Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods 1. Participant eligibility criteria and recruitment

Inclusion criteria

- Diagnosis of COPD according to the current Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (GOLD)[1];
- Optimal pharmacological treatment, including treatment with a combination of a long-acting muscarinic antagonist (LAMA) and a long-acting β-agonist (LABA)[1];
- Grade 2, 3 or 4 dyspnea on the modified Medical Research Council (mMRC) Scale[2];
    - This criterion was expanded to moderate breathlessness (mMRC grade 2) to allow enrollment of predefined patient numbers.
- Optimal non-pharmacological treatment defined as completed a comprehensive pulmonary rehabilitation program[3,4].

Exclusion criteria

- History of substance misuse;
- Exacerbation of COPD within two weeks of study enrolment;
- Waiting list for lung transplantation;
- Pregnant or childbearing potential not using contraception;
- Renal failure (creatinine clearance <15mL/min);
- Age under 18;
- Not being able to read or fill in the questionnaires or diary;
- Allergy for morphine or its excipients;
- Concomitant use of irreversible MAO blockers;
- Use of opioids;
- History of convulsions;
- Head injury;
- Intestinal obstruction;
- Gastroparesis;
- Liver disease.

Recruitment locations

Initially, participants were recruited in CIRO, Horn, The Netherlands, after completion of a PR program.[4] Due to delayed participant enrollment, participants were also recruited in Zuyderland Hospital, Heerlen and VieCuri Hospital, Venlo, The Netherlands after completion of an outpatient PR program.

eMethods 2. Description of outcome measures

Description of measures

Health status

Health status was determined using the COPD Assessment Test (CAT). The CAT is a short and simple instrument that assesses the impact of COPD on health status.[5,6] The questionnaire consists of eight questions, assessing the symptoms on a scale from 0 to 5. The total score ranges from 0 to 40, with higher scores representing worse health status. The minimal clinical important difference (MCID) for the CAT is 2·0 to 3·0 points.[7] The CAT was completed on paper by the participants at T0, T2, T3, and T5.

Respiratory adverse effects

The primary respiratory outcome was arterial partial pressure of carbon dioxide ($PaCO_2$). $PaCO_2$ was assessed by arterial blood gas drawn from the radial artery at T0 and T5. Also, arterial partial pressure of oxygen (PaO_2) and arterial oxygen saturation (SaO_2) were assessed in the arterial blood. A priori, the project group defined a change of 7.5 mmHg in $PaCO_2$ as clinically relevant.[8]
Overnight pulse oxygen saturation (SpO_2) and the time SpO_2 was below 90% during the night was assessed at T0 and T5 using a WristOx2 3150 pulse oximeter (Nonin Medical, Plymouth, USA).
Transcutaneous partial pressure of carbon dioxide ($PtcCO_2$) and transcutaneous SpO_2 were assessed at T0, T2, T3, and T5 using a SenTec Digital Monitoring System (SenTec, Therwil, Switzerland) with an earlobe clip. Respiratory rate (RR) was assessed at T0, T2, T3, and T5. Finally, lung function consisted of a flow-volume measurement and a body box measurement at T0 and T5. During the flow-volume measurement, forced expiratory volume in the first second (FEV_1) and forced vital capacity (FVC) were assessed, of which the Tiffenau index (FEV_1/FVC) was calculated. During the body box measurement, inspiratory capacity (IC), total lung capacity (TLC) and intra thoracic gas volume (ITGV) were assessed and afterwards the IC/TLC ratio was calculated.

Functional performance

Functional performance consisted of three tests. The 6-minute walk test (6MWT) is a valid and reliable measure to estimate functional exercise capacity in patients with chronic respiratory diseases.[9] Participants cover as many distance as possible in 6 minutes. The test was performed according to the ERS/ATS guidelines.[9] The MCID for the 6MWT is 30m.[10] The 6MWT was performed at T0 and T5.
General mobility was examined using the Timed 'Up & Go' (TUG) test.[11] This simple test requests patients to stand up from a chair, walk 3 meters in a comfortable pace, turn, walk back and sit down on the chair again. During the test, the time is recorded. Participants performed this test twice[12] and the best time was used for analysis. The TUG test is valid and responsive in patients with COPD with an MCID of 0.9-1.4 sec.[13] The TUG test was performed at T0, T2, T3, and T5.
Care dependency was examined using the Care Dependency Scale (CDS).[14,15] This instrument consists of 15 items regarding basic and instrumental activities of daily living, which are each scored on a 5-point Likert Scale. Higher scores indicate less care dependency. The CDS was completed on paper by the participants at T0 and T5.

Severity of breathlessness

Severity of breathlessness was assessed using a Numeric Rating Scale (NRS)[16] ranging from 0 to 10, with 0 being not breathless at all and 10 being the worst imaginable breathlessness. The participants completed these items verbally. During all assessments, the mean and worst breathlessness in the last 24 hours was recorded. At baseline, the mean breathlessness in the last week was also determined to estimate if the day of the baseline assessment was an average day of that week. The MCID for the NRS for breathlessness is estimated at 1.0 points.[17]

Other outcomes

At baseline, the following other outcomes were recorded: demographic characteristics (age, gender, Body Mass Index and marital status), medical history (Charlson Comorbidity Index (CCI)[18] and number of exacerbations and hospital admissions in the previous 12 months[19,20]), smoking history, current smoking behavior, use of medication, use of long-term oxygen therapy (LTOT) and use of non-invasive positive pressure ventilation (NIV). At T1, T2, T3, T4, and T5, data on change in medication use, LTOT and NIV, compliance to study intervention, exacerbations and adverse effects were collected.
The CCI was completed based on the patient report and further discussed with the participant for completeness. Compliance to study intervention was recorded by asking the participant during each assessment if they missed a

capsule since the prior assessment. Furthermore, if study medication was handed in at T5, the remaining capsules were counted. The occurrence of exacerbations[21] was assessed by asking the participant if they experienced a worsening of their COPD since the prior assessment. If so, the symptoms were recorded together with given medication and possible contact with a health care professional or admission to the hospital. Collection of adverse effects included nausea, vomiting and retching, drowsiness, constipation, sleeplessness, sleepiness and cognition. Nausea, vomiting and retching, drowsiness, constipation and sleeplessness were recorded during all assessments using NRS (average burden in last 24 hours). The participants completed these items verbally.
At the end of the intervention study, the participants were asked which intervention they assumed to have received.

eTable 1. Covariance structures

	Random Intercept	**Random Intercept + Random Slope**	**Unstructured**
CAT	Chosen	Considered	Considered
Respiratory rate	Chosen	Not applicable	Considered
$PtcCO_2$	Considered	Not applicable	Chosen
SpO_2	Considered	Not applicable	Chosen
TUG	Considered	Considered	Chosen
NRS mean breathlessness	Considered	Chosen	Considered
NRS worst breathlessness	Chosen for both groups	Considered for total group Not applicable for subgroup	Considered for both groups

CAT, COPD Assessment Test; NRS, Numeric Rating Scale; $PtcCO_2$, transcutaneous partial pressure of carbon dioxide; SpO_2, pulse oxygen saturation; TUG, Timed 'Up&Go' test.

eTable 2. Mean difference in CAT score and breathlessness scores per assessment for total study population and subgroup of participants with mMRC grade 3-4

	Mean difference (95% CI), morphine vs placebo			
	Total study population		**Subgroup with mMRC grade 3-4**	
	(n=111)	P value	(n=49)	P value
CAT				
T2	-1.45 (-3.33;0.44)	0.13	-0.34 (-3.16;2.48)	0.81
T3	-1.83 (-3.74;0.08)	0.06	-1.82 (-4.67;1.04)	0.21
T5	-2.18 (-4.14;-0.22)	**0.03**	-1.17 (-4.17;1.84)	0.44
Mean breathlessness (NRS)				
T2	-0.11 (-0.84;0.62)	0.76	-0.41 (-1.46;0.63)	0.43
T3	-0.55 (-1.35;0.26)	0.18	-0.90 (-2.10;0.29)	0.14
T5	-0.60 (-1.55;0.35)	0.21	-1.31 (-2.80;0.17)	0.08
Worst breathlessness (NRS)				
T2	-0.02 (-0.83;0.80)	0.97	-0.63 (-1.73;0.46)	0.26
T3	-0.20 (-1.02;0.62)	0.63	-0.44 (-1.55;0.67)	0.43
T5	-0.56 (-1.41;0.28)	0.19	-1.33 (-2.50;-0.16)	**0.03**

CAT, COPD Assessment Test; NRS, Numeric Rating Scale

eTable 3. Dose increase during the study for total study population

	Morphine group	**Placebo group**	**P value**
	(n=54)	(n=57)	
Increase T2, No (%)	13 (27)	30 (55)	0.001
Increase T3, No (%)	14 (29)	11 (20)	0.28
Decrease T3, No (%)	1 (2)	3 (5)	0.38
Number of capsules per day after T2, mean (SD)	2.26 (0.44)	2.55 (0.50)	0.002
Number of capsules per day after T3, mean (SD)	2.53 (0.50)	2.69 (0.47)	0.10
Final number of capsules per day at T5, mean (SD)	2.55 (0.50)	2.73 (0.45)	0.07
Participants using 3 capsules per day at T5, No (%)	24 (55)	37 (73)	0.07

eTable 4. Numeric Rating Scores for adverse effects

	Mean difference (95% CI), morphine vs placebo			
	Baseline to final assessment		**Maximal difference**	
	Total study population		Total study population	
	(n=111)	P value	(n=111)	P value
Nausea	-0.61 (-1.57;0.35)	0.21	-0.61 (-1.57;0.35)	0.21
Vomiting and retching	-0.27 (-0.69;0.14)	0.20	-0.43 (-1.01;0.14)[a]	0.14
Drowsiness	-0.11 (-.124;1.01)	0.84	1.23 (0.16;2.31)[b]	0.30
Constipation	1.53 (0.44;2.62)	**0.006**	1.53 (0.44;2.62)	**0.006**
Sleeplessness	-0.44 (-1,67;0.80)	0.48	-0.49 (-1.52;0.55)[b]	0.36

[a] Reached at T1
[b] Reached at T2

eTable 5. Participants experiencing worsening of adverse effects

	No (%)		
	Morphine group	**Placebo group**	**P value**
	(n=54)	(n=57)	
Nausea	16 (30)	13 (23)	0.48
Vomiting and retching	8 (15)	10 (18)	0.72
Drowsiness	27 (50)	21 (37)	0.29
Constipation	25 (46)	17 (30)	0.16
Sleeplessness	16 (30)	23 (40)	0.34

A worsening was defined as ≥2 points on the NRS score.

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