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Opioids bring peace to IPF cough

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There are now two positive randomised placebo-controlled phase 2 trials of opioids for the treatment of cough in patients with idiopathic pulmonary fibrosis (IPF). Opioids suppress cough by binding to several types of G protein-coupled endorphin receptors on pre-synaptic neurons in brainstem cough centres, thus modulating neurotransmitter release. A recent trial of nalbuphine, a mixed agonist-antagonist of opioid receptors, demonstrated a 52.5% placebo-adjusted reduction in daytime cough counts (1). In this edition of *The Lancet Respiratory Medicine, Wu et al* report the results of PAciFy-cough in IPF, showing that 2 weeks' treatment with twice daily low-dose morphine sulphate (MST) significantly reduced objective daytime cough counts (by 39.4%) and subjective measures of cough severity, and improved cough-related quality of life compared with placebo.

Chronic cough is a cardinal feature of IPF with a reported prevalence of >80%(2). Cough is associated with poorer quality of life in IPF, and subjective cough measures have been associated with worse IPF outcomes in retrospective studies (3). However, there are no licensed treatments for patients with IPF who suffer from chronic cough.

The mechanism of cough in IPF is the subject of debate. Our understanding of refractory chronic cough (RCC) has been revolutionised by the paradigm of the cough hypersensitivity syndrome (CHS), whereby hypersensitivity of vagal afferents and/or central pathways to normally innocuous stimuli leads to aberrant over-activation of the cough reflex.(4) Capsaicin challenge studies have demonstrated that patients with IPF have a heightened cough reflex sensitivity(5), suggesting a common pathophysiology with CHS. A trial in IPF cough of gefapixant, which reduces cough reflex sensitivity by antagonising the effect of adenosine triphosphate (ATP) on peripheral ATP-gated P2X3 ion channels, didn't meet its primary endpoint.(6). However, the study was fraught with methodological problems and positive signals on secondary endpoints shouldn't be ignored. Distinctive contributing factors to cough in IPF include gastro-oesophageal reflux, neuroimmune crosstalk, abnormal mucus, and stiffness and structural distortion of the lungs.(2) The positive phase 2 trial results with opioids highlight a role for the central neural cough network in IPF cough.

Cough can be measured in many ways. The current gold standard is objective cough counting, particularly awake/daytime cough frequency since patients with CHS cough mostly whilst awake. *Wu et al* assessed cough using an ambulatory cough recorder to count coughs, a subjective visual analogue scale of cough severity, and the Leicester cough questionnaire for cough-related quality of life. These validated patient-reported outcome measures (PROMs)(7) correlate imperfectly with objective cough frequency. PROMs are often overlooked by regulators, yet quality-of-life detriments engendered by cough are of paramount significance to patients. Arguably PROMs should represent the primary outcomes of importance in cough studies.

One of the most striking observations in PAciFy-cough is the near absence of a placebo response. In contrast, trials in patients with RCC typically exhibit large placebo responses. The COUGH-1 and COUGH-2 trials of gefapixant in RCC showed >50% reductions in objective cough counts with placebo.(8) Based on *Wu et al*'s results, we would argue that IPF cough is an example of cough that is commonly truly refractory to placebo.

A disadvantage of using opioids to treat chronic cough is the potential for unwanted effects. In PAciFy-cough, 40% of patients when treated with MST reported an adverse event during the 2-week treatment period compared with 14% on placebo. Constipation was reported by 21% of patients on MST, but no patient required laxatives. This low burden of constipation may reflect the short treatment period; most patients on long-term opioid therapy need to take a regular laxative. Another explanation is that concurrent nintedanib therapy in half of the participants may have abrogated opioid-induced constipation. Longer-term opioid studies should also assess participants' risk of addiction and withdrawal.

Secondary outcome analysis in PAciFy-cough did not demonstrate an effect of MST on breathlessness questionnaire scores. In chronic obstructive pulmonary disease there is good evidence that opioids reduce breathlessness (9). The MABEL trial(10), examining the effect 56 days of low dose MST on chronic breathlessness, has recently completed recruitment. MABEL recruited patients with cardiac or respiratory disease (including IPF) with modified Medical Research Council breathlessness grade ≥3, representing a more severely breathless case mix than PAciFy-cough. Together, these trial results will shed light on the role of opioid therapy in managing the most disabling symptoms of IPF.

PAciFy-cough represents a stride forward in the management of IPF cough. Questions remain around the pathophysiology of IPF cough and how it overlaps with RCC. Further work is required to carefully phenotype cough in IPF patients to identify personalised therapeutic targets.

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