# ILD 환자의 동반 증상 조절


2024.6.29

ILD school

분당서울대학교병원 호흡기내과

박종선

# Symptoms of IPF/ILD

Comorbidities


Medication side effects

van Manen MJ et al, Ther Adv Respir Dis 2017:11(3); 157–169

# Symptoms of IPF/ILD

- Cough
- Dyspnea

- Related to Quality of Life

- Patient Reported Outcome (PRO)
- Patient-Centered Outcome Research (PCOR)

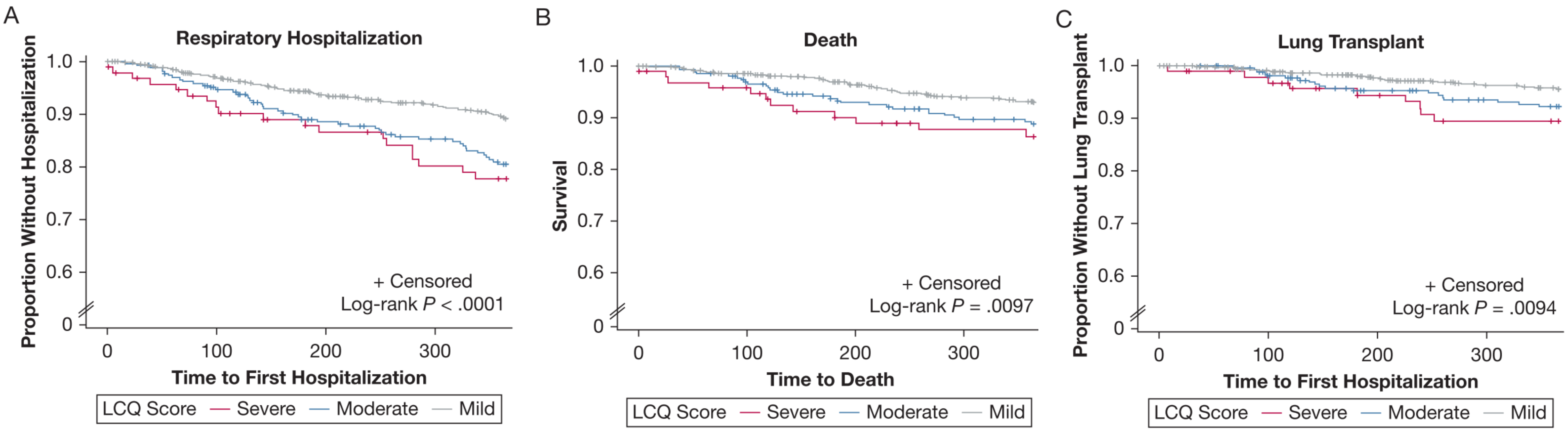
# Cough in Interstitial lung diseases

- Cough is a common symptom (up to 80%) in patients with ILD.
- Cough is frustrating and leads to a substantial impairment in the quality of life of patients with ILD.

Wakwaya Y., et al Chest. 2021:160; 1774-1782

# Cough specific QOL is associated with prognosis in ILD

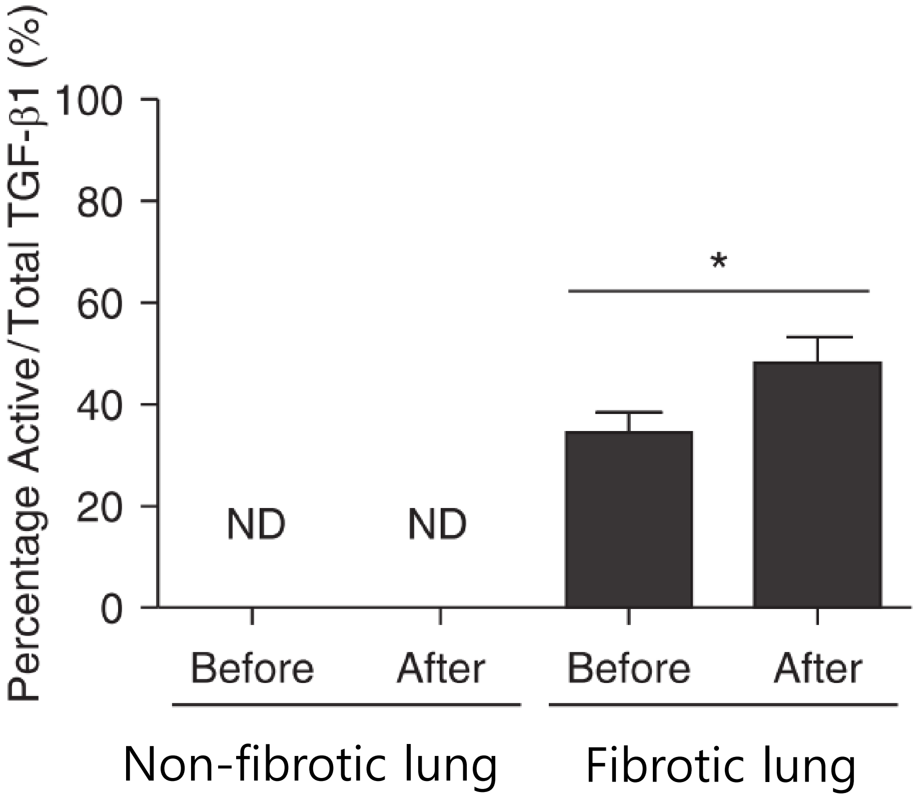
- Pulmonary Fibrosis Foundation Registry (PFFR): 1447 ILD patients
- The Leicester Cough Questionnaire (LCQ): Cough-specified QOL
    - ✓ mild (≥ 14), moderate (10 to < 14), severe (7 to < 10) and very severe (< 7)



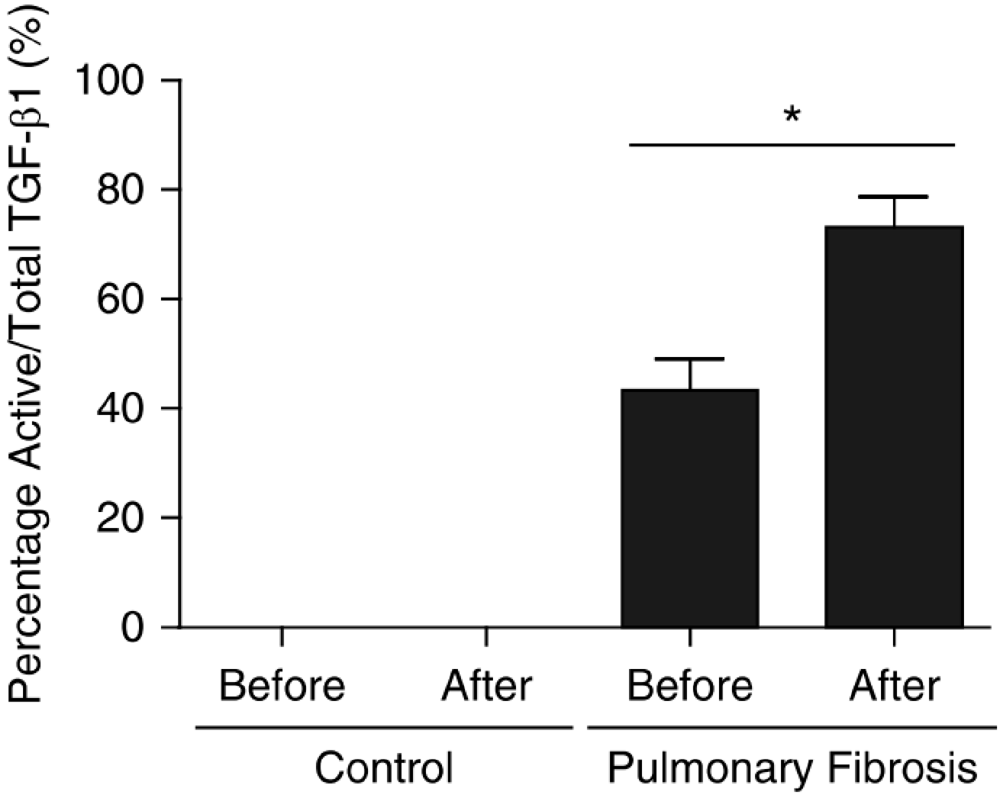

Chest. 2022;162(3):603-613.

# Cough can contribute to a pro-fibrotic feedback

- In vivo study
  - Rat model (fibrotic lung / non-fibrotic)
  - Mechanical stress

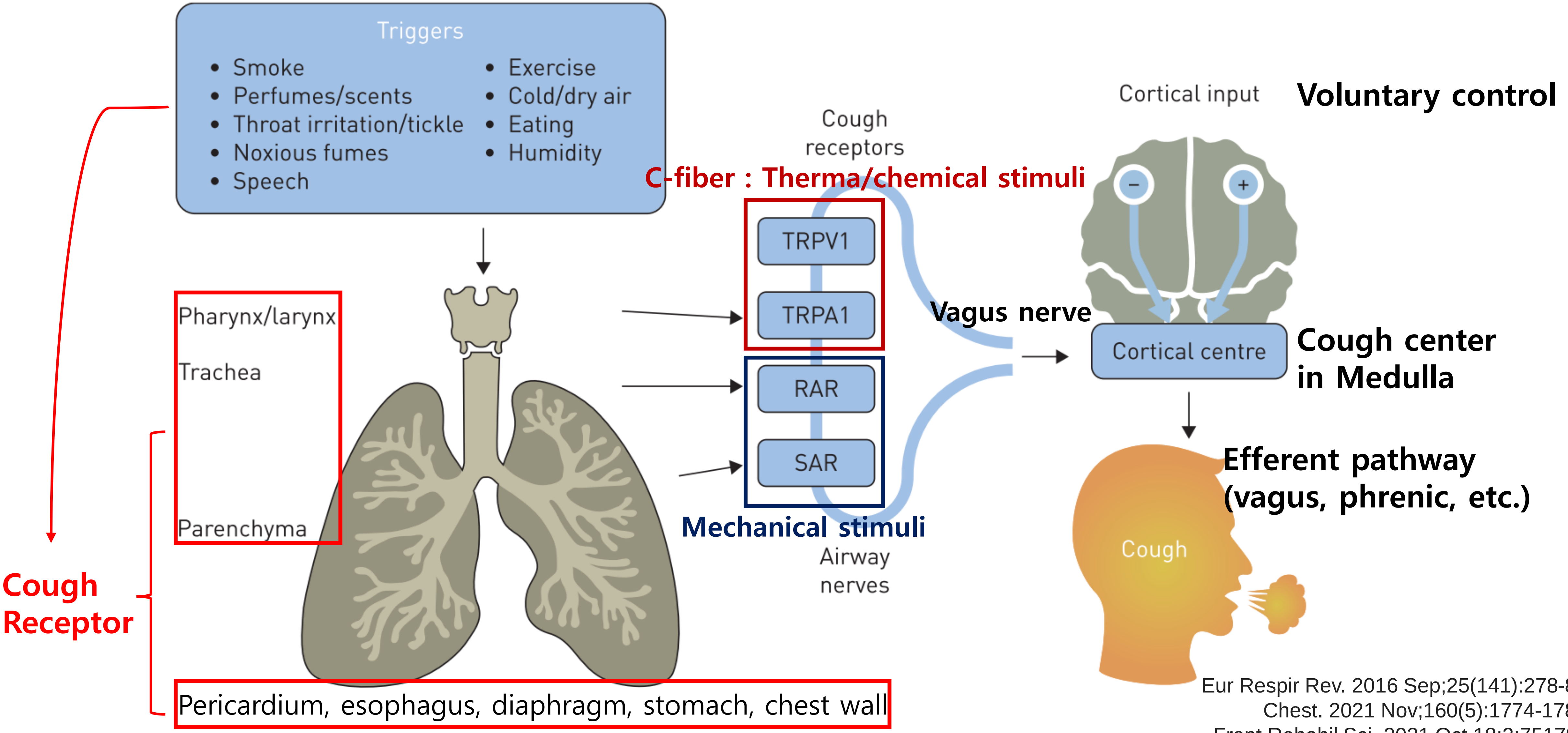



- Ex vivo study
  - Human (UIP lung /Control lung)
  - Mechanical stress




Am J Respir Crit Care Med. 2016 Jul 1;194(1):84-96.

# Cough reflex is important defensive mechanism




Eur Respir Rev. 2016 Sep;25(141):278-86.
Chest. 2021 Nov;160(5):1774-1782.
Front Rehabil Sci. 2021 Oct 18;2:751798.

# Mechanisms of cough in ILD

- Increased cough reflex sensitivity
  - Increased traction forces impacting the function of stretch receptors
  - Destruction of inhibitory nerves by fibrosis or upregulation of vagal sensory fibers

- Change in Mucous Production
  - A common variant in the promoter region of the mucin 5B (MUC5B) gene
  - Increases production of MUC5B, an airway mucin
  - Correlate with severe-coughing clinical phenotype

Am J Respir Crit Care Med. 2003 Oct 15;168(8):995-1002.
Cough. 2014 Mar 25;10:3.

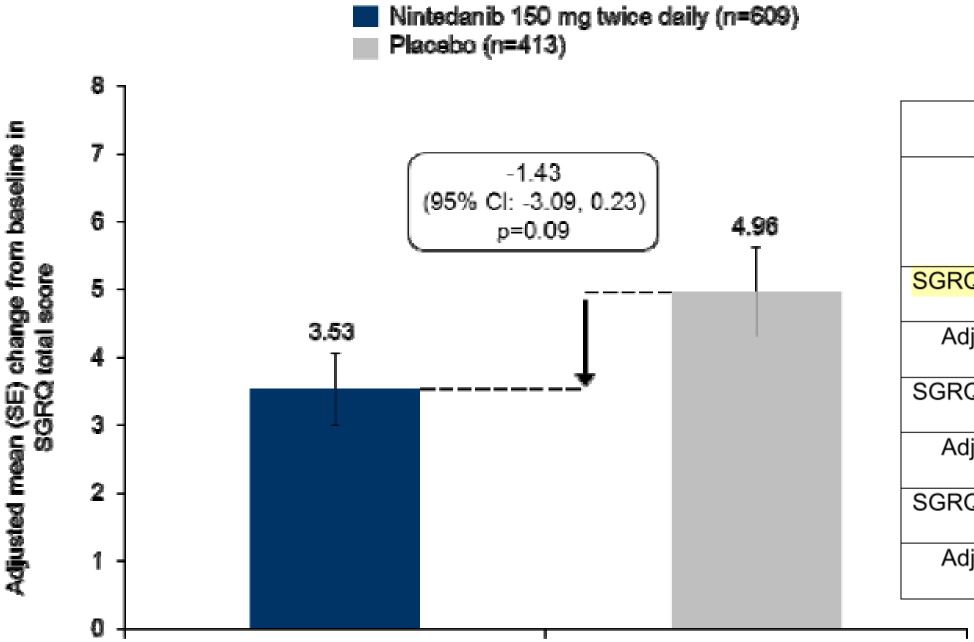
# Comorbid condition associated with IPF

| System | Diagnosis | Proposed mechanisms of cough | Prevalence in IPF |
|---|---|---|---|
| Respiratory and sleep | Infection: tuberculosis, pertussis, lung abscess, protracted bacterial bronchitis | Excess mucous production, loss of ciliary structure, airway inflammation | NA* |
| | Chronic obstructive pulmonary disease, bronchiectasis | Excess mucous production, C-fiber nerve activity | 6–67% (37) |
| | Asthma | Bronchial hyperreactivity | 8.5–18.6% (38)† |
| | Lung cancer | C-fiber nerve activity | 10–30% (39) |
| | Obstructive sleep apnoea | Upper airway inflammation and injury due to airway obstruction | 22–90% (40) |
| Ear nose and throat | Earwax or foreign body | Stimulation of branch of the vagal nerve innervating external auditory canal | NA |
| | Chronic sinusitis | Direct irritation of the vocal cords, sensitization of the cough reflex | NA |
| | Vocal cord dysfunction | Paradoxical vocal cord movement and glottis closure with airway narrowing | NA |
| Gastrointestinal | Gastro-esophageal reflux disease | Microaspiration and direct irritation, sensitization of the cough reflex due to activation of vagal nerve endings in the esophagus | 87–94% (41–44)‡ |
| Cardiovascular | Left ventricular failure | Pulmonary c-fibers activated by pulmonary venous congestion and oedema (45) | 4–26% (37) |
| | Arrhythmia | Mediators of cough (bradykinin and substance *P*) accumulate in the upper airway | NA§ |
| Drugs/toxins | Angiotensin-converting enzyme inhibitor use | Mediators of cough (bradykinin and substance *P*) accumulate in the upper airway | NA¶ |

Front Rehabil Sci. 2021 Oct 18;2:751798.

# Nintedanib in IPF

- IMPULSIS trial
  - Change in SGRQ over 52 weeks in 2nd outcome




| | INPULSIS™-1 and INPULSIS™-2 (pooled data) | | | |
|---|---|---|---|---|
| | Nintedanib 150 mg twice daily | Placebo | Difference vs. placebo (95% CI) | P-value |
| SGRQ symptoms domain* | | | | |
| Adjusted mean (SE) change from baseline | 1.82 (0.765) | 3.67 (0.935) | -1.85 (-4.22, 0.51) | 0.12 |
| SGRQ activity domain† | | | | |
| Adjusted mean (SE) change from baseline | 4.24 (0.625) | 6.54 (0.761) | -2.30 (-4.23, -0.37) | 0.02 |
| SGRQ impact domain‡ | | | | |
| Adjusted mean (SE) change from baseline | 3.83 (0.627) | 4.98 (0.760) | -1.15 (-3.08, 0.78) | 0.24 |

Respir Res. 2020 Jan 30;21(1):36.

# Nintedanib in IPF

**Table 7** Nintedanib-placebo median treatment difference for absolute change from baseline to 52 weeks on each PRO measure, by stratification subgroup (analysis 3)

| PRO measure | Median (95% confidence interval) nintedanib-placebo treatment difference | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | GAP | | FVC | | $DL_{CO}$ | | CPI | | SGRQ | |
| | I | II/III | > 80% | ≤ 80% | > 40% | ≤ 40% | ≤ 45 | > 45 | ≤ 40 | > 40 |
| *N*, range nintedanib; placebo | 240–260; 161–171 | 241–260; 161–173 | 226–245; 148–163 | 255–275; 174–182 | 335–363; 226–242 | 146–157; 96–102 | 211–230; 149–161 | 270–290; 173–183 | 257–277; 183–200 | 214–231; 136–142 |
| SGRQ total | −0.1 (−2.8, 2.6) | −3.3 (−6.1, −0.5) | −0.8 (−3.4, 1.8) | −2.7 (−5.5, 0.1) | −0.9 (−3.1, 1.3) | −3.9 (−7.7, −0.3) | −0.6 (−3.2, 2.2) | −2.8 (−5.5, -0.2) | −1.0 (−3.1, 1.3) | −2.5 (−5.9, 1.1) |
| SGRQ symptom | −2.7 (−6.6, 1.3) | −1.0 (−4.9, 2.7) | −1.8 (−5.7, 2.2) | −2.0 (−5.9, 1.9) | −1.3 (−4.6, 2.0) | −3.3 (−8.2, 1.7) | −1.7 (−5.9, 2.4) | −2.0 (−5.6, 1.6) | −2.7 (−6.1, 0.6) | −0.7 (−5.2, 3.9) |
| SGRQ activity | −0.1 (−5.0, 0.9) | −5.5 (−6.7, −0.4) | −0.6 (−5.8, 0.3) | −4.1 (−6.6, −0.0) | −0.5 (−5.3, 0.1) | −6.0 (−7.6, −0.4) | −0.1 (−5.3, 1.0) | −5.3 (−6.7, −0.3) | −0.3 (−5.5, 0.2) | −4.8 (−6.8, 0.0) |
| SGRQ impacts | 0.3 (−2.8, 3.2) | −2.9 (−6.2, 0.3) | −0.9 (−3.9, 1.9) | −1.8 (-5.2, 1.5) | −0.6 (−3.1, 1.9) | −3.4 (−7.9, 1.0) | −0.3 (−3.3, 2.5) | −2.4 (−5.6, 0.9) | 0.0 (−2.4, 2.1) | −2.8 (−7.0, 1.3) |
| UCSD-SOBQ | 1.0 (−3.0, 4.0) | −4.0 (−7.0, 0.0) | 1.0 (−2.0, 5.0) | −4.0 (−8.0, 0.0) | 0.0 (−3.0, 2.0) | −5.0 (−10.0, 0.0) | 0.0 (−4.0, 3.0) | −3.0 (−6.0, 1.0) | 0.0 (−3.0, 2.0) | −3.0 (−8.0, 2.0) |
| CASA-Q cough symptom* | 0.0 (−0.0, 0.0) | 0.0 (0.0, 8.3) | 0.0 (0.0, 8.3) | 0.0 (-0.0, 8.3) | 0.0 (0.0, 0.0) | 0.0 (−0.0, 8.3) | 0.0 (−0.0, 0.0) | 0.0 (0.0, 8.3) | 0.0 (0.0, 8.3) | 0.0 −0.0, 8.3) |
| CASA-Q cough impact* | 0.0 (−3.1, 3.1) | 3.1 (0.0, 6.3) | 3.1 (0.0, 6.3) | 3.1 (0.0, 6.3) | 3.1 (0.0, 3.1) | 3.1 (0.0, 9.4) | 0.0 (−3.1, 3.1) | 3.1 (0.0, 6.3) | 0.0 (0.0, 3.1) | 3.1 (0.0, 6.3) |
| EQ-5D VAS* | 0.0 (0.0, 5.0) | 4.0 (0.0, 8.0) | 2.0 (0.0, 5.0) | 3.0 (0.0, 6.0) | 1.0 (0.0, 5.0) | 5.0 (0.0, 10.0) | 3.0 (0.0, 5.0) | 1.0 (0.0, 5.0) | 0.0 (0.0, 4.0) | 5.0 (0.0, 10.0) |

$p < 0.05$

$0.05 \leq p < 0.10$

Respir Res. 2020 Jan 30;21(1):36.

# Nintedanib in PPF

## Effects of nintedanib on symptoms in patients with progressive pulmonary fibrosis

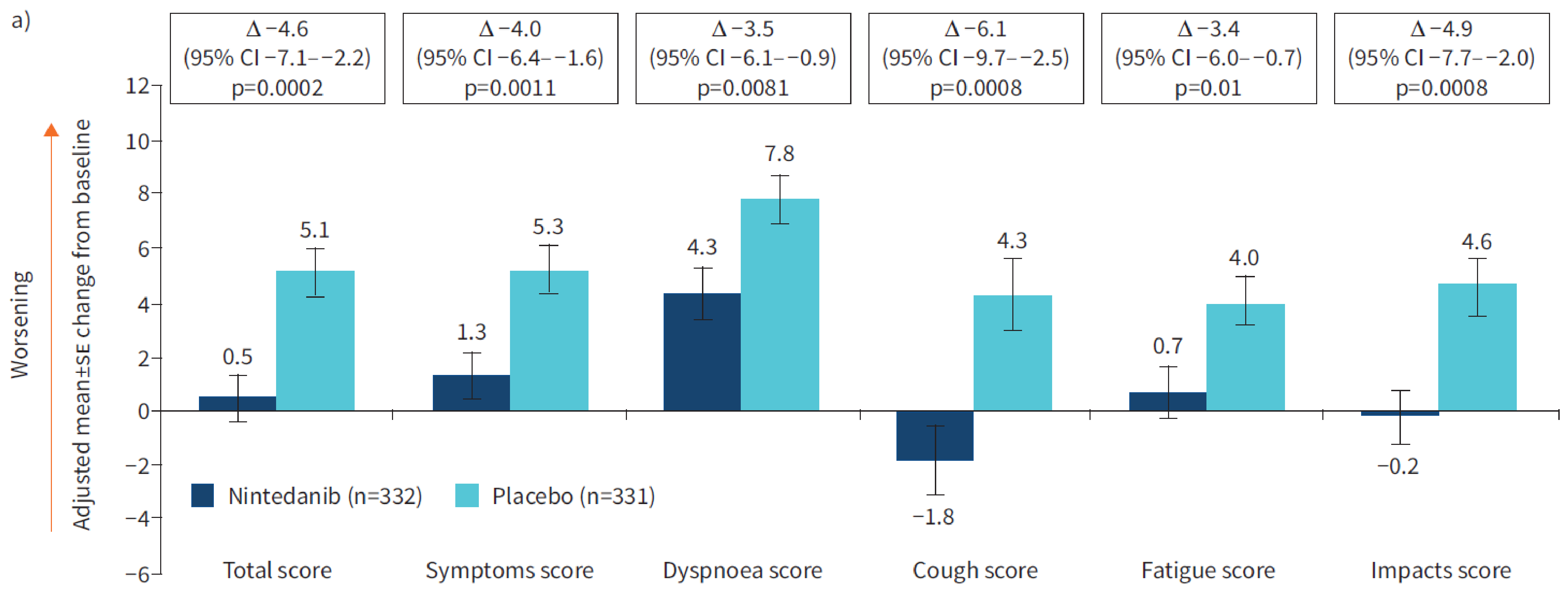
Marlies Wijsenbeek[1], Jeffrey J. Swigris[2], Yoshikazu Inoue[3], Michael Kreuter[4,5], Toby M. Maher[6,7], Takafumi Suda[8], Michael Baldwin[9], Heiko Mueller[10], Klaus B. Rohr[9] and Kevin R. Flaherty[11] on behalf of the INBUILD Trial Investigators

[1]Centre for Interstitial Lung Diseases and Sarcoidosis, Department of Respiratory Medicine, Erasmus MC, University Medical Centre, Rotterdam, The Netherlands. [2]National Jewish Health, Denver, CO, USA. [3]National Hospital Organization Kinki-Chuo Chest Medical Center, Osaka, Japan. [4]Center for Pulmonary Medicine, Department of Pneumology, Mainz University Medical Center, Mainz, Germany. [5]Pulmonary, Critical Care and Sleep Medicine, Marienhaus Clinic Mainz, Mainz, Germany. [6]Inflammation, Repair and Development Section, National Heart and Lung Institute, Imperial College London, London, UK. [7]Keck School of Medicine, University of Southern California, Los Angeles, CA, USA. [8]Department of Internal Medicine, Hamamatsu University School of Medicine, Hamamatsu, Japan. [9]Boehringer Ingelheim International GmbH, Ingelheim, Germany. [10]Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany. [11]Division of Pulmonary and Critical Care Medicine, University of Michigan, Ann Arbor, MI, USA.

- INBUILD trial
- Absolute changes in L-PF questionnaire cough and dyspnea domain scores at week 52 : secondary end-point

Wijsenbeekk M. et al, Eur Respir J 2024; 63: 2300752

# Changes in L-PF questionnaire scores in INBUILD study




Wijsenbeekk M. et al, Eur Respir J 2024; 63: 2300752

# Effect of 12 weeks of pirfenidone treatment on objective and subjective cough and health status measures

| | Baseline | At 12 weeks | Change# (95% CI) | p-value# |
|---|---|---|---|---|
| Subjects n | 43 | 31 | | |
| 24-h cough | 520 (91 to 3394) | 392 (75 to 1746) | −34% (−48 to −15%) | 0.002 |
| Coughs per hour | 23 (4 to 141) | 17 (3 to 73) | −35% (−49 to −17%) | <0.001 |
| Daytime | 28 (5 to 171) | 20 (4 to 121) | −33% (−47 to −14%) | 0.003 |
| Night-time | 7.2 (0.7 to 101) | 3.3 (0 to 54) | −34% (−54 to −5%) | 0.029 |
| LCQ | 12±4 | 15±4 | 2.0 (1.0 to 3.0)¶ | <0.001 |
| VAS cough | 67±15 | 47±27 | −19 (−28 to −10) | <0.0001 |
| VAS urge-to-cough | 68±16 | 49±25 | −18 (−26 to −10) | <0.0001 |
| K-BILD total | 50±22 | 55±23 | 3.4 (−2.3 to 9.1) | 0.245 |
| HADS anxiety | 8.5±4 | 8.5±4 | 0.7 (−0.6 to 1.9) | 0.291 |
| HADS depression | 4.7±3 | 6.0±3 | 1.6 (0.5 to 2.6) | 0.004 |
| GAD-7 | 5.8±6 | 5.9±6 | 0.7 (−0.9 to 2.3) | 0.396 |
| FVC % pred | 78±15 | 79±17 | | |
| $T_{LCO}$ % pred | 51±13 | 51±16 | | |

- Pirfenidone treatment significantly reduces objective 24-h cough counts by 34%, and improves subjective measures of cough

van Manen MJG et al, Eur Respir J 2017; 50: 1701157

ORIGINAL RESEARCH

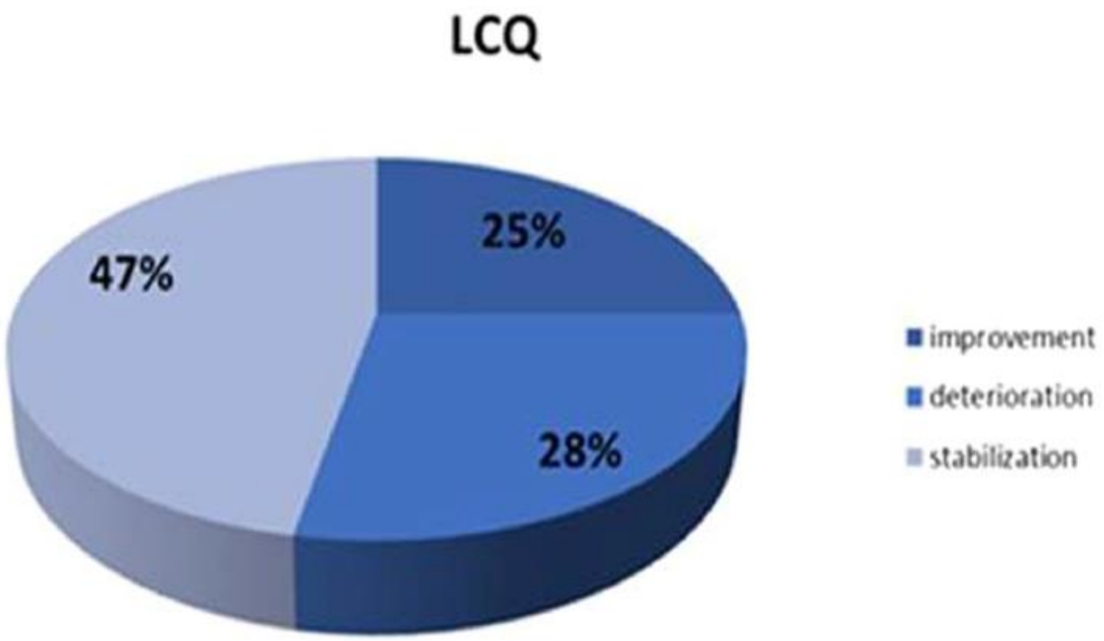
Health Science Reports Open Access WILEY

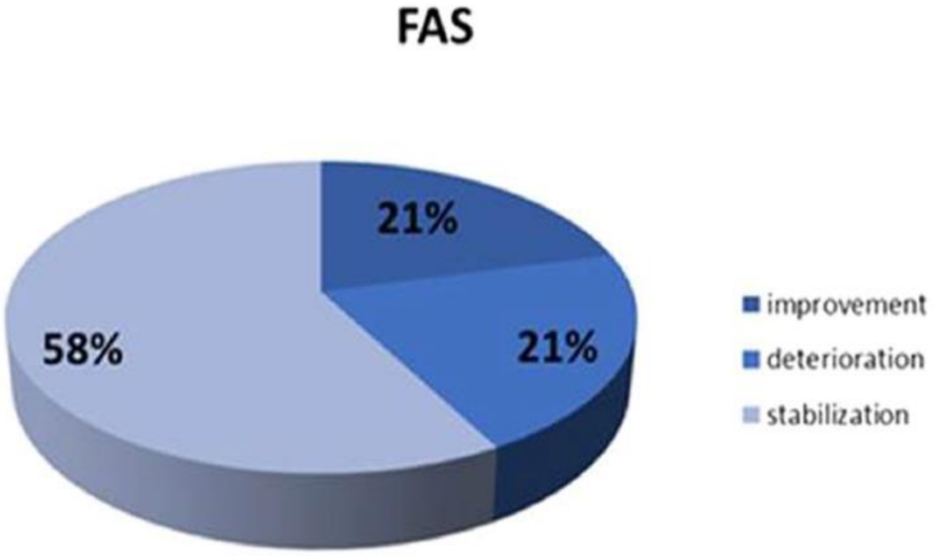
# Expectations, symptoms, and quality of life before and after 1 year of Pirfenidone treatment in patients with idiopathic pulmonary fibrosis: A single-arm, open-label nonrandomized study

Dariusz Jastrzębski[1] | Sabina Kostorz-Nosal[1] | Dagmara Galle[1] | Alicja Gałeczka-Turkiewicz[1] | Joanna Warzecha[2] | Sebastian Majewski[3] | Wojciech J. Piotrowski[3] | Dariusz Ziora[1]

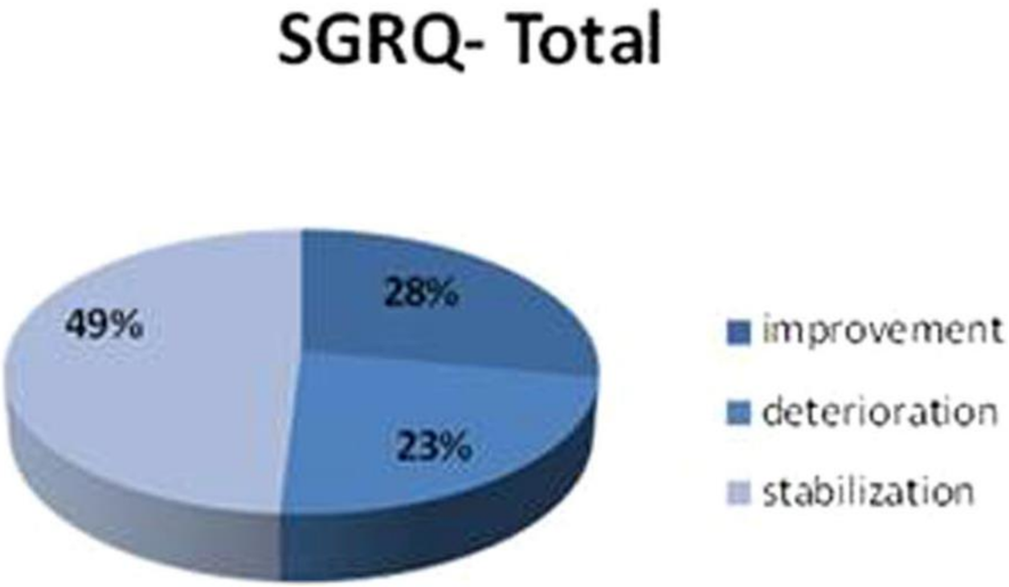
- 52 IPF patients

Jastrzębski D et al, Health Sci. Rep. 2023;6:e1449.




- 52 weeks of follow up period
- Cough sensation
  - 25% of patients: improvements
  - 50% of patients: stabilization



# Changes in cough severity during treatment of ILD

Canadian Registry for Pulmonary Fibrosis (CARE-PF)

**Table S1**. Changes in cough severity at 12 months following treatment initiation in patients with IPF and non-IPF fibrotic ILD

| Parameters | Baseline | | 12 months | | p-value* |
|---|---|---|---|---|---|
| | Measurement | 95% CI | Measurement | 95% CI | |
| **Patients with treatment initiation following baseline evaluation** | | | | | |
| **IPF** | | | | | |
| Nintedanib (n=206) | 27.3 | 23.8, 30.7 | 38.8 | 33.7, 43.9 | 0.92 |
| Pirfenidone (n=110) | 29.5 | 24.7, 34.4 | 40.6 | 33.1, 48.0 | |
| **Non-IPF fibrotic ILD** | | | | | |
| Azathiopine (n=61) | 28.9 | 22.0, 35.8 | 42.2 | 32.9, 51.4 | 0.27 |
| Mycophenolate (n=414) | 26.8 | 24.2, 29.4 | 34.6 | 31.3, 38.0 | |
| **Patients with treatment initiation following baseline evaluation and baseline Cough Severity VAS ≥30mm** | | | | | |
| **IPF** | | | | | |
| Nintedanib (n=77) | 53.6 | 50.3, 57.0 | 54.2 | 49.5, 58.9 | 0.99 |
| Pirfenidone (n=48) | 53.8 | 45.5, 62.2 | 54.5 | 40.2, 68.7 | |
| **Non-IPF fibrotic ILD** | | | | | |
| Azathiopine (n=27) | 52.4 | 46.4, 58.4 | 50.4 | 39.2, 61.5 | 0.54 |
| Mycophenolate (n=162) | 55.6 | 51.1, 60.2 | 58.6 | 50.5, 66.7 | |

Am J Respir Crit Care Med 2024 Mar 27online ahead of print

# Pharmacological treatment of cough in ILD

- Thalidomide
- Omeprazole
- Inhaled Sodium cromoglicate
- Gefapixant
- Opioids

# Thalidomide

- Potent immunomodulatory, anti-inflammatory, anti-angiogenic drug
- Randomized crossover trial with IPF patients in US (N=24)
  - Thalidomide 50~100mg for 12 weeks
  - First clinical trial to demonstrate an effective treatment for cough in IPF

*Table 2.* **CQLQ, VAS, and SGRQ Scores After Placebo and Thalidomide Treatments***

| Measure | Mean Score at Baseline (SD) | Mean Score After 12 wk of Placebo (SD) | Mean Score After 12 wk of Thalidomide (SD) | Mean Difference (95% CI)† | *P* Value† |
|---|---|---|---|---|---|
| CQLQ | 60.5 (12.0) | 58.7 (14.0) | 47.2 (13.4) | −11.4 (−15.7 to −7.0) | <0.001 |
| Cough VAS | 64.8 (21.4) | 61.9 (26.5) | 32.2 (26.1) | −31.2 (−45.2 to −17.2) | <0.001 |
| SGRQ total | 57.4 (18.8) | 56.9 (17.1) | 43.9 (16.0) | −11.7 (−18.6 to −4.8) | 0.001 |
| SGRQ symptom domain | 67.7 (19.7) | 62.0 (18.3) | 50.3 (20.9) | −12.1 (−22.2 to −2.0) | 0.018 |
| SGRQ impact domain | 48.1 (20.7) | 49.0 (19.4) | 34.3 (16.1) | −13.1 (−19.7 to −6.6) | <0.001 |
| SGRQ activity domain | 64.3 (22.7) | 65.8 (18.7) | 60.9 (14.2) | −3.3 (−9.8 to 3.2) | 0.31 |

*Ann Intern Med.* 2012 Sep 18;157(6):398-406

# Omeprazole (PPI) in IPF

- High prevalence of GERD in IPF patients
  - GERD as contributory factor for chronic cough in IPF
  - GERD related to pathogenesis and progression of IPF
- Pilot RCT with IPF patients in UK (N=45)
  - Omeprazole 20mg bid for 3 months vs placebo

**Table 2** Geometric mean cough frequency (coughs/hour) and the ratio (omeprazole:placebo) of geometric means at the end of treatment, adjusted for baseline cough frequency (complete-case analysis set; n=40)

| | Omeprazole (n=20) | | Placebo (n=20) | | |
|---|---|---|---|---|---|
| | Baseline geometric mean (95% CI) | End of treatment geometric mean (95% CI) | Baseline geometric mean (95% CI) | End of treatment geometric mean (95% CI) | Ratio of geometric means at end of treatment, adjusted for baseline (95% CI) |
| 24 hours | 8.2 (5.4 to 12.7) | 4.6 (2.4 to 8.7) | 9.1 (6.8 to 12.2) | 8.3 (5.3 to 12.9) | 0.609 (0.340 to 1.093) |
| Awake/daytime | 10.8 (6.8 to 17.0) | 6.1 (3.2 to 11.8) | 11.8 (8.9 to 15.8) | 10.7 (6.7 to 17.2) | 0.629 (0.354 to 1.119) |
| Asleep/night-time | 1.7 (0.9 to 3.3) | 1.1 (0.6 to 2.0) | 2.3 (1.1 to 4.7) | 2.1 (1.2 to 3.7) | 0.553 (0.267 to 1.146) |

*Thorax.* 2019 Apr;74(4):346-353.

# Inhaled cromolyn sodium

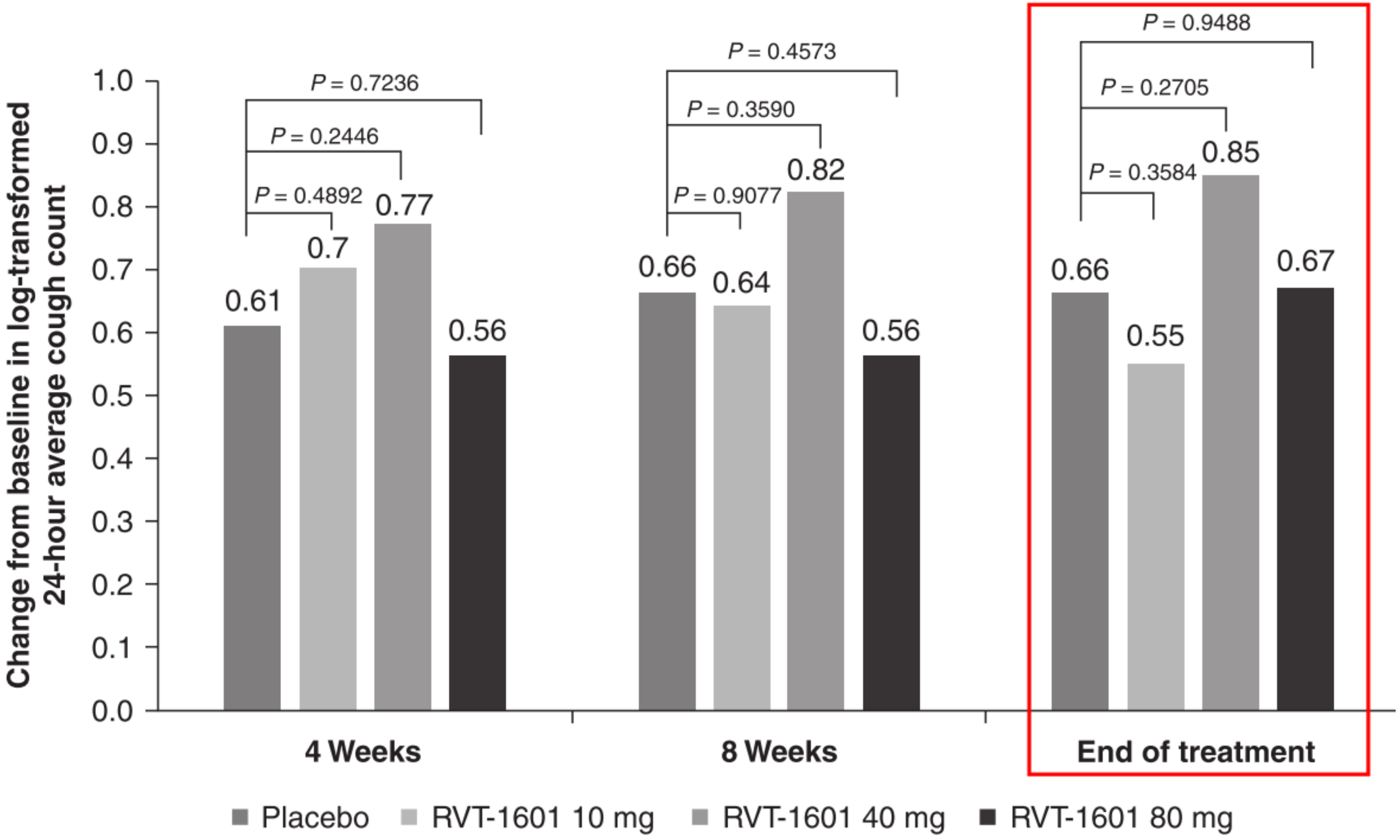
- Mechanism of Cromolyn sodium
  - Inhibit mast cell degranulation → substance P, histamine, serotonin, proteases ↓
  - Reduce C-fiber sensory nerve activity via an orphan Gp coupled receptor, GPR35

- Novel formulation (PA101) of inhaled cromolyn sodium
  - High concentration formulation of sodium cromoglicate
    - physiologically tolerable range of osmolality and pH
  - Using high-efficiency electronic nebulizer, eFlow (PARI, Grafelfing, Germany)
    - Vibrating mesh membrane
  - 5~10-fold higher lung concentration

*Lancet Respir Med.* 2017 Oct;5(10):806-815.
https://www.pari.com/int/products/inhalation-devices-for-the-lungs/eflow-rapid-nebuliser-system/

# Inhaled cromolyn sodium (RVT-1601)

- Phase 2b RCT (SCENIC trial)




*Am J Respir Crit Care Med.* 2022 May 1;205(9):1084-1092.

## 단원 10. 기침의 치료제 – 진해제 및 거담제

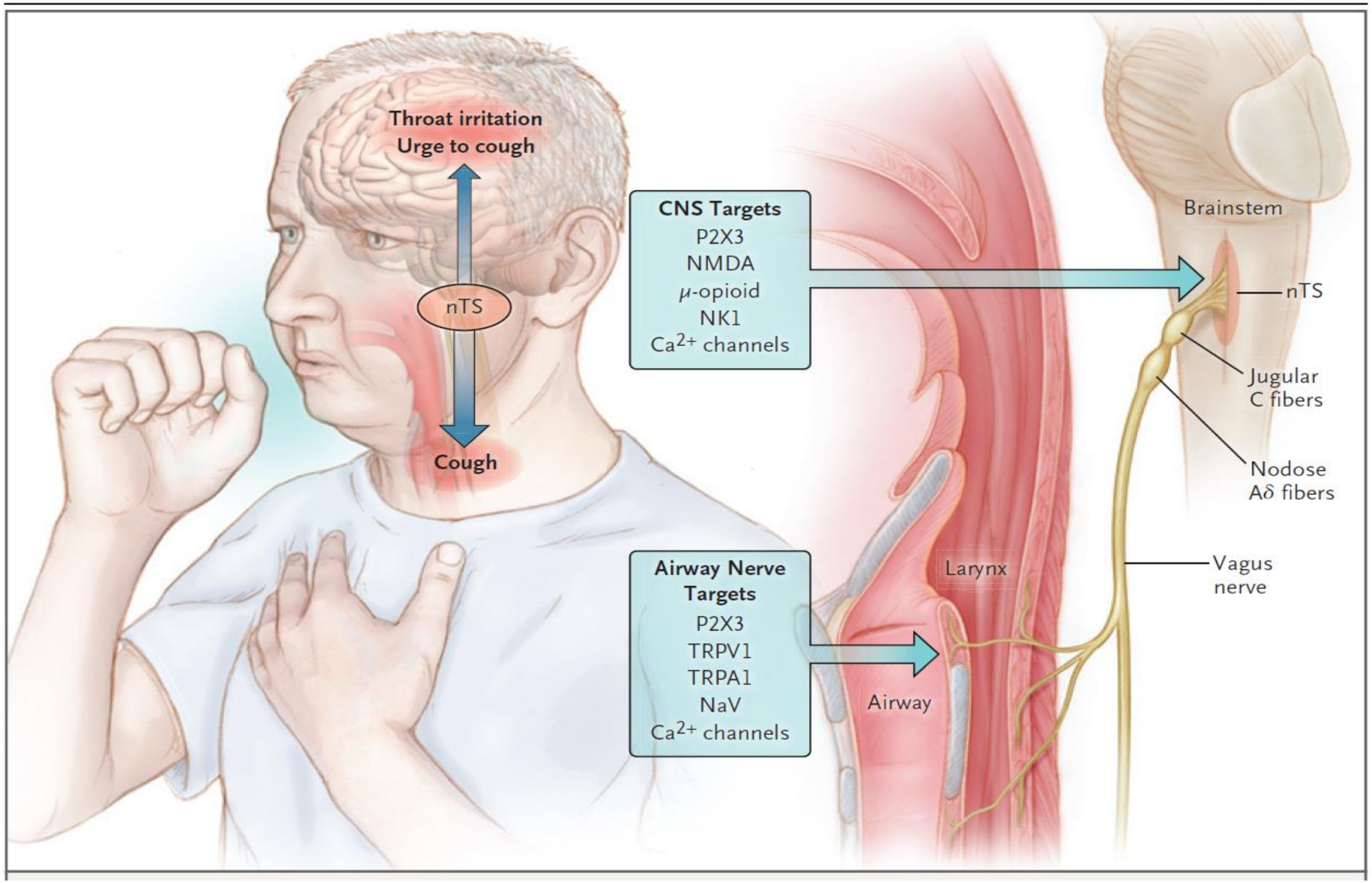
**요점**

- 진해제는 중추성 진해제와 말초성 진해제로 구분한다.
  - 마약성 중추성 진해제: 모르핀(morphine), 코데인(codein)
  - 비마약성 중추성 진해제: dextromethorphan, levopropoxyphene
  - 말초성 진해제: benzonatate, benproperine, theobromine
- 거담제는 분비촉진제, 점액조절제, 점액용해제(점액분해제), 점액활성제로 구분한다.
  - 분비촉진제: 고장성 식염수, 요오드 포함 복합물, guafenesin, 이온통로 조절제
  - 점액조절제: carbocysteine, 항콜린제, 글루코코르티코이드, macrolide계 항생제
  - 점액용해제(점액분해제)
    - 전형적 점액용해제: N-acetylcysteine, N-acetylin, bromhexin, erdosteine, fudosteine
    - 펩타이드 점액용해제: dornase alpha, gelsolin, thymosin $\beta$-4
    - 비파괴성 점액용해제: dextran, heparin
  - 점액활성제: 흡입 속효성베타작용제, 메틸잔틴, 표면활성제, ambroxol, acebrophylline
- 새롭게 시도되고 있는 약제들로는 gabapentin, pregabalin, amitriptyline, gefapixant (P2X3 receptor antagonist) 등이 있다.

# Anti-tuissive in real-world

| 조제약품명 | 한글약품명 | 전문 | 급여 |
|---|---|---|---|
| Codaewon forte(R) 20ml pkg | 코대원포르테시럽 20ml | Y | Y |
| Codaewon S(R) 20ml pkg | 코대원에스시럽 20ml | Y | Y |
| Cough syr(R) 20ml pkg | 코푸시럽 20ml | Y | Y |
| Coughsti(R) syr | 코푸스티 시럽 | | Y |
| Hebron-F(R) | 헤브론에프정 25mg | | Y |
| Levodropropizine 60mg | 레보투스정 60mg | Y | Y |
| Levodropropizine 10ml pkg | 레보투스시럽 10ml/pkg | Y | Y |
| L-dropropizine 6mg/ml | 레보투스시럽 6mg/ml | Y | Y |
| Lomincomp(R) 9ml pkg | 로민콤프시럽 9ml/pkg | Y | Y |
| Synatura(R) syr | 시네츄라시럽 | Y | Y |
| Synatura(R) syr 15ml pkg | 시네츄라시럽 15ml | Y | Y |
| Theobromine 300mg | 애니코프캡슐 300㎎ | Y | Y |

# Neuronal Pathways Controlling Cough, and Targets of Available Antitussive Agents

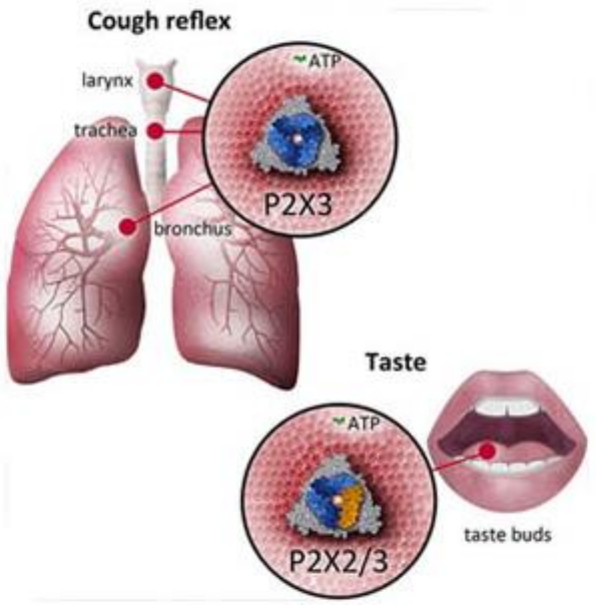



N Engl J Med 2016;375:1544-51.

# Gefapixant, $P2X_3$ receptors antagonist

- Roll of $P2X_3$ receptors
  - ATP-gated ion channels found on sensory C-fibers of the vagus nerve
  - ATP release followed by stimuli from epithelium (Injury, inflammation, infection)
  - Extracellular ATP + $P2X_3$ receptors → C-fiber activation → Cough reflex

- Gefapixant
  - $P2X_3$ receptors antagonist, non-competitive
    - Reduce cough response
  - Partial affinity to $P2X_{2/3}$ receptors
    - Signaling between taste buds and gustatory sensory nerves
    - Common taste-related adverse events

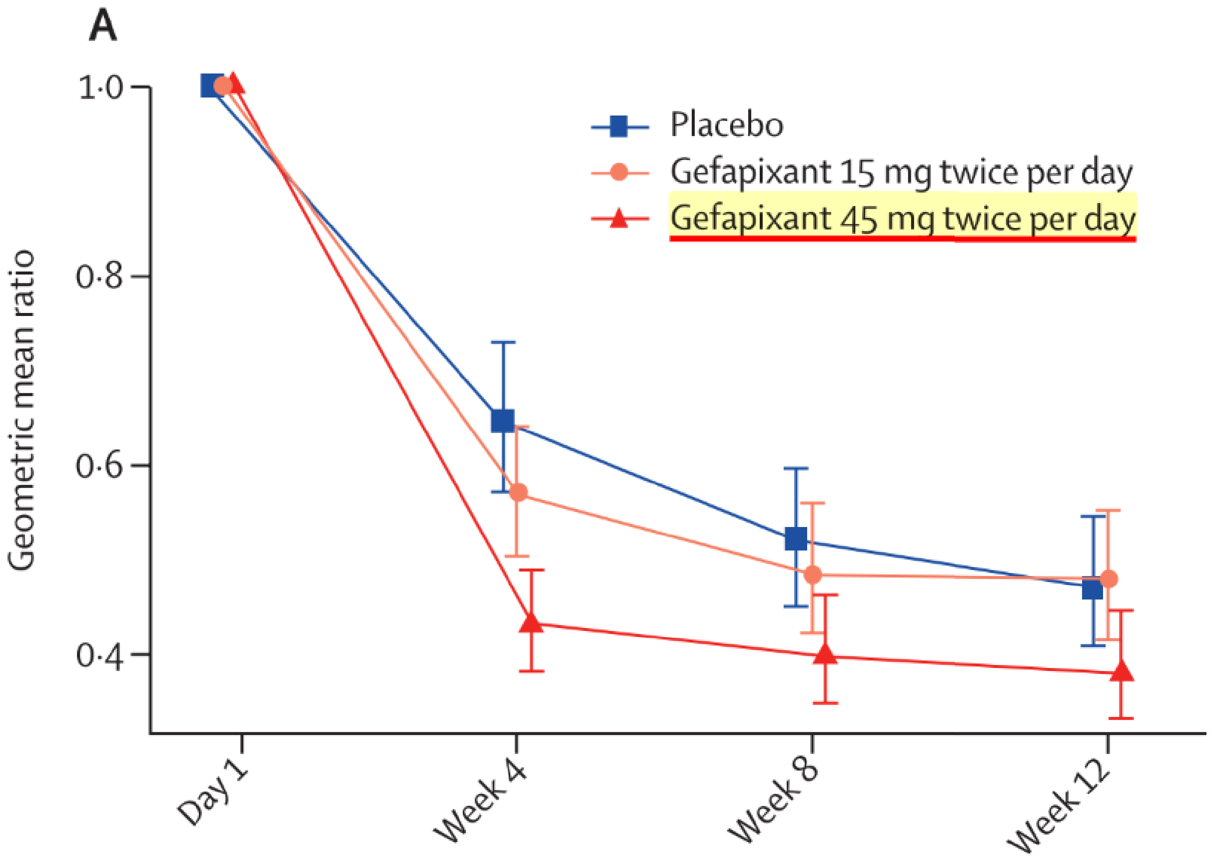



*Eur Respir J.* 2019 Jul 4;54(1):1900889.
*Lancet Respir Med.* 2020 Aug;8(8):775-785.

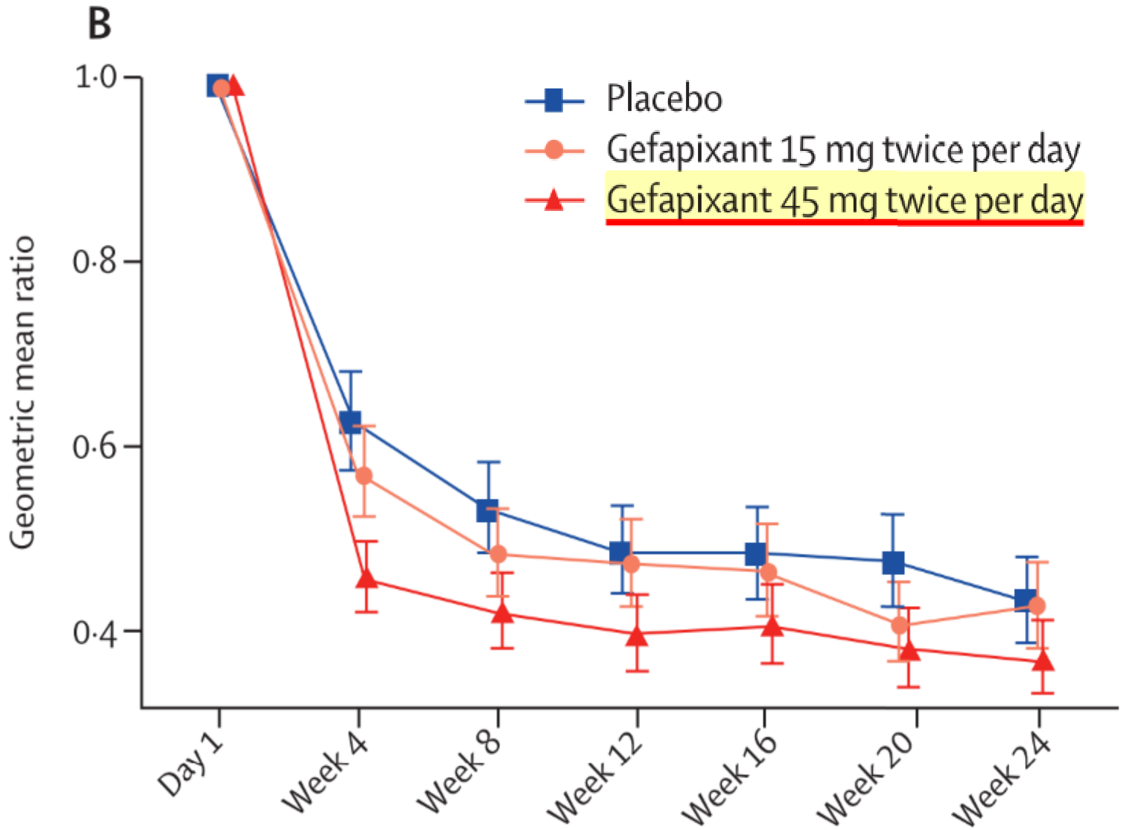
# Gefapixant in unexplained chronic cough

❖ **Objective outcome: 24-h cough frequency**

❖ **COUGH-1**



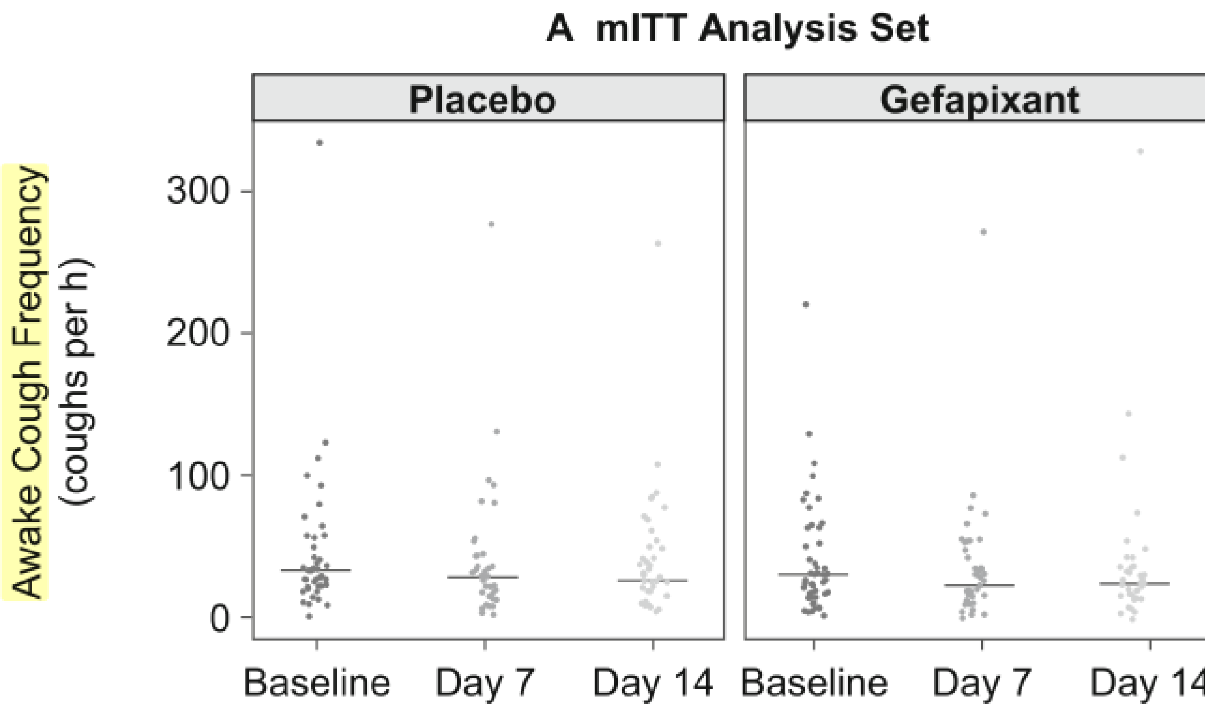

❖ **COUGH-2**

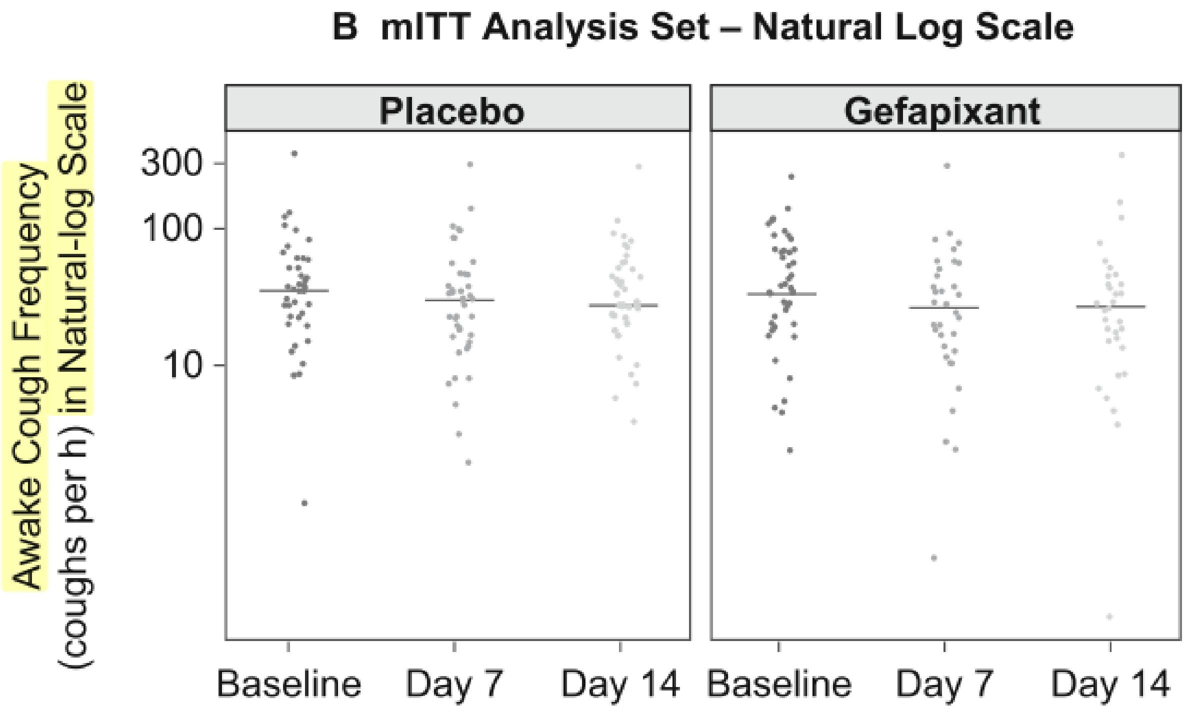



*Lancet.* 2022 Mar 5;399(10328):909-923.

# Gefapixant in IPF?

- Crossover RCT (N=44)




Gefapixant was generally well tolerated but was not associated with a significant improvement in chronic cough in subjects with IPF.

Pulm Ther. 2021 Dec;7(2):471-486

NEJM Evidence

Published May 22, 2023
NEJM Evid 2023; 2 (8)
DOI: 10.1056/EVIDoa2300083

ORIGINAL ARTICLE

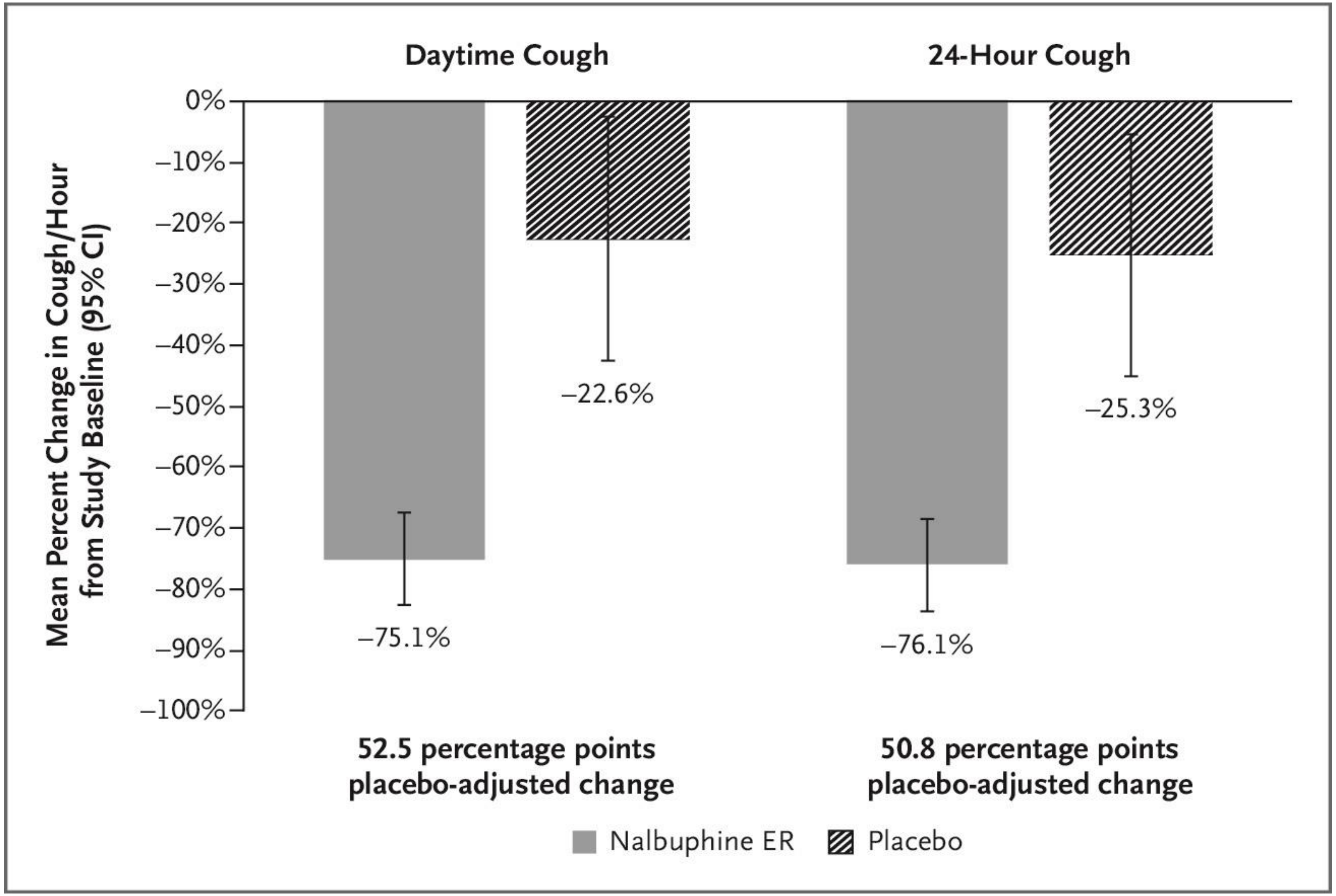
# Nalbuphine Tablets for Cough in Patients with Idiopathic Pulmonary Fibrosis

Toby M. Maher, M.D., Ph.D.,[1,2] Cristina Avram, M.D.,[3] Enoch Bortey, Ph.D.,[4] Simon P. Hart, M.D., Ph.D.,[5] Nikhil Hirani, M.D., Ph.D.,[6] Philip L. Molyneux, M.D., Ph.D.,[2] Joanna C. Porter, M.D., Ph.D.,[7,8] Jaclyn A. Smith, M.D., Ph.D.,[9] and Thomas Sciascia, M.D.[10]

- Nalbuphine ER
  - Mixed agonist–antagonist of opioid receptors
  - Act both centraly in the brain and peripheraly in the lungs via κ-agonist and μ-antagonist opioid receptors
- Primary outcome: percent change in hourly daytime objective cough frequency

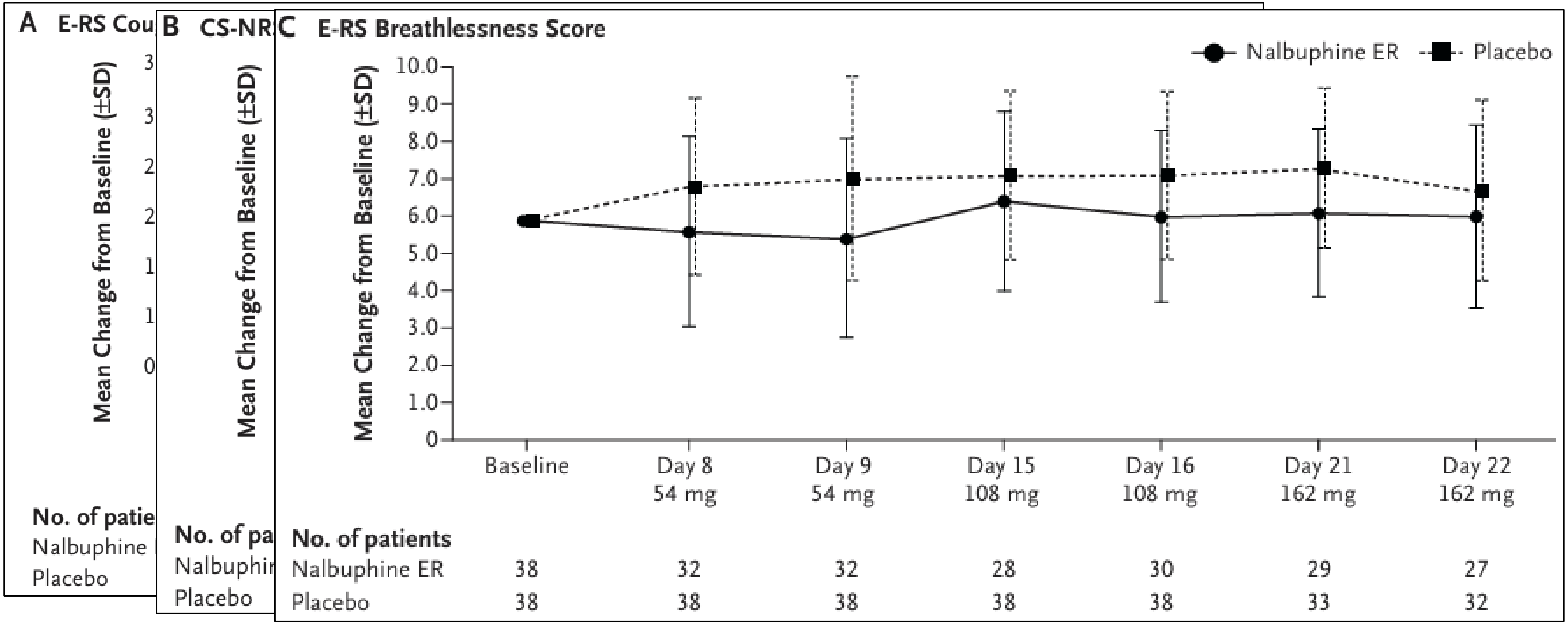
Maher TM et al, NEJM Evid 2023;2(8):EVIDoa2300083

# Changes of cough frequency




Maher TM et al, NEJM Evid 2023;2(8):EVIDoa2300083

# Mean Change from Study Baseline for Patient-Reported Outcomes




Maher TM et al, NEJM Evid 2023;2(8):EVIDoa2300083

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

*Zhe Wu, Lisa G Spencer, Winston Banya, John Westoby, Veronica A Tudor, Pilar Rivera-Ortega, Nazia Chaudhuri, Ira Jakupovic, Brijesh Patel, Muhunthan Thillai, Alex West, Marlies Wijsenbeek, Toby M Maher, Jacky A Smith, Philip L Molyneaux*

- Opioids suppress cough by binding to several types of G protein-coupled endorphin receptors on presynaptic neurons in brainstem cough center.
- Oral morphine 15mg bid
- Primary outcome: percentage change in awake cough frequency

Wu Z et al, Lancet Respir Med 2024;12: 273–80

# Low dose morphine for cough in IPF

| | 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 |

Wu Z et al, Lancet Respir Med 2024;12: 273–80

Observational Study

Medicine

OPEN

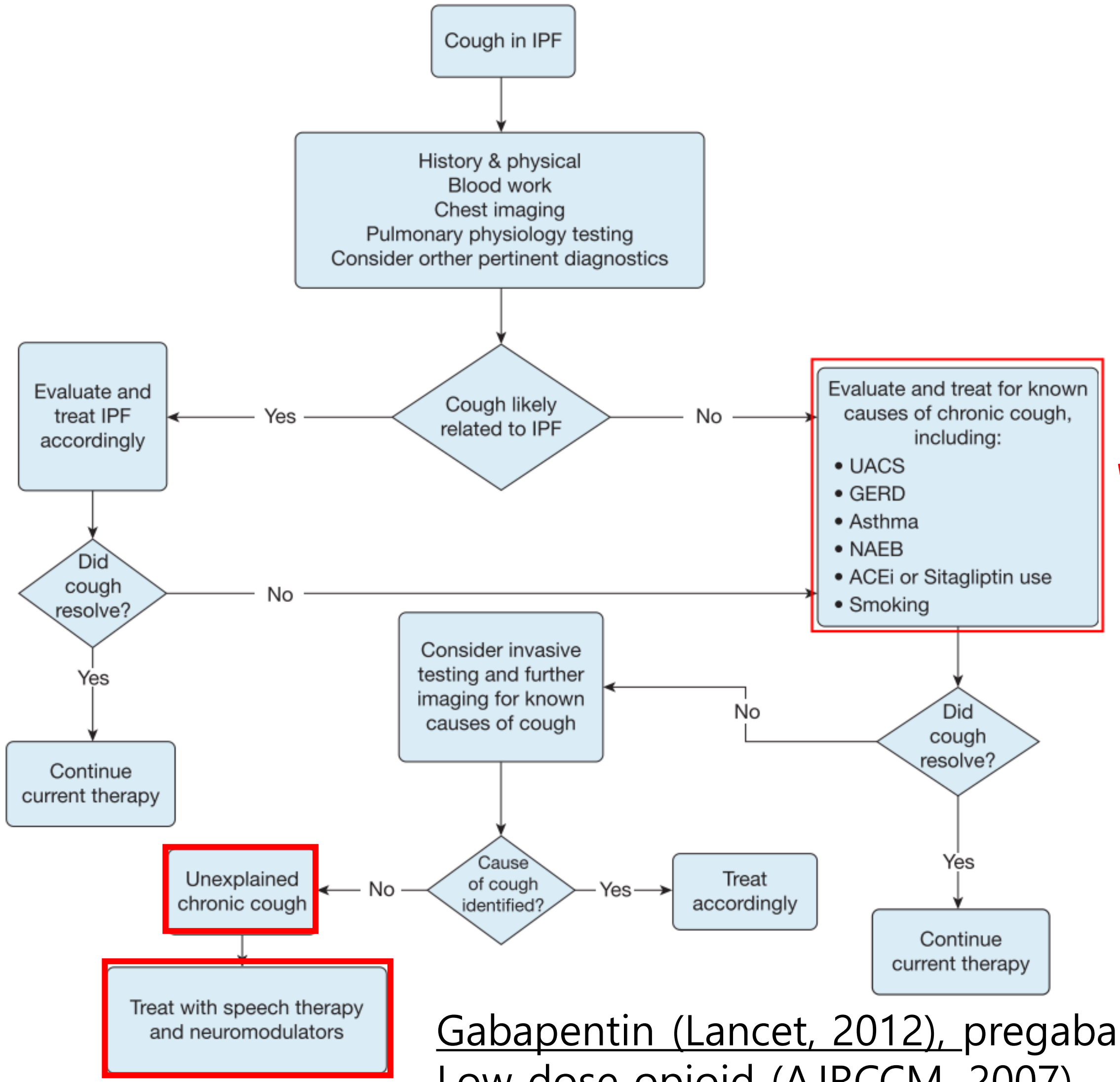
# The clinical efficacy of a mixture of ivy leaf extract and coptidis rhizome in patients with idiopathic pulmonary fibrosis

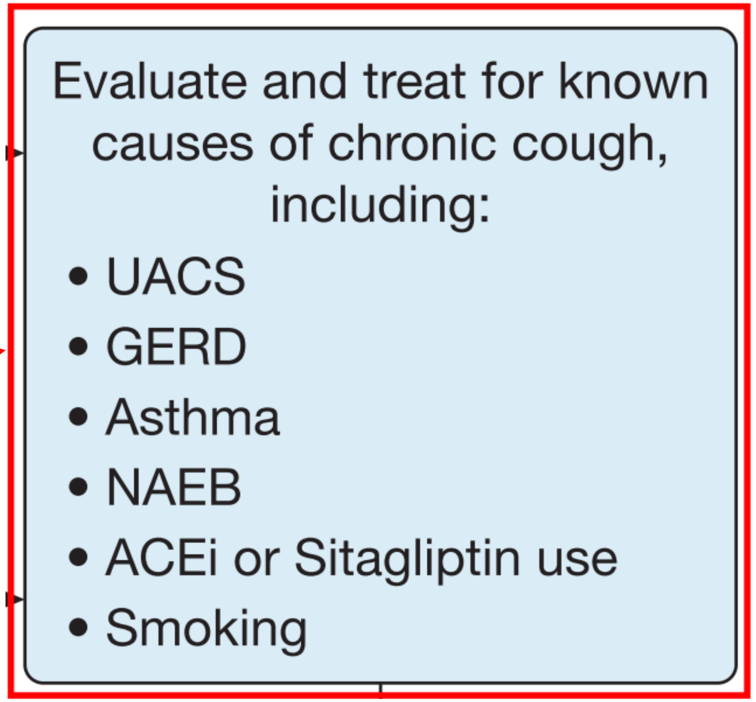
Jae Ha Lee, MD, PhD[a], Ji Hoon Jang, MD[a], Jin Han Park, MD[a], So Young Jung, MD[b], Sunggun Lee, MD, PhD[c], Seong-Ho Kim, MD, PhD[c], Ji Yeon Kim, MD, PhD[d], Junghae Ko, MD, PhD[e], Hee Eun Choi, MD, PhD[f], Tae-Hoon No, MD[g], Hang-Jea Jang, MD[a,*]

- Prospective, open-label, single-center, and single-arm study
- 30 IPF patients with chronic bronchitis
- No significant improvement in LCQ (16.8 [15.6–19.1] vs 17.5 [15.2–18.9], *P* = .772) and SGRQ (30.6 [19.4–37.8] vs 29.9 [19.6–41.8], *P* = .194) scores
- Improved cough-specific life quality in one third patients with IPF.

Lee JH et al, Medicine 2023;102:5(e32786).

# Suggested management algorithm of cough in IPF




\+
Possible combined infection
environmental/occupational exposure

<u>Gabapentin (Lancet, 2012),</u> pregabalin, amitriptyline, and baclofen
<u>Low dose opioid (AJRCCM, 2007)</u>

*Chest.* 2021 Nov;160(5):1774-1782.

# Dyspnea in ILD

- Dyspnea
  - “A subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity”
- Dyspnea and change in dyspnea is also an independent predictor of survival in ILD.
- Result of complex interactions of physiological, psychosocial, and social and environmental factors

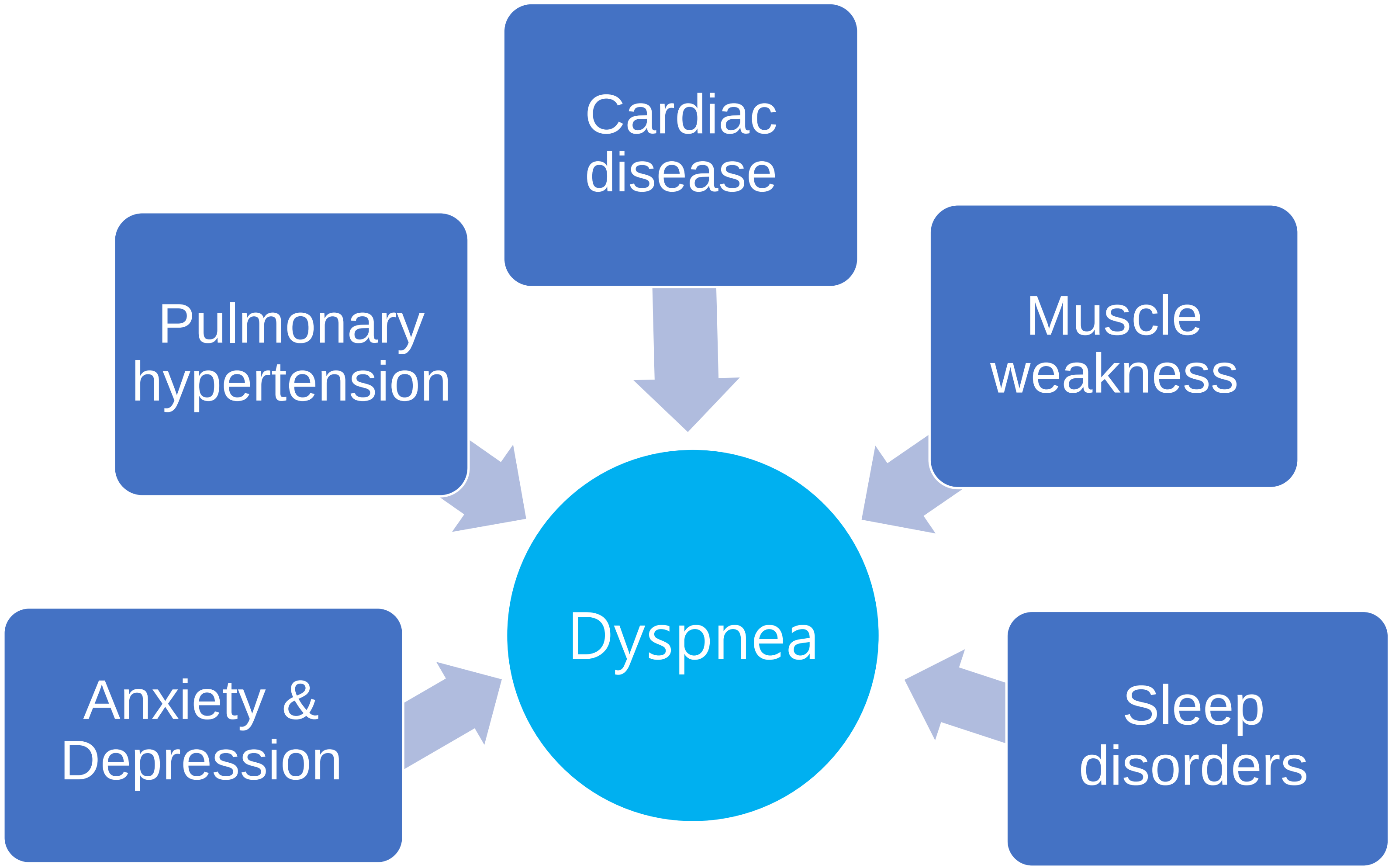
Khadawardi, H. et al, Respirology 22, 501–507 (2017)
Parshall MB et al. Am. J. Respir. Crit. Care Med. 185, 432–452

# Pathophysiology of dyspnea in ILD

- Results from both respiratory and circulatory limitations
  - Reduced lung compliance
  - Loss of lung volume
  - Increased dead space ventilation
  - Increased respiratory drive
  - Gas exchange abnormalities
  - Pulmonary hypertension

Janowiak P et al, Front. Med. 2022:9:917973

# Comorbidities associated with dyspnea




van Manen MJ et al, Ther Adv Respir Dis 2017:11(3); 157–169

# Management of dyspnea in ILD

- Treatment of comorbidities
- Non-pharmacological treatment
  - Fan, air circulation
  - Oxygen treatment
  - Rehabilitation
- Pharmacological treatment
  - Opioids
- Others

# Non-pharmacological treatment of dyspnea

- Fan, air circulation
- Behavior modification
- Pacing
- Aids for activities of daily living
  - eg. Wheelchair, walker
- Involvement of allied health team
  - physiotherapist, occupational therapist, respiratory therapist, nurse

# Fan therapy

- Mechanisms underlying its effects remain unclear
- Direct stimulation of the face, nasal mucosa, pharynx, or changes in facial temperature due to cooling, may affect ventilation patterns
- Inexpensive, portable, and readily available
- Symptomatic benefits in COPD, lung cancer

Sato T et al, Cureus 15(8):e43668

# Handheld Fans (HHFs) in ILD

- Mixed-methods, randomised, single-blinded, controlled pilot study
- ILD patients with mMRC ≥ 2, HHFs for 2 weeks

| | Fan group[a] | | Control group[a] | | | |
|---|---|---|---|---|---|---|
| | Baseline | Week 2 | Baseline | Week 2 | Treatment effect[b] | *p* value |
| Dyspnoea-12 | 16.1 ± 2.2 | 13.4 ± 2.3 | 13.3 ± 2.2 | 12.8 ± 2.2 | − 2.2 (− 6.4, 1.9) | 0.29 |
| K-BILD Breathlessness & Activities | 29.2 ± 3.9 | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] |
| K-BILD Chest Symptoms | 47.0 ± 5.2 | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] |
| K-BILD Psychological Symptoms | 51.7 ± 4.2 | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] |
| K-BILD Total | 48.0 ± 2.5 | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] |
| Self-efficacy[c] | 5.4 ± 0.6 | 5.7 ± 0.7 | 5.5 ± 0.6 | 5.7 ± 0.6 | 0.07 (− 1.9, 2.0) | 0.94 |
| Activities of daily living[d] | 14.4 ± 0.9 | 14.6 ± 1.0 | 15.1 ± 0.9 | 16.9 ± 0.9 | − 2.5 (− 4.8, 0.3) | 0.08 |
| Life-space[e] | 58.6 ± 6.3 | 58.0 ± 6.4 | 66.6 ± 6.1 | 63.7 ± 6.1 | 2.4 (− 10.4, 15.2) | 0.72 |
| Steps per day | 3423 ± 540 | 3620 ± 527 | 3082 ± 453 | 3206 ± 488 | 74 (− 807, 956) | 0.87 |
| Total energy expenditure (kCal/day) | 8269 ± 343 | 8383 ± 340 | 8470 ± 288 | 8481 ± 287 | 104 (− 197, 404) | 0.50 |
| Total METs | 1.10 ± 0.04 | 1.12 ± 0.04 | 1.05 ± 0.03 | 1.06 ± 0.03 | 0.003 (− 0.04, 0.44) | 0.88 |
| Duration of sedentary time per day (mins) | 1129 ± 38 | 1139 ± 36 | 1205 ± 32 | 1149 ± 31 | 66 (− 30, 162) | 0.18 |
| Duration of time ≥ 3 METs per day[a] (mins) | 221 ± 27 | 243 ± 27 | 187 ± 23 | 183 ± 23 | 26 (− 16.1, 68.3) | 0.23 |

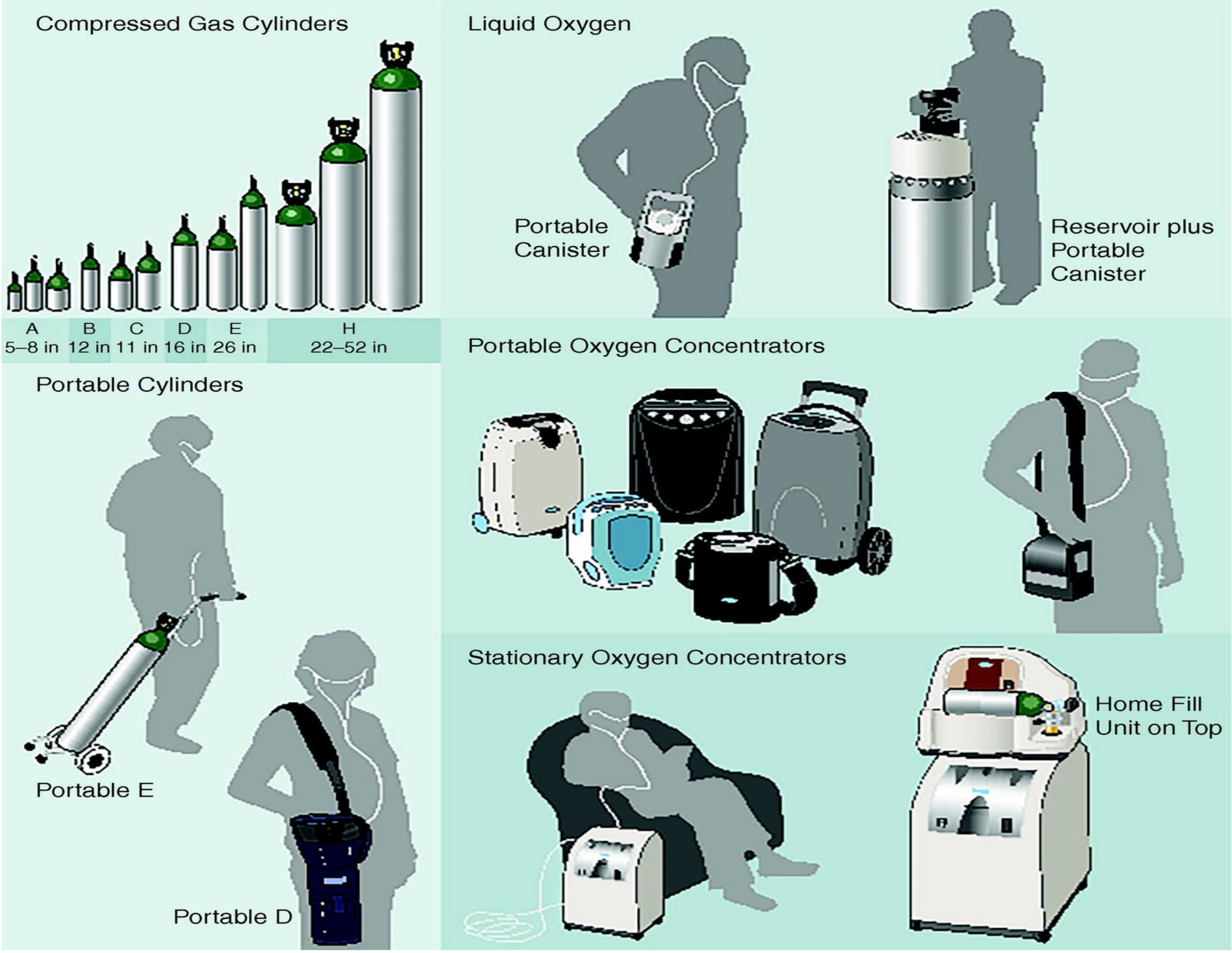
HHF being easier to use, but not as effective for symptomatic relief, compared to oxygen therapy.

Khor YH et al, Sci Rep 2021: 25;11(1):6874

# AMERICAN THORACIC SOCIETY DOCUMENTS

## Home Oxygen Therapy for Adults with Chronic Lung Disease

An Official American Thoracic Society Clinical Practice Guideline




Am J Respir Crit Care Med Vol 2020:202(10); e121–e141

| Question | ATS Recommendation | Strength of Recommendation and Level of Evidence |
| --- | --- | --- |
| COPD | | |
| Question 1: Should long-term oxygen be prescribed for adults with COPD who have severe* chronic resting room air hypoxemia? | In adults with COPD who have severe chronic resting room air hypoxemia, we recommend prescribing LTOT for at least 15 h/d. | Strong recommendation, moderate-quality evidence |
| Question 2: Should long-term oxygen be prescribed for adults with COPD who have moderate† chronic resting room air hypoxemia? | In adults with COPD who have moderate chronic resting room air hypoxemia, we suggest not prescribing LTOT. | Conditional recommendation, low-quality evidence |
| Question 3: Should ambulatory oxygen be prescribed for adults with COPD who have severe exertional room air hypoxemia? | In adults with COPD who have severe exertional room air hypoxemia, we suggest prescribing ambulatory oxygen. | Conditional recommendation, low-quality evidence |
| ILD | | |
| Question 4: Should long-term oxygen be prescribed for adults with ILD who have severe chronic resting room air hypoxemia? | For adults with ILD who have severe chronic resting room air hypoxemia, we recommend prescribing LTOT for at least 15 h/d. | Strong recommendation, very-low-quality evidence |
| Question 5: Should ambulatory oxygen be prescribed for adults with ILD who have severe exertional room air hypoxemia? | For adults with ILD who have severe exertional room air hypoxemia, we suggest prescribing ambulatory oxygen. | Conditional recommendation, low-quality evidence |
| Liquid oxygen | | |
| Question 6: Should portable liquid oxygen be provided for adults with chronic lung disease who are prescribed continuous oxygen flow rates of >3 L/min during exertion? | In patients with chronic lung disease who are mobile outside of the home and require continuous oxygen flow rates of >3 L/min during exertion, we suggest prescribing portable liquid oxygen. | Conditional recommendation, very-low-quality evidence |
| Education | | |
| Education and safety for patients and caregivers | For all patients prescribed home oxygen therapy, we recommend that the patient and their caregivers receive instruction and training on the use and maintenance of all oxygen equipment and education on oxygen safety, including smoking cessation, fire prevention, and tripping hazards. | Best-practice statement |

# Long term oxygen treatment (LTOT)

- Small scale studies suggesting a beneficial effect of supplemental oxygen on dyspnea and exercise capacity in patients with IPF.

- Maintain nadir SpO2 >90% with exertion
- Frequent titrations in clinic and home
- Patients and families have a pulse oximeter and learn how to self-manage their oxygen

- O2 generator vs. O2 tank

Schaeffer MR et al, Curr Opin Support Palliat Care 2019, 3:174–178

# Ambulatory Oxygen in fibrotic ILD

- A Pilot, Randomized, Triple-Blinded, Sham-Controlled Trial
- To examine the feasibility of conducting a clinical trial of ambulatory oxygen delivered via portable concentrators
- Primary outcome: trial feasibility, 6MWD on room air at week 12.

| Walk Test Variables | Week 4 | | | | Week 12 | | | |
|---|---|---|---|---|---|---|---|---|
| | Oxygen Group[a] | Sham Group[a] | Treatment Effect[b] | *P* | Oxygen Group[a] | Sham Group[a] | Treatment Effect[b] | *P* |
| 6MWD on RA (m) | 454 ± 24 | 491± 25 | −37 (−107 to 32) | .29 | 433 ± 24 | 468 ± 26 | −34 (−105 to 36) | .34 |
| mMRC Dyspnea Scale | 1.4 ± 0.2 | 1.0 ± 0.2 | 0.4 (−0.2 to 0.9) | .16 | 1.4 ± 0.2 | 1.4 ± 0.2 | 0 (−0.6 to 0.6) | .98 |
| UCSD SOBQ | 49.3 ± 4.7 | 39.8 ± 5.0 | 9.5 (−4.2 to 23.3) | .17 | 45.7 ± 4.5 | 37.5 ± 5.1 | 8.2 (−5.9 to 22.2) | .25 |
| HADS—Depression | 4.7 ± 0.7 | 4.4 ± 0.8 | 0.3 (−1.8 to 2.5) | .74 | 3.9 ± 0.7 | 4.4 ± 0.8 | −0.5 (−2.7 to 1.7) | .64 |
| HADS—Anxiety | 2.7 ± 0.7 | 3.7 ± 0.8 | −1.0 (−3.1 to 1.1) | .35 | 2.8 ± 0.8 | 4.8 ± 0.8 | −2.0 (−4.2 to 0.2) | .07 |

Khor YH et al, CHEST 2020; 158(1):234-244

# Pulmonary rehabilitation

- Pulmonary rehabilitation probably improves functional exercise capacity, as measured by the six-minute walk test.

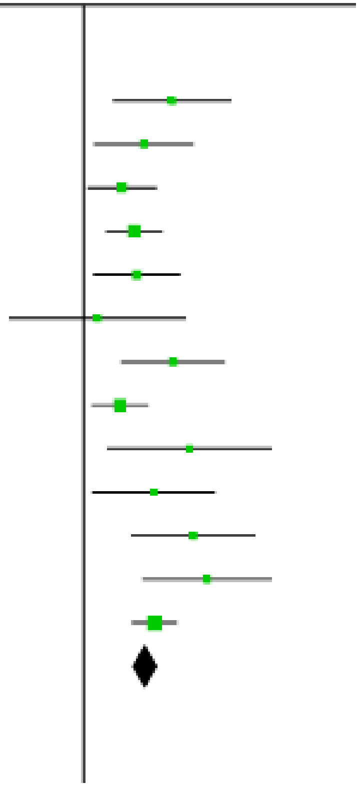
- Reduction in dyspnea and improvement in quality of life

Dowman L, et al, Cochrane Database of Systematic Reviews 2021, Issue 2. Art. No.: CD006322

# Pulmonary rehabilitation effect on 6MWD in ILD

| Study or Subgroup | Pulmonary rehabilitation Mean | SD | Total | Control Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.1.1 All participants** | | | | | | | | |
| Dale 2014 | 71 | 25.7 | 7 | 13 | 34.4 | 4 | 3.6% | 58.00 [19.28 , 96.72] |
| De Las Heras 2019 | 4.3 | 24 | 11 | -35.2 | 47.4 | 10 | 5.1% | 39.50 [6.88 , 72.12] |
| Dowman 2017 | 23 | 68 | 74 | -2 | 69.2 | 68 | 10.6% | 25.00 [2.40 , 47.60] |
| He 2016 | 58.7 | 26.2 | 15 | 25.5 | 25.8 | 15 | 15.7% | 33.20 [14.59 , 51.81] |
| Holland 2008 | 31.2 | 48.6 | 30 | -3.7 | 59.8 | 27 | 6.7% | 34.90 [6.42 , 63.38] |
| Jackson 2014 | -6.2 | 86.91 | 11 | -15.3 | 42.89 | 10 | 1.6% | 9.10 [-48.73 , 66.93] |
| Jarosch 2020 | 54.68 | 85.88 | 34 | -3.83 | 38.02 | 17 | 4.7% | 58.51 [24.45 , 92.57] |
| Ku 2017 | 27 | 30.8 | 20 | 3.2 | 29.1 | 20 | 15.7% | 23.80 [5.23 , 42.37] |
| Naz 2018 | 47 | 33.5 | 9 | -22.6 | 75.4 | 9 | 1.9% | 69.60 [15.70 , 123.50] |
| Nishiyama 2008 | 42 | 50.8 | 13 | -4 | 57.7 | 15 | 3.4% | 46.00 [5.81 , 86.19] |
| Perez Bogerd 2018 | 49 | 80.4 | 30 | -23 | 80.4 | 30 | 3.3% | 72.00 [31.31 , 112.69] |
| Vainshelboim 2014 | 70.4 | 77 | 15 | -10.6 | 35.4 | 17 | 3.0% | 81.00 [38.56 , 123.44] |
| Xiao 2019 | 53.42 | 31.9 | 40 | 6.97 | 32.9 | 34 | 24.7% | 46.45 [31.62 , 61.28] |
| **Subtotal (95% CI)** | | | **309** | | | **276** | **100.0%** | **40.07 [32.70 , 47.44]** |

Heterogeneity: Chi² = 16.25, df = 12 (P = 0.18); I² = 26%
Test for overall effect: Z = 10.66 (P < 0.00001)




Dowman L, et al, Cochrane Database of Systematic Reviews 2021, Issue 2. Art. No.: CD006322

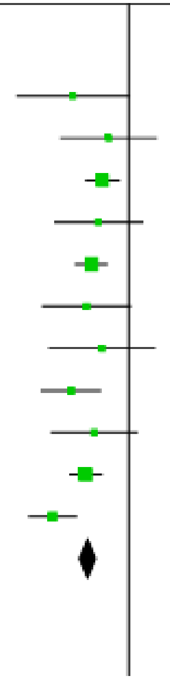
# Pulmonary rehabilitation effect on SGRQ in ILD

| | Pulmonary rehabilitation | | | Control | | | | Mean Difference |
|---|---|---|---|---|---|---|---|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Fixed, 95% CI |
| **1.12.1 All participants** | | | | | | | | |
| Dale 2014 | -6.2 | 14.3 | 7 | 6.4 | 7.3 | 4 | 1.9% | -12.60 [-25.38 , 0.18] |
| De Las Heras 2019 | -7 | 14 | 11 | -2.5 | 11.5 | 10 | 2.6% | -4.50 [-15.42 , 6.42] |
| Dowman 2017 | -4.8 | 11.8 | 74 | 1.1 | 11.9 | 68 | 20.6% | -5.90 [-9.80 , -2.00] |
| Gaunaurd 2014 | -4.1 | 14.7 | 11 | 2.7 | 8.2 | 10 | 3.1% | -6.80 [-16.86 , 3.26] |
| Ku 2017 | -8.89 | 3.6 | 20 | -0.47 | 7.6 | 20 | 23.1% | -8.42 [-12.11 , -4.73] |
| Naz 2018 | -15.4 | 13.2 | 9 | -5.9 | 8 | 9 | 3.1% | -9.50 [-19.58 , 0.58] |
| Nishiyama 2008 | -2.9 | 14.13 | 13 | 3.1 | 18.25 | 15 | 2.2% | -6.00 [-18.01 , 6.01] |
| Perez Bogerd 2018 | -7 | 13.4 | 30 | 6 | 13.4 | 30 | 6.8% | -13.00 [-19.78 , -6.22] |
| Shen 2016 | -9.2 | 13.5 | 16 | -1.4 | 14.3 | 15 | 3.3% | -7.80 [-17.60 , 2.00] |
| Vainshelboim 2014 | -6.9 | 6.5 | 15 | 2.8 | 3.6 | 17 | 22.9% | -9.70 [-13.41 , -5.99] |
| Xiao 2019 | -18.13 | 12.6 | 40 | -1.02 | 11.6 | 34 | 10.3% | -17.11 [-22.63 , -11.59] |
| **Subtotal (95% CI)** | | | **246** | | | **232** | **100.0%** | **-9.29 [-11.06 , -7.52]** |

Heterogeneity: Chi² = 13.64, df = 10 (P = 0.19); I² = 27%

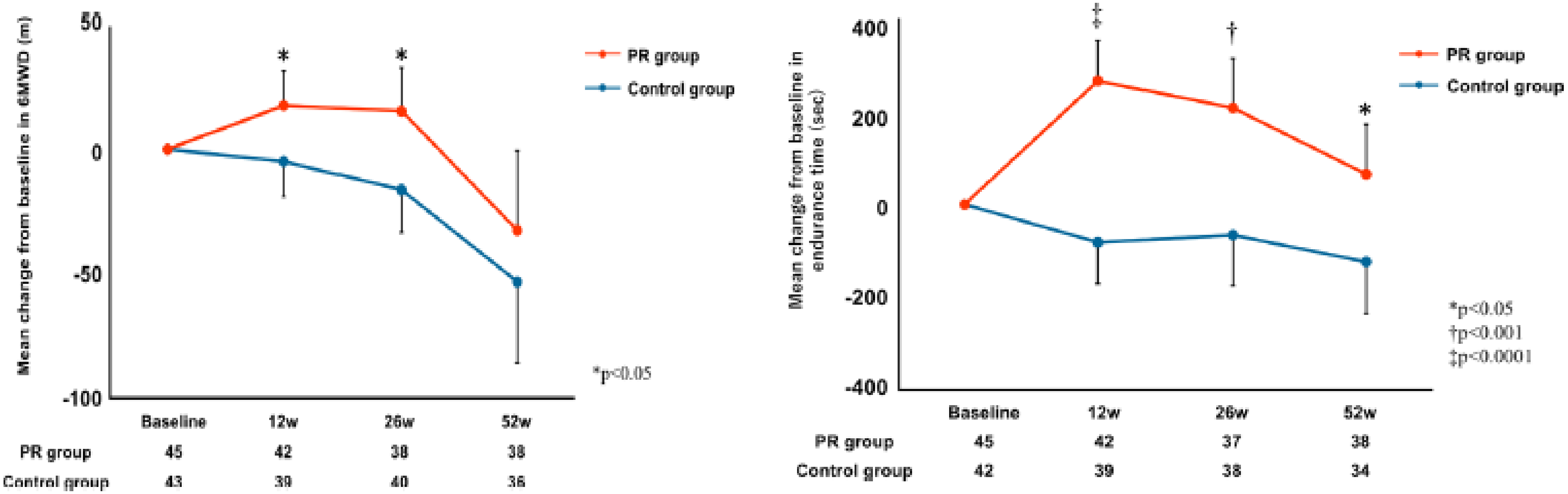
Test for overall effect: Z = 10.27 (P < 0.00001)

**Mean Difference**
**IV, Fixed, 95% CI**



Dowman L, et al, Cochrane Database of Systematic Reviews 2021, Issue 2. Art. No.: CD006322

# Long-term effect of pulmonary rehabilitation in IPF




Although pulmonary rehabilitation in patients taking nintedanib did not improve 6MWD in the long term, it led to prolonged improvement in endurance time.

Kataoka K, et al. Thorax 2023;78:784–791

# Long-term effect of pulmonary rehabilitation in IPF

| | 12 weeks | | 26 weeks | | 52 weeks | |
|---|---|---|---|---|---|---|
| | Difference† (SE) | P value | Difference† (SE) | P value | Difference† (SE) | P value |
| 6 min walking distance | 22.5 (10.1) | 0.029 | 31.7 (12.5) | 0.013 | 20.7 (23.4) | 0.38 |
| Endurance time | 344.1 (62.9) | <0.0001 | 271.0 (77.2) | 0.0007 | 186.8 (77.9) | 0.019 |
| 6 min walking distance, percentage of change | 0.07 (0.02) | 0.0068 | 0.08 (0.03) | 0.0055 | 0.06 (0.05) | 0.28 |
| SGRQ total | −1.03 (2.34) | 0.66 | 1.25 (2.74) | 0.65 | −0.20 (3.72) | 0.96 |
| SGRQ symptoms | −1.12 (3.43) | 0.75 | −0.71 (3.74) | 0.85 | −5.48 (4.34) | 0.21 |
| SGRQ activity | −1.86 (2.96) | 0.53 | 0 (3.19) | 1.00 | 0.52 (4.17) | 0.90 |
| SGRQ impact | −0.89 (2.8) | 0.75 | 1.96 (3.33) | 0.56 | 0.66 (4.31) | 0.88 |
| COPD assessment test | −1.36 (1.24) | 0.28 | −0.15 (1.54) | 0.92 | −0.97 (1.64) | 0.55 |
| Pedometer, step | 274 (401) | 0.50 | 546 (394) | 0.17 | 540 (480) | 0.26 |
| Transitional Dyspnoea Index | 2.32 (0.66) | 0.0005 | 1.97 (0.66) | 0.0035‡ | 1.46 (0.67) | 0.032 |
| Dyspnoea-12 | −0.48 (1.01) | 0.63 | 0.58 (1.16) | 0.62 | 1.35 (1.51) | 0.37 |
| Hospital Anxiety and Depression Scale, Depression | 0.03 (0.61) | 0.96 | −0.16 (0.60) | 0.79 | 0.31 (0.65) | 0.64 |
| Hospital Anxiety and Depression Scale, Anxiety | 0.41 (0.60) | 0.50 | −0.2 (0.67) | 0.76 | 0.56 (0.74) | 0.45 |
| Saturation of percutaneous oxygen ($SpO_2$), stable | 0.44 (0.30) | 0.15 | 0.42 (0.34) | 0.22 | 0.55 (0.47) | 0.24 |

Kataoka K, et al. Thorax 2023;78:784–791

# Opioids for dyspnea

- Acting upon their central and peripheral nervous system receptors
- Decrease anxiety
- Modulate central perception of dyspnea
- Reduce respiratory drive without significant changes in blood gases

- Lack of high quality RCTs

Matsuda Y et al, J Palliat Med. 2018;21(12):1718-1723

Janowiak P et al, Front. Med. 2022:9:917973

# Opioids for dyspnea

- Oral morphine
  - opioid of choice in the treatment of dyspnea
  - no uniform dosing schedule
  - 1.25 to 2.5 mg q4h in non-cancer patients
  - 10mg daily maximum to 30mg daily

- Oxycodone
  - Start with 10mg bid

- Fentanyl
  - potency 100 times greater than morphine
  - accumulates in liver failure, but well tolerated in kidney failure
  - fentanyl buccal tablet, 100–200 µg, provided greater and faster dyspnea relief than immediate-release morphine.

Matsuda Y et al, J Palliat Med. 2018;21(12):1718-1723

Palliative Medicine in Practice 2018

# Morphine equivalent dose

| | Potency | Equivalent dose to 10mg oral morphine |
|---|---|---|
| Codeine phosphate | 0.1 | 100mg |
| Dihydrocodeine | 0.1 | 100mg |
| Hydromorphone | 5 | 2mg |
| Methadone | * | * |
| Morphine | 1 | 10mg |
| Oxycodone | 1.5 | 6.6mg |
| Tapentadol | 0.4 | 25mg |
| Tramadol | 0.1 | 100mg |

| Fentanyl patch strength (microgram/hr) | Oral morphine (mg/day) |
|---|---|
| 12 | 30 |
| 25 | 60 |
| 50 | 120 |
| 75 | 180 |
| 100 | 240 |

Pain Medicine 2012; 13: 562-70

# Safety of benzodiazepines and opioids in interstitial lung disease: a national prospective study

Sabrina Bajwah[1], Joanna M. Davies[1], Hanan Tanash[2], David C. Currow[3], Adejoke O. Oluyase[1] and Magnus Ekström[2,3]

TABLE 3 Benzodiazepines (BDZs) and opioids and adjusted hazard ratio of admission to hospital and mortality in 1603 patients with oxygen-dependent fibrotic interstitial lung disease

| | Adjusted HR (95% CI)# | |
|---|---|---|
| | **Admission** | **Mortality** |
| **BDZs** | | |
| Untreated | 1 | 1 |
| Low dose | 1.19 (0.95–1.49) | 1.13 (0.92–1.38) |
| High dose | 1.27 (0.92–1.73) | 1.46 (1.08–1.97) |
| **Opioids** | | |
| Untreated | 1 | 1 |
| Low dose | 1.21 (0.96–1.52) | 1.22 (0.99–1.50) |
| High dose | 1.08 (0.86–1.35) | 1.11 (0.89–1.39) |

Treatment with BDZs was associated with increased mortality but not in opioids

Bajwah S et al, Eur Respir J. (2018) 52:(6):1801278

# Opioids for dyspnea in ILD

- Opioids reduce breathlessness in COPD.
- Ongoing trial (MABEL trial)
  - Effect of low-dose morphine for chronic breathlessness
  - In patients with cardiac or respiratory disease (including IPF) with mMRC ≥3

Ekström M, et al Ann Am Thorac Soc 2015; 12: 1079–92.
Date K, et al, ERJ Open Res 2023; 9: 00167–2023.

# High flow nasal cannula (HFNC)

- Matches patient's inspiratory demand and washes out $CO_2$ from pharyngeal dead-space.
- Reduction of ventilatory dead-space might in turn improve the ventilation perfusion inequality.
- Oxygen supplementation in HFNC therapy improved exercise tolerance and $SpO_2$.

Janowiak P et al, Front. Med. 2022:9:917973
Respiration 2018;96(4):323-329
Respirology 2024 Jun;29(6):497-504

# Non-invasive ventilation (NIV)

- In terminal cancer patients with respiratory failure, NIPPV was significantly more effective in reducing dyspnea than conventional oxygen therapy in hypercapnic respiratory failure patients with cancer.

- No studies which would assess effect of NIPPV on breathlessness in IPF patients

Janowiak P et al, Front. Med. 2022:9:917973
Eur Respir J. (2017) 50:1602426

# HFNC vs. NPPV in ILD

- Retrospective study in Japan
- HFNC had a survival rate equivalent to that of NPPV and was better tolerated by patients with hypoxemic respiratory failure associated with ILD.

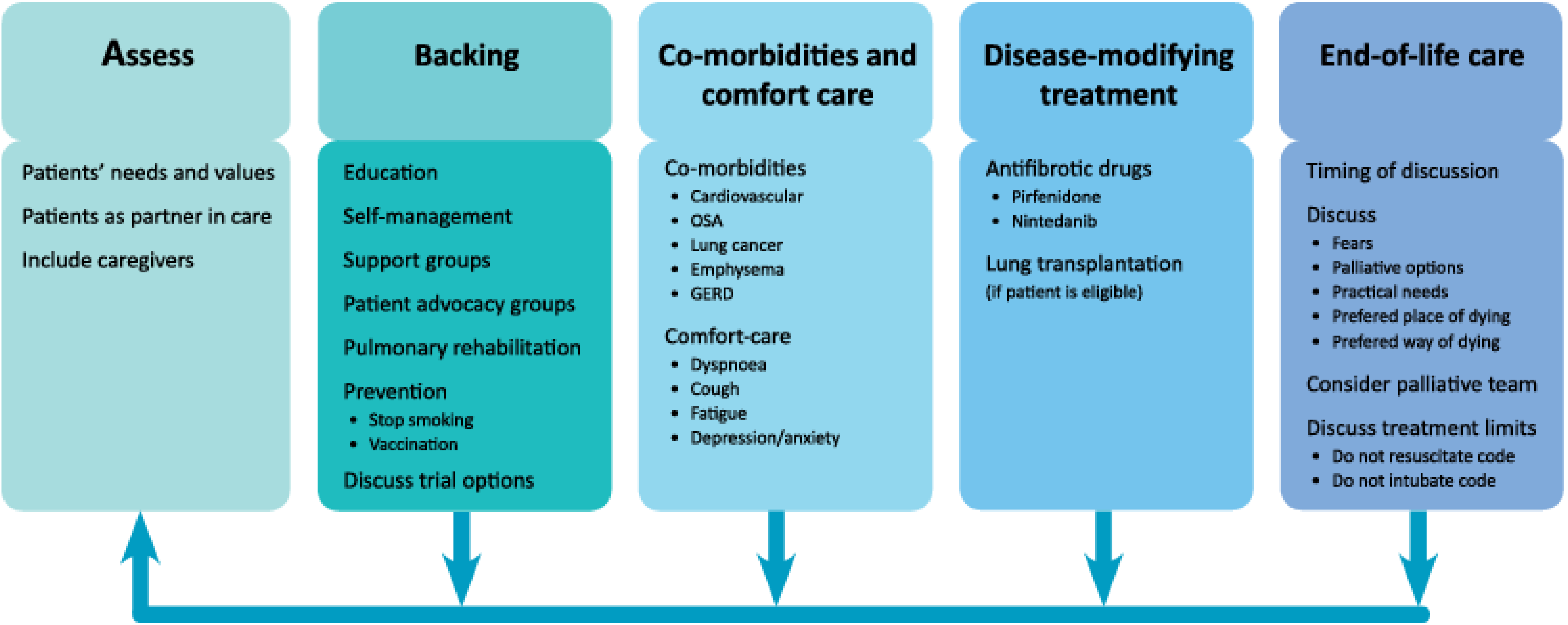
**Table 2.** Outcomes in patients with hypoxemic respiratory failure associated with interstitial lung disease

| Outcome | HFNC group ($n$ = 54) | NPPV group ($n$ = 30) | $p$ value |
|---|---|---|---|
| In-hospital mortality | 43 (79.6) | 25 (83.3) | 0.78 |
| Temporary interruption at the patient's request | 2 (3.7) | 7 (23.3) | 0.009 |
| Discontinuation at the patient's request | 0 (0) | 3 (10.0) | 0.043 |
| Adverse events | 1 (1.9) | 7 (23.3) | 0.003 |

| | HFNC | | | NPPV | | |
|---|---|---|---|---|---|---|
| | pre-HFNC | post-HFNC | $p$ value | pre-NPPV | post-NPPV | $p$ value |
| Respiratory rate, breaths/min | 28.0 (7.0) | 23.8 (4.3) | 0.0001 | 31.2 (8.1) | 32.6 (8.9) | 0.34 |
| STAS-J dyspnea score | 1.14 (0.72) | 0.90 (0.57) | 0.07 | 1.37 (0.69) | 1.30 (0.82) | 0.69 |

Respiration 2018;96(4):323-329

# Care of patients with IPF/PPF




van Manen MJ et al, Ther Adv Respir Dis 2017:11(3); 157–169

# Summary

- Cough, dyspnea is associated with QOL and prognosis of ILD.
- Rule out comorbidities associated with cough and dyspnea.
- Antifibrotics have some effects on QOL but insufficient for symptom control.
- Novel therapeutic approaches for managing cough are actively investigated.
  - Gefapixant, Nalbuphine
- Oxygen therapy and pulmonary rehabilitations are beneficial in improving dyspnea and QOL.
- Need more evidences for the management of symptoms in ILD.