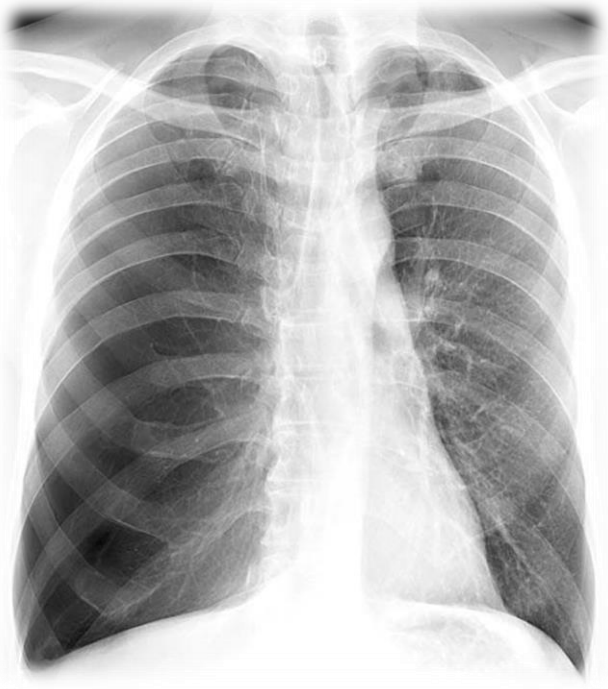
Effects of dronabinol on dyspnea and quality of life in patients with COPD



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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is a leading cause of mortality and morbidity worldwide. In the United States, it is a large contributor to healthcare cost. By nature, COPD is a progressive disease and thus, virtually all patients will require escalating therapy over time. Unfortunately, however, even despite strict adherence to optimal medical therapy, a large proportion of COPD patients are still debilitated by chronic dyspnea. The identification of the central nervous system (CNS) areas involved in the sensation of dyspnea in geographically overlapping areas as the cannabinoid receptor (CB1) warrants an evaluation of cannabinoids such as dronabinol as potential modulators of dyspnea.

Objective: We aim to elucidate the potential role of dronabinol as adjunctive therapy in treatment of chronic dyspnea. We hope to show that dronabinol reduces dyspnea and improves the quality of life of COPD patients who experience chronic dyspnea despite maximal medical therapy.

Research Design: The study will be a prospective randomized, placebo-controlled, double-blind cross-over design.

Methods: We plan to study 21 veterans at the Veterans Affairs Loma Linda Healthcare System who are: diagnosed with COPD on maximal medical therapy, have completed pulmonary rehabilitation, are not smoking tobacco or using cannabinoid products and remain dyspneic. Patients will be excluded if they are in heart failure, are pregnant, have neuromuscular disorders, anemic or allergic to sesame products.
We plan to assess severity of dyspnea and its effects on exercise tolerance and quality of life as measured validated questionnaires such as St. George's Respiratory Questionnaire, Geriatric Depression Scale, Pulmonary Functional Status & Dyspnea Questionnaire, as well as Borg scale during the Incremental Shuttle Walk Test (ISWT).

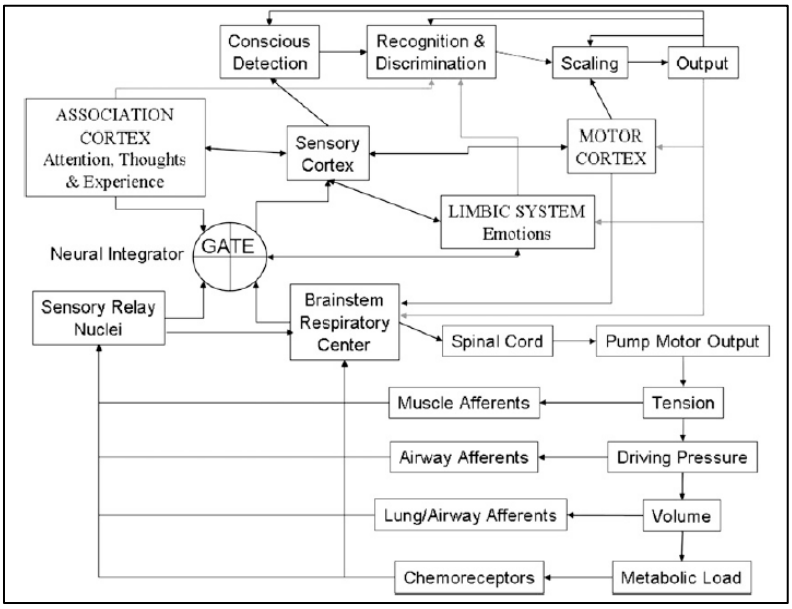
INTRODUCTION

1. **Introduction**

Chronic obstructive pulmonary disease (COPD) affects over 13 million people in the United States[3]; it is a leading cause of disability and death worldwide.[4] The sensation of dyspnea is the most commonly reported symptom impacting quality of life and daily functional status. The current therapeutic modalities include bronchodilators, corticosteroids, mast cell stabilizers, oxygen therapy and pulmonary rehabilitation. However, some patients are still debilitated by dyspnea despite maximal medical therapy.

2. Background

The pathophysiology of dyspnea in COPD is not fully understood and was the subject of a recent roundtable discussion at the American Thoracic Society.[1] According to O'Donnell and colleagues dyspnea has multiple qualitative descriptors and the primary sources stem from: (1) inputs from multiple somatic proprioceptive and bronchopulmonary afferents, and (2) centrally generated signals related to inspiratory motor command output or effort. When there is a mismatch between medullary respiratory motor discharge and peripheral mechano-sensor afferent feedback, a distressing urge to breathe is sensed independently of muscular effort.[1] A "gating system", as shown in *Figure 1*, may help organize some of the proposed interactions.



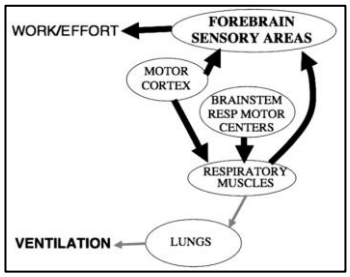


Figure 1. (Left) The respiratory sensory gating system model is a helpful way to organize the hypothesized connections, although it does not fully explain the mechanisms. (Below) Simplified neural pathways underlying work/effort sensation. *From O'Donnell 2007.*[1]

Current therapies aim to improve ventilatory mechanics but no specific therapy exists to target the central neural signaling of dyspnea. In the past, investigators have tried to address this issue but no clearly positive results have been demonstrated. Previous trials have included: inhaled Furosemide[5], oral[6-9] and inhaled[10,11] opiates, opiate analogues[12], naloxone[13], anxiolytics[14-16] and antidepressants[17,18]. Of all of these interventions, only non-inhaled opiates and anxiolytics significantly reduced dyspnea measures in some studies but the studies are heterogeneous and large-scale, controlled trials in COPD patients are lacking. Furthermore, both of these classes of medications produced sedative adverse effects; in some of the opiate studies, constipation was also cited as an additional burden that was noted by patients.

As our understanding of the pathophysiology of dyspnea improves, newer treatment modalities can emerge. Particular attention should be paid to potential modulators of the neuronal component of the perception of dyspnea and "air hunger" that have a relatively clean adverse effect profile.

3. Rationale

Oral cannabinoids may represent a new class of adjunctive therapy in the treatment of dyspnea in COPD patients. Some of the earliest references to the use of *Cannabis sativa* plant date back as far as 4,000 B.C. in China.[19] Since then, the plant has been widely consumed in various forms for recreational and, less widely, for medicinal purposes.[20] The cannabinoids are known to affect neurobehavioral processes which may include the sensation of dyspnea.

In 1974, the most active and clinically relevant component, Δ^9-tetrahydrocannabinol (Δ^9-THC) in *C. sativa* extracts was identified by Mechoulam and Gaoni.[21] Subsequent discovery and cloning of the two cannabinoid receptors, CB1 and CB2, have led to expanded pharmacological research.[22-24] While the CB2 receptors appear to be mainly peripherally located and play a role in immune modulation, the CB1 receptor is predominantly concentrated in neuronal cells of the central nervous system (CNS).[25,26] Of particular interest for the perception and interpretation of breathlessness or air hunger is the presence of CB1 receptors in the frontal cortex, hypothalamus and brain stem at the Solitary Tract Nucleus (STN) –areas which are involved in regulating dyspnea;[2,27] see *Figure 2*. With the use of advanced brain imaging, the exact location, role and importance of these receptors are being explored.

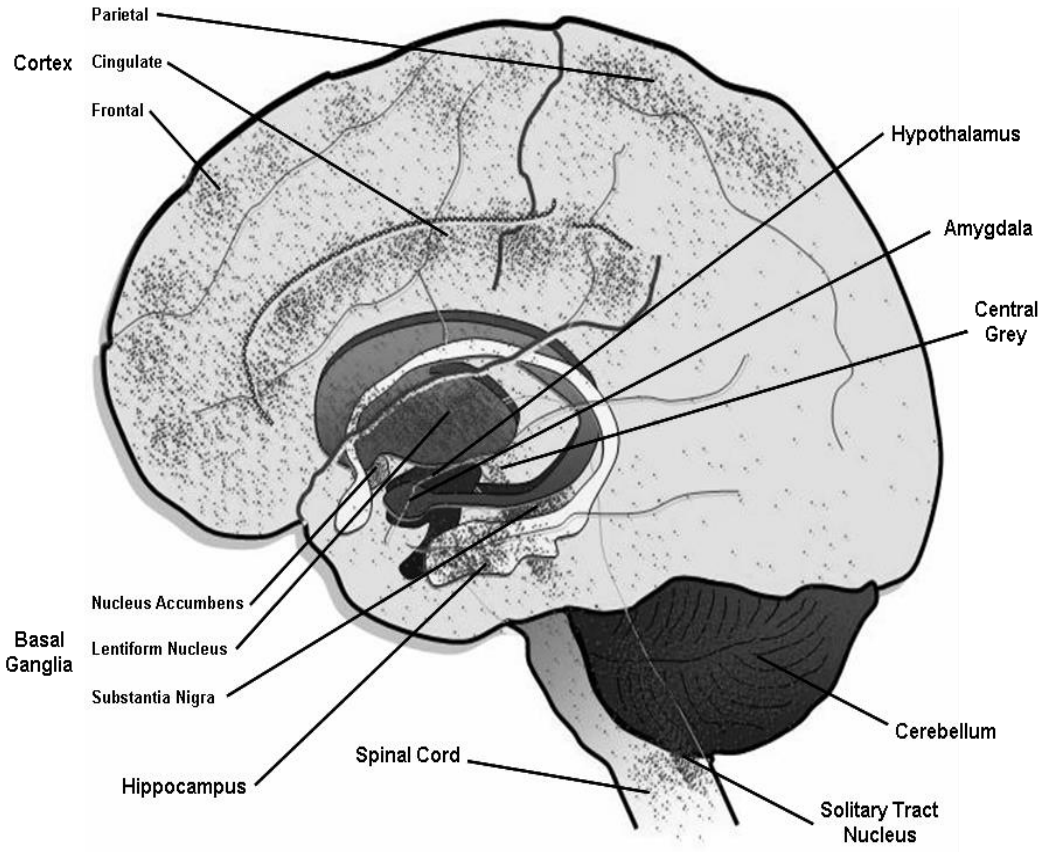


Figure 2. Distribution of CB1 receptors in the central nervous system. *From Otero JM (2005)* [2]

At the time of this proposal, we find no large prospective, randomized controlled trials. A Medline search reveals only one single article reporting on the effects of oral cannabinoids on dyspnea in COPD patients.[28] Pickering and colleagues studied five normal patients and four patients with COPD. They were unable to show significant reduction of dyspnea on a visual analog scale after two single administrations of sublingual dronabinol. However, after drug administration, COPD subjects picked "air hunger" breathlessness descriptors less frequently compared to placebo.

We believe the single dose administration design, the limited outcome evaluation methods, and the small sample size may have falsely masked a favorable result. The fact that even two hours after a single dose of dronabinol, COPD subjects felt less "air hunger" is encouraging.

In the United States, Δ^9-THC is manufactured as dronabinol (Marinol®) in sesame oil based soft gel capsules. It is currently FDA approved for use in HIV-associated cachexia to stimulate appetite and also mitigate nausea and vomiting caused by chemotherapy adverse effects. It is generally well tolerated in these populations and has been used off-label in palliative care medicine for relief of "air-hunger".

Given the current neurophysiological understanding of dyspnea and location of CB1 receptors in the overlapping regions as dyspnea sensation, we propose the following study of prolonged dronabinol treatment.

4. Hypothesis

The administration of oral dronabinol will significantly reduce the sensation of dyspnea at baseline and with exertion and also improve quality of life in COPD patients who are currently symptomatic despite optimal medical therapy.

AIMS

1. Primary Objective

Our primary aim is to evaluate COPD patients who remain symptomatic despite maximal medical therapy in order to answer the following questions: (1) Does the administration of oral dronabinol reduce the intensity of dyspnea and improve the functional status at each patient's individual baseline activity? (2) Does dronabinol improve exercise tolerance as measured by the Incremental Shuttle Walk Test? (3) Does dronabinol decrease the intensity of dyspnea during the Incremental Shuttle Walk Test? (4) Does dronabinol improve the patient's subjective quality of life?

2. Secondary Objective

We also we plan to evaluate the effect dronabinol on weight and mood in COPD patients.

3. Achieving our aims

To achieve our primary aim, we plan to use surveys that have been validated in patients with COPD. See *Table 1*. For measure of disease-specific quality of life the St. George's Respiratory Questionnaire (SGRQ) is one the most widely used and validated tools.[29] Although the shortened Geriatric Depression Scale (GDS-15) was developed as a non-specific measure of quality of life, more recently it has been validated as a useful screening measure for mood disorders in COPD patients.[30]

To evaluate functional status of our patients, the modified Pulmonary Functional Status and Dyspnea Questionnaire[31] (PFSDQ-M) will be utilized. Several other prognostic study tools have been developed and validated in COPD patients, including the Six Minute Walk Test[32,33] (6MWT) and the Incremental Shuttle Walk Test[34,35] (ISWT). Based on our conversation with national COPD expert researchers, we find it most accurate in this research setting to measure endurance and dyspnea using the ISWT instead of the 6MWT. During the ISWT patients are asked to walk a flat 10 meter surface while paced by an audio signal which incrementally increases in speed until fatigue or dyspnea (rated on the modified Borg scale) becomes limiting[36]. As a complement to the Borg score data, a five question subset of the PFSDQ-M called the "dyspnea component" is useful in identifying an overall pattern of shortness of breath not directly linked to specific activities.[31]

Table 1. Validated Questionnaires to measure dyspnea and its effects on exercise tolerance and quality of life in COPD patients.

Title	Primary Assessment	Number of questions	Average time to complete
St. George's Respiratory Questionnaire (SGRQ)	Quality of life survey specific to pulmonary diseases	18	20 minutes
Geriatric Depression Scale – short form (GDS-15)	A "mood scale" used as screening tool for depression and quality of life	15	< 5 minutes
Pulmonary Functional Status & Dyspnea Questionnaire-Modified (PFSDQ-M)	Self-administered, disease specific questionnaire for clinical evaluation of symptoms and functional status	40	7 minutes
PFSDQ-Dyspnea component	Subset of questions that focus directly on the effects of dyspnea in daily life	5	< 2 minute
Incremental Shuttle Walk Test (ISWT)	Prognostic tool used to assess functional status based on symptoms during exertion	n/a	5 minutes
Borg Scale	Visual analog scale to numerically rate the degree of dyspnea and fatigue during an activity (e.g. ISWT)	2	< 1 minute

METHODS

1. Study Design

To evaluate our hypothesis, we plan to conduct a prospective, randomized, placebo-controlled, double-blind cross-over study.

The active drug will be an over-encapsulated dronabinol gel cap that is filled with additional starch. The placebo will consist of an identical self-sealing capsule but only filled with starch.

2. Subjects

a. Patient Selection

We plan to enroll 50 veterans at the Veterans Affairs Loma Linda Healthcare System that meet all inclusion criteria and none of the exclusion criteria.

b. Inclusion criteria

(1) diagnosed with COPD as defined by the American Thoracic Society (ATS) and European Respiratory Society (ERS) to have a forced expiratory volume in one second to forced vital capacity ratio (FEV1/FVC%) below the statistically defined as below 95% confidence interval of normal (i.e. lower limit of normal)[37]

(2) completed pulmonary rehabilitation program (including weight-training, education and support group meetings)

(3) not actively smoking

(4) are still having COPD symptoms despite currently on maximal medical therapy indicated for their level of disease

c. Exclusion criteria

(1) admission urine drug screen positive for THC

(2) are hypercapnic with pCO_2 >45mmHg on admission arterial blood gas testing

(3) have a hemoglobin < 7g/dL (obtained from arterial blood gas sample)

(4) are allergic to sesame seeds or sesame oil

(5) if female, are currently pregnant (A Urine dipstick test will be done prior to Phase I and Phase II. If a positive at any point, the subject will be removed from study and no longer receive drug or placebo.)

(6) have clinical evidence of acute heart failure at the time of study induction

(7) have a history of neuromuscular disease

3. Protocol

a. Recruitment

Patients who are diagnosed with COPD and have not smoked tobacco for at least three months are eligible to enroll in the pulmonary rehabilitation program at Veterans Affairs Loma Linda Healthcare System in Loma Linda, California. Once enrolled, veterans receive weekly exercise, education and group support. Furthermore, the concurrent medical therapy is optimized to the maximum

medical therapy recommended for the stage and symptom with which the patient presents. Dyspnea, functional status and quality of life surveys are completed at several points during the 20 to 24-week period. Some veterans continue to exercise at the hospital facility even after the completion of the program. As a whole, this group of individuals offers a unique opportunity for research given the established (consistent) enrollment criteria including maximal medical therapy as well as the proven track record of compliance with surveys and follow-up visits.

For patient recruitment, we will depend of referral from primary care physicians, pulmonary rehabilitation staff and other colleagues. If patients meet the inclusion criteria and none of the exclusion criteria are met, a member of the research team will contact the patient to ask if he or she is interested in participating in this research study.

b. Study description

If a patient decides to enroll in the study, complete informed consent (see appendix) will be provided and all questions will be answered prior to signing the enrollment forms. The following protocol will be followed (see *Figure 3*):

Enrollment

-sign all forms (e.g. informed consent, HIPPA, etc.)
-focused history and physical exam including weight check
-urine drug screen and if female, urine pregnancy test
-document current medications, amount of home oxygen (if any)
-obtain arterial blood gas (ABG) if not available within the last 30days
-document most recent spirometry data (specifically: FEV1, FVC, and FEV1/FVC)
-using a randomization software, patients are assigned to group A or B

PHASE I

Run-in period I (2 weeks)

Day 0: -fill out questionnaire packet and answer adverse drug reaction screen (see appendix) and perform ISWT.
-start dronabinol 5mg by mouth or placebo daily x 3 days.

Day 3: -answer adverse drug reaction screen
-if no adverse effects reported, increase dose to 5mg by mouth twice a day.

Day 6: -answer adverse drug reaction screen
-if no adverse effects reported, increase dose to 5mg by mouth three times a day.

Day 9: -answer adverse drug reaction screen
-if no adverse effects reported, increase dose to 5mg by mouth four times a day.

Day 12: -answer adverse drug reaction screen.

-if no adverse effects reported, continue 20mg daily in divided doses.

**Note: There will be a sham titration of the placebo arm following the exact same schedule as laid out above.

If at any point during the run-in phase, a patient reports side effects, he or she will be given the option to reduce to the previously well-tolerated dosage and remain in the study.

Treatment period I (4 weeks)

-group A will receive doses of oral dronabinol (Δ^9-THC)

-group B will receive a placebo that is identical in appearance

-at the end of four weeks, patients will fill out the questionnaire packet and perform ISWT

Wash-out period (8-12 weeks)

-patients will stop taking dronabinol or placebo for 8-12 weeks (this range provides flexibility to work around patients' schedules), then be screened for inclusion and exclusion criteria again:

-focused history and physical exam including weight check

-urine drug screen and if female, urine pregnancy test

-document current medications, amount of home oxygen (if any)

-obtain arterial blood gas (ABG)

**Note: if a urine drug screen is positive for THC, the patient will have repeat urine drug screens at one-week intervals until the test is negative for THC to ensure that there will be no carry-over effect.

- patients will fill out the questionnaire packet and perform ISWT

Cross-over

The groups will then be crossed over so that during Phase II, group A will receive placebo and group B will receive dronabinol.

PHASE II

Run-in II and **Treatment period II** will be conducted with an identical protocol as Run-in I and Treatment period I, respectively.

Because dizziness is a known effect of cannabinoid receptor agonist therapy, it will be determined if subjects at the time of enrollment in the study were naive to cannabinoid receptor agonists.

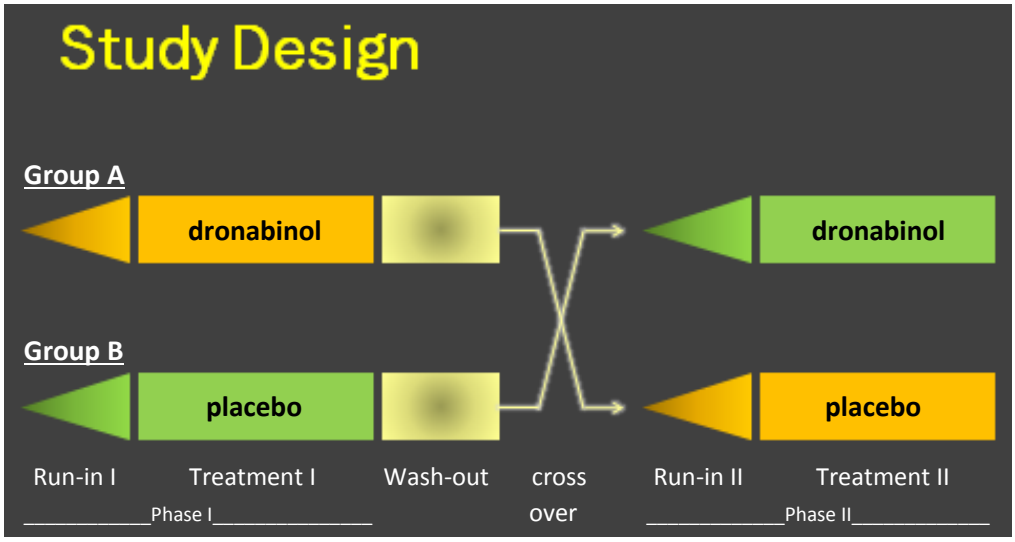


Figure 3. Graphical display of intended study design.

4. **Statistical Analysis**
   a. **Error allowance**
   Alpha (type I error) was accepted as 0.05 and beta (type II error) was taken as 0.2.
   b. **Power Calculation**
   Based on sample sizes in previously published statistically significant studies[6,9,15] of drug interventions for control of dyspnea we anticipated a sample size between 9-31 patients.
   Using GPOWER[38] software we determined, with an alpha of 0.05 and effect size = 0.9, to reach a power of 0.8 a sample size of 42 patients is required. Since we are using a cross-over design and these will be paired data, we conclude that 21 patients are actually needed. Given the possibility of high drop-out rates, we will aim to enroll up to 50 patients in order to have at least 21 patients completing the study.
   We have determined *a priori* to analyze the data after 10 patients have completed the study to determine the feasibility of completion with the current design and possible need to increase the enrollment number.

5. **Registration**
   Upon Institutional Review Board (IRB) and Research & Development Committee (R&D) approval and prior to patient enrollment, we will register this study at www.clinicaltrials.gov.

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