Lessons from negative dyspnoea studies: arguments for the multidimensional evaluation of multidirectional therapeutic approaches

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Dyspnoea-targeted interventions should probably combine multiple approaches (multidirectional) and their evaluation should take the complex nature of dyspnoea into account (multidimensional) http://ow.ly/tLaM30ndprk

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In this issue of the *European Respiratory Journal*, two articles are published that could at a glance appear to be only barely related [1, 2]. One of these articles [1] discusses patients with chronic respiratory diseases who suffer from chronic [3] or persistent [4] breathlessness, that is, who remain crippled by dyspnoea after they received the best known treatments for their underlying conditions. The other article [2] discusses patients with acute respiratory failure, either *de novo* or as complication of an underlying chronic cardiac or respiratory disorder, admitted to an intensive care unit (ICU) and who received noninvasive ventilation (NIV). The two studies yet have two things in common: they both aimed to relieve respiratory discomfort and were both deemed negative because their main outcome was not reached.

In the study by Currow *et al.* [1], 223 patients with chronic breathlessness were randomised at multiple sites to receive either sertraline or a placebo following a double blind, dose increment, parallel arm placebo-controlled adaptive design. Sertraline and placebo were administered to patients in addition to their treatments. The main outcome was defined as the proportion of patients reporting an improvement of breathlessness by more than 15% on a 100 mm visual analogue scale, relative to baseline. This target was not reached. Additionally, no subgroup demonstrated any response in any measure of breathlessness. There was no improvement of functional status, anxiety or depression. In the study by Messika *et al.* [2], 113 patients receiving NIV for acute respiratory failure were included at three medical centres to undergo either standard practice NIV (control), NIV with musical intervention, or NIV with sensory deprivation (acoustic and visual), with random assignment. The primary outcome was a change in respiratory comfort between NIV initiation and the 30th minute of the first NIV session. Again, this target was not reached, neither globally nor after various sensitivity analyses. Variations of respiratory discomfort were not

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significantly different between subsequent time-points nor in subsequent NIV sessions. These two studies can therefore be deemed negative without a doubt.

Interpreting randomised controlled trials that fail to demonstrate statistically significant differences in primary outcomes can be difficult, and one is often unduly tempted to focus on "trends" and secondary outcomes to "salvage" a study [5, 6]. Secondary outcomes can only be reasonably used to try and understand why the main outcome was not attained, or can be resorted to as "signals" to devise further research. In that vein, both the sertraline study and the musical intervention study published in this issue of the *European Respiratory Journal* [1, 2] hold interesting information. The sertraline study by Currow *et al.* [1] showed two things indeed. First, there was a weak signal favouring sertraline over placebo with regard to general quality of life scores. The proportion of patients who reported an improvement in breathlessness of more than 15% from baseline in the placebo group was not significantly different from the equivalent proportion of patients in the sertraline group, but this proportion was very high at 41%, hence the possibility of a floor effect. The musical intervention studies reported by Messika and co-workers showed that the peritraumatic distress inventory score at the time of ICU discharge was reduced by 50% (and significantly so) in patients subjected to musical intervention compared to patients having experienced sensory deprivation as well as control patients [2, 7]. A significant reduction in blood pressure was also noted in patients randomly affected to the music arm during the first NIV session. The study further showed that the numerical values of slopes of changes varied between groups, with respiratory discomfort decreasing faster in the musical intervention group than in the two other groups. Of note, NIV alone (control group) was efficient in reducing respiratory discomfort; this relieving effect could have been expected but is known to be inconstant [8]; it could have also led to a floor effect.

What lessons can we learn from the above "secondary signals" and how can they be useful for future research?

Firstly, the magnitude of the effect observed in the placebo arm of the sertraline study is of major interest [9, 10]. A similar finding has previously been resorted to as to explain the failure of nefopam (a non-opioid analgesic interfering with C-fibres) to alleviate experimental dyspnoea in healthy volunteers [11]. The mechanism at play can either be the placebo effect in the traditional sense (as proposed by Pattinson and Wanigasekera [9] in a letter also published in this issue of the journal) or the Hawthorne effect (as proposed by Currow *et al.* [10] in their response to said letter). The placebo effect could impact breathlessness by modifying anticipatory processes [12] that are increasingly recognised as determinants of the dyspnoea experience [13, 14]. The Hawthorne effect could influence breathlessness through patients realising that their dyspnoea is being observed and thus no longer ignored. Dyspnoea is indeed known to elicit at times unsatisfactory responses from caregivers, or even avoidance ("invisibility of dyspnoea" [15, 16]). This worsens the patients' negative experience through disempowerment [17]. It is therefore not surprising that participation in a dyspnoea-oriented clinical trial would suffice in generating clinical benefits. Offering reassurance and empathy should therefore be highly effective for persistent breathlessness, either chronic (as in the sertraline trial [10]) or acute (as in the music intervention trial [2]). This could and should be the subject of specific studies, with the aim to increase caregivers' sensibility to dyspnoea and improve their training to its management [18].

Secondly, the two studies were perhaps negative only because their primary outcomes were not properly chosen. In both cases, dyspnoea (or breathlessness, or respiratory comfort/discomfort) was assessed using one-dimensional tools evaluating "intensity". Yet, dyspnoea is a complex experience [19]. Its multidimensional nature [20] can be captured clinically by specific tools such as the Multidimensional Dyspnea Profile or the Dyspnoea-12 [21, 22]. The very definition of dyspnoea implies that it features a sensory and an affective dimension that can vary independently of one another [23]. These dimensions correlate differently with different types of patient-related outcomes [24, 25]. For example, in patients suffering from chronic obstructive pulmonary disease (COPD) [24], correlations between the sensory dimension of dyspnoea were stronger with "activity" outcomes (such as the DIRECT disability questionnaire [26]) than with "quality of life" outcomes. Conversely, correlations were stronger between the affective dimension of dyspnoea and "psychological" outcomes (such as the Kessler psychological distress scale [27]). The same general pattern was also observed in patients with amyotrophic lateral sclerosis [25], where the affective dimension of dyspnoea proved to be the main driver of anxiety, according to the hospital anxiety and depression scale. Both sertraline and the musical intervention [1, 2] could have had a positive effect on the "affective dimension" of dyspnoea that was simply not picked up by the one-dimensional scales used to assess their effects. This hypothesis is consistent with some of the observations made in the two studies, such as the improvement in general quality of life in the sertraline arm of the sertraline study [1] and the reduction of acute stress (blood pressure) and peritraumatic stress at the time of ICU discharge in the musical intervention study [2]. Both are likely to relate to the affective dimension of dyspnoea.

Finally, one should remember that when neither the lung nor the brain are accessible to dyspnoea-relieving interventions, coping approaches can have a positive effect and "appease the mind" [28]: COPD patients have demonstrated significant and sustained benefits from mindfulness-based cognitive therapy, even in the absence of dyspnoea improvement [29]. In other words, an intervention that does not relieve dyspnoea can however be beneficial to the well-being of dyspnoeic patients.

The two studies that are the object of this editorial [1, 2] were both rigorously conducted by highly renowned teams and were completed in spite of demanding designs. They are worthy of publication in a high profile journal such as the *European Respiratory Journal* even though their negative nature will probably imply that they may not be widely cited in their respective fields. As in the case of negative studies in general, these publications are useful to spare other research groups futile efforts of a similar nature, and to avoid the unethical exposure of patients to procedures already known as ineffective. But beyond that the results of the two studies remind us that the outcomes of future dyspnoea-targeted studies should take into account the recent understanding of dyspnoea's complex nature: the use of multidimensional tools to evaluate dyspnoea-targeted interventions should thus probably be generalised. The two studies also suggest that gathering data describing the effects of mere human interactions on dyspnoea is necessary: it will allow investigators to better calibrate studies of more specific interventions, be they pharmacological or not. And in the end, these two studies raise the question of how single interventions (pharmacological or otherwise) are likely to be effective in patients with multiple needs in whom dyspnoea cannot be reduced to a symptom but represents a complex (and negative) life experience. Multidirectional approaches (such as the breathlessness support service concept [30, 31]) have proven to be effective, and should probably be favoured when addressing clinical dyspnoea.

One thing remains certain: "negative" dyspnoea studies should not tame our efforts to improve the identification and management of respiratory suffering, a major medical cause [32] that proceeds from no less than human rights issues [17, 33]. In this view, the authors of the two abovementioned studies must be commended not only for undertaking them, but also for not self-censoring themselves when submitting their work for publication.

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