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Morphine for treatment of cough in idiopathic pulmonary fibrosis (PACIFY COUGH): a prospective, multicentre, randomised, double-blind, placebo-controlled, two-way crossover trial

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Summary

Background Idiopathic pulmonary fibrosis is a progressive fibrotic lung disease, with most patients reporting cough. Currently, there are no proven treatments. We examined the use of low dose controlled-release morphine compared with placebo as an antitussive therapy in individuals with idiopathic pulmonary fibrosis.

Methods The PACIFY COUGH study is a phase 2, multicentre, randomised, double-blind, placebo-controlled, two-way crossover trial done in three specialist centres in the UK. Eligible patients aged 40–90 years had a diagnosis of idiopathic pulmonary fibrosis within 5 years, self-reported cough (lasting >8 weeks), and a cough visual analogue scale (VAS) score of 30 mm or higher. Patients were randomly assigned (1:1) to placebo twice daily or controlled-release morphine 5 mg orally twice daily for 14 days followed by crossover after a 7-day washout period. Patients were randomised sequentially to a sequence group defining the order in which morphine and placebo were to be given, according to a computer-generated schedule. Patients, investigators, study nurses, and pharmacy personnel were masked to treatment allocation. The primary endpoint was percentage change in objective awake cough frequency (coughs per h) from baseline as assessed by objective digital cough monitoring at day 14 of treatment in the intention-to-treat population, which included all randomised participants. Safety data were summarised for all patients who took at least one study drug and did not withdraw consent. This study was registered at ClinicalTrials.gov, NCT04429516, and has been completed.

Findings Between Dec 17, 2020, and March 21, 2023, 47 participants were assessed for eligibility and 44 were enrolled and randomly allocated to treatment. Mean age was 71 (SD 7·4) years, and 31 (70%) of 44 participants were male and 13 (30%) were female. Lung function was moderately impaired; mean forced vital capacity (FVC) was 2·7 L (SD 0·76), mean predicted FVC was 82% (17·3), and mean predicted diffusion capacity of carbon monoxide was 48% (10·9). Of the 44 patients who were randomised, 43 completed morphine treatment and 41 completed placebo treatment. In the intention-to-treat analysis, morphine reduced objective awake cough frequency by 39·4% (95% CI −54·4 to −19·4; p=0·0005) compared with placebo. Mean daytime cough frequency reduced from 21·6 (SE 1·2) coughs per h at baseline to 12·8 (1·2) coughs per h with morphine, whereas cough rates did not change with placebo (21·5 [SE 1·2] coughs per h to 20·6 [1·2] coughs per h). Overall treatment adherence was 98% in the morphine group and 98% in the placebo group. Adverse events were observed in 17 (40%) of 43 participants in the morphine group and six (14%) of 42 patients in the placebo group. The main side-effects of morphine were nausea (six [14%] of 43 participants) and constipation (nine [21%] of 43). One serious adverse event (death) occurred in the placebo group.

Interpretation In patients with cough related to idiopathic pulmonary fibrosis, low dose controlled-release morphine significantly reduced objective cough counts over 14 days compared with placebo. Morphine shows promise as an effective treatment to palliate cough in patients with idiopathic pulmonary fibrosis, and longer term studies should be the focus of future research.

Funding The Jon Moulton Charity Trust.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, and invariably fatal fibrotic lung disease of unknown cause.[1] Available treatments for IPF slow disease progression but do not improve symptoms or quality of life. Most patients with IPF report cough, a distressing symptom with substantial physical, social, and psychological consequences, which is associated with rapid disease progression.[2,3] Evidence-based treatment options for cough in IPF are scarce.[4]

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Research in context

Evidence before this study

We searched PubMed from database inception to June 20, 2023, for reports published in any language using the search terms "idiopathic pulmonary fibrosis" AND "cough" AND "clinical trial". In a single centre, 24-week, double-blind, two-treatment, two-period crossover trial, thalidomide was shown to be beneficial for IPF cough. However, only 20% of patients were able to tolerate it. Pirfenidone, one of the novel antifibrotic agents, has shown some promise in an uncontrolled study. A randomised, double-blind, proof-of-concept trial of a nebulised form of sodium cromoglicate showed encouraging results. However, a subsequent larger, phase 2b trial, which was hampered by participant retention, yielded disappointing outcomes. The novel P2X3 receptor antagonist, gefapixant, was also trialled for the treatment of chronic cough in IPF, but the randomised, double-blind, placebo-controlled, crossover study was negative and most participants reported taste-related adverse events. In a more recent phase 2, placebo-controlled, randomised, crossover trial, extended release nalbuphine reduced awake cough frequency by 51·6%, although nearly a quarter of the participants discontinued the nalbuphine regimen due to adverse effects.

Added value of this study

To our knowledge, this study is the first to report a benefit of morphine in IPF-related cough. We included patients with IPF and a self-reported persistent cough for at least 8 weeks. Using objective digital cough monitoring the study showed a reduction in daytime cough after 14 days of treatment with morphine when compared with placebo. This extends the knowledge in the field, in which a previous randomised, double-blind, placebo-controlled, crossover study showed low-dose morphine was efficacious in patients with refractory chronic cough. Given the established safety profile of morphine in IPF, these findings should be rapidly translatable to clinical practice.

Implications of all the available evidence

There is no direct evidence to guide the treatment of cough in IPF. Therefore, the results of this trial are important for almost 85% of patients with IPF who have cough and the clinicians involved in their treatment. The improvements in subjective and objective cough count and associated benefits in quality of life with morphine suggest that the drug offers an effective treatment option for this group of patients. Longer term studies should be conducted to establish the durability of its effects and the impact of improving cough on disease outcomes.

Opioids have long been advocated for the suppression of chronic cough.[5] Morphine is thought to depress the cough reflex, acting directly on the neural pathways in the brain. Antitussive effects might occur with doses lower than those usually required for analgesia. Although morphine is frequently used as a palliative agent for dyspnoea in IPF, its effect on cough has never been tested.[6] The only randomised controlled trial evaluating opioids in refractory chronic cough was conducted by Morice and colleagues[5] in which a starting dose of slow-release morphine 5 mg twice daily was shown to be effective at reducing diary-recorded cough scores. Despite the side-effects of constipation and drowsiness, all patients completed the study, highlighting the tolerability of low dose morphine. A longitudinal cohort study of more than 1600 patients with interstitial lung disease starting long-term oxygen therapy showed that opioids were used in 15% of patients and opioid use was not associated with increased mortality or admission to hospital.[7] These findings were true for both low and high dose opioid therapy, confirming the safety of opioids in this patient population.

To evaluate the efficacy and safety of low dose controlled-release morphine as an antitussive therapy in patients with IPF, we did a placebo-controlled, two-way crossover trial. A crossover design was chosen as it is the standard approach in proof-of-concept cough studies since it minimises effects due to patient variation and improves statistical power.

Methods

Study design

The PACIFY COUGH study is a phase 2, multicentre, double-blind, placebo-controlled, crossover trial of morphine for the treatment of cough in IPF. The trial was conducted across three specialist centres for interstitial lung disease in the UK—namely, the Royal Brompton Hospital, Aintree University Hospital NHS Foundation Trust, and Manchester University NHS Foundation Trust. The study was approved by the London Brent Research Ethics Committee (20/LO/0368). The protocol has previously been published online[8] and is available in the appendix (p 6). The statistical analysis plan is also available in the appendix (p 44).

Participants

Eligible participants were aged 40–90 years, diagnosed with IPF according to the ATS/ERS/JRS/ALAT guidelines[9] within 5 years before screening, reporting a chronic cough (duration >8 weeks), and a cough severity of 30 mm or higher on the visual analogue scale (VAS). We used a cough VAS of 30 mm or higher (using a scale ranging from 0 mm to 100 mm) on the basis of unpublished data, which suggests that, above this threshold, patients with an IPF-related cough have a significantly worse quality-of-life and higher mortality (unpublished). Eligible patients also required a forced vital capacity (FVC) of 45% of predicted or higher, an FEV_1 to FVC ratio of 0·7 or higher, and a diffusion capacity of carbon monoxide (DLCO) corrected for

haemoglobin of 30% of predicted or higher. Lung function tests performed within 12 months of screening was acceptable. The extent of fibrotic changes seen on high resolution CT imaging had to be greater than the extent of emphysema. Patients were excluded if they: were current smokers; had an acute exacerbation of IPF within 6 months; had clinically significant comorbidity with coronary artery disease; had clinically significant hepatic or renal impairment; had a predicted life expectancy of less than 6 months; required long-term oxygen therapy at rest; or had a history of drug or alcohol dependency. Participants with previous intolerance to morphine were also excluded. The following concomitant medications were prohibited: immunosuppressive therapy or antibiotics used within 4 weeks of the screening visit, opioids used within 14 days of the screening visit, and angiotensin converting enzyme inhibitors. Corticosteroids were permitted if a stable dose (equivalent to prednisolone 10 mg/day or less) was used for an indication other than pulmonary disease, as was concurrent use of pirfenidone or nintedanib, if the participant had been taking a stable dose for at least 8 weeks before screening. Details of full inclusion and exclusion criteria are available in the supplementary material (appendix pp 17–18). All participants provided written informed consent.

Randomisation and masking

Participants were randomly assigned (1:1) to receive controlled-release morphine (5 mg twice daily orally) in period 1 followed by placebo (twice daily orally) in period 2 (sequence 1), or placebo in period 1 followed by morphine in period 2 (sequence 2). Using a computer-generated schedule (Sealed Envelope EDC version 7.6.1, patients randomly assigned sequentially to a sequence group defining the order in which morphine and placebo were to be given). Block randomisation of size 4 or 6 was undertaken and a unique kit code was assigned to each treatment kit (one bottle containing 30 capsules of controlled-release morphine or placebo). Morphine (Napp Pharmaceuticals, Cambridge, UK) was an over-encapsulated tablet and both the morphine and the matched placebo capsule were coloured Swedish orange to maintain masking. Patients, investigators, study nurses, and pharmacy personnel were masked to treatment allocation. Emergency unblinding via the electronic database system (Sealed Envelope EDC) was available in cases where knowledge of the treatment was considered essential for the appropriate clinical management or welfare of the participant.

Procedures

At the screening visit, participant's medical history and concomitant medication were reviewed, and blood tests (liver and renal function) and physical examination were performed. Patients were randomly assigned to a sequence of two treatment periods for 14 days separated by a 7-day washout. To reduce the number of on-site visits due to the COVID-19 pandemic, the day 14 visit was conducted remotely. Vital signs including measurements of body temperature, heart rate, blood pressure, oxygen saturation, and respiratory rate were performed to monitor safety at each on-site visit (on days 0, 22, and 36). Participants underwent efficacy measurements 24 h before the first dose of study drug and during the last 24 h of each treatment period (on days 0, 14, 22, and 36). These included 24-h ambulatory cough monitoring, assessment of cough VAS, and patient reported outcomes. Patient reported outcomes were emailed to participants from an electronic database (Sealed Envelope EDC) with instructions to complete them within 24 h of the visit. At the end of each treatment period, the global impression of change for cough, breathlessness, and overall quality of life (better, same, or worse) were recorded. A final follow-up remote telephone call was conducted 2 weeks after administration of the last treatment.

Cough frequency was measured using the VitaloJAK cough monitor (Vitalograph, Buckingham, UK), which is a custom built ambulatory digital recording device with a lapel microphone and contact sensor applied at the sternum. The sound files were processed using validated custom-written software (WH03_V1.12) to remove periods of silence and non-cough sounds.[10] Cough sounds were manually counted with audio-editing software (Adobe Audition, version 3.0).

Outcomes

The primary efficacy endpoint was the percentage change in frequency of daytime or awake cough (coughs per h) from baseline as centrally assessed by objective digital cough monitoring at day 14 (end of period 1) and day 36 (end of period 2). Secondary outcomes were change from baseline in patient reported outcomes (ie, cough VAS, Leicester Cough Questionnaire, Dyspnoea-12, Hospital and Depression Scale, King's Brief Interstitial Lung Disease questionnaire, Living with IPF questionnaire impacts and symptoms); and change from baseline in global impression of change in overall quality of life, cough, and breathlessness. Exploratory analyses of participants with a 20% or more or 50% or more reduction in awake cough frequency were conducted. Adverse events were recorded at each visit and assessed for severity. Trial medication compliance was also recorded.

Statistical analysis

Based on previous data on individuals with IPF[11] who were assessed for 11 days, a sample size of 40 participants was expected to have 90% power to detect a true difference in 24-h cough frequency on the natural log scale (–0.132 or 0.132, equivalent to about a 35% change) with a probability of 0.9; assuming a within-subject SD of 0.310 (natural log scale) and a two-sided p value of 0.05. Allowing for a 10% drop out rate, we aimed to recruit 44 participants for the study.

Baseline characteristics were summarised using means (SD) or median (IQR) for continuous variables, and frequencies for categorical variables. The primary analysis used data from the intention-to-treat population, which included all randomised participants. Only observed data were included and no imputation was used for missing data. A per-protocol analysis was also done for the primary endpoint, which included all participants who received at least 80% of the doses for the treatment period and provided a baseline and post-baseline primary endpoint observation for periods 1 and 2. A sensitivity analysis was performed by imputing worst-case scores for missing data. For cough frequency, the change from baseline was calculated after natural log transformation of the data. Average cough frequency was calculated as geometric means and standard error. To estimate the treatment effect, a generalised estimating equation model was used. This model included a response variable of log transformed awake cough frequency at end of treatment and a covariate of log transformed period-specific baseline awake cough frequency, and was adjusted for treatment, treatment sequence, and period.[12] Estimates were generated for differences between treatments with calculation of corresponding 95% CIs and p values. Statistical significance was determined at a two-sided 5%. No adjustments were made for multiple comparisons. Untransformed changes from baseline patient reported outcomes were analysed using similar generalised estimating equation models, but with appropriate covariates. Outcomes on global impression of change and responder analysis were summarised as frequencies within categories. Safety data were summarised for all patients who took at least one study drug and did not withdraw consent, in accordance with the Common Terminology Criteria for Adverse Events (version 5.0). Treatment adherence was defined as the number of tablets taken as a proportion of the number of tablets that should have been taken as directed by the investigator during a specific treatment period. Statistical analysis was conducted using SPSS, version 28.0. The trial was monitored by an independent data safety monitoring board and is registered with ClinicalTrials.gov, NCT04429516.

Role of the funding source
The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results
Between Dec 17, 2020, and March 21, 2023, 47 individuals were assessed for eligibility, and 44 were randomly assigned, of whom one withdrew consent before treatment. Of the 43 participants, 21 were randomly allocated to receive morphine in period 1 and then placebo in period 2, and 22 received placebo in period 1 and then morphine in period 2; figure 1). 43 participants completed morphine treatment. In the placebo group, before completion of treatment, one patient was excluded due to withdrawal of consent and one patient died. 41 participants completed placebo. The cough recording failed for two patients (ie, poor sound quality) at one time point, and two patients were found to have had less than 80% treatment compliance during a treatment period. These patients were all included in the ITT analysis but excluded from the per-protocol analysis. All 43 participants were included in the analysis for the primary outcome. The mean age was 71 years (SD 7·4) years (table 1). Of 44 participants, 31 (70%) were male and 13 (30%) were female. Mean FVC was 2·7 L (SD 0·76), mean predicted FVC was 82% (17·3), and mean predicted DLCO was 48% (10·9). Of 44 participants, 19 (43%) had gastroesophageal reflux disease, 13 (30%) used proton pump inhibitors, and 26 (59%) were on antifibrotic therapy. Two patients withdrew from the study for personal reasons (one died before starting placebo and one withdrew consent before starting placebo). Overall treatment adherence was 98% in the morphine group
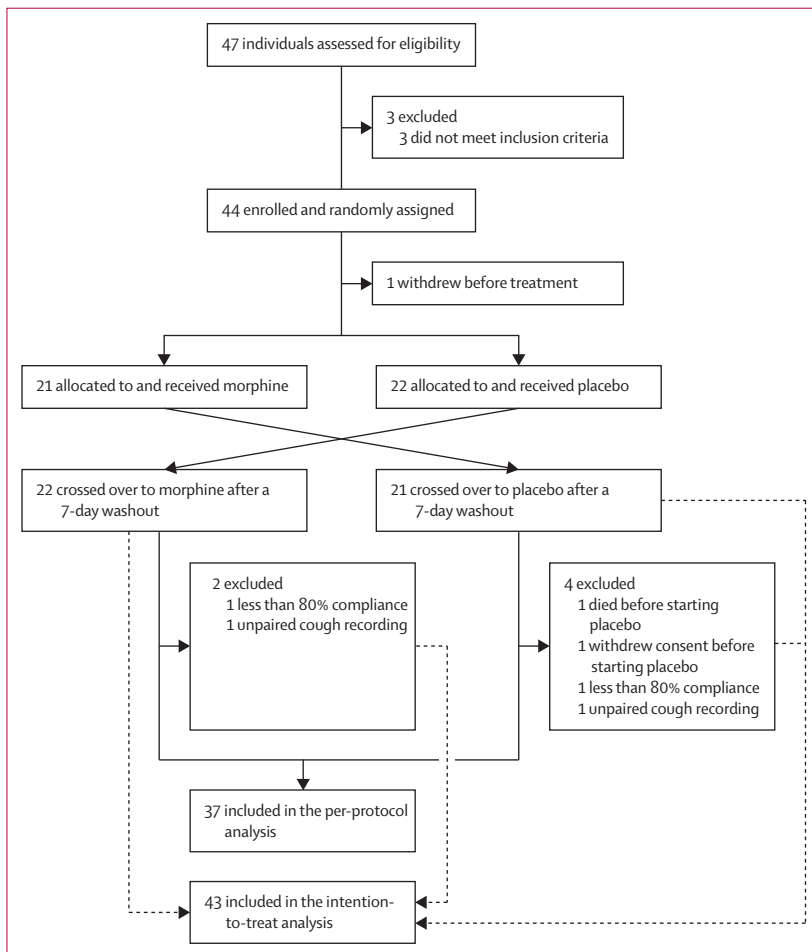

Figure 1: Trial profile
Dashed lines indicate intention-to-treat population and solid lines indicate per-protocol population.

	Total (n=44)
Sex	
Male	31 (70%)
Female	13 (30%)
Age, years	71 (7·4)
Ever smokers	24 (54%)
Ethnicity	
Caucasian	40 (91%)
Indian	4 (9%)
Gastroesophageal reflux disease	19 (43%)
Lung function	
FEV₁, L	2·2 (0·60)
Predicted FEV₁, %	87·1 (18·1)
FVC, L	2·7 (0·76)
Predicted FVC, %	82·4 (17·3)
DLCO, CO min⁻¹ kPa⁻¹	4·0 (1·17)
Predicted DLCO, %	48·5 (10·9)
Antifibrotic therapy	26 (59%)
Nintedanib	22 (50%)
Pirfenidone	4 (9%)
Proton pump inhibitor	13 (30%)
Ambulatory oxygen	4 (9%)

Data are n (%) or mean (SD). FVC=forced vital capacity. DLCO=diffusion capacity of carbon monoxide.

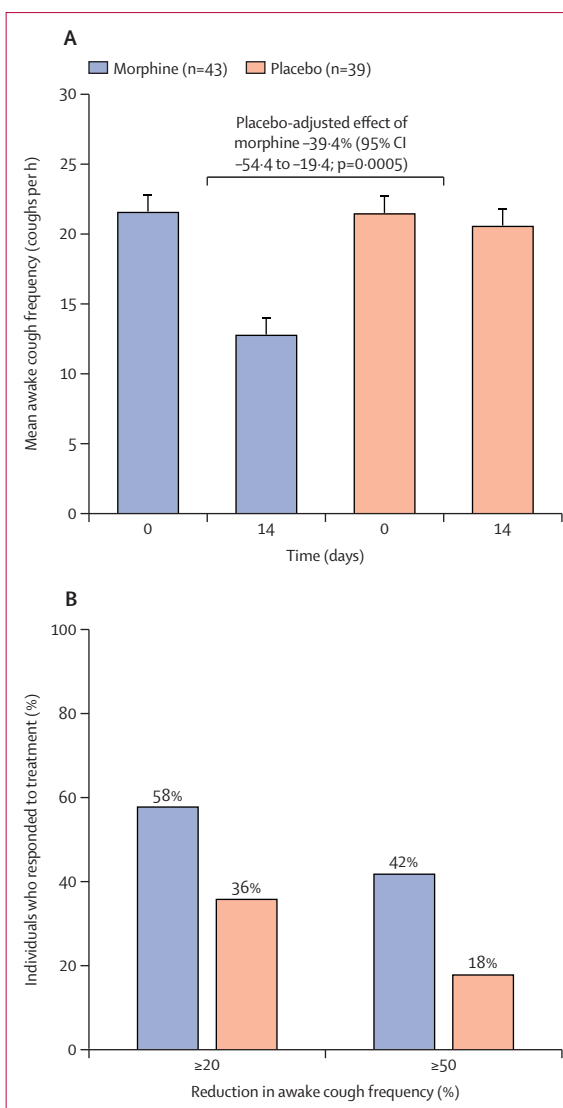***Table 1:* Baseline characteristics**

***Figure 2:* Change in awake cough frequency**
(A) Change in mean awake cough frequency at baseline and day 14.
(B) Responder analysis. Error bars represent SE.

and 98% in the placebo group. Baseline mean and median values for the primary and secondary outcomes are summarised in the appendix (p 2).

In the analysis for the primary outcome, controlled-release morphine treatment reduced daytime cough frequency by 39·4% (95% CI −54·4 to −19·4; p=0·0005) compared with placebo (figure 2A). Mean daytime cough frequency changed from 21·6 coughs per h (SE 1·2) at baseline to 12·8 coughs per h (SE 1·2) on day 14 with morphine treatment (−40·8%, −54·2 to −23·6; p<0·0001), and from 21·5 (1·2) coughs per h at baseline to 20·6 (1·2) coughs per h at day 14 in the placebo group (−4·3%, −21·8 to 17·0; p=0·66). In the per-protocol analysis, treatment with morphine reduced daytime cough frequency by 40·3% (−55·9 to −18·9; p=0·0009) compared with placebo (table 2). There was no significant effect of treatment period or sequence in either analysis (appendix p 3). Sensitivity analyses were consistent with the primary analysis (appendix p 4).

Treatment with controlled-release morphine improved all cough-related patient-reported outcomes: cough VAS reduced by 16·1 mm (95% CI −22·3 to −9·9; p<0·0001) and Leicester Cough Questionnaire increased by 1·8 points (0·9 to 2·8; p=0·0002) from baseline. Scores reduced for L-IPF impacts (−5·2 points, 95% CI −9·9 to −0·4; p=0·033) and L-IPF overall symptoms (−5·2 points, −8·9 to −1·4; p=0·0078) with morphine, with improvement in the cough domain (−10·8 points,

−16·9 to −4·8; p=0·0004). These effects remained significant when adjusting for placebo (table 2). A period effect was observed in the L-IPF Symptoms cough domain, with patients in period 2 reporting higher scores, indicating worse cough (7·5 points, 95% CI 0·35 to 14·57; p=0·040). Morphine had no effect on breathlessness (as measured by Dyspnoea-12 and L-IPF Symptoms dyspnoea domain), anxiety or depression scores (Hospital and Depression Scale), King's Brief Interstitial Lung Disease questionnaire, or L-IPF Symptoms energy domain. With respect to global impression of change, morphine treatment led to an improvement in cough in over half of participants (24 [56%] of 43) and overall quality of life in a third (14 [32%] of 43); appendix p 4). In the cough responder

	Morphine			Placebo			Difference at 14 days	
	Baseline	Day 14	Change	Baseline	Day 14	Change	Placebo-adjusted effect of morphine (95% CI)*	p value
Awake cough frequency (coughs per h; ITT)	21·6 (1·2); n=43	12·8 (1·2); n=43	−40·8% (−54·2 to −23·6); p<0·0001	21·5 (1·2); n=39	20·6 (1·2); n=39	−4·3% (−21·8 to 17·0); p=0·66	−39·4% (−54·4 to −19·4)	0·0005
Awake cough frequency (coughs per h; per protocol)	24·2 (1·2); n=37	13·8 (1·2); n=37	−43·1% (−57·0 to −24·7); p<0·0001	23·6 (1·2); n=37	22·4 (1·2); n=37	−5·2% (−23·2 to 13·6); p =0·62	−40·3% (−55·9 to −18·9)	0·0009
Cough VAS†	61·5 (2·4); n=43	45·5 (3·7); n=43	−16·1 (−22·3 to −9·9); p<0·0001	57·7 (2·8); n=41	57·3 (2·7); n=41	−0·4 (−5·8 to 4·9); p=0·88	−14·6 (−22·8 to −6·5)	0·0004
LCQ‡	13·2 (0·5); n=43	15·0 (0·6); n=43	1·8 (0·9 to 2·8); p=0·0002	13·0 (0·5); n=41	13·6 (0·5); n=41	0·6 (−0·2 to 1·3); p=0·15	1·3 (0·4 to 2·3)	0·0047
Dyspnoea-12§	13·0 (1·2); n=43	12·9 (1·3); n=43	−0·1 (−1·9 to 1·6) p = 0·87	13·5 (1·4); n=41	14·3 (1·4); n=41	0·9 (−0·5 to 2·2); p=0·22	−1·2 (−3·1 to 0·8)	0·24
HADS anxiety¶	5·1 (0·5); n=43	5·2 (0·6); n=43	0·1 (−0·1 to 0·2); p=0·30	4·9 (0·6); n=40	5·0 (0·6); n=40	0·0 (−0·1 to 0·0); p=0·43	−0·2 (−0·9 to 0·6)	0·64
HADS depression¶	5·3 (0·6); n=43	5·3 (0·6); n=43	0·0 (0·0 to 0·0); p=0·68	5·5 (0·7); n=40	5·4 (0·7); n=40	−0·1 (−0·2 to 0·1); p=0·23	−0·2 (−1·0 to 0·6)	0·57
KBILD‖	58·2 (3·1); n=43	57·9 (3·1); n=43	−0·2 (−0·6 to 0·2); p=0·31	55·7 (3·3); n=40	55·9 (3·4); n=40	0·2 (−0·5 to 0·9); p=0·61	2·7 (−2·6 to 8·1)	0·32
L-IPF impacts**	60·9 (3·8); n=42	55·8 (3·8); n=42	−5·2 (−9·9 to −0·4); p=0·033	61·8 (4·0); n=40	60·1 (3·8); n=40	−1·7 (−5·5 to 2·1) p=0·38	−4·5 (−8·3 to −0·7)	0·019
L-IPF symptoms (total)**	40·9 (2·9); n=41	35·7 (3·1); n=41	−5·2 (−8·9 to −1·4); p=0·0078	40·9 (3·3); n=40	41·4 (3·4); n=40	0·5 (−2·5 to 3·4); p=0·75	−6·7 (−11·2 to −2·3)	0·0031
Dyspnoea domain	31·9 (3·7)	28·8 (3·6)	−3·1 (−7·9 to 1·8); p=0·22	32·1 (3·9)	31·9 (4·0)	−0·1 (−2·6 to 2·5); p=0·95	−1·5 (−6·2 to 3·2)	0·53
Cough domain	50·3 (3·7)	39·5 (3·8)	−10·8 (−16·9 to −4·8); p=0·0004)	50·1 (3·6)	49·6 (3·8)	−0·5 (−6·2 to 5·1); p=0·85	−11·9 (−18·7 to −5·1)	0·0006
Energy domain	44·2 (3·3)	44·8 (3·6)	0·6 (−4·3 to 5·6); p=0·81	44·5 (3·9)	47·9 (3·9)	3·4 (−1·3 to 8·2); p=0·16	−3·3 (−8·3 to 1·6)	0·19

Data are mean (SE); n, unless otherwise specified. HADS=Hospital Anxiety and Depression Scale. ITT=intention to treat. KBILD=King's Brief Interstitial Lung Disease. LCQ=Leicester Cough Questionnaire. L-IPF=Living with Idiopathic Pulmonary Fibrosis. VAS=visual analogue scale. *Generalised estimating equation model with baseline measurement as covariate and adjusting for treatment, treatment sequence, and period. †The cough severity score ranges from 0 mm to 100 mm, indicating no cough to the worst cough. ‡The LCQ is a cough-specific quality-of-life score that ranges from 3 to 21, with higher values indicating a better quality of life. § The Dyspnoea-12 score assesses subjective breathlessness, with 12 items. The range of scores is between 0 and 36, with higher scores representing greater levels of dyspnoea. ¶The HADS score is divided into the anxiety and depression domains. Each domain has a score ranging from 0 to 21, with higher scores suggestive of greater impairment. Scores 0–7 represents normal impairment, 8–10 is borderline abnormal impairment, and 11–21 is abnormal impairment. ‖The KBILD is a specific quality-of-life tool in interstitial lung disease, notably with the absence of cough specific questions. Scores range from 0 to 100, with higher scores indicating a better quality of life. **The L-IPF is a 35-item survey. The symptoms module (with subdomains in dyspnoea, cough, and energy) contains 15 items assessing the past 24 h. The impacts module consists of 20 items asking recall over the past 7 days. Each score, including the subdomains, ranges from 0 to 100. Higher values denote greater impairment.

Table 2: **Primary and secondary outcomes**

	Morphine (n=43)	Placebo (n=42)
Any adverse event	17 (40%)	6 (14%)
Serious adverse events	0	1 (2%)
Gastrointestinal disorders		
Nausea	6 (14%)	3 (7%)
Vomiting	2 (5%)	1 (2%)
Constipation	9 (21%)	0
Nervous system disorders		
Hypersomnia	4 (9%)	2 (5%)
General disorders		
Lethargy	2 (5%)	0
Respiratory disorders		
Lung infection	1 (2%)	1 (2%)

Data are n (%). The single serious adverse event with placebo treatment resulted in death.

Table 3: **Adverse events**

analysis, morphine reduced awake cough frequency by 20% or more in 25 (58%) of 43 participants and by 50% or more in 18 (42%) of 43 participants (figure 2B). In the placebo group, awake cough frequency reduced by 20% or more in 14 (36%) of 39 participants and by 50% or more in seven (18%) of 39 participants.

Adverse events were observed in 17 (40%) of 43 participants in the controlled-release morphine treatment group and six (14%) of 42 participants in the placebo group (table 3). The most common side-effects with morphine were constipation (nine [21%] of 43 participants) and nausea (six [14%] of 43 participants). Initiation of laxatives was not required during treatment with morphine. One participant developed nausea (moderate) and hypersomnia (severe) with morphine treatment and discontinued treatment, having taken half of the prescribed regimen. Only one severe adverse event occurred (lung infection resulting in death during placebo treatment), which was attributed to underlying IPF disease trajectory.

Discussion

This multicentre study shows that low-dose controlled-release morphine is effective in reducing awake cough frequency and improving quality of life in participants with significant IPF-related cough. Morphine reduced daytime cough frequency by at least 20% and improved the global impression of change in cough in more than half of patients. The improvements seen in patient reported outcomes were robustly mirrored across multiple tools. Treatment was generally well tolerated by most participants.

There is a large unmet need for treatments that improve quality of life in individuals with IPF and address highly prevalent and frequently disabling symptoms like cough. A recent study assessing the longitudinal effects of cough burden on quality of life in IPF highlighted the stability of this symptom over time.[13] Insufficient clarity about the pathogenic mechanisms driving cough in IPF has limited the therapeutic options available to patients and clinicians. Individuals with IPF have been shown to have a more sensitive cough reflex than healthy volunteers.[14] Cough is mediated by vagal afferents that innervate the larynx and airways and synapse in the brainstem. Although much can be learnt from studies on refractory chronic cough when considering the treatment of IPF-related cough, the biological mechanisms that contribute to cough probably differ in these conditions. This difference is evidenced by the contrasting results observed between refractory chronic cough and IPF with gefapixant, a peripherally acting P2X3 receptor antagonist.[15,16]

Use of opioids in patients with chronic respiratory disease is often curbed due to concerns about side-effects and the potential for addiction and abuse. In a recent trial, extended release nalbuphine, a dual acting κ-opioid agonist or μ-opioid antagonist, reduced awake cough frequency in individuals with IPF by 51·6%.[17] However, almost a quarter of participants discontinued treatment during nalbuphine treatment due to side-effects. Further studies are required to establish a dose that preserves clinical benefit with optimal tolerability. By contrast, in our trial only one participant discontinued low-dose controlled-release morphine treatment and a lower proportion of participants developed side-effects than participants in the nalbuphine study. Safety assessments conducted during study visits were reassuring. Moreover, the stability of scores in the Hospital and Depression Scale and L-IPF Symptoms energy domain suggests there were no changes in mood or excessive fatigue with morphine.

The corroborative findings of improvements in cough-related patient reported outcomes and reduction in objective cough counts support the role of low-dose controlled-release morphine as an antitussive in IPF. Studies on refractory chronic cough have established that reductions in cough frequency of 20–30% and improvement in Leicester Cough Questionnaire by 1·3 points or more are clinically meaningful.[18] Swigris and colleagues showed that a 4-point to 5-point change in the cough domain of an adapted version of the L-IPF survey, targeting individuals with progressive non-IPF interstitial lung disease, represented a meaningful difference.[19] In our study, treatment with morphine reduced cough frequency by 39·4% at 14 days compared with placebo, improved Leicester Cough Questionnaire scores by 1·8 points compared with baseline, and reduced L-IPF cough domain scores by 10·8 points compared with baseline. Morphine did not alleviate breathlessness. However, a change in dyspnoea was not the primary objective of our study and patients with severe disease were excluded. Therefore, baseline Dyspnoea-12 scores were lower than scores in other published cohorts.[20,21]

Our study has some limitations. Patients with severe fibrosis, in particular individuals requiring long-term oxygen therapy and with a life expectancy of less than 6 months, were excluded. Although the antitussive effect of morphine is expected to be maintained in individuals with severe IPF, caution would need to be taken when monitoring for potential adverse effects. Although we did not examine subjective opioid withdrawal measures, there were no documented withdrawal symptoms during the study or follow-up period. A 7-day washout window has been used in previous trials of morphine[22] and was used here, and although morphine clearance was not tested, the absence of a treatment sequence effect suggests that there was no carry-over effect of morphine. A fixed dose of morphine was used in this study; however, titrating or escalating dosages might be beneficial for individuals who did not respond to treatment, which should be the focus of future studies. Treatment with morphine was only administered for 2 weeks. Therefore, the durability of the antitussive effect of morphine and its long-term safety should be assessed in randomised controlled trials.

Treatment with low dose controlled-release morphine significantly improved objective and subjective cough measures in patients with IPF-associated cough. Given the negative effects of cough in individuals with IPF, these findings merit its short-term use in clinical practice. Longer term studies should be the focus of future research.

References
1 Maher TM, Wells AU, Laurent GJ. Idiopathic pulmonary fibrosis: multiple causes and multiple mechanisms? *Eur Respir J* 2007; **30**: 835–39.
2 Rajala K, Lehto JT, Sutinen E, Kautiainen H, Myllärniemi M, Saarto T. mMRC dyspnoea scale indicates impaired quality of life and increased pain in patients with idiopathic pulmonary fibrosis. *ERJ Open Res* 2017; **3**: 84–2017.
3 Ryerson CJ, Abbritti M, Ley B, Elicker BM, Jones KD, Collard HR. Cough predicts prognosis in idiopathic pulmonary fibrosis. *Respirology* 2011; **16**: 969–75.
4 Chung KF, Birring SS, Morice AH, et al. Tackling the neuropathic cough of idiopathic pulmonary fibrosis (IPF): more needs to be done. *Lung* 2022; **200**: 673–75.
5 Morice AH, Menon MS, Mulrennan SA, et al. Opiate therapy in chronic cough. *Am J Respir Crit Care Med* 2007; **175**: 312–15.
6 Kohberg C, Andersen CU, Bendstrup E. Opioids: an unexplored option for treatment of dyspnoea in IPF. *Eur Clin Respir J* 2016; **3**: 30629.
7 Bajwah S, Davies JM, Tanash H, Currow DC, Oluyase AO, Ekström M. Safety of benzodiazepines and opioids in interstitial lung disease: a national prospective study. *Eur Respir J* 2018; **52**: 1801278.
8 Wu Z, Banya W, Chaudhuri N, et al. PAciFy Cough—a multicentre, double-blind, placebo-controlled, crossover trial of morphine sulphate for the treatment of pulmonary fibrosis cough. *Trials* 2022; **23**: 184.
9 Raghu G, Remy-Jardin M, Myers JL, et al. Diagnosis of idiopathic pulmonary fibrosis: an Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *Am J Respir Crit Care Med* 2018; **198**: e44–68.
10 Smith JA, Holt K, Dockry R, et al. Performance of a digital signal processing algorithm for the accurate quantification of cough frequency. *Eur Respir J* 2021; **58**: 2004271.
11 Key AL, Holt K, Hamilton A, Smith JA, Earis JE. Objective cough frequency in idiopathic pulmonary fibrosis. *Cough* 2010; **6**: 4.
12 Wellek S, Blettner M. On the proper use of the crossover design in clinical trials: part 18 of a series on evaluation of scientific publications. *Dtsch Arztebl Int* 2012; **109**: 276–81.
13 Saunders P, Wu Z, Fahy WA, et al. The burden and impact of cough in patients with idiopathic pulmonary fibrosis: an analysis of the prospective observational PROFILE study. *Ann Am Thorac Soc* 2023; **20**: 1267–73.
14 Hope-Gill BDM, Hilldrup S, Davies C, Newton RP, Harrison NK. A study of the cough reflex in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2003; **168**: 995–1002.
15 Martinez FJ, Afzal AS, Smith JA, et al. Treatment of persistent cough in subjects with idiopathic pulmonary fibrosis (IPF) with gefapixant, a P2X3 antagonist, in a randomized, placebo-controlled clinical trial. *Pulm Ther* 2021; **7**: 471–86.
16 McGarvey LP, Birring SS, Morice AH, et al. Efficacy and safety of gefapixant, a $P2X_3$ receptor antagonist, in refractory chronic cough and unexplained chronic cough (COUGH-1 and COUGH-2): results from two double-blind, randomised, parallel-group, placebo-controlled, phase 3 trials. *Lancet* 2022; **399**: 909–23.
17 Maher TM, Avram C, Bortey E, et al. Nalbuphine tablets for cough in patients with idiopathic pulmonary fibrosis. *NEJM Evid* 2023; published online May 22. https://doi.org/10.1056/EVIDoa2300083.
18 Nguyen AM, Schelfhout J, Muccino D, et al. Leicester Cough Questionnaire validation and clinically important thresholds for change in refractory or unexplained chronic cough. *Ther Adv Respir Dis* 2022; **16**: 17534666221099737.
19 Swigris JJ, Bushnell DM, Rohr K, Mueller H, Baldwin M, Inoue Y. Responsiveness and meaningful change thresholds of the Living with Pulmonary Fibrosis (L-PF) questionnaire dyspnoea and cough scores in patients with progressive fibrosing interstitial lung diseases. *BMJ Open Respir Res* 2022; **9**: e001167.
20 Ekström MP, Bornefalk H, Sköld CM, et al. Minimal clinically important differences and feasibility of Dyspnea-12 and the Multidimensional Dyspnea Profile in cardiorespiratory disease. *J Pain Symptom Manage* 2020; **60**: 968–975.e1.
21 Yorke J, Swigris J, Russell A-M, et al. Dyspnea-12 is a valid and reliable measure of breathlessness in patients with interstitial lung disease. *Chest* 2011; **139**: 159–64.
22 Al-Sheklly B, Mitchell J, Issa B, et al. S35 Randomised control trial quantifying the efficacy of low dose morphine in a responder group of patients with refractory chronic cough. *Thorax* 2017; **72** (suppl 3): a242–25.