Online Supplement
Effects of Dronabinol on Dyspnea and Quality of Life in Patients with COPD.

Abdul H. Zaid, MBBS[1] Suman B. Thapamagar, MBBS[2] James D. Anholm, MD[3] Laura Weaver-Carnahan, RN, RRT[3] Lien Duong, PharmD[3] Lennard Specht, MD[3]

[1]Pulmonary-Critical Care, Loma Linda University Medical Center, Loma Linda, California, United States

[2]Pulmonary-Critical Care, Riverside University Health System, Moreno Valley, California, United States

[3]Pulmonary-Critical Care, VA Loma Linda Healthcare System, Loma Linda, California, United States

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