Common Cormorbidities of ILD

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Comorbidities in ILD

- Gastroesophageal reflux
- Pulmonary hypertension
- Cough
- Fatigue

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See Dr. LaCamera: Treatment of IPF

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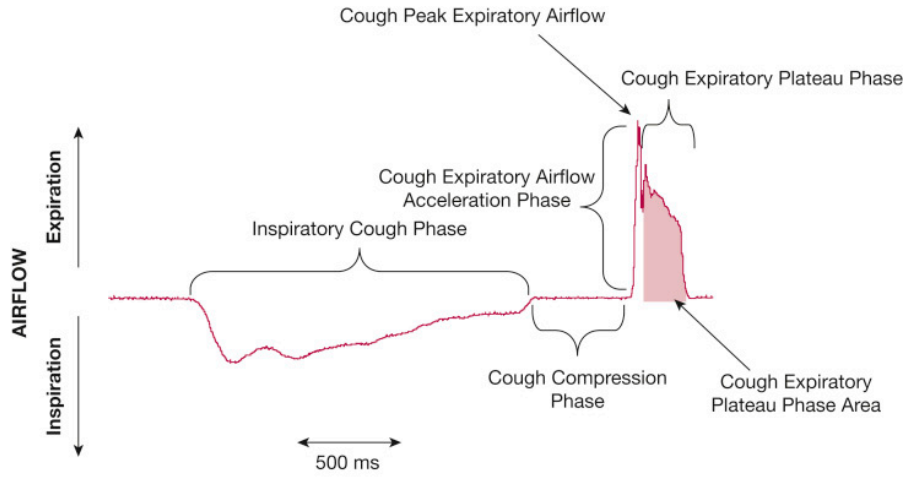
Cough Basics

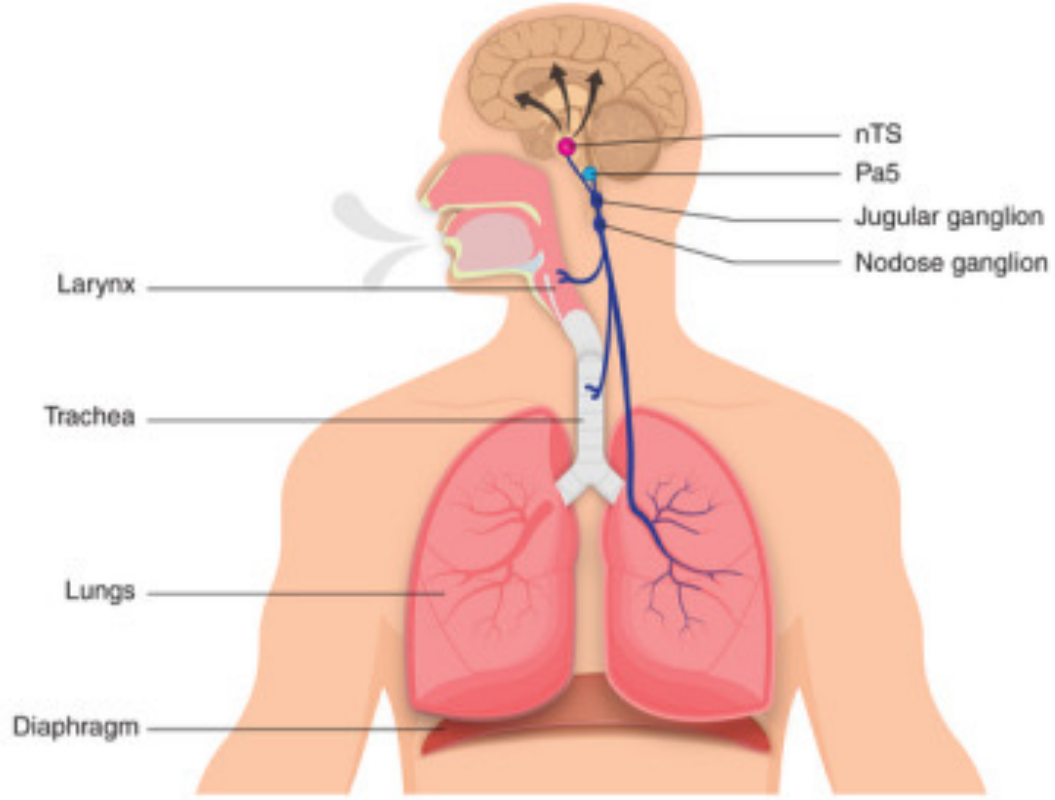
- Brief inspiration, expiration against closed glottis, reopening of glottis with large expulsive airflow phase



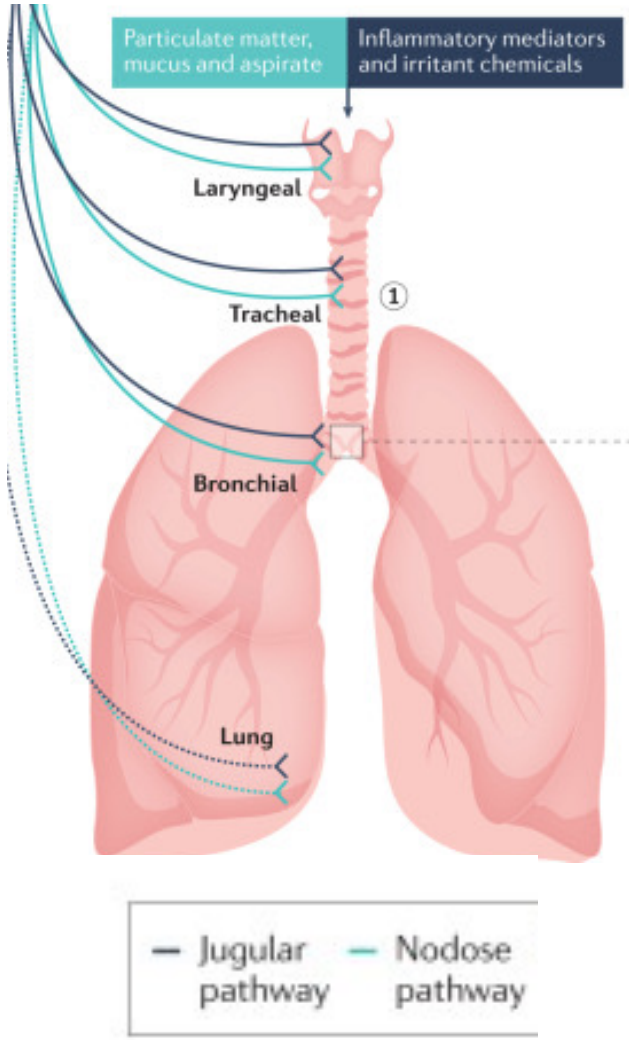
- Coordinated by brainstem respiratory pattern generator
- Reflex cough - in response to irritant stimulus
- “Cough hypersensitivity” – overreactive response

Lee et al. *Chest* 2021

Neural pathways of chronic cough



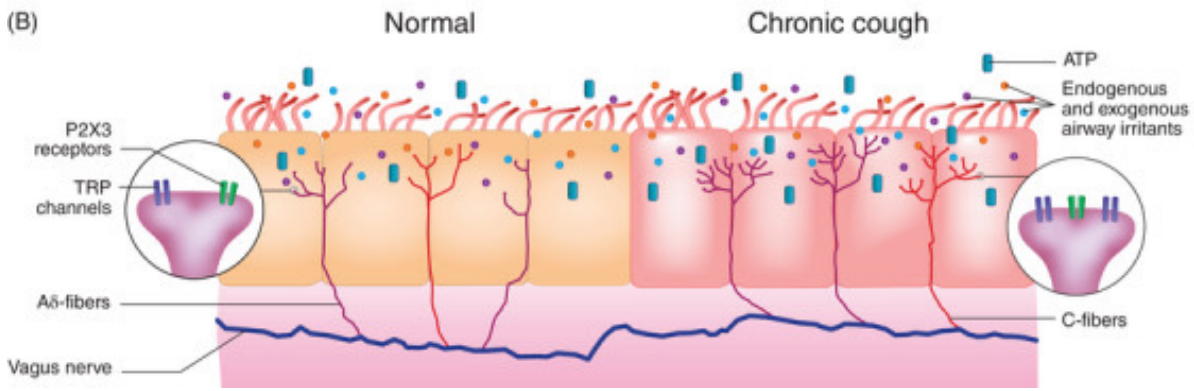
nTS, nucleus of the solitary tract; Pa5, paratrigeminal nucleus

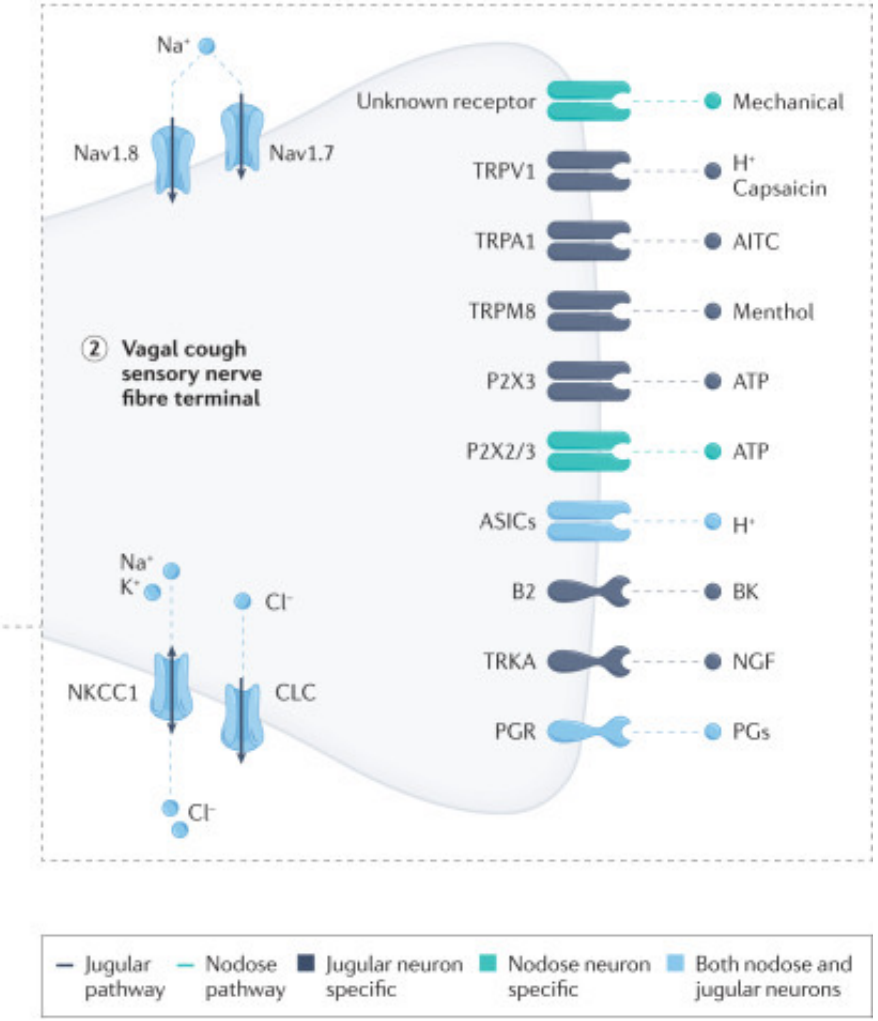


Nodose ganglia: vagal Aδ fibers:
Mechanical stimuli - particles, mucus, gastric contents

Jugular ganglia: vagal C fibers: irritant chemicals inflammatory mediators

Neural pathways of chronic cough



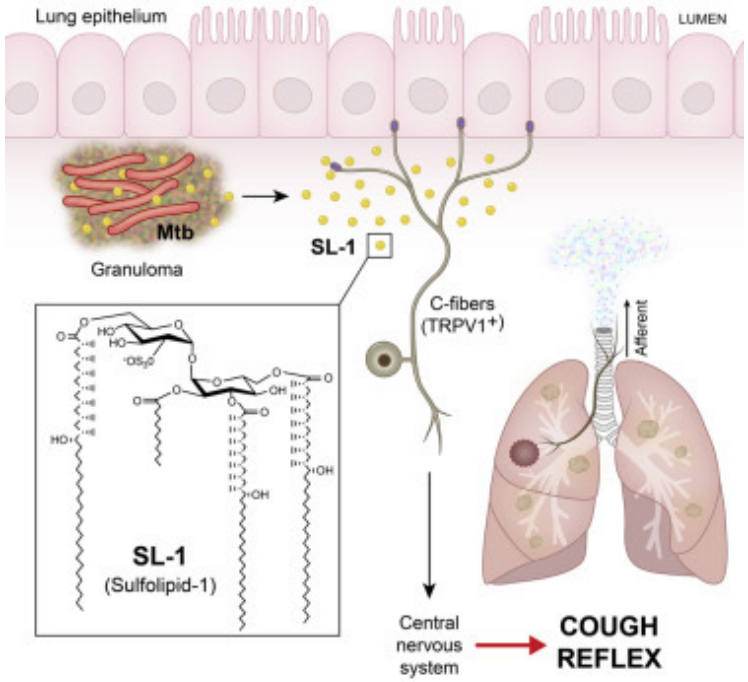


Pathogens can directly stimulate cough

Article

Cell

***Mycobacterium tuberculosis* Sulfolipid-1 Activates Nociceptive Neurons and Induces Cough**



Cough in ILD

- Described in the majority of ILD patients
  - 87% of IPF patients
  - 83% of chronic HP patients
  - 68% of SSc-ILD
- Similar sputum production as seen in chronic cough patients
- Small study suggested increased cough sensitivity in IPF patients
- Variable correlation with other underlying etiologies
  - GERD, UACS, ACE inhibitor use

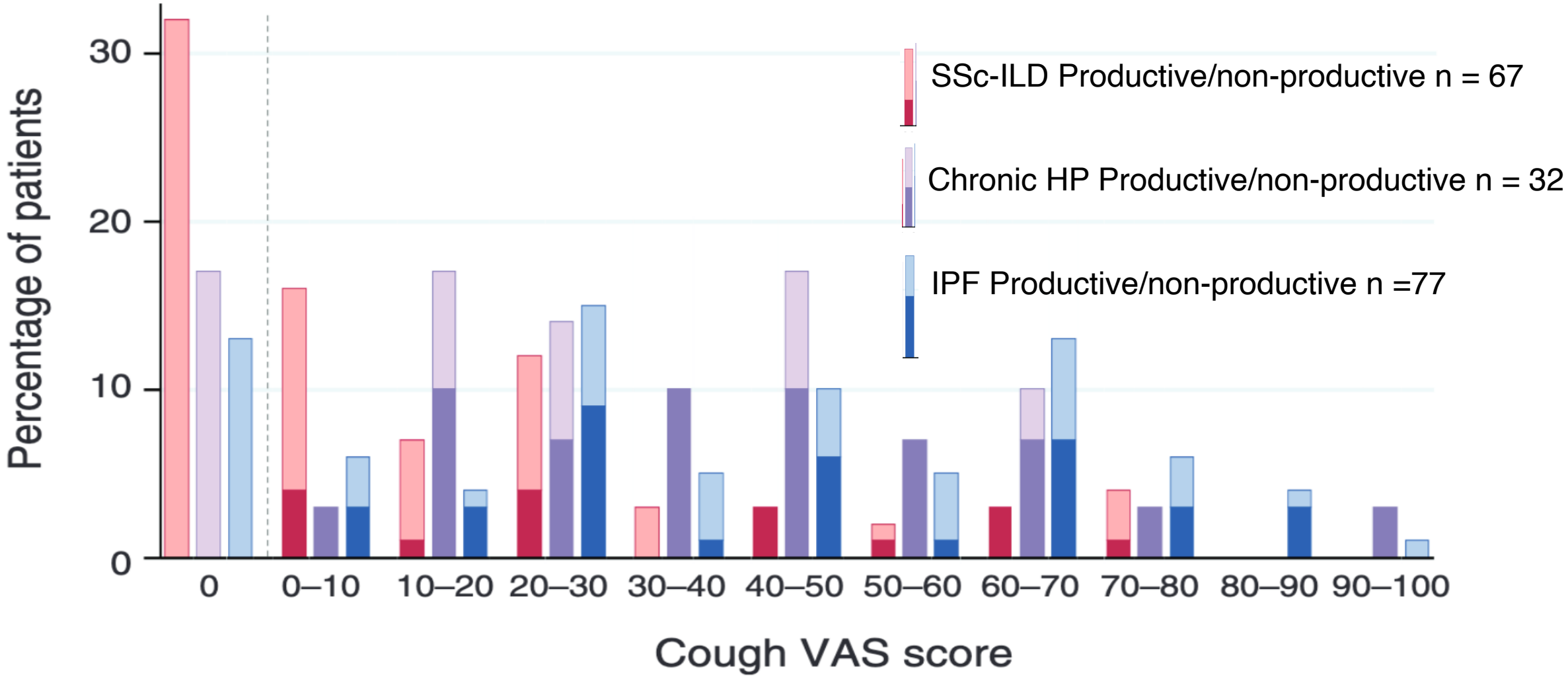
Ryerson *Respirology* 2011 Key et al *Cough* 2010; Saari *BMC Pulm Med.* 2023; Hope-Gill et al. *Am J Respir* Cheng… Ryerson *Respirology*. 2017. *Crit Care Med* Vol 168. Irwin R.S.*Curr. Opin. Pulm. Med.* 2005

Cough and other comorbidities coexist

Comorbidity	Frequency in IPF (%)
GORD	21–94
OSA	59–88[#]
Emphysema	30–55
ACE inhibitor use	9–15
Chronic sinusitis/UACS	17–34
Lung cancer	4.4–16
Infection	11–20

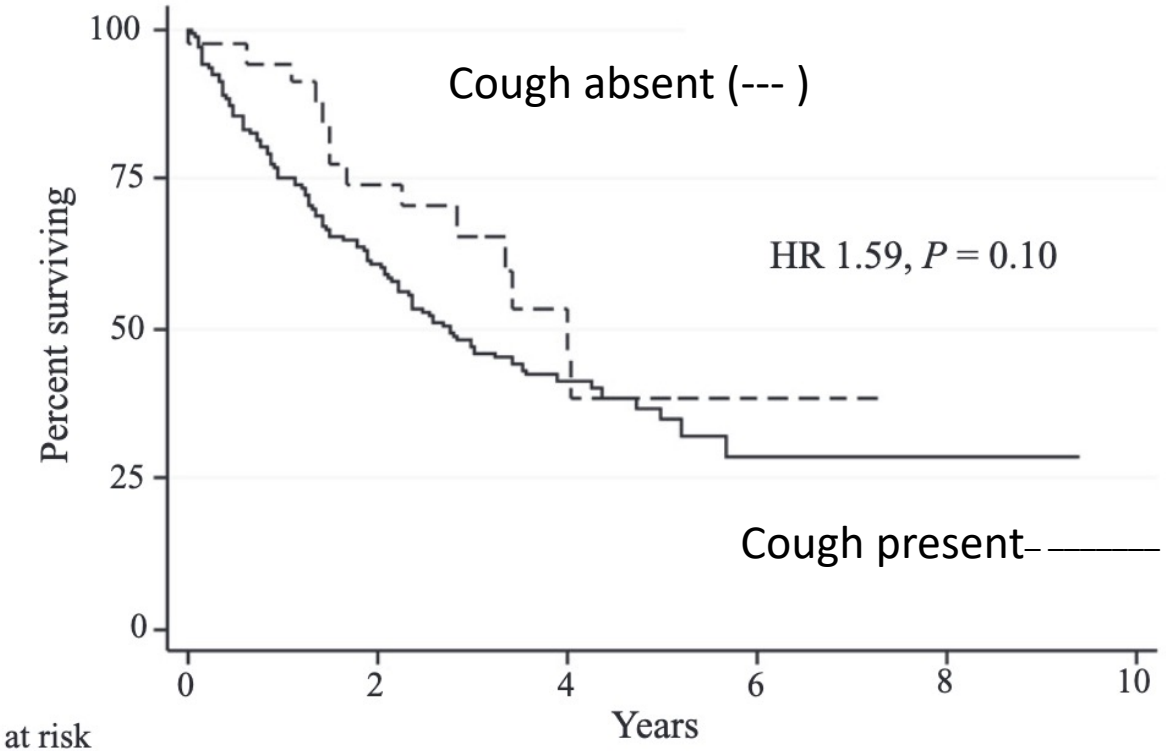
GORD: gastro-oesophageal reflux disease; OSA: obstructive sleep apnoea;
ACE: angiotensin converting enzyme; UACS: upper airway cough syndrome.
[#]: with high mean body mass index of 28–32 $kg \cdot m^{-2}$.

Cough severity varies among ILDs



Cheng... Ryerson *Respirology* (2017) 22, 1592–1597

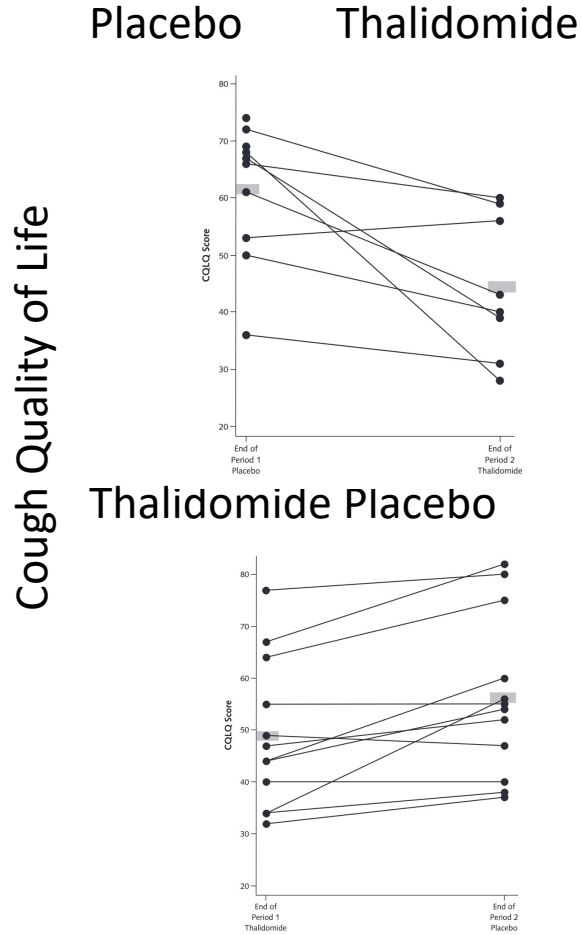
Cough correlated with mortality in IPF



Number at risk					
Cough absent	38	22	8	2	0
Cough present	204	85	36	6	5

Treatment for cough in IPF

- Thalidomide
  - 24 IPF patients double blinded RCT (Horton *2012*
  - Cough Quality of Life (lower means less impact of cough); VAS, SGRQ)
  - All improved after thalidomide
- Pirfenidone
  - Observational study of 43 IPF patients starting pirfenidone
  - 24 hour cough decreased 34% at week 12; cough recordings better in 20 of 27 patients (Van Manen et al. 2017)
  - Recent observational study of 52 patients ->no change in cough score (LCQ) (Jastrzębski et al. 2023)
  - No change in cough score in 253 pts with unclassifiable ILD *(Maher 2020)*

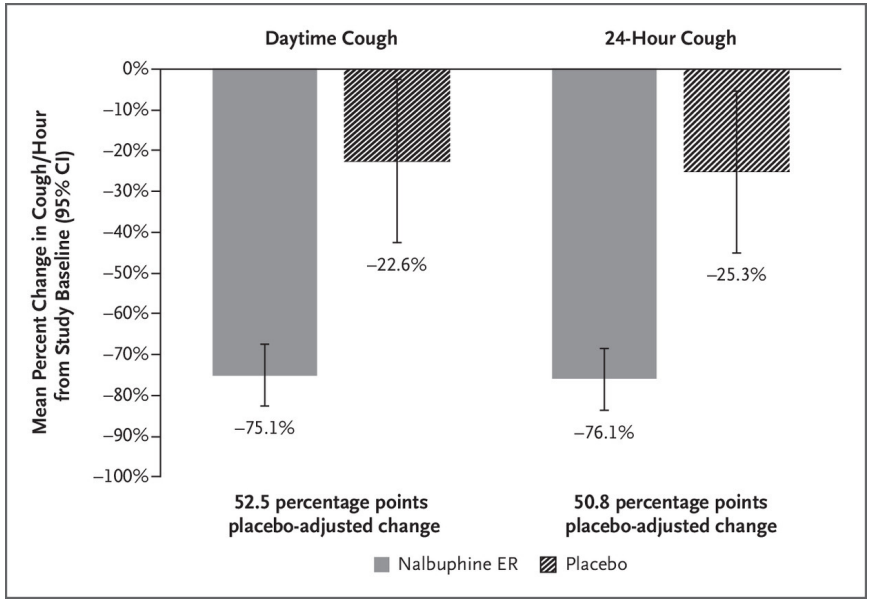


Horton et al. *Ann Intern Med* 2012

Horton et al. *Ann Intern Med* 2012; van Manen et al. *Eur Respir J*. 2017; Maher…Cottin *Lancet Respir Med* 2020 Jastrzębski et al. *Health Sci Rep;* Maher…Cottin *Lancet Respir Med* 2020

Nalbuphine for Cough in IPF

- Randomized, double-blind, placebo-controlled, crossover of 41 pts
- Day 21 75% daytime cough reduction vs 22.6%
  - 12/42 discontinued drug (9 AEs, 3 COVID-19)
  - Nausea, fatigue, constipation very common
- Larger study: Cough Reduction in IPF With Nalbuphine ER (CORAL) not yet recruiting *NCT05964335*



Maher et al. *NEJM Evid* 2023;2(8)

Therapies without proven efficacy

Nintedanib – no change in self reported CASA-Q in INPULSIS patients

638 nintedanib vs 423 placebo

Acid suppression

- Possible improvement in omeprazole 20 mg bid *(*Dutta 2018)
- No change in cough after high dose PPI, possible increased non acid reflux (Kilduff 2014)

Inhaled cromolyn sodium - mast cell stabilizer

- 108 patients randomized; 66 completed study (Martinez 2022)
- trial terminated May 2020 COVID19
- No change in IPF cough

Gefapixant – antagonist of $P2X_3$ receptor

- Approved in Japan for chronic cough
- Small pilot in IPF – no discernable effect (Martinez 2021)

Trials for Cough in IPF

Orvepitant - NK-1 R antagonist (Receptor for substance P)

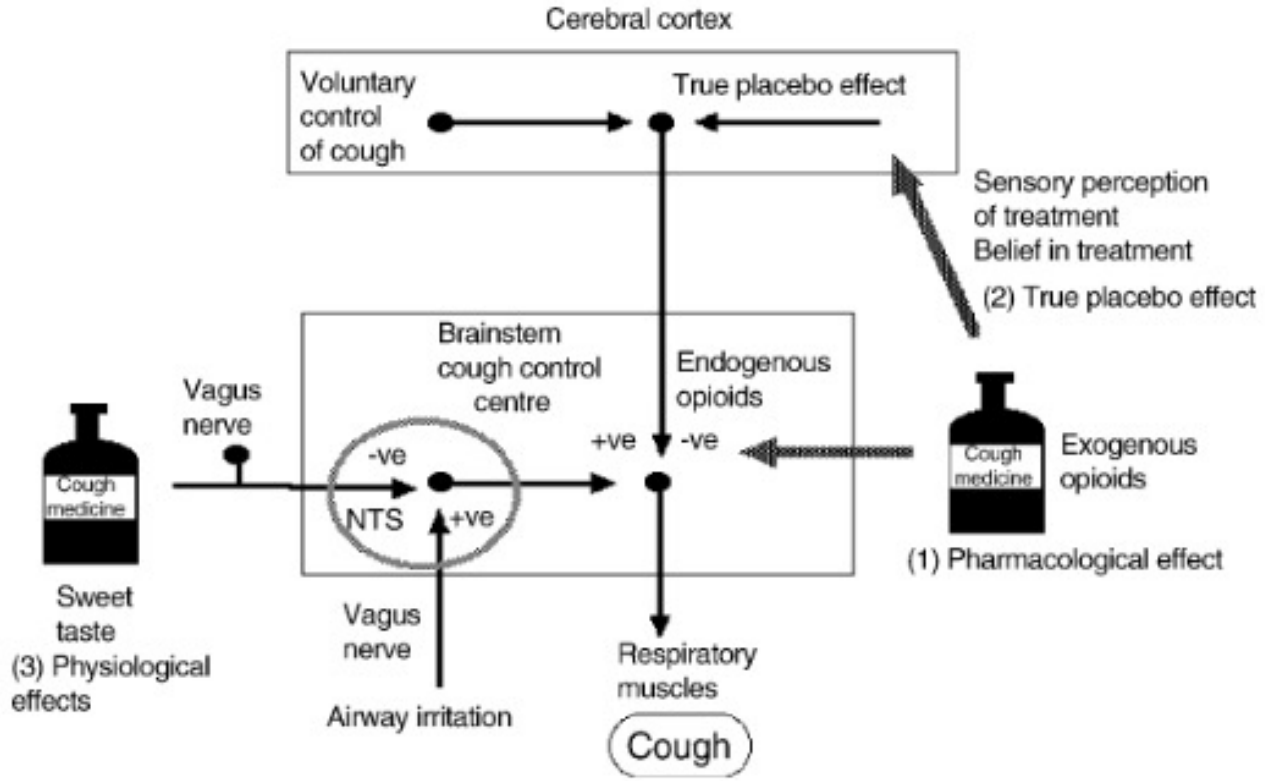
Phase 2 pilot in chronic cough some benefit, Phase 2 completed NCT05185089, NCT02993822

Phase 2 in IPF cough recruiting IPF-COMFORT NCT05185089

Morphine – Double blind crossover of 5mg morphine ER bid NCT04429516

Nalbuphine - Cough Reduction in IPF With Nalbuphine ER (CORAL) not yet recruiting NCT05964335

Placebo quite powerful in cough



ACTIVE INGREDIENT
Guaifenesin 20mg/ml

→ PHARMACOLOGICAL EFFECT

SWEETNERS
Glucose,liquid
Glycerol
Sucrose
Sucralose

FLAVOURS
Levomenthol
Bitterness blocking flavour 84E260
Honey flavour SN781458
Lemon flavour 557579CW8
Cooling flavour 539692T
Tingling flavour 538723T
Hot mix flavour 538842T
Non-alcohol enhancer SC008414
Caramel (E150)

GELLING AGENT
Carbomer

→ PLACEBO EFFECT

BUFFERING AGENTS
Sodium citrate
Citric acid monohydrate

SOLVENTS / PRESERVATIVES
Ethanol 96%
Sodium benzoate (E211)
Purified water

Eccles, R, *Lung* 2020 Eccles, R, *Respir Physiol Neurobiol* 2006 Jul 28;152(3):340-8.

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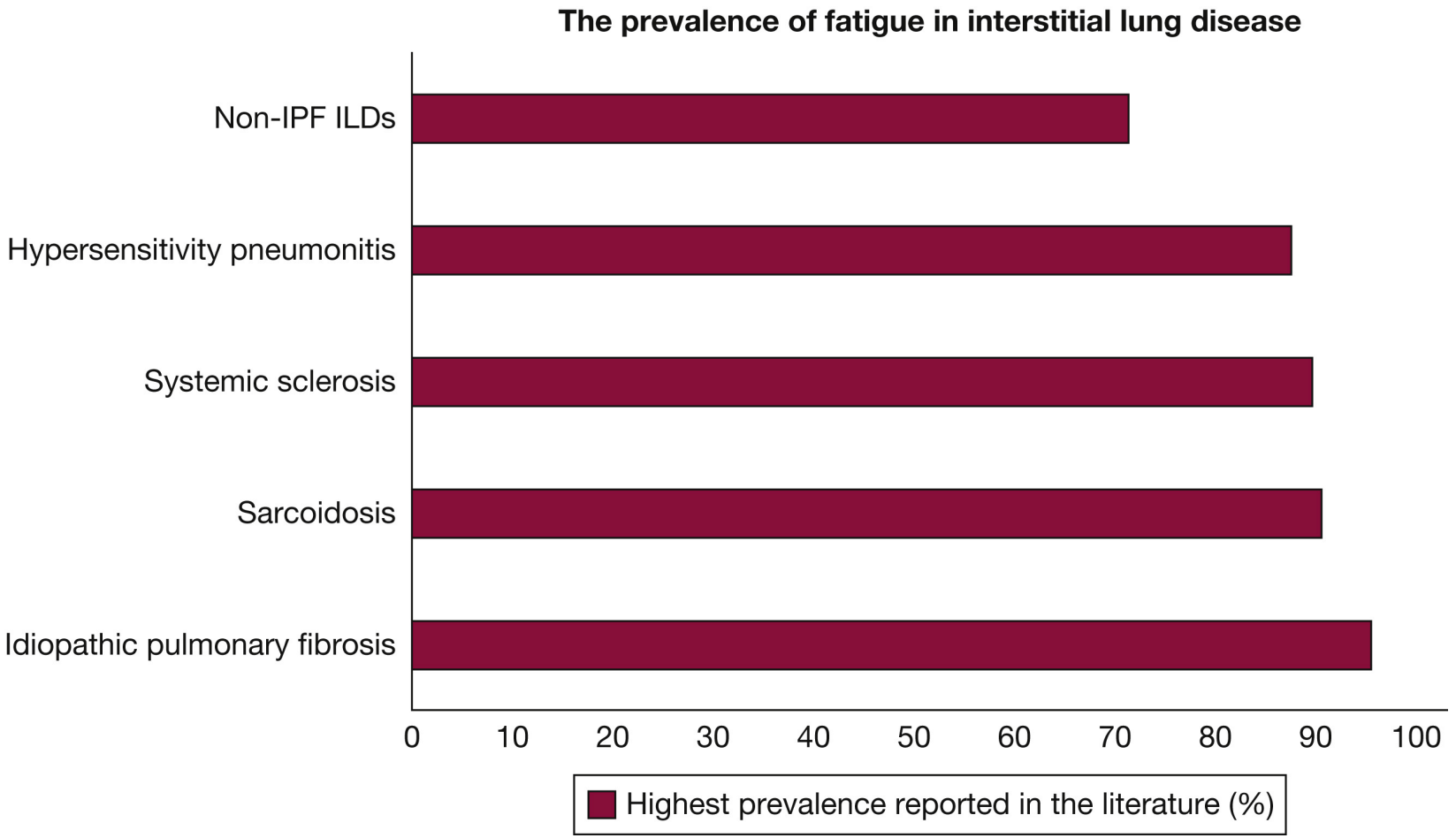
What does tired mean?

Fatigue: lack of both physical and emotional energy and motivation (tiredness, exhaustion, low energy)

Sleepiness: the desire to fall asleep (drowsiness)

Depression: persistent feelings of sadness, disappointment and hopelessness, along with other emotional, mental, and physical changes that interfere with daily activities.

Fatigue in ILD



Kahlmann et al. *Chest* 2020 Nov;158(5):2026-2033.

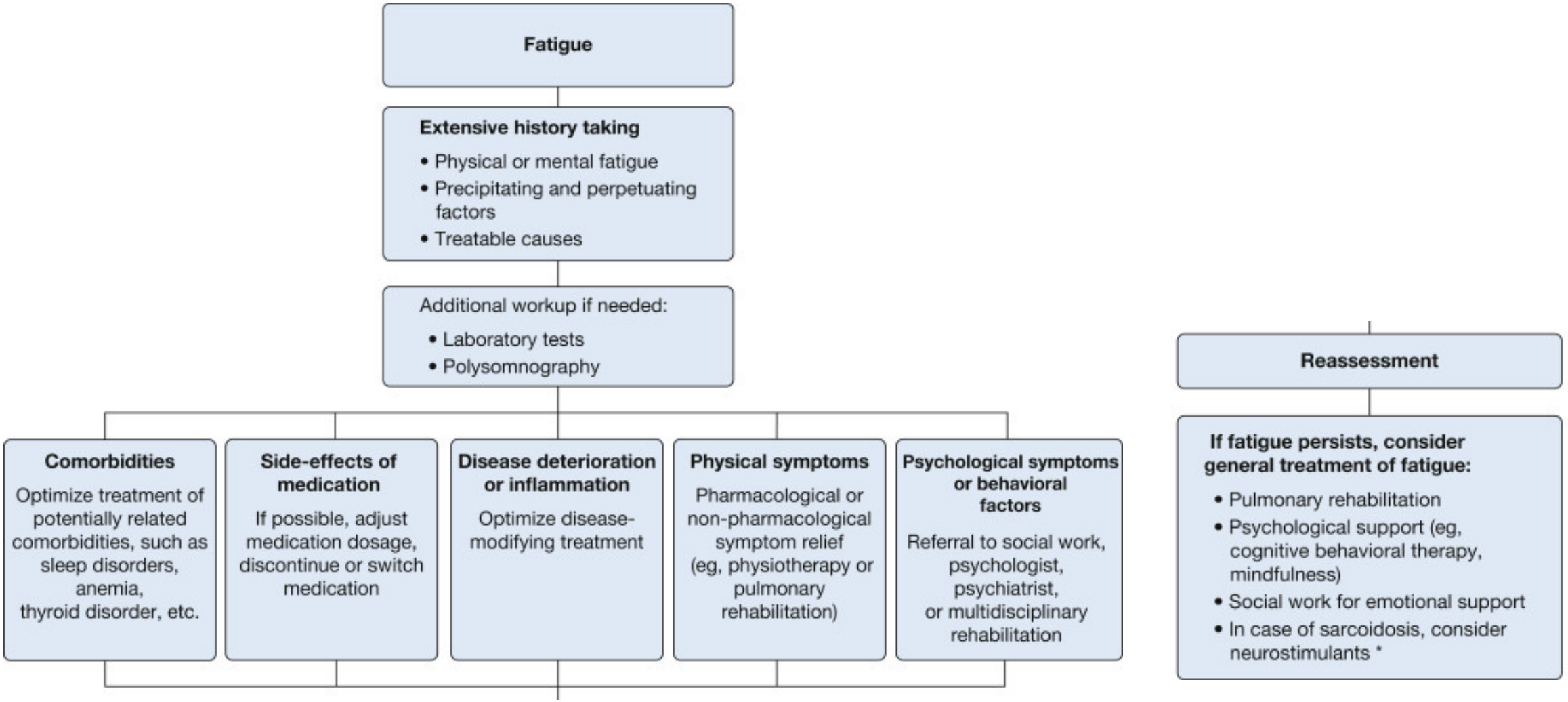
Workup of Fatigue

- Medical comorbidities
  - Anemia, coronary disease, thyroid disorder, electrolytes
  - Sleep disruption - GERD, cough, OSA, urinary symptoms
- Medications
  - Beta blockers, opioids, steroids
- ILD
  - Hypoxia, deconditioning

- Depression or anxiety

- **Almost definitely multifactorial**

Workup of Fatigue



Kahlmann *Chest* 2020 Nov;158(5):2026-2033.

Obstructive Sleep Apnea in ILD

- Meta-analysis prevalence in IPF ~76% vs 16% in non IPF
  - IPF 88%
  - 45% of sarcoidosis subjects vs 31% of control subjects
  - Prevalence ranges (44–83%) in various ILDs
    - Scleroderma-ILD, ankylosing spondylitis, chronic hypersensitivity pneumonitis
- Unclear impact on disease
  - Small studies suggest treatment is beneficial
  - Retrospective review of 130 ILD-OSA patients found no change in mortality with CPAP

Lancaster *Chest*. 2009 Sep; 136(3): 772–778. Karuga J *Clin Med* 2020, Boulloukaki Breathe (Sheff). 2022 Bosi et al *Lung* (2017) Papadogiannis *J Clin Sleep Med,*.Roeder *J Clin Sleep Med* 2022, Adegunsoye, *Chest*. 2020

Screening for OSA

Full PSG

Home sleep study

WatchPAT

Sci Rep 2019 Dec 18;9(1):19392.
COPD. 2020 Feb;17(1):34-39.

Take Home Points

Cough is prevalent and bothersome

Etiology multifactorial and heterogeneous

Strong placebo effect expected

Novel therapies being tested – Nalbuphine, Orvepitant, morpheme

Fatigue is common

OSA is prevalent, unclear impact on disease progression

Thank you

References

Lee et al. Chest. 2021 Jan; 159(1): 282–293

Madison JM, Irwin RS. Curr Opin Pulm Med 2005; 11: 412–416

Martinez et Al. Am J Respir Crit Care Med 2022 May 1;205(9):1084-1092.
Martinez et al. *Pulm Ther* 2021 Dec;7(2):471-486. Irwin et al/ Chest. 2018;153:196–209

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

Hope-Gill et al. Am J Respir Crit Care Med 2003 Oct 15;168(8):995-1002

Jastrzębski et al. *Health Sci Rep* 2023 Aug 16;6(8):e1449

Wu, Z *et al.* PAciFy Cough. *Trials* **23**, 184 (2022)

References

Eccles, R, *Lung* 2020 Feb;198(1):13-21.

Eccles, R, *Respir Physiol Neurobiol* 2006 Jul 28;152(3):340-8.

Lancaster *Chest*. 2009 Sep; 136(3): 772–778.

Karuga J Clin Med. 2022 Sep; 11(17): 5008.

Boulloukaki Breathe (Sheff). 2022 Sep; 18(3): 220073. Bosi et al *Lung* (2017) 195:643–651

Papadogiannis et al. *J Clin Sleep Med*. 2021;17(3):533–544.

Roeder et al. *J Clin Sleep Med* 2022 Oct 1;18(10):2415-2422

Adegunsoye et al. *Chest* 2020 Oct; 158(4): 1701–1712.