



Enabling patients in effective self-management of breathlessness in lung cancer: the neglected pillar of personalized medicine

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Practice points

- Current management of breathlessness focused on treatment of underlying disease and pharmacological interventions is inadequate.
- Comprehensive breathlessness services that integrate self-management support are ideal for improving breathlessness and quality of life but need implementation on a wider scale.
- Engagement of patients in effective self-management of breathlessness is the neglected participatory pillar of personalized cancer medicine and requires greater attention globally.
- Support of patients in effective self-management of breathlessness should be integrated in routine lung cancer care to reduce breathlessness, suffering and optimize quality of living.

Globally, engagement of patients in the self management of disease and symptom problems has become a health policy priority to improve health outcomes in cancer. Unfortunately, little attention has been focused on the provision of self-management support (SMS) in cancer and specifically for complex cancer symptoms such as breathlessness. Current management of breathlessness, which includes treatment of underlying disease, pharmacological agents to address comorbidities and opiates and anxiolytics to change perception and reduce the sense of breathing effort, is inadequate. In this perspective paper, we review the rationale and evidence for a structured, multicomponent SMS program in breathlessness including four components: breathing retraining, enhancing positive coping skills, optimizing exertional capacity and reducing symptom burden and health risks. The integration of SMS in routine lung cancer care is essential to improve breathlessness, reduce psychological distress, suffering and improve quality of life.

First draft submitted: 9 June 2020; Accepted for publication: 20 May 2021; Published online: 2 July 2021

Keywords: lung cancer • self-management • perspective • breathlessness

Due to earlier detection and advances in systemic treatment (i.e., immunotherapy) and targeted precision medicine therapies, death rates have been declining in lung cancer leading to a better outlook for some individuals [1]. Despite better survival, lung cancer patients are often multisymptomatic and experience a myriad of physical symptoms (pain, fatigue, cough, breathlessness) and high rates of psychological distress (depression and anxiety) [2]. Breathlessness (dyspnea, shortness of breath) remains one of the most terrifying symptoms of lung cancer with rates ranging from 15% in early stage disease to 90% at the end of life [3]. Breathlessness is a subjective symptom that varies in intensity with dynamic, continuous (chronic) and acute-episodic features that trigger fear of 'suffocation' in patients and their families with negative impacts on multiple domains of quality of life (QOL) [4,5]. Breathlessness is differentiated from objective measures of respiration of increased respiratory and ventilatory rate; low oxygen saturation blood levels and severity is poorly correlated with pathology and pulmonary function tests [6,7].

Current management of breathlessness focuses on treatment of underlying disease (chemotherapy, radiotherapy, surgery, targeted therapies, immunotherapy, etc.), and complications such as pleural effusions alongside pharmacological agents to address pre-existing comorbidities such as chronic obstructive pulmonary disease (COPD) [8]. In

Direct	<ul style="list-style-type: none"> Pulmonary parenchymal involvement Lymphangitic carcinomatosis Airway obstruction by tumor Pleural tumor or effusion Pericardial effusion Ascites/liver enlargement Multiple tumor micro emboli Pulmonary leukostasis Superior vena cava syndrome
Indirect	<ul style="list-style-type: none"> Cachexia Electrolyte abnormalities Anemia Pneumonia Pulmonary emboli Paraneoplastic syndromes Muscle deconditioning
Adverse effects of cancer treatment	<ul style="list-style-type: none"> Lung resection Radiation pneumonitis or fibrosis Chemotherapy induced pulmonary toxicity Chemotherapy induced cardiomyopathy Radiation induced cardiac disease
Other comorbidities	<ul style="list-style-type: none"> Chronic obstructive pulmonary disease Congestive heart failure Asthma Interstitial lung disease Psychological distress (anxiety, depression) Chest wall deformity Pulmonary vascular disease Obesity Neuromuscular disorders

advanced disease, opiates are used to alter the perception of breathlessness and patients’ sense of breathing effort [9] and may be combined with anxiolytics for their sedative properties [10], but with limited effectiveness shown in recent Cochrane systematic reviews [11].

While the optimization of medical and pharmacological treatment for managing breathlessness in lung cancer is imperative, this biomedical approach is insufficient to address the complexity of breathlessness and interrelationships among physiological/biochemical, psychological, social and environmental factors that induce secondary physiological, emotional and behavioral responses [4,7]. Consequently, two main models of support have emerged in the literature including: comprehensive breathlessness services comprised of multi-professional teams to address multifactorial causes of breathlessness and supportive care focused on education, rehabilitation, behavioral and psychological interventions; and self-management support (SMS) programs or interventions to enable and empower patients (and families) in effective self-management of breathlessness. While comprehensive breathlessness services have shown positive results [12], greater attention must still be focused on SMS [13]. Engagement of patients in self-management remains the neglected ‘participatory’ component of P4 personalized cancer medicine (predictive, preventive, personalized, participatory) [14] resulting in breathlessness being overlooked and poorly managed in routine clinical care. In this perspective paper, an overview of the rationale and evidence for proactive SMS to activate patients in effective self-management of breathlessness is emphasized.

Pathophysiology & mechanisms for breathlessness

The pathophysiology and mechanisms of breathlessness in lung cancer are complex and multifactorial (Table 1) and include impaired ventilation, increased ventilatory demand or a combination of both of these [15]. Impaired ventilation occurs as a result of either a restrictive ventilatory deficit due to decreased stretch capacity of the lung parenchyma, pleura or chest wall or from a reduction in maximum force by the respiratory muscles as evidenced in pulmonary function tests as decreased total lung capacity (TLC), and decreased residual volume (RV) [16]. Impaired ventilation also occurs as a result of obstruction or narrowing of the lumen of the airway (obstructive ventilatory deficit), due to tumor infiltration, mucus, inflammation or edema shown on PFTs as reduced FEV1/FVC and an increase in TLC, residual volume (RV) and functional capacity (FRC) [17].

Increased ventilatory demand due to interruption of the perfusion capacity in the lung due to vascular obstruction, emboli or the effects of chemotherapy or radiation treatment can also occur. The direct effects of cancer or treatment

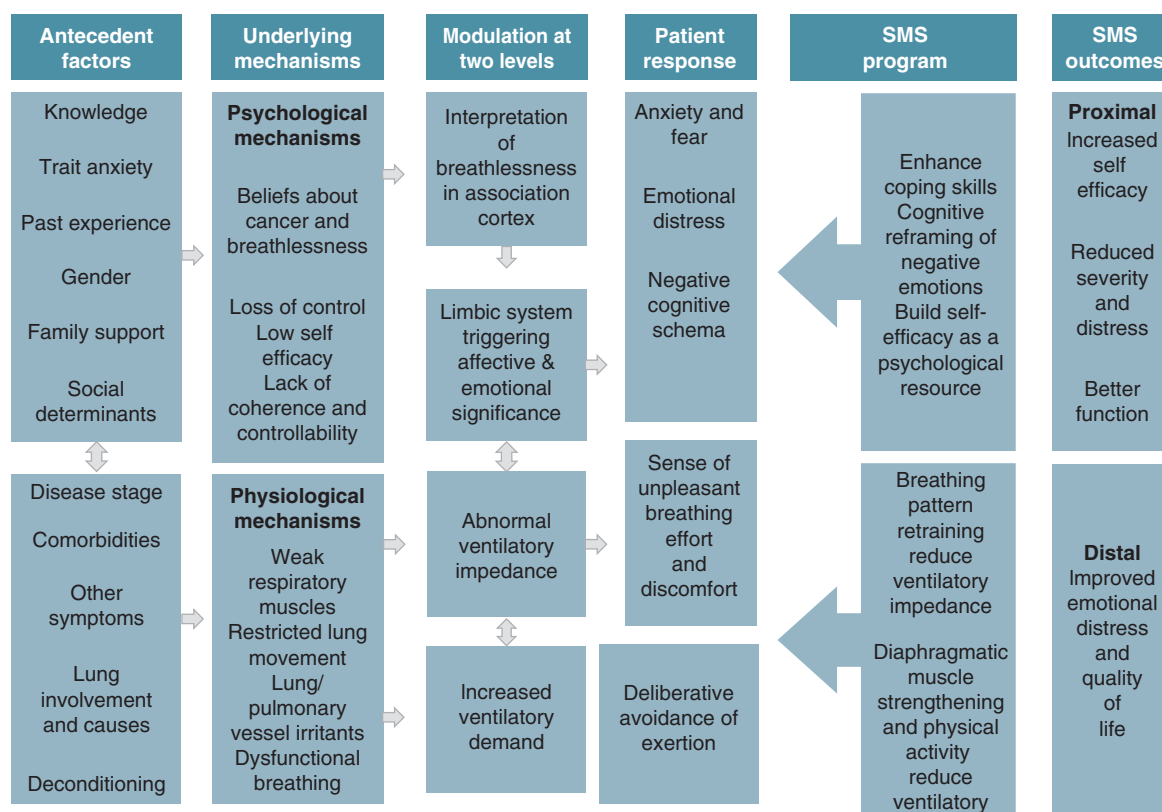


Figure 1. Mechanistic targets for SMS programs for breathlessness and outcomes for measurement of effectiveness. SMS: Self-management support.

on the cardio-respiratory or pulmonary system as a result of metastasis, interstitial or vascular complications are shown empirically to cause breathlessness [18]. Secondary mechanisms include skeletal muscle wasting, myopathy of the peripheral muscles, respiratory muscles or myocardium [19] and reduced perfusion capacity as a result of surgical resection of lung tissue [20] or due to comorbid conditions (i.e., COPD) that lead to a further reduction in perfusion capacity or ischemic heart disease and oxygen exchange problems [21].

Psychological distress can also increase ventilatory demand [22]. Like all symptoms, the evaluation and perception of breathlessness is highly subjective with modulation of the intensity and quality of breathlessness as part of a complex psychological information processing system in the higher cortical centers of the brain [23]. The intensity and distress of breathlessness is modified based on its meaning (cognitive symptom schema) [24,25], triggering affective distress particularly fear and anxiety [26,27], and feelings of loss of control [28], that can exacerbate acute, episodic breathlessness [29]. Consequently, pulmonary function tests such as forced expired volume in one minute (FEV1) and peak flow measures (PEF) [30] and objective disease-stage variables are poorly correlated with a patient's subjective sense of breathing effort, its perceived severity, and the disruptions it causes on daily living [31]. The emotive or affective aspect is an important part of the experience of breathlessness as it alters patient's behavior, that is, the deliberate avoidance and restriction of activities to avoid triggering of breathlessness [32] and is also a direct predictor of psychological distress (i.e., depression) [33]. Breathlessness is often accompanied by anxiety, fear, panic and a sensation of impending death that can compound psychological distress [28].

While underlying physiological mechanisms may be less mutable in lung cancer compared with other respiratory conditions, the inconsistent relationship between the sensation and perception of breathlessness, effort of breathing and underlying pathology, suggests that modulation of this symptom can be achieved by targeting mutable mechanisms and altering subjective perception and interpretation in the central brain. Self-management interventions or programs (SMI) are essentially cognitive-behavioral interventions that entail modification of thought, behavior and attention to symptoms; and the application of specific behaviors and skills that can reduce ventilatory impedance and ventilatory demand [34]. The mechanisms targeted through SMS are shown in Figure 1 alongside how these

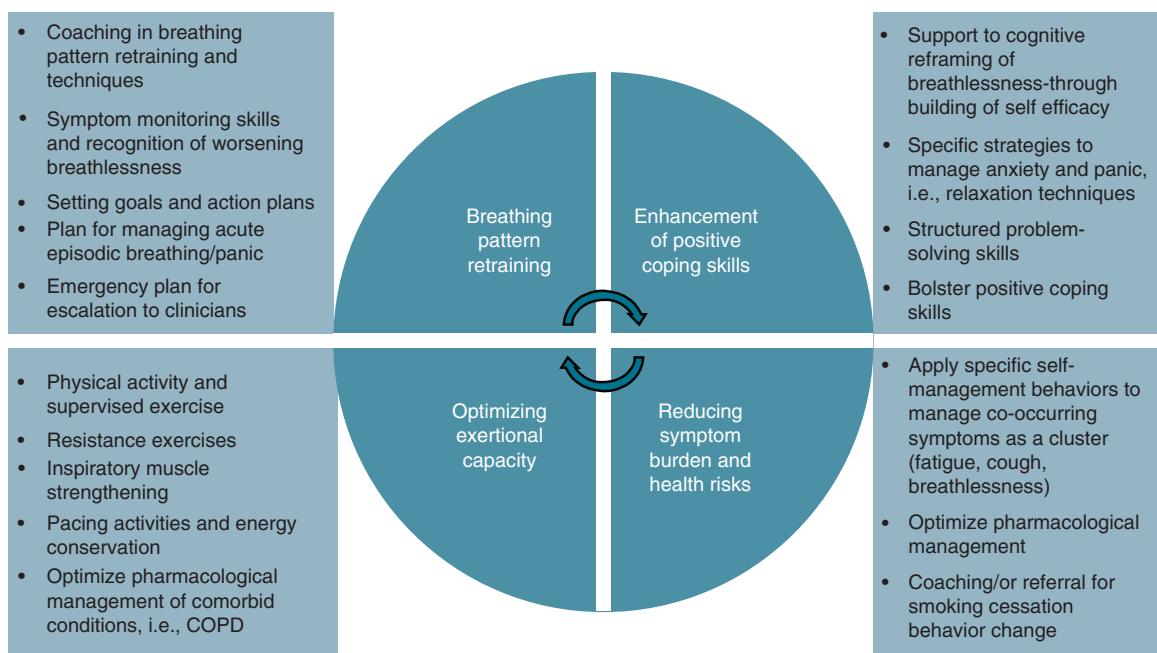


Figure 2. Core components of self-management programs for breathlessness in lung cancer. COPD: Chronic obstructive pulmonary disease.

can translate into measurable health outcomes.

Self-management & self-management support

Globally, it is recognized that patients could benefit from active engagement in self-management of chronic conditions and health challenges with efficacy shown for improved clinical outcomes, symptom reduction and lower healthcare utilization and costs [35]. In cancer, self-management (what patients do) involves a cluster of behaviors that individuals must undertake to manage the medical aspects of cancer and symptoms (i.e., adhering to lifelong treatment regimens), coping with emotional consequences and adapting/adjusting life roles and relationships (i.e., work/employment) to accommodate illness, and applying lifestyle behaviors (e.g., physical activity, healthy eating, smoking cessation) to reduce risks and optimize health [36]. Effective SMS includes instructions that support patient application of core skills for self-management such as problem solving with solution implementation for daily decision-making, effective provider communication, use of support resources, goal setting/action planning and coaching to facilitate uptake and enhanced abilities for self-tailoring of behaviors to the changeable and dynamic nature of disease and symptoms such as breathlessness in the context of daily life [37].

SMS (what practitioners do) [38] has been further defined for respiratory conditions, as personalized, structured and multi-component programs, with the goals of motivating, engaging and supporting patients to positively adapt their health behavior(s), and apply core skills to better manage their disease [39]. SMS programs focus on healthcare professionals or peers working in a collaborative relationship with patients to build their self-efficacy (confidence), which is facilitated by a structured programmatic approach that emphasizes practice, feedback, role-modeling and reattribution of negative experiences [40].

There is a wealth of research on SMS interventions in other respiratory conditions such as COPD, which have shown improvements in breathlessness severity, exercise capacity and reductions in hospital admissions and overall healthcare use [41,42]. However, the evidence for SMS in lung cancer is more limited and fragmented with heterogeneity in included components as shown in Table 2, and the benefits may differ given the dynamic nature of breathlessness, underlying physiological mechanisms, and since the level of physical or psychological burden of disease is usually high [43]. SMS programs for breathlessness management in lung cancer are structured and multicomponent and target four modifiable mechanisms: breathing pattern retraining; enhancement of positive coping skills; optimizing exertional capacity and reducing overall symptom burden and health risks (Figure 2).

Table 2. Self-management components and core skills emphasized in breathlessness randomized controlled trials in lung cancer.

Study (year)	Intervention	Pacing	Physical activity plan	Breathing retraining	Plan for crisis	Goals/action plans	Problem-solving support	Performance feedback	Training in symptom self-monitoring	Strategies to manage anxiety	Enhancement of coping skills	Ref.
Corner <i>et al.</i> (1999)	Supportive counseling and training sessions 3–8 sessions	✓	X	✓	X	✓	X	X	X	✓	✓	[47]
Bredin <i>et al.</i> (2009)	Supportive counseling and training sessions 3–8 sessions	✓	✓	✓	✓	✓	X	X	X	✓	✓	[48]
Barton <i>et al.</i> (2010)	Written materials, DVD, 3 training sessions	✓	✓	✓	X	X	X	✓	X	✓	✓	[49]
Johnson <i>et al.</i> (2015)	Three sessions compared with one session of training	X	✓	✓	X	X	X	X	X	✓ Calming hand and PMR	X	[50]
Chan <i>et al.</i> (2011)	1 session plus coaching, with a FU	Information packet	X	✓	X	X	X	X	X	✓ PMR	X	[69]
Yorke <i>et al.</i> (2015)	Breathing training, cough techniques, acupressure 2 session, 1 telephone call	Information packet	Information packet	✓	X	X	X	X	X	✓ Calming hand	X	[88]
Higginson <i>et al.</i> (2014)	Multidisciplinary and palliative care assessment written materials, DVD 3 sessions	✓	✓	✓	✓	X	✓	✓	X	✓ Breathing mantra	X	[97]
Farquhar <i>et al.</i> (2009)	Multidisciplinary service, 1–4 sessions	✓	✓	✓	✓	X	X	X	X	✓	✓	[98]
Farquhar <i>et al.</i> (2016)	Multidisciplinary service, 1–4 sessions	✓	✓	✓	✓	X	X	X	X	✓	✓	[99]

X: Not specified; ✓: Component emphasized; FU: Follow up.

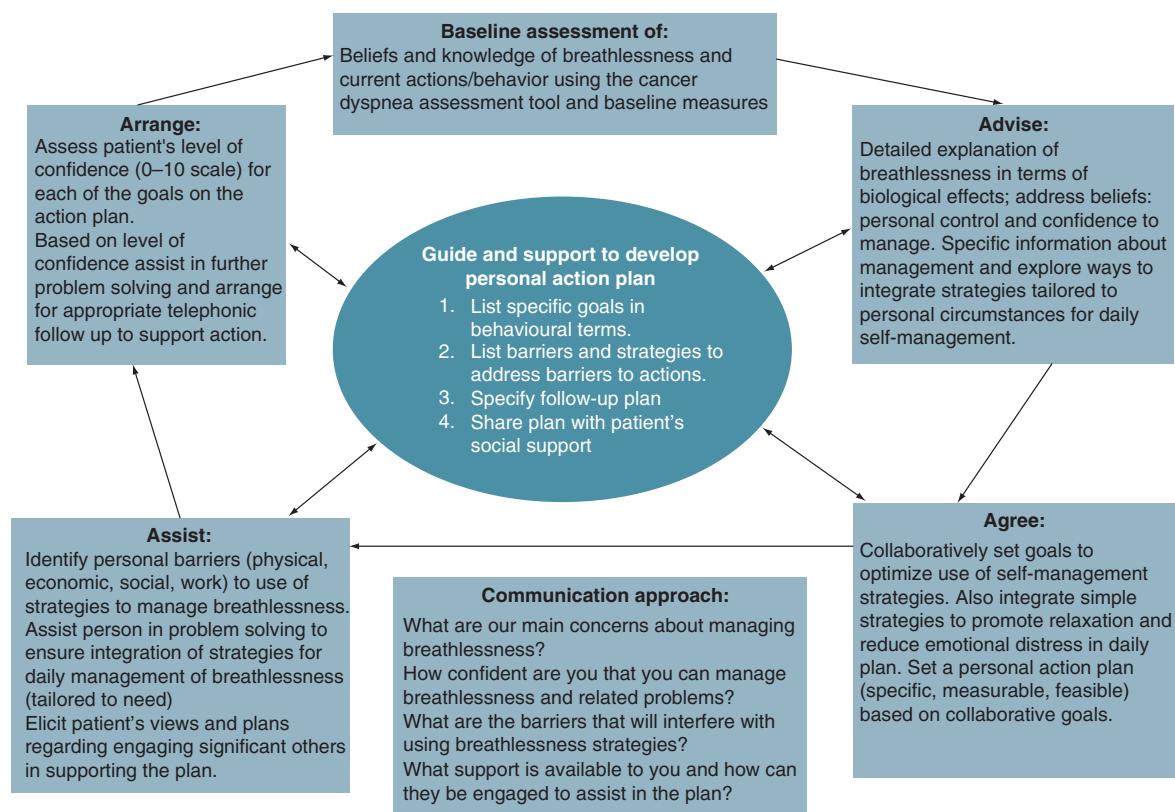


Figure 3. Adapted 5As for counseling in behavior change for breathlessness self-management.

Component 1: breathing pattern retraining

Breathing pattern retraining targets dysfunctional or inefficient breathing patterns characterized as rapid, shallow breathing, involving breathing from the upper chest with greater recruitment of upper rib cage motion compared with the lower rib cage [44]. Dysfunctional breathing patterns occur due to diaphragmatic weakness or as a physiological response to stress or as a patterned response or deliberative attempt by patients to avoid triggering of breathlessness and cough.

Breathing pattern retraining involves education and coaching of patients in the practice of breathing techniques, particularly diaphragmatic breathing (abdominal breathing) and/or pursed lip breathing during rest and activities to maximize breathing capacity and promote better gas exchange unless contraindicated in lung cancer (i.e., upper airway blockage) [45,46]. Breathing techniques have been widely applied for management of breathlessness in lung cancer with reduction in breathlessness severity at worst, and at best with reduction in breathlessness distress depending on measures used in studies [47–52]. Diaphragmatic breathing (abdominal breathing) may be particularly beneficial for reducing the affective response to breathlessness as it has been shown in stress disorders to address the shared physiological basis underlying breathing, emotion and cognition, involving the autonomic nervous system [53]. Emotional distress and anxiety are reduced when diaphragmatic breathing is applied at least three-times/day in mental health disorders [53]. However, a recent systematic review of low intensity educational interventions including breathing retraining for chronic breathlessness found variable effects on severity [54] supporting the notion that patient education alone is insufficient and coaching to motivate behavior change necessary. Coaching patients in behaviors has been shown to be essential for managing breathlessness in COPD [55] and for reducing symptom severity in cancer [56]. We have adapted a practical behavior change counseling process based on the 5As (assessment, advise, agree, assist, arrange) [57] for coaching uptake of behaviors for management of breathlessness that may have utility for integration in routine clinical care (Figure 3).

Explicit goals/action plans to apply breathing techniques for managing continuous and acute, episodic periods of breathlessness (with support of trained family members) is critical for integration of breathing techniques within the patient's behavioral repertoire for managing breathlessness [58]. Recovery and escape positioning techniques

(i.e., leaning against a wall or over a table), activity pacing, and specific breathing techniques for managing panic and an emergency plan are also reported as beneficial by patients for inclusion in action plans [59]. Hand-held fans can also help to reduce breathlessness [60]. Patients also require skills in symptom monitoring and the specific signs and symptoms that should alert them to a need to escalate a change in breathlessness to clinicians. Symptom recognition is a complex cognitive skill [61] and patients often adapt to low levels of functioning, thus, failing to recognize when breathlessness is more severe or what changes warrant urgent attention. Enhancing the patient's symptom monitoring skills is also crucial to guide tailoring and adjustment of their behaviors to symptom severity using daily diaries and symptom severity scales.

Component 2: enhancement of positive coping skills

Lung cancer is a dreaded disease that is associated with high psychological morbidity. Clinically significant depression rates ranging from 15 to 44% have been reported and is usually comorbid with anxiety [62]. Prompt treatment of anxiety and depression is essential to mitigate exacerbation of breathlessness since untreated depression can interfere with motivation for self-management [63], and this impacts on QOL and overall survival [64]. A combination of psychological therapies (i.e., cognitive-behavioral therapy, psychotherapy) combined with pharmacological agents are recommended with special consideration for prescribing to mitigate adverse reactions in combination with cancer treatment regimens [65].

SMS interventions for breathlessness have primarily focused on supportive counseling inclusive of active listening, mobilizing social support, and enhancing positive coping skills (i.e., structured problem solving) to facilitate adjustment to breathlessness and lung cancer with reductions in anxiety [66], but seldom depression. SMS interventions must be specifically targeted to behaviors that are effective in reducing depression (i.e., coping skills training) versus a generic SMS program to achieve an effect [67]. Moreover, specific self-management strategies are required to address situational anxiety, a distinct type of anxious response and anticipatory fear and dread that is triggered by breathlessness and can reach phobic proportions [68]. For most patients, anxiety impacts self-control and the ability to remain or restore calm, thus patients require specific training in the management of situational anxiety and panic triggered by breathlessness. Training patients in relaxation techniques such as progressive muscle relaxation or mindfulness has been shown to reduce anxiety and triggering of breathlessness [69,70].

Lung cancer patients are vulnerable to getting caught in a 'vicious cycle' of breathlessness-anxiety-fatigue-deconditioning [71]. Vicious cycles can trigger negative cognitive schema ("nothing can be done") and low self-efficacy ("I don't know how to change this") and are difficult to interrupt in the context of the existential distress posed by a lung cancer diagnosis. This further exacerbates psychological distress and contributes to suffering [72]. Vicious cycles are difficult to interrupt unless patients have adequate information, skills, confidence and the 'know-how' for applying the behaviors necessary to reduce chronic and episodic breathlessness that can improve functioning in daily life.

Building of a patient's self-efficacy in the application of core skills including structured problem solving and other positive problem-oriented coping skills (i.e., breathing techniques) and emotion regulation such as reframing of negative emotions or meaning in illness interventions can reduce symptom amplification and emotional distress [73]. Structured problem-solving is a core skill emphasized in SMS programs that teaches the patient a systematic approach to proactively solve their problems and take actions to manage illness or symptom challenges has shown positive effects [74]. Teaching patients the process of problem-solving empowers their ability to directly work on illness challenges that can be applied as other problems occur across the lung cancer trajectory. Cognitive-behavioral approaches that emphasize reframing of negative schema related to breathlessness and adapted for lung cancer patients with advanced disease have shown improvement in breathlessness severity, quality of life and mood [75].

Component 3: optimization of exertional capacity & peripheral muscle strength

Most patients typically experience worse breathlessness with exertion and in response may deliberately avoid activities that trigger this symptom resulting in further deconditioning. Exercise to optimize physiological breathing capacity (i.e., reducing ventilatory demand) has the strongest evidence for improving exertional capacity and reducing severity of breathlessness in COPD [76].

Potential mechanisms of effect for exercise include reduced central motor drive related to increased metabolic acidosis, slower breathing patterns, reduced dynamic hyperinflation, increased function of the respiratory muscles and desensitization to anxiety [77]. While the evidence for exercise is more limited across types and stages of lung cancer, supervised exercise programs usually as part of a pulmonary rehabilitation program have shown significant

improvements in 6-min walk tests post-lung cancer resection [78,79]. Other reviews have also shown benefits for exercise in lung cancer even in advanced stages of disease on objective measures indicative of improvements in cardio-respiratory outcomes but also in reducing breathlessness as a secondary outcome [80]. It is recommended that a specialist in cancer exercise should design a personalized and supervised program of exercise and resistance training that is graded to the individuals' exertional capacity and takes into consideration precautions in lung cancer. Precautions that need to be taken into consideration for exercise programs in lung cancer include pulmonary (e.g., inadequate ventilator capacity), musculoskeletal (e.g., bone pain and metastasis) and cardiovascular issues as described earlier re: mechanisms of breathlessness [81]. A review of combined yoga and physiotherapist-led resistance training in lung cancer also showed improvements in a 6-minute walk test, pulmonary capacity and improved QOL [82]. Targeted strengthening of breathing muscles using incentive spirometry to improve breathing muscle efficiency has also been shown to reduce worse breathless severity [83,84].

Component 4: reducing overall symptom burden & health risks

Lung cancer patients are multisymptomatic with symptoms often co-occurring as a cluster of symptoms such as fatigue, breathlessness, pain and weakness [85]. Optimization of symptom self-management to reduce other symptoms is essential and can help to mitigate exacerbation of breathlessness, building self-efficacy so that self-management actions can reduce overall symptom burden (outcome expectancy) [86]. Self-management components for breathlessness such as supervised exercise could also have a cross-over effect on co-occurring symptoms such as fatigue since its efficacy is well established for reducing fatigue severity [87]. It is recommended that the 'triad' of breathlessness, cough and fatigue be specifically targeted for intervention [88] and the use of pharmacological treatments (demulcents, opioids, peripherally acting antitussives or local anesthetics) as per best practice guidelines for managing cough [89].

Smoking cessation counseling using motivational interviewing combined with adjunct pharmacological treatment is now considered an integral part of lung cancer treatment given the potential for reversal of genomic alterations and improved survival in those who quit smoking during active treatment [90]. Additionally, continued smoking after a lung cancer diagnosis is associated with increased risk of cancer recurrence, development of a new primary malignancy, treatment toxicity, mortality and decreased efficacy of cancer treatments and quality of life [91]. A recent study using a digital platform for motivating smoking cessation demonstrated the implementation and effectiveness of this approach on smoking cessation in a 'real-world' cancer setting [92]. A number of immediate benefits of cessation include improved oxygenation, reduced breathlessness, lowered blood pressure, improved smell, taste, circulation and breathing, increased energy and improved immune response [93] and is an important behavior change target in SMS.

Discussion

A diagnosis of lung cancer is life altering and associated with significant physical, psychological and existential distress including feelings of hopelessness and helplessness that can lead to a desire for hastened death [94]. While optimization of disease-focused therapies in lung cancer is crucial, SMS in routine care targeting patient activation in management of breathlessness is equally important as ultimately it is patients and families that shoulder the burden for self-management of this and other symptoms outside clinical visits. Unfortunately, patients continue to report feeling unprepared and unaware of the strategies that can be used to manage breathlessness and consequently become 'housebound' and struggle to reduce its impact on functioning in daily life [28]. It is imperative to focus on integration of best practices in SMS for breathlessness management as an essential programmatic approach in routine lung cancer care. Spathis and colleagues have devised a practical clinical model to address the breathing, thinking and feeling components of breathlessness, which are aligned with components of SMS that could be tested in routine clinical care [95].

Many of the core components of SMS programs have been embedded within comprehensive, multidisciplinary breathlessness support services that are focused on optimizing pharmacological and non-pharmacological approaches to address the clinical complexity of lung cancer as part of a 'holistic' approach [96-99]. A number of reviews have documented benefits of these service delivery models in terms of reduced breathlessness intensity, reduced distress due to breathlessness and improved mastery over breathlessness [12,100,101]. However, the components and core skills for effective SMS programs may vary within comprehensive services. Moreover, wide scale spread of these services across cancer settings has not been sustained outside of Europe [102] and further research on cost-effectiveness is required to influence health policy to ensure uptake of these models as standard of care is needed. Perhaps a stepped

approach that ensures all patients have access to SMS for managing breathlessness with intensification of services for patients who require a more comprehensive intervention approach based on risk stratification in lung cancer particularly in under-resourced cancer programs may be required.

It is appealing to think about patients taking an active role in disease and symptom self-management, however there is a need to be cognizant that when therapeutic responsibility passes from the healthcare provider to patient so does the burden of care [103]. Additionally, SMS must be tailored to the individual's capacity and capability and take into consideration the many factors such as age, disease stage, etc. [104] that can impede patient involvement in self-management. Consideration must also be given to the preparation of family caregivers or the patients social support network as they play a critical role in supporting patients in breathlessness self-management. Engagement of patients and their caregivers in self-management requires access to appropriate and relevant SMS, ongoing follow up and monitoring of goals and action plans to build the patients self-efficacy and habituation of skills and techniques to ensure they are able to sustain these behaviors in response to the dynamic (chronic and episodic features) nature of breathlessness and in times of stress; and with tailoring of approaches as the illness progresses and disease burden increases.

Breathlessness still remains an invisible symptom and requires active elicitation using patient reported outcomes for routine surveillance and identification in routine clinical care [105]. Patients often underreport this symptom as they may assume nothing can be done about it or they have adapted to a low level of functioning and when asked may deny breathlessness. This leaves lung cancer patients vulnerable to worse health outcomes and quality of life and adds to suffering. The evidence base for engagement of patients in self-management of chronic disease has shown that this approach can help to achieve 'triple aim' healthcare reform goals of improved health outcomes and better patient experience of care at lower costs [106].

Conclusion & future perspective

In conclusion, SMS programs for breathlessness should be considered an essential service for lung cancer patients and survivors and its integration in routine care should be promoted globally. This will require a whole-system approach that includes upskilling of clinicians in the provision of SMS, patient training in self-management, a shift in the care culture toward patients as partners in achieving better health outcomes; and an emphasis on practice improvement to ensure application of SMS in routine care. Most important, patient engagement in healthcare needs to be recognized as an important evolution in personalized cancer medicine and as equally important as big data analytics and genomic medicine, as it is often a neglected component of the P4 medicine approach.

Author contributions

D Howell, conception and writing.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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