Effect of Morphine on Breathlessness and Exercise Endurance in Advanced COPD: A Randomized Crossover Trial

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Online Data Supplement

Participants. Participants included men and women aged ≥40 yrs with clinically stable Global Initiative for Obstructive Lung Disease stage 3 or 4 COPD (1) and chronic breathlessness syndrome (2), defined as a modified Medical Research Council (mMRC) dyspnoea score of ≥3 (3), a Baseline Dyspnoea Index (BDI) focal score of ≤6 (4) and/or an Oxygen Cost Diagram rating of ≤50% full scale (5) despite optimal treatment with bronchodilators, corticosteroids and/or phosphodiesterase inhibitors (1). Exclusion criteria included: smoking history <20 pack-years; change in medication dosage and/or frequency of administration in preceding 2-weeks; exacerbation and/or hospitalization in preceding 6-weeks; arterialized capillary PCO_2 ($P_{ac}CO_2$) >50 mmHg at rest; presence of other medical condition(s) that could contribute to breathlessness and/or exercise intolerance; important contraindications to cardiopulmonary exercise testing (CPET); self-reported history of addiction and/or substance abuse; use of anti-seizure drugs or opioids; use of daytime oxygen; and exercise-induced oxyhemoglobin desaturation to <80% on room air.

Study design. This single-center, randomized, double-blind, placebo-controlled, crossover trial (ClinicalTrials.gov identifier NCT01718496) consisted of two intervention periods separated by a washout period of ≥48 hrs. Participants were randomized in a 1:1 ratio to receive immediate-release oral morphine sulphate (0.1 mg/kg body mass to a maximum dose of 10 mg; Statex™, Paladin Labs Inc., Montreal, QC, Canada) or diluted simple syrup (placebo) prepared in 250 ml of orange juice. A computer-generated block randomization schedule was prepared by a third-party not involved in the trial. The study protocol and informed consent form received ethical

approval from Health Canada (File No. 9427-M1647-48C) and the Research Ethics Board of the Research Institute of the McGill University Health Centre (MP-CUSM-12-325-T).

After providing written informed consent, participants completed a screening/familiarization visit followed by two randomly assigned treatment visits. *Visit 1* included: medical history; clinical assessment; evaluation of participant-reported breathlessness (3-5), health status (6) and anxiety/depression (7); measurement of $P_{ac}CO_2$ at rest; post-bronchodilator (400 μg salbutamol) pulmonary function testing; and a symptom-limited incremental CPET to determine peak power output (PPO), defined as the highest power output that the participant was able to sustain for ≥30-sec. At the start of *Visits 2 and 3*, participants inhaled 400 μg of salbutamol to standardize the time since last bronchodilator administration. Fifteen minutes thereafter, participants completed the opioid-related symptom distress scale (ORSDS) (8, 9) followed by blood sampling for measurement of $P_{ac}CO_2$ and of plasma concentrations of morphine ([MOR]) and its two metabolites, morphine-3-glucuronide ([M3G]) and morphine-6-glucuronide ([M6G]). Participants were then administered oral morphine or placebo. Thirty-minutes thereafter, participants completed the ORSDS and blood for measurement of $P_{ac}CO_2$, [MOR], [M3G] and [M6G] was collected. Participants then completed a symptom-limited constant-load cycle CPET at 75% PPO.

Procedures. Spirometry, plethysmography and single-breath diffusion capacity of the lung for carbon monoxide were performed using automated equipment and recommended techniques (10-13). Measurements were referenced to predicted normal values (14-17): predicted normal

inspiratory capacity (IC) was calculated as the difference between predicted normal total lung capacity and predicted normal functional residual capacity.

Symptom-limited exercise tests were conducted on an electronically braked cycle ergometer (Lode Corival, Lode B.V. Medical Tech., Groningen, The Netherlands) using a computerized CPET system (Vmax Encore^{TM} 29C). Incremental CPETs consisted of a steady-state rest period of at least 6-min, followed by 1-min of unloaded pedalling and then 5 W/min increases in power output. Constant-load CPETs consisted of a steady-state rest period of at least 6-min, followed by 1-min of unloaded pedaling and then a step increase in power output to 75% PPO. Cardiac, metabolic, breathing pattern and gas exchange parameters were collected and analyzed as previously described (18). Inspiratory capacity (IC) maneuvers were performed at rest, every 2-min during CPET, and at end-exercise (19, 20). Measurements of PPO and of peak oxygen uptake and peak heart rate were referenced to the predicted normal values of Jones and colleagues (20). Using Borg's modified 0-10 category ratio scale (21), participants rated the intensity and unpleasantness of their breathlessness, as well as the intensity of their leg discomfort at rest, every 2-min during CPET, and at end-exercise. In a subgroup of 7 consenting adults, breath-by-breath measures of the crural diaphragm electromyogram (EMGdi) were recorded and analyzed using published methods (22, 23). Participants verbalized their main reason(s) for stopping exercise; quantified the percentage contribution of breathlessness and leg discomfort to exercise cessation; and identified qualitative phrases that best described their breathlessness at end-exercise (24). Each participant's blinded treatment preference was assessed at the end of *Visit 3* by having them identify the visit wherein "exercise felt easier" and providing a reason for their selection.

Blood for measurement of $P_{ac}CO_2$ was drawn from a warmed earlobe (Finalgon® Cream, Boehringer Ingelheim GmbH) into a pre-heparinized capillary tube (safeCLINITUBES, D957P-70-125; Radiometer Copenhagen, Denmark) and analyzed immediately using an OPTI™ CCA-TS2 blood gas analyzer (OPTI Medical Systems Inc., Roswell, GA, USA).

Plasma [MOR], [M3G] and [M6G] were analyzed by high-performance liquid chromatography mass spectrometry (EliaPharma Services Inc., Montreal, QC, Canada). Proteins from 20 µl of plasma were precipitated with the addition of 3 volumes of acetonitrile containing 2 ng of morphine D6 (internal standard). The molecules of interest were isolated by mixed mode strong cation exchange solid phase extraction (Strata-X-C, Phenomenex, Torrance, USA). A 9 points standard curve ranging from 0 to 500 ng/ml of each of the molecules was prepared in plasma alongside the samples (r^2 = 0.99 for morphine, 0.97 for M3G and 0.98 for M6G). Acquisition was performed in positive mode with a Sciex TripleTOF 5600 (Sciex, Concord, Canada) equipped with an electrospray interface with 50 µm iD capillary and coupled to an Eksigent µUHPLC (Sciex,Concord, Canada). Analyst TF 1.7 software was used to control the instrument and for data processing and acquisition. Acquisition was performed in MRM mode with the following transitions, declustering potential and collision energy: 286.1 → 165.06, DP : 100V, CE : 49V for morphine; and 462.18 → 207.03, DP: 100V, CE : 50V for both M3G and M6G. Separation was performed on a reversed phase HALO PFP column 0.5 mm i.d., 2.7 µm particles, 50mm long (Advance Materials Technology, Wilmington, USA) For the 3-min liquid chromatography gradient, the mobile phase consisted of solvent A (0.2% v/v formic acid in water) and solvent B (0.2% v/v formic acid + 50% methanol + 49.8% acetonitrile). Molecule

quantification was done using peak area with a 0.05 Da extraction window with the MultiQuant software (Sciex, Concord, Canada).

Primary outcome variables. The primary outcome was the post-dose difference in breathlessness intensity ratings during exercise at isotime, defined as the highest equivalent 2-min interval of exercise completed by a given participant during each of the constant-load CPETs. The co-primary outcome was the post-dose difference in exercise endurance time (EET), defined as the duration of loaded pedaling during constant-load CPET.

Secondary outcome variables. $P_{ac}CO_2$ at rest; plasma [MOR], [M3G] and [M6G]; OSRDS-derived measures of opioid-related side effects; physiological and perceptual parameters measured at rest, at standardized submaximal times during constant-load CPETs and at end-exercise; reasons for stopping exercise; percentage contribution of breathlessness and leg discomfort to exercise cessation; qualitative descriptors of breathlessness at end-exercise; and participant's blinded treatment preference

Statistical analyses. Using a two-tailed paired subject formula with α=0.05, β=0.90, and an expected effect size of 0.80 (25), we estimated that 20 participants were needed to detect a minimal clinically important difference (MCID) of 1 Borg unit in breathlessness intensity during exercise at isotime (26) and of 101-sec or 1.68-min in EET (27) after taking morphine vs. placebo.

All participants who completed both morphine and placebo arms of the trial were

included in the analysis. Linear mixed-models regression with random intercepts was used to analyze post-dose differences in EET as well as in all physiological and perceptual responses to constant-load CPET, accounting for period and sequence effects.

Post-dose differences in the percentage contribution of breathlessness and leg discomfort to exercise cessation, and in the intensity and bothersomeness of each symptom assessed on the ORSDS were analyzed using two-tailed paired t-tests.

Post-dose differences in the selection frequencies of each symptom on the ORSDS, the individual reasons for stopping exercise, and the individual descriptors of breathlessness at end-exercise were analyzed using the chi-squared test.

Linear mixed-model regression with random intercepts was used to examine treatment, time and treatment*time interaction effects on $P_{ac}CO_2$. Multiple imputations (n=30) were performed to impute missing $P_{ac}CO_2$ values.

A secondary analysis was conducted after examination of the data showed that 11 participants reported a morphine-induced decrease in breathlessness intensity at isotime by the MCID of ≥1 Borg unit (responders [R]) compared with the remaining 9 participants who did not (non-responders [NR]). Baseline characteristics were compared between-groups using two-tailed unpaired t-tests. The effect of oral morphine vs. placebo on EET was analyzed using two-tailed paired t-tests within each group. A two-tailed two-way repeated measures analysis of variance with Tukey's HSD post-hoc test was used to examine treatment, time and treatment*time interaction effects on physiological and perceptual parameters measured at rest and during exercise within each group.

Data were analyzed using SAS statistical package, version 9.1.3 (SAS Institute Inc., Cary,

NC, USA) and SigmaStat, version 3.5 (Systat Software Inc., San Jose, CA, USA). Statistical significance was set at $p<0.05$ and values are reported as mean±SEM unless stated otherwise.

Table E1. Baseline characteristics of the participants with advanced COPD and chronic breathlessness syndrome that did (Responders) and did not (Non-Responders) report a decrease in breathlessness intensity of ≥1 Borg unit during exercise at isotime after taking oral morphine vs. placebo.

Parameter	Responders	Non-responders
Male:Female, n	9:2	6:3
Age, yrs	63.3 ± 6.9	64.0 ± 7.8
Height, cm	171.7 ± 8.9	165.7 ± 6.4
Body mass, kg	69.1 ± 15.7	74.6 ± 13.0
Body mass index, kg · m^{-2}	23.4 ± 4.9	27.3 ± 2.0
Smoking history, pack years	57.6 ± 18.0	61.3 ± 28.7
$P_{ac}CO_2$, mmHg [range] †	38.2 ± 3.6 [32 – 45]	37.1 ± 3.0 [35 – 44]
Incremental cycle exercise time, min	6.2 ± 2.4	6.8 ± 3.2
Peak incremental power output, watts (% predicted)	38.6 ± 20.0 (26 ± 12)	36.7 ± 15.4 (27 ± 9)
Peak incremental $\dot{V}O_2$, ml · kg · min^{-1} (% predicted)	12.8 ± 2.8 (53 ± 14)	12.5 ± 2.5 (57 ± 15)
GOLD stage, 3:4	5:6	6:3
Post-bronchodilator pulmonary function		
FEV_1, % predicted	32 ± 7	40 ± 9
FEV_1/FVC, %	33 ± 6	40 ± 14
TLC, % predicted	129 ± 17	123 ± 16
RV, % predicted	227 ± 71	206 ± 34
FRC, % predicted	180 ± 42	167 ± 35
IC, % predicted	70 ± 19	75 ± 12
D_LCO, % predicted ††	59 ± 27	65 ± 15
sRaw, % predicted †††	1131 ± 687	992 ± 924
Breathlessness and health status		
mMRC score, 0-4	2.8 ± 0.75	3.1 ± 0.33
BDI focal score, out of 12	4.3 ± 1.9	3.3 ± 2.0
Oxygen cost diagram, % full scale	40 ± 18	38 ± 12
CAT score, out of 40	22.4 ± 7.7	19.9 ± 4.6
CAT breathlessness item, out of 5	4.2 ± 0.9	4.1 ± 0.9
CAT activity limitation item, out of 5	2.9 ± 1.6	3.8 ± 1.1
HADS score, out of 42	12.9 ± 6.8	11.2 ± 5.4
COPD Medication Summary		
LABA + LAMA, n	2	2
LABA + LAMA + ICS, n	8	6
LABA + LAMA + PI, n	0	1
LABA + LAMA + ICS + PI, n	1	0

Values are means ± SD. †n=10 for responder and 8 for non-responder. ††n=10 for responders and 7 for non-responders. †††n=9 for both responders and non-responders. $P_{ac}CO_2$, partial pressure of carbon dioxide in arterialized capillary blood; $\dot{V}O_2$, rate of oxygen uptake; GOLD, Global Initiative for Obstructive Lung Disease; FEV_1, forced expiratory volume in 1-sec; FEV_1/FVC, forced expiratory volume in 1-sec to forced vital capacity ratio; TLC, total lung capacity; RV, residual volume; FRC, functional residual capacity; IC, inspiratory capacity; D_LCO, diffusing capacity of the lung for carbon monoxide; sRaw, specific airway resistance; mMRC, modified Medical Research Council Dyspnoea Scale; BDI, Baseline Dyspnoea Index; CAT, COPD Assessment Test; HADS, Hospital Anxiety and Depression Scale; LABA, long-acting β_2 agonist; LAMA, long-acting muscarinic antagonist; ICS, inhaled corticosteroid; PI, phosphodiesterase inhibitor.

References

1. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, Chen R, Decramer M, Fabbri LM, Frith P, Halpin DM, Lopez Varela MV, Nishimura M, Roche N, Rodriguez-Roisin R, Sin DD, Singh D, Stockley R, Vestbo J, Wedzicha JA, Agusti A. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report: Gold executive summary. *American journal of respiratory and critical care medicine* 2017.
2. Johnson MJ, Yorke J, Hansen-Flaschen J, Lansing R, Ekstrom M, Similowski T, Currow DC. Towards an expert consensus to delineate a clinical syndrome of chronic breathlessness. *Eur Respir J* 2017;49.
3. Fletcher CM, Elmes PC, Fairbairn AS, Wood CH. The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. *Br Med J* 1959;2:257-266.
4. Mahler DA, Weinberg DH, Wells CK, Feinstein AR. The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. *Chest* 1984;85:751-758.
5. McGavin CR, Artvinli M, Naoe H, McHardy GJ. Dyspnoea, disability, and distance walked: Comparison of estimates of exercise performance in respiratory disease. *British medical journal* 1978;2:241-243.
6. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the copd assessment test. *The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology* 2009;34:648-654.
7. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta psychiatrica Scandinavica* 1983;67:361-370.
8. Apfelbaum JL, Gan TJ, Zhao S, Hanna DB, Chen C. Reliability and validity of the perioperative opioid-related symptom distress scale. *Anesth Analg* 2004;99:699-709, table of contents.
9. Yadeau JT, Liu SS, Rade MC, Marcello D, Liguori GA. Performance characteristics and validation of the opioid-related symptom distress scale for evaluation of analgesic side effects after orthopedic surgery. *Anesth Analg* 2011;113:369-377.
10. Macintyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten CP, Brusasco V, Burgos F, Casaburi R, Coates A, Enright P, Gustafsson P, Hankinson J, Jensen R, McKay R, Miller MR, Navajas D, Pedersen OF, Pellegrino R, Wanger J. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology* 2005;26:720-735.
11. Miller MR, Crapo R, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J, Force AET. General considerations for lung function testing. *The European respiratory journal* 2005;26:153-161.
12. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J, Force AET. Standardisation of spirometry. *The European respiratory journal* 2005;26:319-338.
13. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, Casaburi R, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Hankinson J, Jensen R, Johnson D, Macintyre N, McKay R, Miller MR, Navajas D, Pellegrino R, Viegi G. Standardisation of the measurement

of lung volumes. *The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology* 2005;26:511-522.
14. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general u.S. Population. *American journal of respiratory and critical care medicine* 1999;159:179-187.
15. Crapo RO, Morris AH, Clayton PD, Nixon CR. Lung volumes in healthy nonsmoking adults. *Bulletin europeen de physiopathologie respiratoire* 1982;18:419-425.
16. Burrows B, Kasik JE, Niden AH, Barclay WR. Clinical usefulness of the single-breath pulmonucy diffusing capacity test. *The American review of respiratory disease* 1961;84:789-806.
17. Briscoe WA, Dubois AB. The relationship between airway resistance, airway conductance and lung volume in subjects of different age and body size. *The Journal of clinical investigation* 1958;37:1279-1285.
18. Jensen D, Alsuhail A, Viola R, Dudgeon DJ, Webb KA, O'Donnell DE. Inhaled fentanyl citrate improves exercise endurance during high-intensity constant work rate cycle exercise in chronic obstructive pulmonary disease. *Journal of pain and symptom management* 2012;43:706-719.
19. Guenette JA, Chin RC, Cory JM, Webb KA, O'Donnell DE. Inspiratory capacity during exercise: Measurement, analysis, and interpretation. *Pulmonary medicine* 2013;2013:956081.
20. Jones NL, Makrides L, Hitchcock C, Chypchar T, McCartney N. Normal standards for an incremental progressive cycle ergometer test. *The American review of respiratory disease* 1985;131:700-708.
21. Borg GA. Psychophysical bases of perceived exertion. *Medicine and science in sports and exercise* 1982;14:377-381.
22. Mendonca CT, Schaeffer MR, Riley P, Jensen D. Physiological mechanisms of dyspnea during exercise with external thoracic restriction: Role of increased neural respiratory drive. *J Appl Physiol (1985)* 2014;116:570-581.
23. Schaeffer MR, Mendonca CT, Levangie MC, Andersen RE, Taivassalo T, Jensen D. Physiological mechanisms of sex differences in exertional dyspnoea: Role of neural respiratory motor drive. *Experimental physiology* 2014;99:427-441.
24. O'Donnell DE, Hong HH, Webb KA. Respiratory sensation during chest wall restriction and dead space loading in exercising men. *J Appl Physiol (1985)* 2000;88:1859-1869.
25. Faul F, Erdfelder E, Buchner A, Lang AG. Statistical power analyses using g*power 3.1: Tests for correlation and regression analyses. *Behav Res Methods* 2009;41:1149-1160.
26. Ries AL. Minimally clinically important difference for the ucsd shortness of breath questionnaire, borg scale, and visual analog scale. *Copd* 2005;2:105-110.
27. Puente-Maestu L, Villar F, de Miguel J, Stringer WW, Sanz P, Sanz ML, de Pedro JG, Martinez-Abad Y. Clinical relevance of constant power exercise duration changes in copd. *The European respiratory journal* 2009;34:340-345.