.1%)
Metformin	0 (0%)	1 (9.1%)
Angiotensin receptor antagonist	1 (9.1%)	1 (9.1%)
COPD related medications		
Albuterol	11 (100%)	11 (100%)
Budesonide-Formoterol	8 (72.7%)	8 (72.7%)
Oladaterol-Tiotropium	1 (9.1%)	1 (9.1%)
Salmeterol	0 (0%)	1 (9.1%)
Tiotropium	10 (90.9%)	10 (90.9%)
Azithromycin	0 (0%)	2 (18.1%)
Roflumilast	0 (0%)	1 (9.1%)
Urine drug screen		
Negative for all substances	9 (81.8%)	8 (72.7%)
Opioids	2 (18.1%)	2 (18.1%)

Barbiturates	1 (9.1%)	1 (9.1%)
Benzodiazepine	0 (0%)	1 (9.1%)

Table S2: Primary outcomes

Variables	Dronabinol group	Placebo group	Total Treatment effect[a]	Significance (paired t-test)
Borg Dyspnea score, at rest, n=11				
Before treatment, mean ± SD	1.4 ± 1.3	1.6 ± 1.6		
After treatment, mean (±SD)	1.1 ± 1.1	1.4 ± 1.3		
Treatment effect, mean difference (95% CI)	0.27 (-0.59 to 1.14)	0.23 (-0.71 to 1.07)	-0.04 (-1.43 to 1.34)	p=0.94
Borg Dyspnea score, after exercise, n=11				
Before treatment, mean ± SD	5.4 ± 1.8	6.6 ± 2.5		
After treatment, mean ± SD	4.5 ± 1.8	6.27 ± 1.95		
Treatment effect, mean difference (95% CI)	0.8 (-0.6 to 2.2)	0.4 (0.1 to 2.8)	- 0.4 (-3.7 to 0.6)	p=0.69
PFSDQ dyspnea score, n=11				
Before treatment, mean ± SD	39.8 ± 20.3	43.7 ± 19.7		
After treatment, mean ± SD	39.2 ± 21.0	38.7 ± 17.3		
Treatment effect, mean difference (95% CI)	0.6 (-3.9 to 5.2)	5.0 (-6.3 to 16.3)	-4.4 (-14.0 to 5.2)	p=0.43
ISWT - Walk distance, meters, n=11				
Before treatment, mean ± SD	307.0 ± 103.2	317.0 ± 103.7		
After treatment, mean ± SD	327.7 ± 133.8	330.6 ± 128.1		
Treatment effect, mean difference (95% CI)	20.7 (-21.5 to 62.9)	13.7 (-24.9 to 52.2)	7.0 (-31.3 to 45.3)	p=0.69

Abbreviations: SD, Standard deviation; 95% CI, 95% Confidence interval; PFSDQ, Pulmonary Function Status & Dyspnea Questionnaire; ISWT, Incremental Shuttle Walk Test; [a] Total treatment effect is the difference of mean difference between Dronabinol group and Placebo group.

Table S3: Adverse events in completers and dropouts

Events	Participants who completed the study (n=11)	Participants who dropped out after 1st dose of study medication (n=11)	Total study population (N=22)
Adverse events (AEs)			
Bradycardia	0	1	1
COPD exacerbation	0	3	3
Dizziness/ lightheadedness	1	3	4
Hypotension	0	1	1
Otitis media	0	1	1
Rhinitis, unspecified	0	1	1
Urinary retention	0	1	1
Total AEs	1	11	12
Serious adverse events (SAEs)			
Mechanical fall and femur fracture	0	1	1
Total AE and SAEs	1	12	13
Adverse Events Assessments: Relationship to study medication			
Unlikely related			7
Possibly related			1
Likely related			3
Adverse Events Assessments: Severity of AEs			
Mild			1
Moderate			10
Adverse Events Assessments: Resolution of AEs			
Resolved			11

Table S4: Baseline characteristics- additional details

	Completers (n=11)	Drop-outs (n=13)	Difference in proportion (95% CI)	p-value
Medical History				
Hypertension	11 (100%)	9 (69%)	0.31 (0.008 – 0.61)	0.0465
Coronary artery disease	4 (36%)	3 (23%)	0.13 (-0.54 to 0.80)	0.711
GERD	4 (36%)	4 (31%)	0.05 (-0.60 to 0.70)	0.881
OSA	1 (9%)	4 (31%)	*	
Anxiety/Depression	3 (27%)	6 (46%)	0.224 (-0.31 to 0.75)	0.331
COPD Medications				
Short acting bronchodilators	11 (100%)	13 (100%)	NA	
ICS	0	3 (23%)	*	
LABA	0	1 (8%)	*	
ICS+LABA	8 (73%)	10 (77%)	-0.04 (-0.44 to 0.36)	0.845
LABA+LAMA	1 (9%)	0	*	
LAMA	10 (91%)	11 (85%)	0.06 (-0.22 to 0.34)	0.674
Others (Azithromycin, Roflumilast)	0	3 (23%)	*	
Other Concomitant medications				
Beta-blockers	5 (45%)	1 (8%)	0.37 (-0.32 to 1.06)	0.488
ACE-I /ARB	5 (45%)	4 (31%)	0.14 (-0.49 to 0.77)	0.668
CCB	6 (55%)	2 (15%)	0.4 (-0.24 to 1.04)	0.325
PPI	4 (36%)	3 (23%)	0.13 (-0.54 to 0.80)	0.711
Psychoactive medications	2 (18%)	6 (46%)	-0.28 (-0.95 to 0.39)	0.482
* = insufficient data for analysis, NA = not applicable ICS= Inhaled corticosteroids, LABA = Long acting bronchodilators, LAMA= Long acting antimuscarinic agent ACE-I: Angiotensin converting enzyme inhibitors, ARB: Angiotensin receptor blocker, CCB= Calcium channel blocker; PPI: Proton Pump inhibitors				

Table S5: Differences in shuttle walk distance based on subjects' COPD severity.

Paired Comparison of difference in walk distance between study drug and placebo group by COPD severity				
	Diff in walk distance (study drug – placebo), in meters		t-test* (mean diff, 95% CI, p value)	Wilcoxon singed rank test
COPD Severity	Drug	Placebo		
FEV$_1$ ≥50% n=7				
Mean (+/-SD)	34.8 (71.67)	18.9 (65.0)	15.8 (-46.5 to 78.2; p=0.56)	
Median (IQR)	43.3 (20 to 80)	20 (-30 to 87)		p=0.55
FEV$_1$ <50% n=4				
Mean (+/-SD)	-4.0 (40.1)	4.5 (48.41)	- 8.45 (-63.9 to 47.0; p=0.66)	
Median (IQR)	5.0 (-30.6 to 22.6)	13.4 (-31.6 to 40.5)		p=0.58
*Paired t-test				

Comparison of difference in walk distance in study drug and placebo group by COPD severity				
	COPD Severity		t-test (mean diff, 95% CI, p value)	Wilcoxon rank-sum test
Diff in walk distance (in meters)	FEV$_1$ ≥50% n=7	FEV$_1$ <50% n=4		
Drug				
Mean (+/-SD)	34.8 (71.67)	-4.0 (40.1)	38.7 (-50.5 to 128.0; p=0.35)	
Median (IQR)	43.3 (20 to 80)	5.0 (-30.6 to 22.6)		p=0.09
Placebo				
Mean (+/-SD)	18.9 (65.0)	4.5 (48.41)	14.4 (-70.6 to 99.5; p=0.71)	
Median (IQR)	20 (-30 to 87)	13.4 (-31.6 to 40.5)		p=1.0