Cognitive and behavioral intervention for the management of episodic breathlessness

Inaugural Dissertation

zur

Erlangung des Doktorgrades
philosophiae doctor (PhD)
der Medizinischen Fakultät
der Universität zu Köln

vorgelegt von

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Referenten:	Prof. Dr. Christian Albus
	Prof. Dr. Martin Hellmich
Datum der Mündlichen Prüfung:	08.04.2022

The present thesis was prepared as a cumulative dissertation based on the following publications (sorted by ascending year numbers)**:**

1. **Schloesser, K.,** Bergmann, A., Eisenmann, Y., Pauli, B., Hellmich, M., Oberste, M., Hamacher, S., Tuchscherer, A., Frank, K. F., Randerath, W., Herkenrath, S., Simon, S.T. (2022). “Only I know now, of course, how to deal with it, or better to deal with it”: A mixed methods phase II single-arm study of a cognitive and behavioral intervention for the management of episodic breathlessness. *Journal of Pain and Symptom Management*, *63*(5), 758-768. DOI: 10.1016/j.jpainsymman.2021.11.003.

1. **Schloesser, K.,** Eisenmann, Y., Bergmann, A., & Simon, S. T. (2021). Development of a Brief Cognitive and Behavioral Intervention for the Management of Episodic Breathlessness—A Delphi Survey With International Experts. *Journal of Pain and Symptom Management*, *61*(5), 963-973. DOI: 10.1016/j.jpainsymman.2020.09.034.

The following papers were also prepared during the PhD period (sorted by ascending year numbers):

1. Bergmann, A., **Schloesser K.,** Simon, S.T. (2022). Atemnotattacken: Kognitive und verhaltensorientierte Kurzintervention: Ergebnisse eines wissenschaftlichen Projekts. *pflegen: Palliativ*, *2022*(53), 40-43.

2. Reitzel, T., Bergmann, A., **Schloesser, K.,** Pauli, B., Eisenmann, Y., Randerath, W., Tuchscherer, A., Frank, K., Pralong, A., Simon, S.T. (2022). The experience of episodic breathlessness from the perspective of informal caregivers: A qualitative interview study. *Annals of Palliative Medicine*, *11*(7), 2225-2234. DOI: 10.21037/apm-21-3361.

3. Bausewein, C., Hodiamont, F., Berges, N. , … **Schloesser, K.,** & Simon, S.T. for the PallPan Study Group. (2022). National strategy for palliative care of severely ill and dying people and their relatives in pandemics (PallPan) in Germany - study protocol of a mixed-methods project. *BMC Palliative Care, 21* (10). DOI: 10.1186/s12904-021-00898-w.

4. Pauli, B., Strupp, J., **Schloesser, K.,** Voltz, R., Jung, N., Leisse, C., Bausewein, C., Pralong, A., Simon, S.T. (2022). "It's like standing in front of a prison fence” - Dying during the SARS-CoV2 pandemic: a qualitative study of bereaved relatives' experiences. *Palliative Medicine, 36*(4), 708-716. DOI:10.1177/02692163221076355.

5. **Schloesser, K.,** Simon, S. T., Pauli, B., Voltz, R., Jung, N., Leisse, C., ... & Strupp, J. (2021). “Saying goodbye all alone with no close support was difficult”-Dying during the COVID-19 pandemic: an online survey among bereaved relatives about end-of-life care for patients with or without SARS-CoV2 infection. *BMC Health Services Research*, *21*(1), 1-11.DOI: 10.1186/s12913-021-06987-z.

Acknowledgement

Mein herzlicher Dank gilt Prof. Dr. med. Steffen Simon. Dankschön für die Betreuung dieser Arbeit, die vielen mut-schenkenden, spannenden und inspirierenden Gespräche im Laufe unserer Zusammenarbeit und die unterstützende Begleitung in den letzten Jahren. Neben der Förderung meiner wissenschaftlichen Arbeit erfreut es mich besonders, mit dem Bild des „bunten Blumenstrauß voller Möglichkeiten“, einen wunderbaren Blick auf die unterschiedlichen fachlichen und persönlichen Optionen mitgegeben bekommen zu haben, die vor mir liegen.

Vielen Dank an Prof. Dr. Martin Hellmich und Prof. Dr. Christian Albus für die interessanten und konstruktiven Gespräche, die zu neuen Ideen angeregt haben. Außerdem vielen Dank an Frau Dr. Mutschler für das geduldige Beantworten der zahlreichen Fragen.

Herzlichen Dank an meine lieben Kolleg*innen aus dem Zentrum für Palliativmedizin, für die vielen beruflichen und nicht beruflichen Gespräche! Merci!

Dankeschön außerdem an Euch. – was für ein Glück, Euch in meinem Leben zu haben.
Namentlich genannt werden müssen Kathrin und Hermann Schlösser, die besten Großeltern, die ich mir jemals hätte wünschen können.

Kurzfassung

Atemnotattacken sind durch eine starke Zunahme der Atemnotintensität, die nach Empfinden der Patient*innen außerhalb der normalen Schwankungen von Atemnot liegt, gekennzeichnet und belasten Patient*innen mit fortgeschrittenen, lebenslimitierenden Erkrankungen stark. Ein Kreislauf aus Atemnot-Angst/Panik-Atemnot führt immer wieder zu Notfallsituationen, die selten durch pharmakologische Interventionen gelindert werden können. Obwohl die Forschung zu Atemnotattacken in letzter Zeit zugenommen hat, mangelt es an Behandlungsstrategien, um das Symptom wirksam zu lindern. Die kurze Dauer der meisten Atemnotattacken schränkt die Wirksamkeit pharmakologischer Interventionen ein, da die Dauer bis Wirkungseintritt der Medikamente häufig länger ist, als die Atemnotattacken andauern. Aus diesem Grund spielen nicht-pharmakologische Strategien eine wichtige Rolle. Zur Behandlung von ***chronischer Atemnot*** z.B. in Atemnotambulanzen in England und München werden nicht-pharmakologische Strategien bereits eingesetzt und von Patient*innen als hilfreich beschrieben. Die Evaluierung nicht-pharmakologischer Strategien für ***Atemnotattacken*** steht noch aus, auch wenn es Hinweise gibt, dass Patient*innen davon profitieren können: So berichteten Patient*innen, dass sie unterschiedliche Strategien (z.B. den Kutschersitz) zur Linderung der Atemnotattacken anwenden, diese kombinieren und entsprechend ihrer Bedürfnisse anpassen. Die Entwicklung und Evaluierung einer auf nicht-pharmakologischen Strategien basierenden kognitiven und verhaltensorientierten Kurzintervention für den Umgang mit Atemnotattacken ist das Ziel der vorliegenden Promotion. Das ersten Dissertationsprojekt (DP 1) beschreibt die Entwicklung der kognitiven und verhaltensorientierten Kurzintervention. Dazu wurden im Rahmen eines Online-Delphiverfahrens mit multiprofessionellen Expert*innen 15 kognitive und verhaltensorientierte Strategien zum Umgang mit Atemnotattacken konsentiert. Zusätzlich zu Strategien, wie bspw. atemerleichternde Körperhaltungen, die mit den Patient*innen geübt werden können, werden andere Aspekte zum Umgang mit Atemnotattacken in einer Patient*innenedukation vermittelt (z.B. Umgang mit Auslösern von Atemnotattacken). Basierend auf der Expert*innenmeinung, zeichnet sich eine optimale Kurzintervention für den Umgang mit Atemnotattacken durch folgende Merkmale aus: anpassbar an die individuellen Bedürfnisse der einzelnen Patient*innen; ein hoher Anteil an Kommunikation zwischen Patient*innen und der Person, die die Intervention durchführt; kurze Dauer (1-2 Stunden); Einbezug von Angehörigen und Nutzung eines Modells, um den Zusammenhang zwischen emotionaler Reaktion und Atemnot zu erläutern. Trotz Standardisierung erlaubt die Kurzintervention zum besseren Umgang mit Atemnotattacken eine Anpassung an die individuellen Bedürfnisse der Patient*innen.

Im zweiten Dissertationsprojekt (DP 2) wurde die Machbarkeit, Sicherheit, Zufriedenheit sowie die potenziellen Effekte der kognitiven und verhaltensorientierten Kurzintervention in einer einarmigen Pilotstudie (Phase II) untersucht. Zwischen 02/2019 und 02/2020 wurden 49

Patient*innen, die unter Atemnotattacken aufgrund einer lebenslimitierenden Erkrankung litten, in die Studie eingeschlossen. 46 Patient*innen füllten den Fragebogen zur Basiserhebung aus (24 Frauen, 36 Patient*innen mit dauerhaft atemwegsverengende Lungen-Erkrankung, engl. Chronic Obstructive Pulmonary Disease; COPD, mittleres Alter: 66 Jahre), 38 nahmen an der 1-2 stündigen Kurzintervention teil, 32 beendeten die Studie und 22 hatten Interesse, ihre Erfahrungen mit der Intervention in einem Interview zu schildern. Ein mixed-methods Ansatz wurde genutzt. Dazu wurden neben den Interviews quantitative Befragungen zwei, vier, und sechs Wochen nach der Intervention durchgeführt, der Fokus lag dabei auf Veränderungen im Umgang mit Atemnot. Der Umgang mit Atemnot verbesserte sich nach der Intervention und in den Interviews beschrieben die Patient*innen einen positiven Einfluss auf ihre Kompetenzen hinsichtlich des Umgangs mit Atemnotattacken und auf die Angst während einer Attacke. Die kognitive und verhaltensorientierte Kurzintervention und die Forschung erwies sich als durchführbar, sicher und wurde gut akzeptiert.

Wir können eine positive Veränderung im Hinblick auf den Umgang mit Atemnotattacken bei den Patient*innen nach der Intervention beschreiben, dennoch muss dies in einer randomisiert-kontrollierten Phase-III-Studie evaluiert werden. Bei gegebener Effektivität der Kurzintervention würde sie sich aufgrund der flexiblen Anwendbarkeit im klinischen Alltag oder z.B. in einer Atemnotambulanz gut einsetzen lassen.

Summary

Episodic breathlessness is characterized by an increase in the intensity of breathlessness, beyond the normal fluctuations, and is burdensome for patients with advanced, life-limiting diseases. A cycle of breathlessness-anxiety/panic-breathlessness repeatedly leads to emergencies that pharmacological interventions can rarely alleviate. Although research on episodic breathlessness has increased recently, there is a lack of treatment strategies to relieve the symptom. The short duration of most breathlessness episodes limits the efficacy of pharmacologic treatments, as the time to onset of drug action is often longer than the duration of the episodes. For this reason, non-pharmacological strategies play an essential role. For the treatment of ***chronic*** breathlessness, non-pharmacological strategies, such as in the breathlessness services in England and Munich, are already used and described as helpful. However, the evaluation of non-pharmacological strategies for ***episodic*** breathlessness remains missing. Nevertheless, there are indications that patients could benefit from them: patients report that they use different non-pharmacological strategies (e.g., forward lean) to relieve episodic breathlessness, combine them, and adapt them according to their needs. The present dissertation aims to develop and evaluate a brief cognitive and behavioral intervention to manage episodic breathlessness, comprising non-pharmacological strategies.

Dissertation project 1 (DP 1) describes the development of the brief cognitive and behavioral intervention. To this end, international multi-professional experts agreed upon 15 cognitive and behavioral strategies for managing episodic breathlessness via an online Delphi survey. Some strategies (e.g., forward lean) can be actively taught and practiced, while other aspects for managing episodic breathlessness need to be discussed in patient education (e.g., dealing with triggers of episodic breathlessness). Based on the experts' opinion, an appropriate brief intervention for managing episodic breathlessness is characterized by the following features: adaptable to the individual needs of each patient, substantial communication between patient and intervention deliverer, short duration (1–2 hours), involvement of relatives, and use of a model to explain the relationship between emotional response and breathlessness. Despite standardization, the brief intervention for better managing episodic breathlessness allows for adaptation to patients' individual needs.

In dissertation project 2 (DP 2), the feasibility, safety, acceptability, and potential effects of the cognitive and behavioral brief intervention were evaluated in a single-arm phase II study. Between 02/2019 and 02/2020, 49 patients suffering from episodic breathlessness due to a life-limiting disease were enrolled in the study. Forty-six patients filled out the baseline assessment (24 women, 36 COPD patients, mean age: 66 years), 38 participated in the 1–2-hour brief intervention, 32 completed the study, and 22 were interested in describing their experience with the intervention in in-depth interviews. A mixed-methods approach was used. In addition to the interviews, quantitative assessments were conducted two, four, and six

weeks after the intervention. The focus was set on changes in patients' mastery with breathlessness. Mastery improved after the intervention, and patients described in the interviews as having a positive impact on their competencies regarding the management of breathlessness episodes and anxiety during an episode. The brief cognitive and behavioral intervention and the research methods proved to be feasible, safe, and well accepted.

A positive change was observed in the patients' management of episodic breathlessness after the intervention, yet this needs to be evaluated in a randomized-controlled phase III trial. Given the effectiveness of the brief intervention, it would be well suited for use in clinical practice or, for example, a breathlessness service due to its flexible applicability.

List of abbreviations

ATS	American Thoracic Society
BIS	Breathlessness Intervention Service
BTF model	Breathing Thinking Functioning Model
BSS	Breathlessness Support Service
CHF	Chronic heart failure
COPD	Chronic Obstructive Pulmonary Disease
DGP	Deutsche Gesellschaft für Palliativmedizin
DP	Dissertation project
ILD	Interstitial Lung Disease
MBS	Munich Breathlessness Service
NRS	Numeric Rating Scale
RCT	Randomized controlled trial
WHO	World Health Organization

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1. Introduction

Palliative care considers symptom control to be a core aspect to improve and maintain patients‘ quality of life (1–5). Symptom burden is high in patients with advanced stages of life-limiting diseases, and it negatively affects their quality of life (6–10). Therefore, successful symptom management can have a beneficial effect on patients‘ quality of life and even on their survival (11–17). Chronic breathlessness is one of the most frequent and severe symptoms, and it often occurs despite optimal treatment (18, 19). Chronic breathlessness (or breathlessness in general) comprise both continuous breathlessness and episodic breathlessness (acute/severe/attack/dyspnea-crisis/acute-on-chronic breathlessness may refer to the same symptom (20). Differentiating episodic breathlessness from chronic breathlessness is complicated and is not the aim of the present dissertation. This dissertation considers episodic breathlessness to be a form of chronic breathlessness and to occur with and without continuous breathlessness (21). Brief episodes of increased symptom intensity and accompanying panic characterize episodic breathlessness (21–23). It is essential to assess whether a patient suffers from episodic breathlessness to provide appropriate symptom control (e.g., anxiety reduction). While opioids appear beneficial for relieving chronic breathlessness (24–26), the short duration of breathlessness episodes (27, 28) challenges their use, as the onset of action often takes longer than the episode lasts. Thus, non-pharmacological treatment options seem promising for managing breathlessness episodes, especially as patients have reported that they use and combine different non-pharmacological strategies for episode management (23, 29). While non-pharmacological treatment options for the relief of chronic breathlessness are the focus of clinical practice and research (30–33), research concerning their use for managing episodic breathlessness is lacking. Non-pharmacological methods appear to benefit patients with chronic breathlessness either as single non-pharmacological strategies discussed with the patients (30, 34, 35), as a combination in cognitive-behavioral interventions (36–38), or as part of breathlessness services offering a holistic treatment approach (39–41). Given their promising results for chronic breathlessness, an evaluation of non-pharmacological management strategies for episodic breathlessness is warranted.

This present dissertation investigates the research gap in symptom management of episodic breathlessness. Therefore, the first project of this dissertation involved the development of a brief cognitive and behavioral intervention for managing episodic breathlessness, comprising various non-pharmacological strategies. The second step was the evaluation of the consented brief intervention regarding its feasibility, safety, acceptability, and potential effects in a subsequent single-arm phase II study.

1.1 Structure of the present dissertation

The theoretical background of this dissertation is described in Chapter 2. It focuses on palliative care, breathlessness, episodic breathlessness, and management options. The third chapter describes the dissertation's aim, including the specific objectives. The fourth chapter focuses on the methods applied for the dissertation projects. The results of the projects are outlined in Chapter 5, providing two peer-reviewed scientific publications. Finally, in Chapter 6, the findings of the dissertation projects are discussed, and a summarizing conclusion is presented in Chapter 7.

2. Theoretical Background

2.1 Palliative care

Each year, around 56.8 million people require palliative care worldwide, including 25.7 million in the last year of life (19). In German, palliative care is referred to as palliative medicine (Palliativmedizin). The *Deutsche Gesellschaft für Palliativmedizin* (DGP) defines palliative care as an active, holistic treatment of incurable, progressive, and advanced diseases with limited life expectancy. Palliative care aims to relieve physical symptoms of illness and support patients and their relatives with psychological, social, and spiritual problems. The main goal of palliative care is to improve the quality of life for patients and their relatives (even beyond the dying phase; 2). The World Health Organization (WHO) established a revised definition of palliative care for adults and children in 2020 (last modified 04/2021; 19):

"*Palliative care is an approach that improves the quality of life of patients (adults and children) and their families who are facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and correct assessment and treatment of pain and other problems, whether physical, psychosocial or spiritual.* "

Given the aging population and the rising burden of communicable and non-communicable diseases, the global need for palliative care will continue to grow (1). Patients with a range of diseases require palliative care, of which respiratory diseases are the third most common (10.3%) preceded by cardiovascular diseases (38.5%) and cancer (34%; 1). A core aspect of palliative care delivered by multi-professional teams is symptom control (1–5). In general, symptom burden is high in patients with advanced stages of a life-limiting disease and negatively affects these patients' quality of life (6–10). Successful symptom management may improve the quality of life for both patients and their families (11–13). It enhances treatment compliance (14, 42) and brings advantages for survival (14–17, 43). There is supporting evidence for the positive effect of palliative care teams on symptom control (44). Next to pain, breathlessness is the most frequent and severe symptom from which patients with life-limiting diseases suffer (1), with over 75 million people suffering from it every year (40).

2.2 Chronic breathlessness

2.2.1 Terminology and definition

Breathlessness is a distressing symptom in advanced diseases like cancer, chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), and chronic heart failure (CHF; 8, 45, 46). The American Thoracic Society (ATS) defines breathlessness as

"… *a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiological, psychological, social, and enviromental factors, and may induce secondary physiological and behavioral responses.*" (47)

Definitions of chronic breathlessness vary slightly. However, they have in common that the breathlessness is long lasting, persists despite optimal treatment of the underlying disease, and requires symptomatic treatment (21, 47–57). Palliative care often focuses on chronic breathlessness (25, 58–61). Chronic breathlessness refers to both continuous breathlessness and episodic breathlessness. Episodic breathlessness, as defined by Simon et al. (21), describes episodes of breathlessness with increased symptom intensity, which are short, are often accompanied by panic, and occur with or without continuous breathlessness. The section *episodic breathlessness* explores this phenomenon more closely.

2.2.2 Prevalence

Higginson et al. estimate that, worldwide, 75 million people suffer from chronic breathlessness each year (40). Breathlessness is a symptom associated with various advanced diseases, such as COPD, cancer, or CHF (8). COPD is *"a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitations (…)"* (62). It is the third leading cause of death worldwide, with 3.23 million deaths in 2019 (World Health Organization, 2021). Among COPD patients, the prevalence of breathlessness varies between 90–95% (8). Cancer accounted for nearly 10 million deaths worldwide in 2020, with lung cancer being the most common cause of cancer death (63). The prevalence of breathlessness among cancer patients lies between 10–70% (8). A nationwide survey (from 2006 to 2008) reported that 72.2% of the patients with primary lung cancer and 75.8% of the patients with pulmonary metastasized cancer suffered from breathlessness (64). CHF has a prevalence of 1–2% of adults (65–68), but as studies typically only include diagnosed heart failure, this number is likely higher (69). Breathlessness is a typical symptom of CHF (70), and 60–88% of the patients suffering from CHF report breathlessness (8). Overall, the prevalence of chronic breathlessness increases in the three months leading to death, especially in patients with lung cancer (71).

2.2.3 Breathlessness is a multidimensional sensation

Breathlessness is a multidimensional sensation with physiological, psychological, environmental, and social factors interacting (20, 47). How patients perceive breathlessness only moderately correlates with objective measures like pulmonary function or the 6-minute walking test (72). It is weakly associated with physiological measures (73).

The ATS (47) defines three different domains of breathlessness: The *sensory-perceptual experience* captures how a patient experiences breathlessness, *affective distress* describes the unpleasantness a patient suffers from when breathless, and the *symptom impact or burden* includes health-related quality of life and the functional status. Complementarily, Lovell et al. (74) developed the concept of *total breathlessness* to capture the experiences of breathless patients. Total breathlessness synthesizes the multidimensional concerns people suffering from breathlessness have by summarizing them into domains. Next to the domains physical impairment, psychological concerns, social impact, and spiritual distress, deriving from the framework of *total dyspnea* (75, 76), total breathlessness adds the factors of context and control (74). Context concerning chronic breathlessness and relating to an episode of breathlessness is essential. The context under which breathlessness occurs should be considered when developing management strategies for (episodic) breathlessness. The perceived control is present across the domains. Therefore, it can be interpreted as perceived control “over” (episodic) breathlessness but also in the broader context of losing control over the patient’s daily life due to breathlessness. The *Breathing Thinking Functioning* (BTF) model describes how a patient’s cognitive and behavioral reactions to breathlessness in the domains of breathing, functioning, and thinking maintain and worsen breathlessness by causing vicious cycles (77).

Given the multidimensional character of the sensation of breathlessness, management strategies, whether pharmacological or non-pharmacological, can only be successful when considering not only the physical aspects but all components that result in the experience of breathlessness and impact the patients’ lives.

2.2.4 Impact of breathlessness on patients

Breathlessness is a symptom that occurs in different advanced diseases (8) and, independently from the diagnosis, substantially impacts a patient’s functional status and quality of life (78). Some research has focused on specific patient groups, resulting in mixed findings regarding the similarities and differences in the impact of breathlessness between the patient groups. Others have assessed breathlessness-associated aspects independently from the diagnosis.

Compared to lung cancer patients, COPD patients are likely to live longer with symptom burden, as breathlessness occurs earlier in the disease trajectory (71, 79). Palliative care

needs and symptom burden are similar between patients with advanced primary and secondary lung cancer and patients with severe COPD, though COPD patients survive longer (80). Moreover, a study described that patients with COPD experience greater breathlessness severity and distress levels than patients with lung cancer (81). In addition, a systematic review revealed that breathlessness and its impacts on functioning were worse in COPD patients than in lung cancer patients (82).

Patients with COPD interpret breathlessness as an immediate threat to life, often resulting in hospitalization (83). Independently from the diagnosis, chronic breathlessness leads to increased health service utilization, whereby more severe chronic breathlessness is associated with more frequent contact with health services and longer hospitalization periods (84). Qualitative studies and reviews with cancer and non-cancer patients have demonstrated a multifaced impact of breathlessness on the emotions and daily lives of patients and their families, such as acute fear of death and hopelessness (78, 85, 86). Among cancer patients, breathlessness interferes with daily activities (87), decreases their will to live (88), and is associated with a higher risk of panic disorder (89). Psychological symptoms, such as fear, depression, anxiety, or panic, often accompany breathlessness in chronic respiratory diseases (90).

The anxiety-dyspnea-anxiety cycle (91) describes the close relationship between the emotional component of breathlessness and the sensation of breathlessness: It postulates that the patient's anxiety exacerbates the perception of breathlessness, in turn aggravating anxiety. Bailey (92) underpins the interaction between anxiety and breathlessness but concludes, based on interviews with COPD patients, that anxiety is not the underlying reason for breathlessness but is an indicator that a patient is breathless. She essentially postulates the same relationship as that proposed by Carrieri-Kohlman et al. (1993) but starting with breathlessness; thus, she describes the dyspnea-anxiety-dyspnea cycle. Anxiety is often perceived in breathlessness, but it interacts particularly with episodic breathlessness.

2.3 Episodic breathlessness

2.3.1 Definition

Episodic breathlessness is one form of chronic breathlessness, next to continuous breathlessness, that causes additional burden for patients (86, 93). Intermittent, increased symptom intensity of breathlessness that recurs with varying frequency is experienced by patients with or without continuous breathlessness (22, 87). This phenomenon is referred to by a range of expressions, including *acute* (94), *attack* (95), or *breakthrough* (87, 96) breathlessness. A 2013 ATS workshop defined *dyspnea crisis* as a *"sustained and severe resting breathing discomfort that occurs in patients with advanced, often life-limiting illness and overwhelms the patient and caregivers' ability to achieve symptom relief"* (97). A dyspnea crisis

is described as a consequence of the following factors interacting: worse breathlessness, carers who are unprepared to appropriately respond to the situation, and a heightened psycho-social-spiritual response (97). Finally, Simon et al. defined episodic breathlessness in an international consensus process in 2014 as follows (21):

"*Episodic breathlessness is one form of breathlessness characterized by a severe worsening of breathlessness intensity or unpleasantness beyond usual fluctuations in the patient's perception. Episodes are time-limited (seconds to hours) and occur intermittently, with or without underlying continuous breathlessness. Episodes may be predictable or unpredictable, depending on whether any trigger(s) can be identified. There is a range of known triggers which can interact (e.g., exertion, emotions, comorbidities or external environment. One episode can be caused by one or more triggers."*

A dyspnea crisis and breathlessness episodes are similar, but dyspnea crises can be considered a longer-lasting form of episodic breathlessness (98). In contrast to the definition of episodic breathlessness, Mularski et al. (97) describe the importance of the carer's reaction and focus more explicitly on the emotional response than Simon et al. (21). Simon et al. (21) acknowledge the trigger that leads to breathlessness episodes. The present dissertation refers to Simon et al.'s definition of breathlessness episodes (21), including their short duration, the severe worsening in breathlessness intensity, and the importance of trigger.

2.3.2 Prevalence

The prevalence of episodic breathlessness in patients with life-limiting diseases has been poorly studied. In cancer patients (diverse entities) with breathlessness, a prevalence of 68–71% (87, 99) has been described. In a prospective, longitudinal cohort study, 81–97% of patients with COPD and 75–88% of patients with lung cancer reported breathlessness episodes in each monthly interview over 13 months (28).

2.3.3 Characteristics of episodic breathlessness

Patients perceive breathlessness episodes as severe, with mean ratings > 5 on a modified Borg Scale (0–10, higher ratings indicate a higher severity level; 27, 28). Sixty-four percent of the patients in a cohort study experienced severe episodes (rating on Borg Scale > 5), with the majority of the patients being diagnosed with COPD (78%) versus lung cancer (33%). Patients suffering from COPD also rated the peak severity higher than cancer patients (28). Episodes' severity correlated positively with the frequency of occurrence (28). Breathlessness episodes were found to occur frequently, with mainly one to three episodes per day (28). The same research team assessed the frequency of episodes depending on the disease (i.e., COPD, lung cancer, CHF, and motor neuron disease). There was no significant difference in the frequency of the episodes between the disease groups, and the majority of each group

experienced one to ten episodes daily (27). Eighty-one percent of the patients reported that breathlessness episodes occurred almost exlusive during the day (28). Breathlessness episodes were predominantly of short duration (median 5 minutes), and nine out of ten episodes were shorter than 20 minutes (28). Researchers have additionally found that episodes can be triggered, which means that patients can identify one or more triggers for their breathlessness episodes (21, 22). The most common triggers are exertion and emotions (93), especially anxiety and panic (92, 100, 101). Anxiety/panic is not only a trigger for episodic breathlessness but may also result from a breathlessness episode, which impacts patients' lives (29) and can result in a vicious cycle leading to fear of death (22).

2.3.4 Impact of episodic breathlessness on patients

As research on episodic breathlessness is limited, information on the impact on the patients derives partially from a few studies that have analyzed chronic breathlessness and described episodic breathlessness as a subgroup (86, 87). For many patients, episodic breathlessness is closely linked to anxiety and panic: On the one hand, anxiety/panic and even fear of death are common consequences of breathlessness episodes (29). Therefore, patients experience episodic breathlessness as frightening and stressful (29). On the other hand, anxiety and panic causally trigger or aggravate existing breathlessness (21). Many patients with breathing difficulties describe a vicious cycle that leads to an escalating feeling of panic (77), and most patients are afraid to experience this situation again (29). Here again, the dyspnea-anxiety-dyspnea cycle (92), as well as the anxiety-dyspnea-anxiety cycle, describing the same mechanism (91), are helpful to understand the interaction. The thinking domain of the BTF model (77) is particularly useful for describing the interaction: A (slight) feeling of breathing discomfort activates memories of past breathlessness episodes, which draws attention to one's current breathing difficulties and may increase their fear of suffocation. This can lead to anxiety/panic, which results in an increased breathing rate and muscle tension, aggravating breathing even more (see Fig. 1; 77). The affective component of breathlessness is processed in the limbic system, which is also associated with the processing of emotions (102).

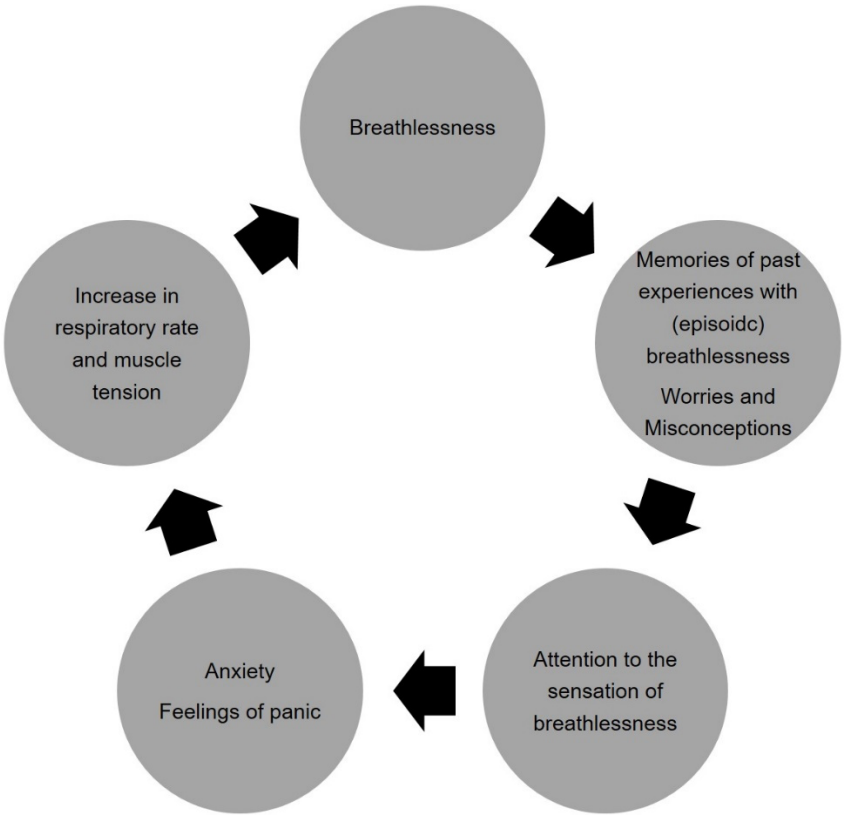

Figure 1. Thinking domain of the BTF model, adopted from Spathis et al. (77).

Episodic breathlessness can cause not only panic (23, 29) but also fear of death (22, 95, 101, 103) and distress for patients and their caregivers (86, 87, 93). Breathlessness episodes are also associated with fatigue (87, 104). An analysis revealed a moderate to severe interference of breathlessness episodes with general activity, mood, walking ability, normal work, relations with others, sleep, and enjoyment of life (87).

2.3.5 Assessment of episodic breathlessness

Given the relative novelty of the definition of episodic breathlessness, specific outcome measures for assessing episodic breathlessness are lacking. The S3 Leitlinie Palliativmedizin (105) recommends assessing the episodes‘ intensity/severity, unpleasantness, and impairment in daily life caused by the episodes. The difference between breathlessness intensity and unpleasantness warrants further investigation, as a longitudinal clinical study demonstrated that the measures were highly correlated with similar variability and varied more between than within patients suffering from chronic breathlessness (106). Just as with chronic breathlessness, patient-reported (episodic) breathlessness is considered a gold standard due to the subjective experience of (episodic) breathlessness (47, 73, 107). Numeric rating scales are validated for assessing breathlessness (108) and are useful to assess episodic breathlessness characteristics such as intensity, impairment, and unpleasantness. As

episodic-breathlessness-specific outcome measures beyond NRS are missing, tools for assessing chronic breathlessness are used (e.g., Chronic Respiratory Questionnaire; 109).

2.4 Managing chronic breathlessness

There are various approaches for the symptomatic treatment of chronic breathlessness: These include pharmacological and non-pharmacological strategies and interventions based on non-pharmacological strategies, as well as breathlessness services, which remain rare but offer promising effects (39–41). There is little evidence-based research concerning the most beneficial treatment for episodic breathlessness. The few available studies are presented in Section 2.5.

2.4.1 Pharmacological strategies

Beyond opioids and oxygen, there is no robust evidence regarding the management of chronic breathlessness, according to the European Respiratory Society (ERS) and the ATS (47).
The use of opioids to treat breathlessness is suggested by, for example, the ESMO Clinical Practice Guideline (110) and the S3 Leitlinie Palliativmedizin (105). They have supporting evidence, but optimal dosing and potential disadvantages caused by long-term use of opioids need to be considered (24, 25, 75, 111, 112). There is an ongoing controversy regarding the beneficial effect of opioids (25, 111). A systematic review described the beneficial use of fentanyl for breathlessness relief, but randomized controlled studies to evaluate its effectiveness are missing (113). Moreover, the evidence does not support the use of nebulized opioids (25), and a systematic review and meta-analysis failed to demonstrate the effectiveness of benzodiazepines in preventing breathlessness among patients with malignant and non-malignant diseases (114, 115). Recently, antidepressants have been explored to treat breathlessness, but research on the use of antidepressants for breathlessness is still at its beginning. Our research team is part of a randomized controlled trial (RCT) that is testing whether mirtazapine is an effective treatment for chronic breathlessness among patients needing palliative care.
According to the Esmo Clinical Practice Guideline (110), supplemental oxygen, non-invasive ventilation, and high flow can be considered for treating breathlessness. Oxygen is indicated in hypoxic patients who are breathless, but for non-hypoxemic patients, there is no difference between oxygen and medical air regarding the effect on the relief of breathlessness (116, 117).

2.4.2 Non-pharmacological strategies

In addition to pharmacological strategies, non-pharmacological strategies are crucial in relieving and managing chronic breathlessness. Non-pharmacological strategies complement pharmacological treatment options and have shown strong evidence in treating chronic

breathlessness among patients in advanced stages of malignant and non-malignant diseases (30, 34). Therefore, they are recommended by the Asco Guideline for managing breathlessness in advanced cancer (118). As there are many non-pharmacological strategies, they are summarized according to the areas where they most support the patient's management and relief from breathlessness. While some non-pharmacological strategies help with managing breathlessness by focusing on breathing or positioning, others focus on panic and anxiety control, aiming to relax the breathing. The first are referred to as *behavioral* strategies and the latter *cognitive* strategies. Next to these two groups of non-pharmacological strategies, there are different strategies directed at the patient's general lifestyle and habits. Therefore, common assumptions and thoughts about breathlessness are discussed with the patients. Moreover, to date, a few studies have evaluated cognitive-behavioral intervention programs comprising various non-pharmacological strategies.

Breathing techniques address altered breathing patterns. Two reviews focusing on non-pharmacological strategies for breathlessness among patients with life-limiting diseases recommend breathing techniques (30, 34). A single session of breathing training compared to three sessions was found to be sufficient to reduce the worst breathlessness over the previous 24 hours (119). Three standard breathing techniques include pursed-lip breathing, breathing control, and deep, slow breathing (30, 34). Pursed-lip breathing is defined as *"the generation of positive pressure within the airways by expiration against partially closed lips."* It has the strongest evidence among all breathing techniques used in breathlessness management and is recommended for management in patients suffering from COPD (120). Breathing control promotes the return to an appropriate respiratory rate and tidal volume (121). To achieve this, patients can benefit from visual help to prolong exhales and, thus, decrease their respiratory rate and relieve the breathing accessory muscles. The Breathlessness Intervention Service (BIS) (122) suggests discussing a *breathing rectangle* (34) with patients to support them in controlling their breathing. According to this method, when trying to control their breathing, patients can follow the edges of a rectangle with their eyes: The patient breathes out when looking along the longer side and breathes in when looking along the shorter side. Rectangles can easily be found anywhere in a patient's environment (e.g., a book or a window). Teaching patients diaphragmatic/slow deep breathing can also promote more effective ventilation (120). Patients who struggle with slow, deep breaths may place their hands on their tummy with their fingertips just touching: Breathing in leads to their fingertips separating, and, when breathing out, the fingertips touch again.

Physiotherapeutic experts recommend positions to relieve breathlessness in respiratory care (120). Fixation of the shoulder girdle can increase the thoracic volume and improve ventilation (120). Thus, patients should learn different positions to fix the shoulder grindle to optimize ventilatory muscle efficiency and relieve breathlessness (120). A common position is the

forward lean: The patient sits and rests their elbows on their knees or a table or standing with the arms supported on a wall or another suitable surface (121).

There is additional evidence that facial airflow (e.g., directed at the cheeks) reduces the sensation of breathlessness (123). A systematic review and meta-analysis concluded that airflow substantially relieved chronic breathlessness and suggested considering it as a treatment option for managing breathlessness (123). The effect presumably results from the airflow stimulation independently of the gas (oxygen or room air). It is assumed that the benefit derives from cooling nasal receptors and moderating afferent signals to the respiratory center (77, 107, 116, 124). Accordingly, using a handheld fan is a simple intervention for a patient's self-management of breathlessness. It is portable and has only a few disadvantages, such as potential feelings of embarrassment in public or perceiving the cooling as aversive (32). A randomized cross-over trial with patients with advanced disease who did not receive supplemental oxygen demonstrated the beneficial effect of a handheld fan directed at the face: The patients who directed a handheld fan toward their face vs. their leg for five minutes indicated significantly decreased breathlessness when the airflow was directed toward their face (35). A further randomized controlled feasibility trial (125) demonstrated that the handheld fan did not only support recovery from breathlessness but was also perceived by the patients as a helpful self-management strategy. Contrasting with this, a randomized phase II trial did not yield preliminary evidence of the effectiveness of a handheld fan. The authors discussed the challenge of finding an appropriate control for a visible intervention like the handheld fan. They chose a wristband (labeled "*breathe easy"*, which the patients should pull and flit when feeling breathless), assuming that distraction provide by the wristband could serve as a placebo, and considered it more realistic than directing the fan toward the leg (31, 35).

Besides the aforementioned behavioral strategies, cognitive strategies, as another type of non-pharmacological strategy, have been shown to support patients' management of chronic breathlessness (34).

Given the strong interaction between breathlessness and anxiety, a relevant approach to positively influence the patient's experience of chronic breathlessness is to support them in anxiety/panic reduction. An increasing body of evidence underlines the benefits of anxiety management techniques such as relaxation for controlling pain (126, 127). While anxiety management techniques are often used in managing breathlessness in clinical practice, robust evidence is lacking, and further definition and research is needed (30). A Cochrane Systematic Review (30) did not find sufficient data to analyze techniques directed at anxiety when a patient is breathless. Booth et al. (34) suggest that all patients should learn appropriate strategies, such as anxiety reduction, for managing breathlessness. The same research team describes different strategies for anxiety management, such as relaxation training and distraction (121): How patients distract or relax is unique, as are their strategies during breathlessness. While

some patients are familiar with structured relaxation techniques such as visualization techniques or progressive muscular relaxation, others have their own way of achieving a feeling of relaxation (e.g., thinking of a peaceful place). The same is true for distraction; if a patient manages to focus on something other than their anxiety when feeling breathless, it can be beneficial, as reduced anxiety positively impacts the breathing pattern. Watching TV, listening to music, or listening to a partner talk can be helpful strategies to manage anxiety in breathlessness. Distracting oneself or feeling relaxed when suffering from breathlessness requires practice in a situation when the patient feels comfortable (121). The BIS promotes the use of a "poem" that patients choose for empowerment and calming down ("*Ich schaff' das schon!*"; 39).

Among strategies that may address breathlessness or anxiety, some cannot be trained with the patients. They primarily refer to daily habits and misinformation but need to be discussed. Patient education can comprise the following: First, patients can benefit from advice on energy conservation. This means discussing ways to avoid extremes of rest or activity, carefully planning and structuring their daily lives and pacing themselves during activities (128, 129). Due to fear of becoming breathless, patients often avoid exercise and activities altogether. However, regular exercise and activity improve breathlessness, as patients stay conditioned and keep their muscles trained (86). Thus, empowering a patient to be active and maintain some exercise is important and recommended for COPD (130), cancer (131), and CHF (132). Reduction of physical activity can also lead to self-isolation and greater dependency on others (86). Common misperceptions include the need for oxygen or the idea that patients will die "gasping" for air (121). The S3 Leitlinie Palliativmedizin (105) recommend providing patients with information concerning their disease, adapting their daily rhythm to the "breathlessness rhythm", and instructions for economic mobility. When discussing available options to manage breathlessness, the BTF model can be useful (77). It covers the different domains of breathlessness that interact, maintain, and worsen the experience.

A few cognitive and behavioral interventions which deliver different cognitive and behavioral strategies summarized in an intervention or program have been evaluated for the management of breathlessness. Unfortunately, there is not enough data to assess the overall evidence (30), but the results of most studies are promising.

Williams et al. (2015) developed and implemented a cognitive behavioral therapy program for the sensation of breathlessness. The program includes the following steps*: recognize sensations, explore thoughts and beliefs, validate thoughts as useful or harmful,* and *evolve and change behavior*. It was tested among participants of an eight-week comprehensive pulmonary rehabilitation program. The program was feasible and well accepted by COPD patients (38).

A single-group pilot study evaluated the feasibility and utility of a manualized intervention for patients with advanced lung cancer. In two sessions with nurse practitioners, patients were taught breathing and relaxation techniques. The completion rate was high, and patients reported improvements in breathlessness, anxiety, depression, and quality of life (36). A group cognitive-behavioral intervention for elderly patients suffering from COPD comprised the following themes: understanding of COPD, medication, anxiety, panic, and depression; activity pacing; relaxation; breathing training; and goal setting. It showed significant improvements in depression and health status. Furthermore, Accident & Emergency department attendance was significantly reduced, and patients felt less anxious (non-significant; 133).

The same research team compared a cognitive-behavioral manual with an information booklet on health service use, mood, and health status. It demonstrated, in the cognitive-behavioral manual compared to the information booklet group, a reduction of Accident & Emergency visits by 42%; reduction in hospital admissions and bed days; and significant improvement in depression, anxiety, and breathlessness (37).

A randomized controlled trial with patients suffering from moderate to severe COPD showed no significant differences in anxiety, depression, breathlessness, and exercise capacity between patients attending comprehensive pulmonary rehabilitation and those attending a comprehensive pulmonary rehabilitation program that included a specific cognitive behavioral therapy program for breathlessness. The researcher discussed the possibility that comprehensive pulmonary rehabilitation comprises components of cognitive-behavioral therapy due to coaching and supervision of the rehabilitation deliverer (134).

2.4.3 Breathlessness services

To provide appropriate non-pharmacological management strategies and pharmacological treatment options, breathlessness services for patients suffering from advanced diseases emerged over the last 15–20 years. Specialist breathlessness services usually last a few weeks and include appointments in the clinic and at the patient's home. Patients have appointments with a multi-professional team that aims to meet the demands of breathlessness in all domains (e.g., physiotherapists, psychologists, clinicians, and palliative care providers; 39–41). They provide patients with techniques and informational material to improve patients' self-management of breathlessness. The treatment is tailored to each patient's individual needs and comprises pharmacological and non-pharmacological strategies like cognitive and behavioral strategies. The effectiveness of breathlessness services has been supported in three single-center RCTs (39–41). Participating in the BIS led to reduced distress due to breathlessness, fear, and worries, as well as increased confidence in managing breathlessness (39). Attending the Breathlessness Support Service (BSS) in London improved patients‘ mastery of breathlessness (40), and the most recently evaluated Munich

Breathlessness Service (MBS) confirmed improvements in the mastery of breathlessness and health-related quality of life, at moderate excess costs (41). Although it can be assumed that many patients who are attending breathlessness services also suffer from episodic breathlessness, they are not explicitly mentioned in the service manuals, and the strategies described do not focus on them. Given the high symptom burden due to breathlessness episodes (23, 29, 37, 135), patients would likely benefit from service components that focus on breathlessness episodes (in addition to chronic breathlessness).

2.5 Managing episodic breathlessness

While research focusing on pharmacological and non-pharmacological treatment options for the relief of chronic breathlessness is growing, the scientific data on appropriate management options for episodic breathlessness is minimal. Although episodic breathlessness can be seen as a form of chronic breathlessness, occurring with and without continuous breathlessness, it is essential to recognize episodic breathlessness and its characteristics (e.g., short duration, close connection to panic) to ensure appropriate treatment.

2.5.1 Pharmacological strategies

To date, there are no satisfactory pharmacological treatment options for the relief of episodic breathlessness. An RCT with midazolam as adjunctive therapy to morphine did not demonstrate a relieving effect for breathlessness episodes (95). Furthermore, a Cochrane review assumed a high risk of bias in this trial, as a crossover method was used (midazolam for the morphine group and vice versa), confounding separate analysis (115). Efficacy measures in a feasibility phase II study with fentanyl buccal tablets to relieve episodic breathlessness among cancer patients predominantly favored the drug (136). Still, this trial included only 10 patients, and the results need further evaluation. While opioids are recommended for breathlessness palliation (105), the duration of most breathlessness episodes is shorter (27, 28) than the time it takes for the effect to occur. The brief duration of most episodes (27, 28) is a general problem for the pharmacological treatment of breathlessness episodes: It challenges most pharmacological treatment options, as the onset of action of even fast-acting drugs (such as fentanyl) takes longer than the episodes last.
Thus, due to the limited studies on the pharmacological treatment of episodic breathlessness and the challenges regarding the short duration of most breathlessness episodes, a focus for the relief of episodic breathlessness should be set on non-pharmacological strategies.

2.5.2 Non-pharmacological strategies

Thus far, non-pharmacological strategies have not been evaluated primarily for episodic breathlessness, whether as single strategies or combined in cognitive-behavioral programs. However, patients use non-pharmacological strategies to manage and relieve episodic breathlessness (23, 29).

A qualitative interview study (23), focusing on the patients‘ non-pharmacological strategies, revealed that patients‘ strategies include different components of cognitive and behavioral strategies. The described non-pharmacological strategies can be summarized as *cognitive and psychological strategies*, *breathing techniques and positions*, *air and oxygen*, *environmental and other strategies*, and *reduction of physical exertion* (23). A further qualitative interview study (29) aiming to deepen the understanding of unpredictable breathlessness episodes also described management strategies categorized as *cognitive and psychological strategies* and *breathing techniques and positioning*. In addition, it can be useful for patients to identify triggers for their breathlessness, as it gives them the possibility to more easily control the feeling or avoid their triggers (81).

Despite the findings that patients who suffer from episodic breathlessness use and combine non-pharmacological strategies to ease breathlessness episodes (23), research is still lacking. Nevertheless, developing appropriate and effective management strategies is vital, especially given the limited drug treatment options.

2.6 Summary of the introducion

Breathlessness episodes are a common symptom at the patient’s end of life. They are burdensome, characterized by increased breathlessness intensity, a short duration and often accompanied by anxiety up to fear of death. The brief duration of most episodes limits pharmacological treatment options as the onset of action of, even fast-acting, drugs lasts longer than the episode. For this reason non-pharmacological management strategies are promising for the management of episodic breathlessness. In fact, patients report that they use different non-pharmacological strategies, alone or in combination to manage and relief breathlessness episodes. But the evaluation of non-pharmacological management options for episodic breathlessness is lacking. Therefore, we have developed a brief cognitive and behavioral intervention for the management of episodic breathlessness, comprising different non-pharmacological strategies. The developed intervention was then evaluated regarding its feasibility, safety, acceptability, and potential effects in a subsequent single-arm phase II study.

3. Aim and objectives of the dissertation projects

This dissertation aims to support patients who suffer from life-limiting diseases in managing episodic breathlessness to maintain/increase the patients' mastery of breathlessness and, thus, their quality of life.

The aim is addressed through the following objectives:

1. The objective of DP 1 is to develop a brief cognitive and behavioral intervention for the management of episodic breathlessness for patients suffering from life-limiting diseases using a Delphi survey with multi-professional experts.

2. The objective of DP 2 is to evaluate the feasibility, safety, acceptability, and potential effects of the brief cognitive and behavioral intervention for the management of episodic breathlessness among patients with life-limiting diseases.

4. Methods of the dissertation projects

Aiming to support the management of patients suffering from episodic breathlessness, a brief cognitive and behavioral intervention was developed and evaluated. Two different methodological approaches, building on each other, were applied to address the research objectives (see Table 1).

Development of the brief cognitive and behavioral intervention (DP1): A Delphi survey with international, multidisciplinary experts in the field of breathlessness was used to develop the brief cognitive and behavioral intervention for managing episodic breathlessness. Eighty-seven experts were invited via e-mail to participate in the Delphi survey between January and July 2018. The Delphi survey comprised three rounds, each lasting two to four weeks. Based on a literature search guided by systematic reviews and non-pharmacological interventions to manage breathlessness (30, 93), the study team pre-identified 31 cognitive and behavioral strategies to manage breathlessness. In the first round, the experts rated these strategies regarding their relevance for managing episodic breathlessness, and open-ended questions enabled the addition of further strategies and comments. The second and third rounds were used to develop and consent to the brief cognitive and behavioral intervention, comprising the non-pharmacological strategies selected in round one. In addition to closed-ended questions, free-text fields were provided. The a priori target agreement for closed-ended questions was 70%, only questions answered by a least 50% of the experts were considered for analysis, and abstention was considered non-participation. Data were pseudonymized before analysis. The open-ended questions and free-text comments were analyzed following content analyses and discussed by the study team. For descriptively analyzing the quantitative data (percentages of agreement, median, IQR), SPSS was used. The guideline on conducting and reporting Delphi surveys in palliative care (137) was applied.

Evaluation of the brief cognitive and behavioral intervention (DP2): The subsequent single-arm pilot study (phase II) assessed the feasibility, safety, acceptability, and potential effects of the brief cognitive and behavioral intervention (conducted between February 2019 and February 2020). Before conducting an RCT, pilot studies represent a fundamental phase of the research process (138), providing important information concerning the feasibility, safety, acceptability, and implementation of the intervention (139). This is particularly true for research in palliative care, as recruitment, for example, is difficult due to acceptability and increasing morbidity and death (140). Thus, for the present single-arm phase II study, 49 patients with life-limiting diseases suffering from episodic breathlessness were enrolled. A mixed-methods approach, collecting quantitative and qualitative data, was used. The 1-to 2-hour intervention followed the baseline assessment. In weeks two, four, and six following the intervention, the outcomes were assessed, and in week six, a qualitative interview and the final

assessment were conducted. Recruitment took place at in-/outpatient clinics of the University Hospital of Cologne and the Bethanien Hospital Solingen. Based on sample size calculations, 49 patients were required to enable statistical analysis and test the intervention's feasibility. Feasibility was defined by the enrollment rate within the study period, study completion rate, drop-out reasons, and dates. Reasons for refusal and the sociodemographics of patients who denied participation while being eligible were assessed. To assess the safety of the study, participants were asked about burdens resulting from the intervention and study procedure, both in questionnaires and in the in-depth interviews. Next to the primary outcome *mastery* of breathlessness (Chronic Respiratory Questionnaire; 109), patients' quality of life, palliative care needs, specific symptoms, experiences of anxiety and depression, intensity of their episodic breathlessness, and impairment due to breathlessness episodes were assessed. Complementary to validated questionnaires and scales, qualitative, in-depth interviews improved the understanding of the patients' experiences with the intervention. Quantitative data were managed and collected using REDCap electronic data capture tools and analyzed using SPSS. Moreover, descriptive analyses were performed. Due to deviations from the normal distribution, Wilcoxon Signed Rank Tests were used to test for significant changes between baseline and each post-intervention outcome (α-level was set at .05). Exploratory subgroup analyses concerning the outcome *mastery* of breathlessness were conducted. Using MAXQDA (2020), content analysis (141) was applied to analyze the qualitative data. The MORECare Statement on evaluating complex interventions in end-of-life care was used (142). This trial was registered with ClinicalTrials.gov (NCT04630743).

While DP 1 and DP 2 reported on the development and evaluation of an intervention focused on supporting patients suffering from episodic breathlessness, carers were also invited to participate in the phase II study following the recommendations of the Delphi survey. Within the patient education, the intervention deliverer addressed the carers, aiming to provide them with information, answer questions, and support the patient and carer to develop a common strategy for how to react when the patient is suffering from a breathlessness episode. For this reason, the intervention was also rated by the carers regarding its feasibility, safety, and acceptability. While the results will be reported in the respective, soon-to-be-published paper (accepted 01/2022, Annals of Palliative Medicine), they will not be detailed in the present thesis.

Table 1: Summary of dissertation project methods

Objective	Study design	Data collection	Data analysis	Study participants
Development of a brief cognitive and behavioral intervention for the management of episodic breathlessness	• Online Delphi survey	• Open/closed-ended questions and free-text options	• Descriptive statistics • Combined inductive & deductive coding following content analyses	• Expertise and experience in (episodic) breathlessness in a scientific or clinical context • Multi-professionalism • Broad geographic spread
Evaluation of the feasibility, safety, acceptability, and potential effect of a brief cognitive and behavioral intervention for the management of episodic breathlessness	• Single-arm pilot trial (phase II)	• Mixed-methods approach with validated questionnaires, numeric rating scales, and qualitative in-depth semi-structured interviews • Feasibility evaluation: enrollment rate, study completion rate, drop out reasons, and dates	• Descriptive analyses • Wilcoxon Signed-Rank Tests to detect changes between baseline and post-intervention assessment • Exploratory subgroup analysis • Content analysis for the qualitative interviews	• Suffering from episodic breathlessness despite treatment of the underlying condition due to any life-limiting and progressive disease • Estimated life expectancy ≥ 8 weeks • ≥ 18 years • Comprehension of German language • Cognitive capacity to give informed consent (143) • ECOG status 0-3 (144)

Funding

Both DPs were conducted within the project, “Cognitive and Behavioral Intervention for the Management of Episodic Breathlessness in patients with advanced disease: a single-arm therapeutic explanatory trial (phase II),” funded by the Federal Ministry of Education and Research (No.01GY1716).

Ethical approval and consent to participate

Ethical approval was obtained from the Ethics Commission of Cologne University’s Faculty of Medicine (Delphi survey: 11/2017; No. 17-398; Feasibility trial: 12/2018, No. 18-209), and written informed consent was obtained from all participants prior to participation.

Consent for publication

This dissertation, including the peer-reviewed publications, presents pseudonymized participant data; thus, consent to publish is not required.

5. Results: Scientific publications of the dissertation projects

The following sections display the results of the two DPs in the form of peer-reviewed journal publications.

5.1 Dissertation project 1

Development of a brief cognitive and behavioral intervention for the management of episodic breathlessness: A delphi survey with international experts

Karlotta Schloesser

Yvonne Eisenmann

Anja Bergmann

Steffen T. Simon

Journal of Pain and Symptom Management, DOI: 10.1016/j.jpainsymman.2020.09.034, published 05/2021

5.1.1 Synopsis: Dissertation project 1

Abstract

Context

Episodic breathlessness is characterized by a severe worsening of breathlessness intensity that goes beyond usual fluctuations. Episodes are usually short; therefore, nonpharmacological strategies (cognitive and behavioral) seem most promising to be beneficial. Which strategies—delivered separately or in combination—might be most effective and feasible remains unclear.

Objectives

The Delphi survey selects and determines different nonpharmacological strategies for coping with episodic breathlessness to develop a brief cognitive and behavioral intervention for the management of episodic breathlessness.

Methods

Using an online Delphi survey comprising three rounds, international, multidisciplinary experts in breathlessness summarized and determined cognitive and behavioral strategies. The *a priori* target agreement for close-ended questions was 70%.

Results

Experts (*n* = 41/87; *n* = 45/85; *n* = 36/85) agreed on 15 of the 31 cognitive and behavioral strategies. Based on the experts' opinion, the final version of the cognitive and behavioral intervention comprised the following characteristics: individually tailored intervention, a high amount of communication, short duration, the involvement of carers, and use of the *Breathing Thinking Functioning Model* of Spathis et al. (77). Consensus upon the delivery of the subsequent strategies within the intervention was reached: handheld fan, forward lean, diaphragmatic breathing, distraction, pursed lips breathing, long breaths out, and relaxation training (see Fig. 2).

Conclusion

Using the consented nonpharmacological strategies, a brief cognitive and behavioral intervention was developed that balances between individualization and standardization of the intervention.

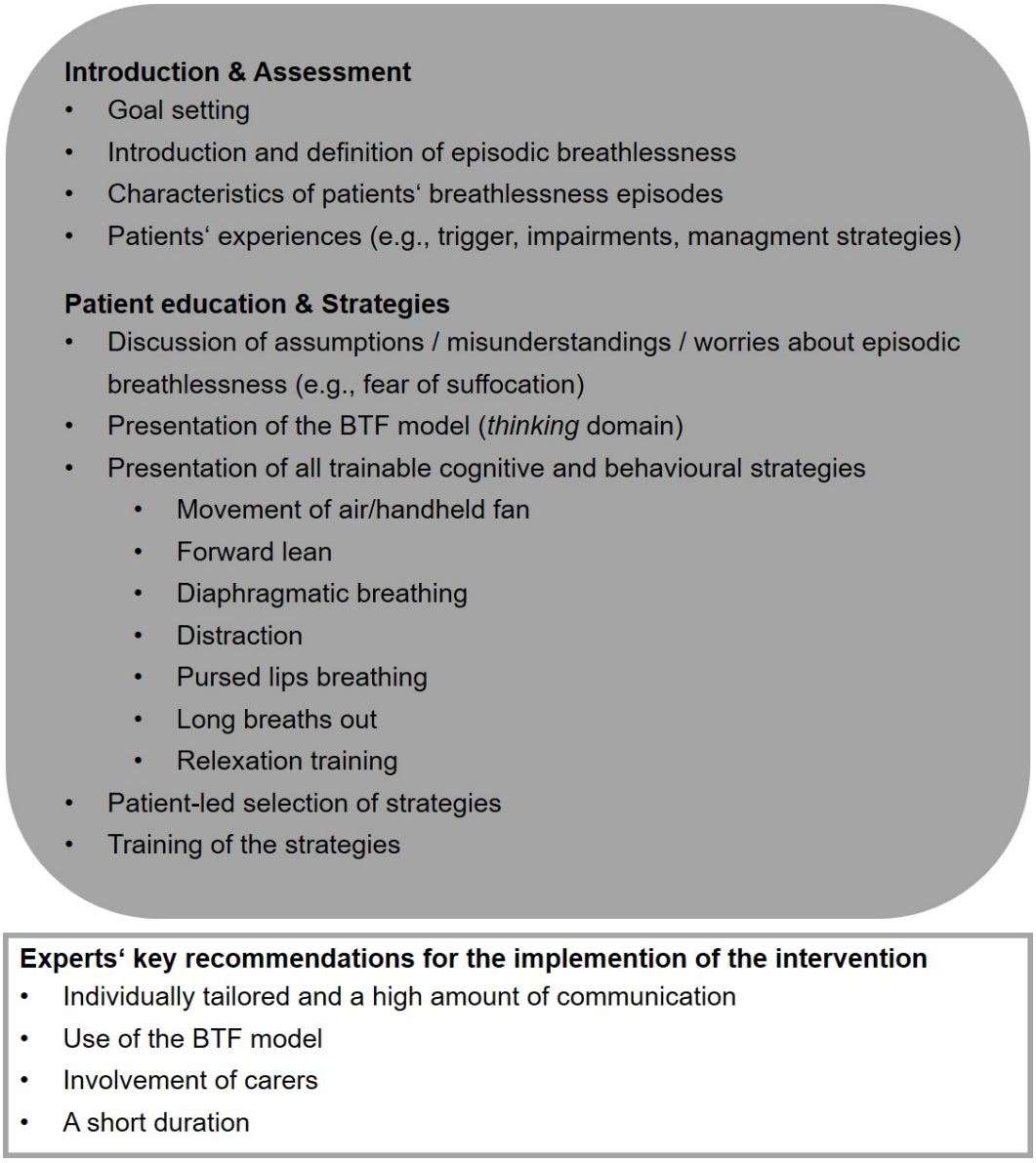

Figure 2. Expert-consented draft of the brief cognitive and behavioral intervention for the management of episodic breathlessness, including the key recommendations for delivering the intervention.

Contribution of Karlotta Schlösser

- Development of study procedure
- Literature search as preparation of the content for the first Delphi round
- Organization of the pilot testing and following revision of the different Delphi rounds
- Identification and contact with the experts who were invited for participation
- Conduction of the different rounds of the online survey
- Analysis of the results
- Interpretation of the results and development of the following round according to the results of the previous round
- Writing of the manuscript

Original Article

Development of a Brief Cognitive and Behavioral Intervention for the Management of Episodic Breathlessness—A Delphi Survey With International Experts

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Abstract

Context. Episodic breathlessness is characterized by a severe worsening of breathlessness intensity that goes beyond usual fluctuations. Episodes are usually short; therefore, nonpharmacological strategies (cognitive and behavioral) seem most promising to be beneficial. Which strategies—delivered separately or in combination—might be most effective and feasible remains unclear.

Objectives. The Delphi survey selects and determines different nonpharmacological strategies for coping with episodic breathlessness to develop a brief cognitive and behavioral intervention for the management of episodic breathlessness.

Methods. Using an online Delphi survey comprising three rounds, international, multidisciplinary experts in breathlessness summarized and determined cognitive and behavioral strategies. The a priori target agreement for close-ended questions was 70%.

Results. Experts ($n = 41/87$; $n = 45/85$; $n = 36/85$) agreed on 15 of the 31 cognitive and behavioral strategies. Based on the panellists' opinion, the final version of the cognitive and behavioral intervention comprised the following characteristics: individually tailored intervention, a high proportion of communication, short duration, the involvement of carers, and use of the *Breathing, Thinking, Functioning Model* of Spathis et al. Consensus upon the delivery of the subsequent strategies within the intervention was reached: handheld fan, forward lean, diaphragmatic breathing, distraction, pursed lips breathing, long breaths out, and relaxation training.

Conclusion. Using the consented nonpharmacological strategies, a brief cognitive and behavioral intervention was developed that balances between individualization and standardization of the intervention. J Pain Symptom Manage 2021;61:963–973.

Key Words

episodic breathlessness, Delphi, cognitive-behavioral

Key message

Based on an online Delphi survey, international, multidisciplinary experts in breathlessness developed the brief cognitive and behavioral intervention for the management of episodic breathlessness: The intervention focuses on the balance between individualization and standardization of the intervention and

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Accepted for publication: September 22, 2020.

0885-3924/$ - see front matter
https://doi.org/10.1016/j.jpainsymman.2020.09.034

comprises patient education and nonpharmacological strategies for the relief of episodic breathlessness.

Introduction

The American Thoracic Society defines breathlessness as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity".[1] The syndrome "chronic breathlessness"[2] occurs despite optimal treatment of the underlying disease and requires symptomatic treatment.[3] Breathlessness is a common symptom in advanced diseases with a prevalence of up to 98% among patients with chronic obstructive pulmonary disease (COPD) that increases toward the end of life[4,5] and has a substantial impact on functional status and quality of life of the patients.[5,6] As one form of breathlessness (in general, chronic or refractory), international experts define episodic breathlessness as a "severe worsening of breathlessness intensity or unpleasantness beyond usual fluctuations in the patient's perception. Episodes are time-limited (seconds to hours) and occur intermittently, with or without underlying continuous breathlessness. Episodes may be predictable or unpredictable, depending on whether any trigger can be identified […]".[7] More than 70% of patients with advanced cancer present episodic breathlessness.[8] Episodes are short (75% less than 10 minutes), severe (mean numeric rating scale: 6,5/10) and occur daily but the frequency is highly variable.[9] Opioids are the only drug group with supporting evidence for symptom relief of breathlessness.[10–12] But the short duration of most breathless episodes[9,13] challenges pharmacological management options: the onset of action takes often longer than the episode lasts. Therefore, cognitive and behavioral strategies[14,15] are most probably useful for the management of episodic breathlessness due to their independence from the short duration of breathless episodes. For the management of continuous breathlessness, nonpharmacological strategies appear to be beneficial[16–18] and holistic breathlessness services for example in London,[19] Munich[20] and Cambridge[21] provide pharmacological and nonpharmacological strategies. Indeed qualitative research revealed that patients suffering from episodic breathlessness adopt cognitive and behavioral strategies for palliation—separately or in combination.[22] But the evaluation of cognitive and behavioral strategies for the management of episodic breathlessness remains warrant. Considering the potential importance of these strategies, they need to be investigated scientifically. In a recently published international Delphi survey, experts with clinical/research expertise in breathlessness define the optimization, exploration, and development of effective (nonpharmacological) interventions for breathlessness as a research priority.[23] Therefore, the present Delphi survey aims to determine cognitive and behavioral strategies to manage episodic breathlessness and to rate the nonpharmacological strategies' relevance by international experts for breathlessness. Subsequently, the most promising strategies will be embedded in a brief cognitive and behavioral intervention (which follows this Delphi survey).

Methods

Study Design

An online Delphi survey comprising 3 rounds was conducted to summarize and determine nonpharmacological strategies for episodic breathlessness and to develop a brief cognitive and behavioral intervention for the management of episodic breathlessness. This Delphi survey is part of the project called "Cognitive and Behavioral Intervention for the Management of Episodic Breathlessness in patients with advanced disease: a single-arm therapeutic exploratory trial (phase II)" (CoBeMEB; funded by the Federal Ministry of Education and Research [funding code: 01GY1716], conducted at the Department for Palliative Medicine, University Hospital of Cologne). The results of the trial will be published separately. The Delphi method has been successfully used in medical and nursing research.[24,25] It is a formal consensus technique with the main purpose to "obtain the most reliable consensus of a group of experts".[26] Ethical approval was provided from the Ethics Commission of Cologne University's Faculty of Medicine (11/2017; No. 17-398).

Expert Panel and Recruitment

To ensure broad and varied expertise in the field of (episodic) breathlessness, the experts building the panel composed the following characteristics: 1) experience and expertise in breathlessness in a scientific or clinical context, 2) multiprofessionalism, and 3) broad geographic spread.

Sufficient expertise was ensured by inviting persons:

1. Who were part of the former National Cancer Research Institute, Palliative Care Breathlessness Subgroup (including experts proposed by former members)
2. First and last authors of relevant publications on nonpharmacological interventions for (episodic) breathlessness
3. Authors of the 27 studies included in the systematic review by Simon et al.[27]
4. Authors of all articles of a Systematic Cochrane Review on the management of breathlessness[16]

Based on these criteria, 87 experts were invited via e-mail to participate in the Delphi survey.

Online Delphi Survey

Data were collected via SurveyMonkey[28] between January and July 2018 within 3 rounds each lasting between 2 and 4 weeks (Fig. 1). Reminders were sent twice. Each round of the Delphi survey was piloted regarding clarity and understanding and revised accordingly. All rounds of the Delphi survey included study information, informed consent, the personal identification code, and the collection of sociodemographic data on a voluntary basis. In round two and three, the experts received feedback from the previous round. Experts indicated (dis-) agreement on Likert scales (from 1 = totally disagree to 5 = totally agree) with the option to choose not applicable (N/A) or unknown strategy.[7,29] The survey language was English.

First Round

Based on a literature search orientated on the systematic reviews on nonpharmacological interventions for the management of breathlessness,[16,27] the study team preidentified 31 cognitive and behavioral strategies for the management of episodic breathlessness. Two independent health-care professionals verified the preliminary completeness of the strategies and added *Breath-stimulating embrocation* (with balm). The first round intended to collect further and to evaluate the presented cognitive and behavioral strategies for the management of episodic breathlessness. Experts were asked to rate the relevance of the strategies especially for the management of episodic breathlessness on a five-point Likert scale. Open-ended questions gave the option to add and to comment on the strategies.

Second round

Based on the results of round one, panellists of the second round answered an open-ended question about which nonpharmacological strategies they considered important for a brief cognitive and behavioral intervention. They rated characteristics of the preliminary version of the intervention on five-point Likert scales. Free-text fields gave the experts the option to add further important aspects or to comment on unnecessary aspects of the intervention and its characteristics and to recommend how the strategies should be presented to the patients. Closed questions with options to choose from were used to determine interventions' characteristics as the duration, the number of strategies the patients should select, and the accompanying information material.

Final round

Resulting from the findings of the second round, the study team adjusted the final draft of the brief cognitive and behavioral intervention. Experts indicated their agreement on the suitability of the intervention for managing episodic breathlessness and to what extent they (dis-)agreed to the two parts of the planned intervention 1) introduction and assessment and 2) patient education and strategies on a five-point Likert scale. Free-text fields gave the option to add further comments on the intervention.

Data Analysis

Data were pseudonymized before analysis. The study group used content analysis for the free-text fields and comments. To analyze quantitative data resulting from close-ended questions, descriptive statistics (IBM SPSS Statistics for Windows, version 25.0) were used. The percentages of agreement (selecting answers *I rather/totally agree*) and disagreement (answers *I rather/totally disagree*), median and interquartile

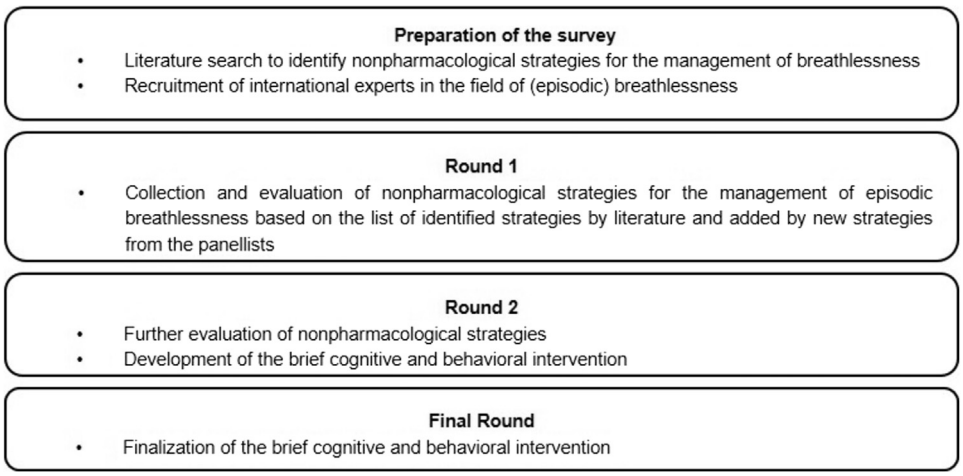

Fig. 1. The Delphi procedure.

range were calculated based on all responses after each round. Abstention (*N/A*) and selecting *unknown strategy* (round 1) were considered as nonparticipation. Only questions answered by at least 50% of the experts were considered for analysis. A priori, a consensus criterion was defined: ≥ 70%[2,7,25] of the experts needed to agree to an item to consider consensus, only the consented items had been presented in the following round. Similarly, if more than 30% of the experts disagreed on an item it was excluded. Panellists' demographic data were analyzed descriptively.

Results

Panellists

The study team contacted 87 of the 88 identified experts for round one, for one expert no valid e-mail address could be found. In the second round, two panellists declined as they considered their clinical experience with episodic breathlessness to be insufficient, resulting in 85 experts contacted in round two and three. Forty-one (47.1%), 45 (52.9%), and 36 (42.4%) experts participated in round one, two, and three, respectively (Fig. 2). Experts mainly worked in

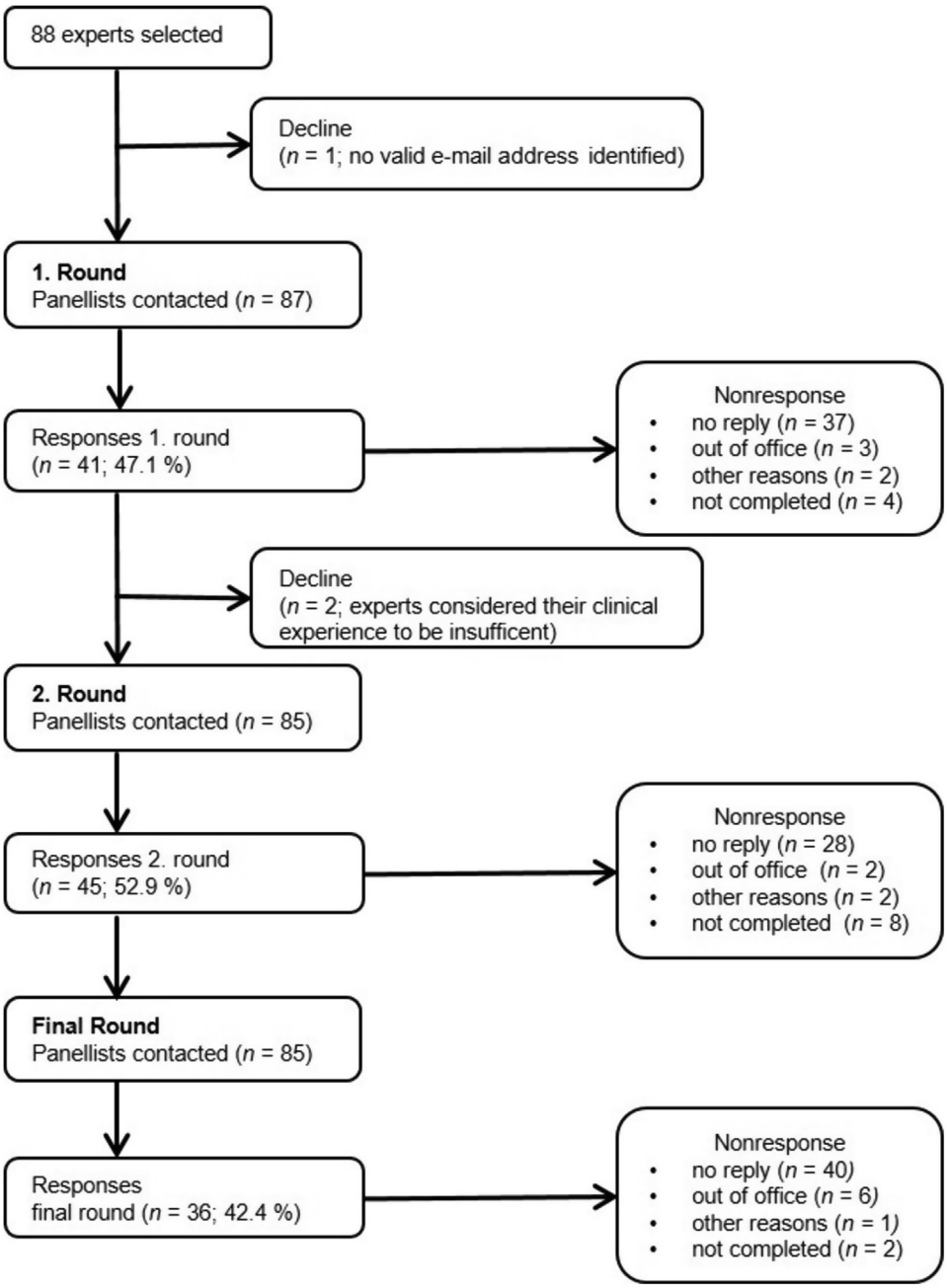

Fig. 2. Flowchart of the panellists in the Delphi survey.

both, research and clinical settings as physicians, nurses, psychologists, physiotherapists, and health/social scientists. Most of them cared for patients with cancer or COPD. They rated their clinical experience and/or scientific skills as quite to highly specialized. The proportion of female and male participants was almost equally distributed over the three rounds (proportion of women in rounds 1/2/3: 48.7%/55.0%/42.9%) and the mean years of experience in breathlessness research were about 13 years and in caring for breathless patients about 17 years (Table 1).

Main Results of the Delphi Survey

Round 1. Agreement of at least 70% was achieved for 15 of the 31 presented strategies in round one (Fig. 3). The strategy *movement of air* (97.4% agreement) reached the highest whereas *actively confronting a breathless episode* yield the lowest agreement (16.7%). *Breath-stimulating embrocation* was unknown to 66.7% of the experts and therefore not included in the analysis. All consented strategies had a median of four or more on the Likert scale (*rather/totally agree*) with an interquartile range of one or two. Answering the open-ended question (round 1; $n = 19$, 46.3%) concerning not listed strategies, the experts suggested the *availability of social support* and *reducing of fear/anxiety* as important strategies.

> "It seems that the experienced severity of breathlessness and dyspnea-related fear are related, which is why I would add a strategy focusing on anxiety as well"
>
> (Research Associate)

Furthermore, panellists requested an explanation of the significance of general fitness/exercises and addressing breathlessness-related misconceptions as further "strategies." In the open-ended fields, 14 experts (round 1, 34.1%) stressed the importance of an individually tailored intervention instead of a one-fits-all intervention for managing episodic breathlessness to make it adjustable to each patient's needs.

> "I feel that the selection of techniques should be based on individual assessment rather than a one size fits all approach"
>
> (Respiratory Specialist Physiotherapist)

As only parts of the strategies can be practised actively and on-site (e.g. *pursed lips breathing*), the remaining strategies are delivered as patient education (e.g. *Identifying triggers of episodic breathlessness*).

Round 2. Experts considered strategies summarized as *breathing techniques* (e.g. *diaphragmatic breathing, long/relaxed breaths out*) and *education* (e.g. *understanding how thoughts and feelings are linked to breathing difficulties; knowledge about episodic breathlessness, its course and that it does not kill*) to be most important for the cognitive and behavioral intervention. About 95.2% of the experts supported the involvement of carers in the intervention and considered the *Breathing, Thinking, Functioning Model*[30] (BTF model) helpful for explaining the strategies to the patients (95.3%). The majority of the experts suggested keeping the intervention short (up to 90 minutes; 76.2%), to equip patients with a patient leaflet (comprising either only the *individually selected strategies* [n = 21; 51.2%] or a booklet with *all cognitive and behavioral strategies* [n = 20; 48.8%]) and a patient-led number of selected strategies (50%; in the open-ended questions they consider 1-3 to be sufficient). Panellists agreed to the preliminary draft of the cognitive and behavioral intervention (88.1%). They agreed to the relevance of addressing the patients' medical history (90.5%) and experiences of episodic breathlessness (100%) within the intervention. Within the open-ended questions, experts emphasized the need for a high proportion of conversation between the health-care professional and the patient, that means to listen carefully what the patient reports and to ask questions to get a comprehensive impression of the patient and the impairments. This allows an individually tailored intervention that is adaptable to the patients' wishes and needs. In the implementation, the cognitive and behavioral intervention should be simple and easy to understand, patients should be instructed to practice and try what works best for them.

Round 3. According to the results from the first and second round, the study group developed the final draft of the brief cognitive and behavioral intervention. All panellists considered the complete intervention suitable for managing episodic breathlessness ($n = 36$; 91.7%). They also agreed to the parts introduction and assessment (88.9%) and patient education and strategies (91.7%) which the intervention comprises. Using the free-text fields for additional comments, the experts stressed the patient-centered approach and the usefulness of the BTF model.[30]

> "Using the BTF model and writing their experiences in the model can be helpful to enable the patient to make sense of it, giving written information, demonstrating techniques, and explaining rationale behind them"
>
> (Occupational Therapist)

Within the introduction and assessment, besides assessing the characteristics of episodic breathlessness, the health-care professional should listen to the patient's (medical/social/breathlessness) history, should pay attention to psychological impairments that might be related to breathlessness (e.g. anxiety; dyspnea-anxiety circle) and the patient's individual

Table 1
Characteristics of Panellists

Characteristics	First Round N	First Round %	Second Round n	Second Round %	Final Round n	Final Round %
Participation	41	47.1	45	52.9	36	42.4
Age, years, median (range)[a]	40-49	28.2	50-59	35	50-59	34.3
N/A	2		5		1	
Gender						
Female	19	48.7	22	55	15	42.9
Male	20	51.3	18	45	20	57.1
N/A	2		5		1	
Country of employment						
UK	10	25.6	13	34.2	9	28.1
Other European countries	14	35.9	14	36.8	12	37.5
USA	8	20.5	6	15.8	4	12.5
Australia	3	7.7	2	5.3	4	12.5
Canada	3	7.7	2	5.3	2	6.3
Hong Kong	1	2.6	1	2.6	1	3.1
N/A	2		7		4	
Employment setting						
Research	10	26.3	12	30	11	33.3
Clinical	3	7.9	5	12.5	6	18.2
Both	24	63.2	21	52.5	14	42.4
Other	1	2.6	2	5	2	6.1
N/A	3		5		3	
Background: If clinician[b,c]						
Medicine	19		18		15	
Psychology	2		2		2	
Nursing	5		4		3	
Physiotherapy	3		3		2	
Other	1		1		2	
Background: If researcher[b,c]						
Medicine	17		14		12	
Psychology	4		4		3	
Nursing	6		6		6	
Physiotherapy	3		3		3	
Health or social sciences	2		3		3	
Other	1		1		1	
Primary caring for[b]						
Cancer	25		23		14	
COPD	22		20		17	
Chronic heart failure	14		13		8	
Motor neurone disease	9		5		6	
Other disease	10		8		5	
Scientific knowledge						
General	1	2.6	1	2.6	0	0
Slightly specialized	4	10.3	5	12.8	6	18.2
Moderately specialized	7	17.9	9	23.1	6	18.2
Quite specialized	21	53.8	10	25.6	10	30.3
Highly specialized	6	15.4	14	35.9	11	33.3
N/A	2		6		3	
Clinical experience						
General	2	5.4	4	10.5	5	16.1
Slightly specialized	3	8.1	3	7.9	2	6.5
Moderately specialized	8	21.6	9	23.7	5	16.1
Quite specialized	12	32.4	10	26.3	11	35.5
Highly specialized	12	32.4	12	31.6	8	25.8
N/A	4		7		5	
Years of experience(n; mean; SD; range)						
In the field of breathlessness research	37; mean = 13.59 SD = 8.65; range = 2-35		40; mean = 13.77 SD = 7.80; range = 1-30		32; mean = 13.88 SD = 8.72; range = 2-35	
In caring for breathless patients with advanced diseases	39; mean = 17.87 SD = 10.61; range = 0-35		40; mean = 17.38 SD = 10.08; range = 0-40		31; mean = 15.52 SD = 10.24; range = 0-35	

N/A = not applicable; COPD = chronic obstructive pulmonary disease.
[a]Median/range of categories (18-29; 30-39; 40-49; 50-59; 60-69; 70-79; >79).
[b]Multiple answers are possible.
[c]Clinician = 30/28/24 participants in total in the first/second/third round; Researcher = 33/31/28 participants in total in the first/second/third round.

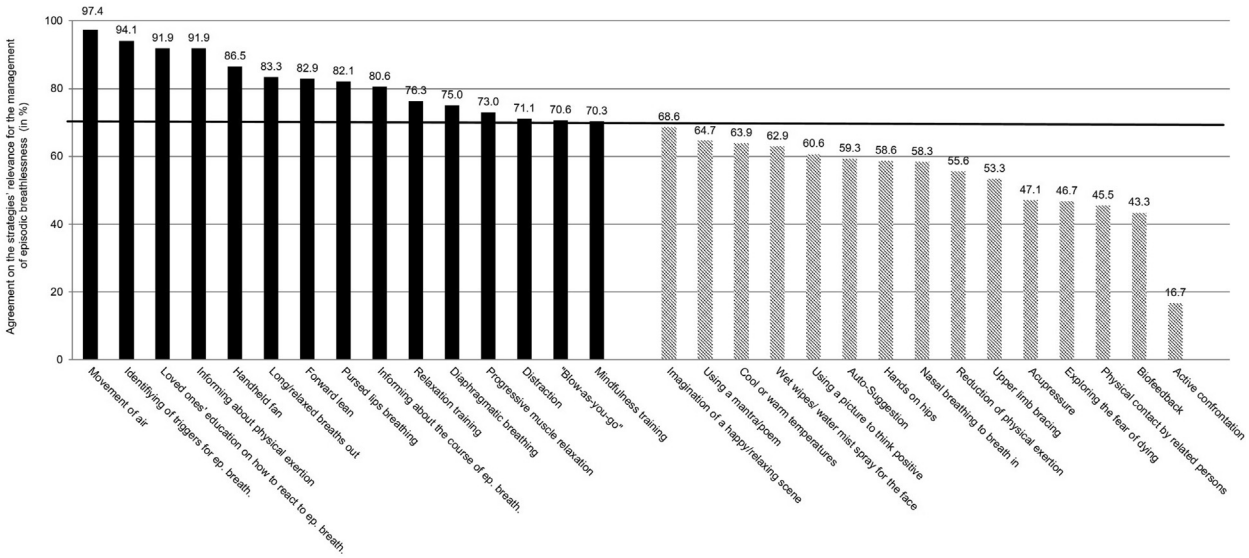

Fig. 3. Overview of the cognitive and behavioral strategies for the management of episodic breathlessness (ep. breath.). Filled bars indicate agreement (rather/totally agree) of at least 70%; hatched bars of less than 70%.

experiences suffering from episodic breathlessness, she/he should ask for triggers and existing coping strategies for episodic breathlessness. Based on the communication with the patient, it should be determined which aspects of episodic breathlessness are most burdensome for the patient and where support is needed. In the following part patient education and strategies, assumptions about episodic breathlessness and related fears should be discussed (as fear of suffocation, duration and course of episodic breathlessness or need for physical exertion) and the trained health-care professional should discuss the BTF model[30] with the patient. After presenting all strategies, the patient has the opportunity to choose her/his strategies, taking into consideration individual (emotional) experiences and needs, cognitive/psychological impairments, and so forth. If desired/needed, the health-care professional should assist in the selection of the strategies. Practicing the strategies should be adaptable to the patients' conditions.

The Final Draft of the Proposed Brief Cognitive and Behavioral Intervention for the Management of Episodic Breathlessness

The brief cognitive and behavioral intervention included the consented strategies (either explained and practised together or discussed within the patient education). For implementation, the experts provided comments from which the study team derived the following key recommendations:

1. An individually tailored intervention and a high proportion of communication to assure the assessment of the patients' experiences, patient education upon episodic breathlessness and a patient-led selection of strategies
2. The use of the BTF model[30]
3. The involvement of carers
4. A short duration of the intervention

The final draft of the cognitive and behavioral intervention that incorporates the experts' comments of round 3 and their key recommendations are shown in Figure 4.

Discussion

The Delphi survey of international, multidisciplinary experts in the field of breathlessness attained consensus on parts and important characteristics of a brief cognitive and behavioral intervention for the management of episodic breathlessness. A range of different nonpharmacological strategies was collected and rated regarding their relevance by the experts. Some consented strategies are explained to and practised with the patients (*handheld fan*, *forward lean*, *diaphragmatic breathing*, *distraction*, *pursed lips breathing*, *long breaths out*, *relaxation training*), others are summarized and discussed within a patient education (e.g. identifying triggers). Based on the panellists' opinion, the brief cognitive and behavioral intervention was developed by focusing on the balance between individualization and standardization of the intervention.

Brief Cognitive and Behavioral Intervention for the Management of Episodic Breathlessness

An Individualized but Standardized Approach. One of the key suggestions of the panellists stated repeatedly

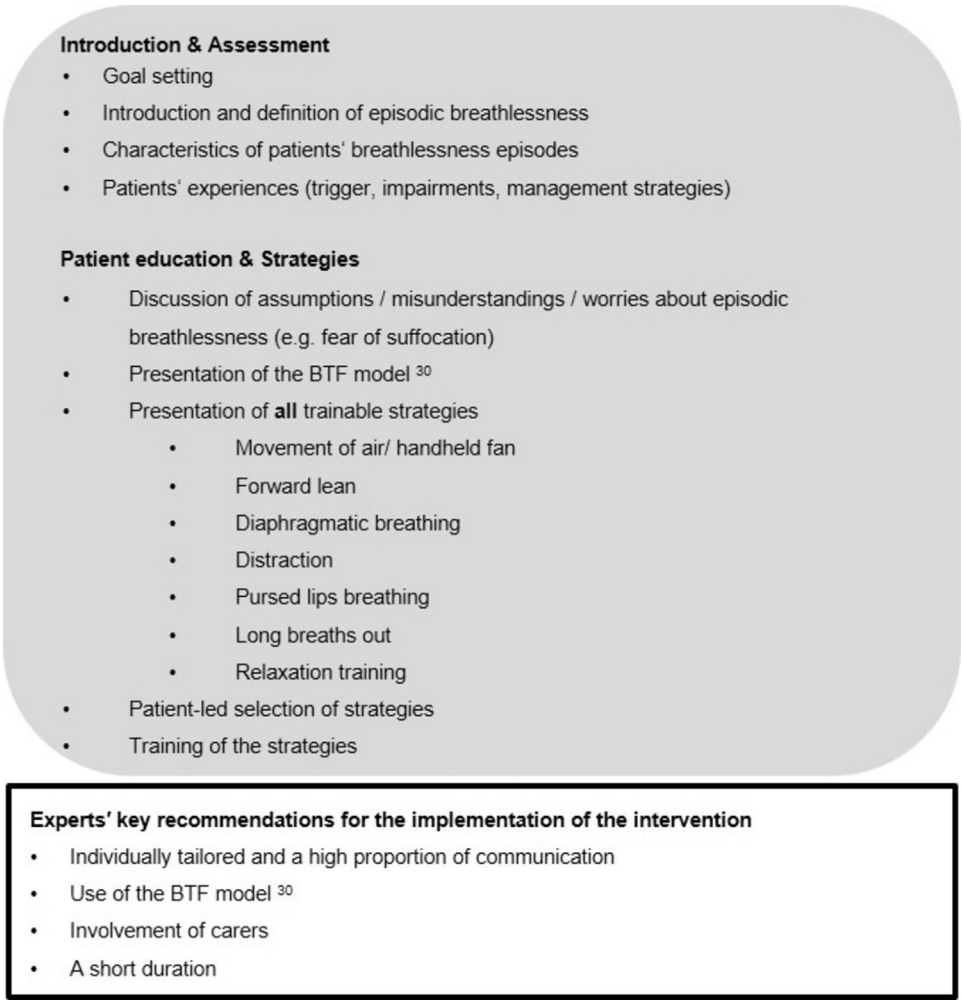

Fig. 4. The final draft of the brief cognitive and behavioral intervention for the management of episodic breathlessness as consented by the experts in the final round and the key recommendations for delivering the intervention.

in the free-text fields was to guarantee an individually tailored intervention instead of a one-fits-all model. Accordingly, the option to individualize the intervention forms the basis of the brief cognitive and behavioral intervention. A high proportion of conversation reflects this approach throughout the intervention. Using the patient-centered approach as a foundation of an intervention is in line with the recommendations of Williams et al.[23] They suggest that patient-centered communication in explaining breathlessness should comprise the acknowledgment of the distress the patient suffers, the importance of the sensation, and the clarification of maladaptive believes. The approach is reflected in the developed intervention. Breathlessness services that support patients suffering from breathlessness in general focus on individually tailored interventions as well.[19,21]

Use of the Breathing, Thinking, Functioning Model. Following the recommendations of the experts, the BTF model[30] is used to explain episodic breathlessness as a multimodal experience to the patients. The empirical model was developed by the Cambridge Breathlessness Intervention Service[21] and does not only show evidence from a methodological point of view but is also widely used by health-care professionals as an educational tool in clinical practice.[30] It is theoretically based on the "vicious flower", a model used in cognitive-behavioral therapy.[31] The BTF model describes three vicious circles that arise from cognitive and behavioral reactions to breathlessness that maintain or even worsen the symptom. Besides the breathing domain and the functioning domain, the thinking domain is of particular interest for the cognitive and behavioral intervention for the management of episodic breathlessness.[30] Similar to the dyspnea-anxiety-dyspnea cycle,[32] the thinking domain of the BTF model describes how a (slight) feeling of breathlessness can activate memories and experiences of breathlessness in the past, draws attention to the breathlessness, and gives rise to the fear of suffocation. This can lead to anxiety/panic, which in turn

increases breathing rate and muscle tension, making breathing even more difficult.[30] Indeed, for many patients, episodic breathlessness is closely linked to anxiety and panic: on the one hand, anxiety/panic or even mortal fear is often a consequence of breathless episodes;[33] on the other hand, anxiety/panic triggers or aggravates episodic breathlessness.[34] Therefore, episodic breathlessness is very frightening and stressful for many patients.[33] Most patients with breathing difficulties experience the vicious circle that leads to an escalating feeling of panic[30] and are afraid to experience this situation again.[33] The experts recommended the BTF model for the brief cognitive and behavioral intervention to address patients' experience of the vicious circle and to explain the interactions, in particular the connection and reinforcement of anxiety and panic with breathlessness. Furthermore, the BTF model helps to select suitable strategies by identifying the patients' domains with the main impairments.

Involvement of Carers. Carers of patients suffering (episodic) breathlessness report a high burden because of the patients' symptom.[6] At the same time, the mere presence of another person might reduce the burden by breathlessness among patients.[35] Hence, following the recommendation of the panellists' to involve carers in the intervention might be relieving not only for the carers but also for the patients. As carers are often insufficiently informed about the illness and possible management strategies for the patients' breathlessness, which leaves them helpless and anxious,[6] carers could be encouraged to ask questions and some information could be directly addressed to the carer (e.g. paying attention to maintaining calm breathing when the patient is suffering a breathless episode). Together with the health care professional, patients and carers could discuss what the patient needs in a moment of suffering episodic breathlessness beyond the mere attendance of a (close) person.

Strategies. All consented strategies actively delivered to the patients (e.g. *forward lean*, *handheld fan*, *diaphragmatic breathing*, *distraction*, *pursed lips breathing*, *long breaths out*, *relaxation training*) are already used in the management of chronic breathlessness.[14–18] Their positive effect had been shown in clinical studies, reviews[14–18,36–38] and as components of breathlessness services.[19–21] It is of great importance to train patients with episodic breathlessness how to react to an episode as drug treatment has its limits due to the short duration of the breathless episodes[9,13] These strategies mentioned by the experts are in particular effective for episodes of breathlessness and should be incorporated in a brief cognitive and behavioral intervention.

Implementation. The intervention should be brief (max. 90 minutes) as most of the targeted patients are severely ill and have a limited functional status with limited capacity to absorb the information and instructions of the intervention. The session can be delivered at home or in a clinical setting followed by a refreshing session via telephone. The duration of the intervention corresponds to the usually chosen duration for cognitive and behavioral therapy sessions for the management of breathlessness[39] and the interventions delivered in the breathlessness services.[19–21] Delivering the intervention over repeated sessions was no more effective than a single session.[40]

Strengths and Limitations

The response rate was acceptable (round 1: 47.1%; round 2: 52.9%; round 3: 42.4%) and comparable to other Delphi surveys in this area,[7,23] but the results need to be interpreted with caution as around a half of the experts did not participate. However, the total number of experts was high. Most panellists defined themselves as clinician and researcher, the majority of whom worked as medical doctors. This leaves psychologists, nurses, physiotherapists, or health and social scientist underrepresented. This may have influenced or distorted the focus the experts set on the main topics of the cognitive and behavioral intervention. Using a predefined eligibility criterion, relevant aspects and experiences from the much wider pool of health-care professionals might not have been included. Inviting patients to take part in the Delphi survey could have been advantageous even though the strategies presented in round one had been identified based on studies with patients. To achieve consensus, we used a formal consensus technique with an a priori defined consensus criterion of 70%. This is a valid method of achieving consensus in areas were no gold standard is given.

Conclusion

In an online Delphi survey with international, multidisciplinary, specialized experts working in the field of breathlessness as researcher or clinician, current non-pharmacological strategies for the management of episodic breathlessness were collected and consented. Based on these strategies, a brief cognitive and behavioral intervention, that focuses on the balance between individualization and standardization, for the management of episodic breathlessness was developed. It serves as preparation for an exploratory trial.

Disclosures and Acknowledgments

The authors have nothing to disclose. The study group would like to thank all Delphi panellists for their opinion and time in supporting this survey. The work is part of the project "Cognitive and Behavioral Intervention for the Management of Episodic Breathlessness in patients with advanced disease: a single-arm therapeutic exploratory trial (phase II)" (CoBeMEB; funded by the Federal Ministry of Education and Research [funding code: 01GY1716]. Ms. Schloesser, Ms. Bergmann, Dr. Eisenmann and Prof. Dr Simon report grants from Federal Ministry of Education and Research (01GY1716), during the conduct of the study. The funding source had no involvement in study design, in the collection, analysis, and interpretation of the data nor the writing of the report.

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Appendix I

Samples of items from the Delphi rounds

Round 1

Please indicate how strongly you agree that the following nonpharmacological strategies are relevant for the management of episodic breathlessness. In case you are not familiar with a certain strategy, please select *unknown strategy.*

	I Totally Disagree	I Rather Disagree	Neither, Nor	I Rather Agree	I Totally Agree	Unknown Strategy
Forward lean	○	○	○	○	○	○
Hands on hips	○	○	○	○	○	○
Upper limb bracing: e.g. hands behind the head, hands in belt loops	○	○	○	○	○	○
"blow-as-you-go": breathing out on effort, stretching or bending (vs. instinctive breath holding in such circumstances)	○	○	○	○	○	○
Pursed lips breathing	○	○	○	○	○	○
Long/relaxed breaths out	○	○	○	○	○	○
Diaphragmatic breathing (might help to place a hand on the tummy)	○	○	○	○	○	○

Round 2

- Which **nonpharmacological strategies** do you consider the most important for the **brief cognitive and behavioral intervention** we are developing? (Free-text field)
- To what extent do you agree that the BTF-model is useful to explain how the non-pharmacological strategies should help managing episodic breathlessness? (Likert scale)
- **Assessment of individual experiences of episodic breathlessness**

  Assessing: trigger for ep. breath, most burdensome aspects, individual objectives of the intervention, helpful strategies, already used, Exploring of misconceptions: course of ep. breath, fear of suffocation, need for oxygen, short duration, fear as intervening factor.

  Discussing of prevention strategies: education about physical exertion, energy saving, pacing, awareness and reduction of fear.

  Question: Which additional individual aspects of episodic breathlessness do you consider important to discuss? Do you consider any aspects unnecessary? (Free-text-field)

  Question: To what extent do you agree that the aspects we have listed above are relevant to discuss with the patient? (Likert-Scale)
- So far, the planned duration of the intervention is two hours. Based on your experience, what do you suggest as the maximum duration of the intervention?
  - o up to 30 minutes
  - o up to 60 minutes
  - o up to 90 minutes
  - o up to 120 minutes

Round 3

- To what extent do you agree to the Patient education & Strategies? (Likert-Scale)
- Additional comments? (Free-text-field)

5.2 Dissertation project 2

“Only I know now, of course, how to deal with it, or better to deal with it”: A mixed-methods phase II study of a cognitive and behavioral intervention for the management of episodic breathlessness

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Journal of Pain and Symptom Management, DOI: 10.1016/j.jpainsymman.2021.11.003, published 05/2022

Supplementary material associated with this article can be found in the online version at doi:10.1016/j. jpainsymman.2021.11.003.

5.2.1 Synopsis: Dissertation project 2

Abstract

Context

Episodic breathlessness is characterized by increased breathlessness intensity and it is burdensome for patients. A vicious cycle of breathlessness-anxiety/panic-breathlessness leads to emergencies that can rarely be alleviated by drugs. Non-pharmacological interventions seem to be beneficial: Can a brief cognitive and behavioral intervention help patients to manage episodic breathlessness better?

Objectives

To evaluate the feasibility, safety, acceptability, and potential effects of a brief cognitive and behavioral intervention for the management of episodic breathlessness.

Methods

Between February 2019 and February 2020, 49 patients with life-limiting diseases suffering from episodic breathlessness were enrolled in the single-arm phase II study. The baseline assessment was followed by the 1- to 2-hour intervention. In weeks two, four, and six after the intervention, the outcomes (primary outcome of potential effects: mastery of breathlessness) were assessed, and in week six, a qualitative interview, and the final assessment took place. A mixed-methods approach was used to evaluate mainly the feasibility, including interviewing carers.

Results

46/49 patients (24 female; 36 with COPD; mean age: 66.0 years) participated in the baseline assessment, 38 attended the intervention, 32 completed the final assessment, and 22 were interviewed. Study procedures and the intervention were feasible and mainly well accepted and patients did not experience burdens caused by it (28/32). In the interviews, patients described a positive change in their competencies in managing episodic breathlessness and feelings of anxiety during the episode. Mastery of breathlessness improved after the intervention.

Conclusion

The brief cognitive and behavioral intervention and the study procedures are feasible, safe, and well accepted. We can describe a change for better management of episodic breathlessness in patients after the intervention, still, this needs to be evaluated in a Phase III trial for inclusion in the management of episodic breathlessness.

Contribution of Karlotta Schlösser

- Development of the study procedure
- Organization of the study over the entire period
- Preparation of the study
    - ethics application, writing of the study protocol, registration in ClinicalTrials.gov
    - contact with cooperation partners
    - development of a recruitment strategy (incl. information material for recruiters, flyer for patients)
    - creation of study material (patient booklet, key cards, patients' folders, flow charts for the different appointments, organization of questionnaires, contact with IMSB for the implementation of the questionnaires in RedCap)
- Study conduction
    - screening of patients
    - baseline, follow-up, and final assessment
    - conduction of the brief cognitive and behavioral intervention, the refresher, and the qualitative interviews
- Results (development of an analysis plan, participation/conduction of the quantitative and qualitative analysis)
- Writing of the manuscript

Original Article

Only I Know Now, of Course, How to Deal With it, or Better to Deal With it: A Mixed Methods Phase II Study of a Cognitive and Behavioral Intervention for the Management of Episodic Breathlessness

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Abstract

Context. Episodic breathlessness is characterized by increased breathlessness intensity, and it is burdensome for patients. A vicious cycle of breathlessness-anxiety/panic-breathlessness leads to emergencies that can rarely be alleviated by drugs. Non-pharmacological interventions seem to be beneficial: Can a brief cognitive and behavioral intervention help patients to better manage episodic breathlessness?

Objectives. To evaluate the feasibility, safety, acceptability, and potential effects of a brief cognitive and behavioral intervention for the management of episodic breathlessness.

Methods. Between February 2019 and February 2020, 49 patients with life-limiting diseases suffering from episodic breathlessness were enrolled in the single-arm phase II study. The baseline assessment was followed by the one- to two-hour intervention. In weeks two, four, and six after the intervention, the outcomes (main outcome of potential effects: mastery of breathlessness) were assessed, and in week six, a qualitative interview, and the final assessment took place. A mixed-methods approach was used to evaluate mainly the feasibility, including interviewing informal carers.

Results. 46/49 patients (24 female; 36 with COPD; mean age: 66.0 years) participated in the baseline assessment, 38 attended the intervention, 32 completed the final assessment, and 22 were interviewed. Study procedures and the intervention were feasible and mainly well accepted and patients did not experience burdens caused by it (28/32). In the interviews, patients described a positive change in their competencies in managing episodic breathlessness and feelings of anxiety during the episode. Mastery of breathlessness improved after the intervention.

Conclusion. The brief cognitive and behavioral intervention and the study procedures are feasible, safe, and well accepted. We can describe a change for better management of episodic breathlessness in patients after the intervention, still, this needs to

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Accepted for publication: 8 November 2021.

0885-3924/$ - see front matter
https://doi.org/10.1016/j.jpainsymman.2021.11.003

be evaluated in a Phase III trial for inclusion in the management of episodic breathlessness. J Pain Symptom Manage 2022;000:1−11.

Key Words

Non-pharmacological, episodic breathlessness, cognitive-behavioral intervention, dyspnea, palliative care, breathlessness, pilot study, single-arm phase II study

Key Message

The brief cognitive and behavioral intervention shows a positive change in the management of episodic breathlessness in patients with life-limiting diseases by reducing panic and anxiety in breathlessness episodes and promoting a feeling of competence in managing the episodes. It is safe, feasible, and acceptable.

Introduction

Millions of patients around the world suffer from breathlessness.[1] It's a distressing symptom in advanced diseases like cancer, chronic obstructive pulmonary disease (COPD), and chronic heart failure (CHF[2]). The prevalence among these patients rises to 98% in COPD.[2−4] It is defined by the American Thoracic Society as ''a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity".[5] It increases towards the end of life and has a substantial impact on the patients' functional status and quality of life.[3,6] The syndrome "chronic breathlessness"[7] occurs despite optimal treatment of the underlying cause requiring symptomatic management.[8] Breathlessness is continuous or episodic. An international expert panel defined the latter as a "severe worsening of breathlessness intensity or unpleasantness beyond usual fluctuations in the patient's perception. Episodes are time-limited (seconds to hours) and occur intermittently, with or without underlying continuous breathlessness. (...)".[9] Episodes are often severe, short (75%: < 10 min), and occur daily, with variable frequency.[10] Even though opioids have supporting evidence for symptom relief of breathlessness,[11−13] the short duration of the episodes[10,14] challenges pharmacological management options, as the onset of action of the drugs often takes longer than the episode lasts. Thus, non-pharmacological strategies play a major role in the management of episodic breathlessness and appear to be beneficial.[15−19] Qualitative studies showed that patients combine non-pharmacological strategies for the management and relief of episodic breathlessness.[20] The breathlessness services combine non-pharmacological and pharmacological strategies for the relief of breathlessness in general.[21−23] However, they warrant more evaluation for the treatment of episodic breathlessness in particular to support patients suffering from this burdensome symptom. Cognitive and behavioral strategies to manage breathing difficulties and rising panic seem beneficial.[15,17,18,24] Therefore, we tested a brief cognitive and behavioral intervention for better management of episodic breathlessness in patients with life-limiting diseases to determine the feasibility, safety, acceptability, and potential changes associated with the intervention.

Methods

Study Design

This phase II study will be used to prepare a fully-powered RCT. Following a mixed-methods approach data from the participants were assessed.[25] Ethical approval was provided by the Ethics Commission of Cologne University's Faculty of Medicine (12/2018; No. 18− 209). This study was registered with ClinicalTrials.gov (NCT04630743). The MORECare Statement on the evaluation of complex interventions in end-of-life care was used.[26]

Participants

Recruitment took place at in-/outpatient clinics of the University Hospital of Cologne and the Bethanien Hospital Solingen. Written informed consent was obtained before participation from all participants.

Patients meeting the eligibility criteria were invited to participate:

- suffering from episodic breathlessness due to any life-limiting and progressive disease (e.g., cancer stage III/IV, COPD GOLD classification stage III/IV, chronic heart failure NYHA classification stage III/IV)
- Criteria applied to determine whether patients suffered from episodic breathlessness: recurrent breathlessness episodes (more than once per week), characterized by a severe increase of breathlessness intensity beyond usual fluctuations, that means an intensity change of ≥ 3 on a Numeric Rating Scale (NRS). Episodes occur despite a stable underlying disease and there are no reversible causes (e.g., pneumonia, acute exacerbation) that could explain the breathlessness episodes
- estimated life expectancy: ≥ eight weeks
- ≥ 18 years

- comprehension of the German language
- cognitive capacity to give informed consent[27]
- ECOG Status 0− 3[28]

Patients were asked if there was an informal carer they suggested for study participation (hereinafter referred to as carers), if yes, they were invited to participate in the study. Please see the sample size calculation in Supplement 1.

Study Procedure

Potential participants were approached by a researcher personally/by telephone to check their eligibility and interest in study participation. Reasons for non-eligibility and declining to participate were recorded. The researcher conducted the baseline assessment with the eligible patients after signing of informed consent forms. The intervention took place at the patients' current location of living. One week after the intervention, patients were called to clarify potential questions from the patients' side concerning the content of the intervention. Two, four, and six weeks after the intervention, a researcher conducted the outcome assessments in person at the patient's current living location whenever possible otherwise by phone. At week six, the final assessment was made and in-depth face-to-face interviews were scheduled with those patients interested in sharing their experiences. Carers were surveyed and, if interested, interviewed simultaneously concerning the feasibility, safety, and acceptability of the intervention and accompanying research. For an overview of the study procedure, see (Fig. 1).

Brief Cognitive and Behavioral Intervention

The 1− 2 hour intervention was developed using a Delphi survey with experts in the field of breathlessness.[29] See Fig. 2 for a description of the intervention and Supplement 2 for the key cards. A nurse, a psychologist, or a physician delivered the intervention and attended training before delivery to ensure the intervention's standardization and comparability.

Measurements

Participant Characteristics. Patients' sociodemographic and medical data and carers' sociodemographics were recorded. Patients rated the average breathlessness intensity over the last 24 hours, the average intensity of their breathlessness episodes, and impairment due to their episodes in their daily lives (NRS, 0 to 10[31]). They reported the episodes' frequency, duration, and predictability through closed-ended questions (response options, see Table 1).

Feasibility. Feasibility was defined by the enrolment rate within the 12 months (±1 month) recruitment period, study completion rate, and drop-out rates. Attrition was

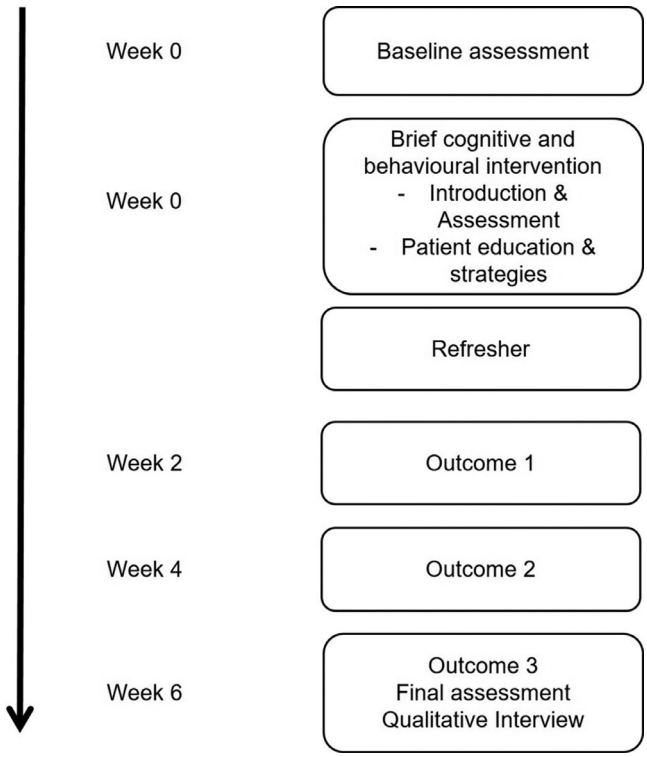

Fig. 1. Overview of the study procedure.

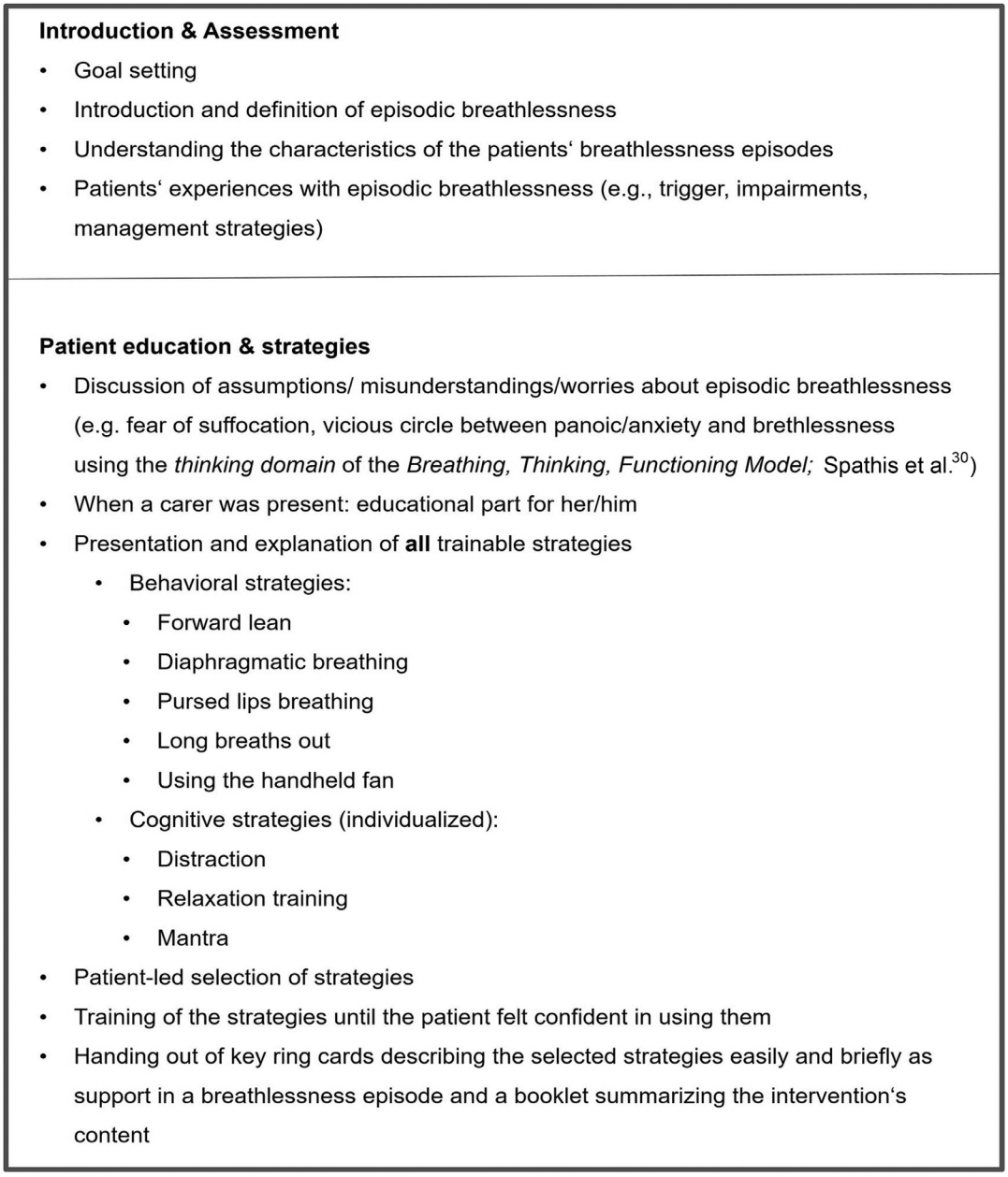

Fig. 2. Structure of the brief cognitive and behavioral intervention for the management of episodic breathlessness.[30]

categorized as *attrition due to death* (ADD), *attrition due to illness* (ADI), or *attrition at random* (AaR[26]). Reasons for the decline of participation and sociodemographics of eligible patients who declined to participate were assessed. Conclusions concerning the feasibility of the intervention and the study procedure were drawn from the interviews.

Safety and Acceptability. To assess the safety of the study, participants were asked about burdens due to the intervention and study procedure. The acceptability of the questionnaires, study procedure, and intervention was determined via closed-ended questions and asked during the interviews.

Potential Effects. The main outcome of the potential effects was patient-reported breathlessness mastery measured with the *mastery* domain of the Chronic Respiratory Questionnaire (CRQ[32]). Changes in intensity of the breathlessness episodes and the impairment caused were assessed with NRSs. Higher values indicated stronger intensity/impairment.[31] To calculate the patients' quality of life, their responses in all four CRQ domains (*mastery, fatigue, dyspnea, and emotional functioning*) were summed up (the higher the value, the weaker the impairment; score 1− 7). The Integrated Palliative Care Outcome Scale (IPOS[33]) assessed changes in palliative care needs and specific symptoms. The higher the value, the stronger the

Table 1
Patients' Characteristics ($n = 46$)

Sociodemographics	*n* (%) or mean (*SD*)
Age (mean, ys)	66.0 (7.3)
Gender	
female	24 (52.2%)
male	22 (47.8%)
Diagnosis	
COPD (stage III / stage IV: $n = 13/23$)	36 (78.3%)
Chronic Heart Failure (all stage III)	2 (4.3%)
Cancer (all stage IV)	7 (15.2%)
Pulmonary Hypertension	1 (2.2%)
Time since diagnosis (mean, ys)	10.0 (7.8)
Current family status	
single	2 (4.3%)
married/in a relationship	31 (67.4%)
widowed, separated/divorced	13 (28.3%)
Episodic breathlessness	
Average intensity of breathlessness episode [b]	7.0 (2.1)
Duration	
seconds	1 (2.2%)
1 − 5 minutes	26 (57.8%)
6 − 10 minutes	7 (15.6%)
11 − 20 minutes	5 (11.1%)
21 − 60 minutes	3 (6.7%)
other	3 (6.7%)
Frequency	
< 1 per day	13 (28.9%)
1-3 per day	19 (42.2%)
> 3 per day	9 (20.0%)
other	4 (8.9%)
Trigger [a]	
exertion	41 (89.1%)
emotions	23 (50.0%)
external environment	17 (37.0%)
comorbidities	9 (19.6%)
Unpredictable breathlessness episodes	
no	24 (60.0%)
yes	16 (40.0%)
Average intensity of breathlessness last 24 hours [b]	5.4 (2.4)
Impairment on daily life caused by episodic breathlessness [c]	8.3 (1.5)

[a]Multiple answers possible
[b]NRS: (0 = no breathlessness; 10 = worst imaginable breathlessness)
[c]NRS: (0 = no impairment; 10 = worst imaginable impairment)

need (score 0− 68). The Hospital Anxiety and Depression Scale measured patients' anxiety and depression (higher values indicated stronger emotions, score 0− 21; HADS[34]).

Qualitative In-Depth Interviews. Participants were asked to report their experience regarding the study procedure, questionnaires, and intervention in semi-structured, face-to-face, in-depth interviews. Interviews were conducted considering the patients' ratings in the final assessment.

Data Collection and Management

Data collection was conducted between 02/2019− 03/2020 and data were managed using REDCap electronic data capture tools hosted at the University of Cologne.[35,36] The baseline, the follow-up, and the final assessments were carried out in person whenever possible, and alternatively by telephone (a patient-held folder comprising the printed questionnaires aimed to facilitate the understanding by allowing the patients to read the questions simultaneously). In the qualitative interviews, the patients' ratings were used to deepen the understanding of their opinions regarding the intervention and study procedure, therefor quantitative and qualitative data collection occurred together and data was integrated for analysis.[25]

Data Analysis

The final analysis included all completers: all patients/carers who gave informed consent and completed the final assessment. Descriptive analyses (mean, standard deviation, median, IQR, percentages, and frequencies) were performed. Significant deviations from normal distribution were detected using Kolmogorov-Smirnov Normal Tests. For this reason, and to keep analyses homogenous, separate Wilcoxon Signed Rank Tests were used to test for statistically significant changes between baseline and each post-intervention outcome. The α-level was set at 0.05. Exploratory subgroup analyses concerning *mastery* were conducted. Quantitative data were analyzed using SPSS Statistics (IBM Corp., Armonk, NY, USA). For analyzing qualitative data, content analysis was applied.[37] The interviews were audio-taped, transcribed, and pseudonymized for analysis. Central aspects of the patients' experiences were summarized into main categories deductively drawn from the interview guide and inductively formed from the data material. Codings were discussed, revised, and finalized by the research team. Based on this, the entire data set was coded using MAXQDA (2020). Emerging themes were discussed with all authors.

Results

Patients were well balanced in terms of gender and the majority suffered from COPD. Summarized patients' characteristics at baseline assessment can be found in (Table 1).

Feasibility

Over the 13-month recruitment period, 157 patients were suggested for participation, 146 were screened, and 93/146 were eligible. Main reason for non-eligibility was the absence of episodic breathlessness (36/53). Forty-four eligible patients declined to participate, 20 of those due to a lack of interest and due to concerns, it would be too exhausting (see Supplement 1, Table 1). Finally, 49 patients gave informed consent, 46 filled out the baseline assessment, 38 took part in the intervention, 32 filled out the final assessment and 22 took part in the interviews. This results in an enrolment rate of 49/146 (34%) within the 13-month recruitment period and a study completion rate of 65% (32/49). The main reason for dropout was ADI (9/17; 53%). For patient participation and attrition during the phase II study,

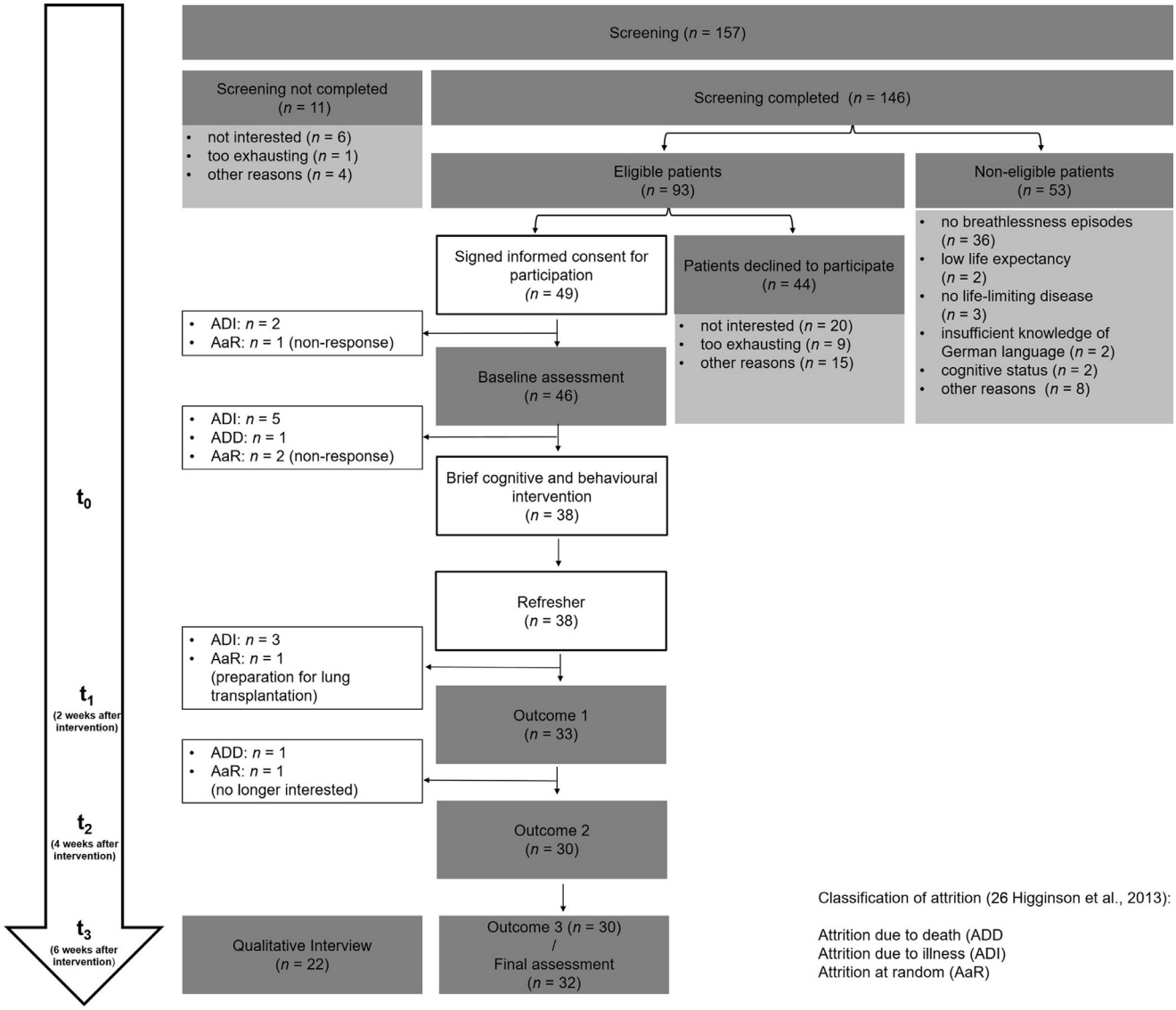

Fig. 3. Flow chart depicting the study procedure.

see Fig. 3. The duration of the intervention was 1–2 hours, as planned.

In the interviews, 12/22 patients described their motivations for participation as to pass on their own experience, to help others, to find a way through illness through many conversations, to take advantage of all offers that could help, or to satisfy their curiosity.

I do everything I can do to defuse the situation or help to stabilize it, but that's all I can do. (COPD-146)

Six patients had suggestions for improvement including inviting patients in an earlier stage of the disease and paying more attention to other diseases/psychological aspects.

Safety

Most patients did not report disadvantages due to the intervention (28/32) or study procedure (29/32; Supplement 1, Table 2). In the interviews, two patients reported the time commitment and burden as causes for the disadvantages they experienced.

Acceptability

The majority of the patients were satisfied with the intervention (25/32) and the study procedure (27/32; Supplement 1, Table 2). During breathlessness episodes, most patients *always* used pursed lips breathing (23/32), forward lean (19/32), and long breaths out (19/32). 27/32 patients *never* used the mantra (Supplement 1, Table 3). Patients described that they tried different strategies and continued to use the ones that suited them best. The strategies were often individualized (e.g., patients developed their own ways of distraction) and combined (e.g., distraction and forward lean). Patients experienced the contact with the healthcare professionals as beneficial. Four patients had

Table 2

Wilcoxon Signed Rank Tests of Potential Effects

	Change from Baseline to Week 2						Change from Baseline to Week 4						Change from Baseline to Week 6					
	n	Median	IQR		95% CI		*z*	*n*	Median	IQR		95% CI		*z*	*n*	Median	IQR		95% CI		*z*
CRQ																					
Total Score	33	0.09	-0.22	0.45	-0.14	0.36	0.72	27	0.30	-0.08	1.05	0.58	0.79	2.31	27	0.20	-0.16	0.82	-0.04	0.63	1.69
Mastery	33	0.00	-0.75	0.75	-0.38	0.63	0.46	26	0.25	-0.56	1.50	-0.13	1.25	1.48	27	0.00	-0.50	1.75	-0.25	1.00	1.04
Fatigue	33	0.25	-0.50	0.50	-0.25	0.38	0.50	26	0.25	-0.52	1.00	-0.25	0.63	0.91	27	0.25	-0.25	0.75	-0.04	0.83	1.70
Dyspnea	33	-0.20	-0.80	0.30	-0.50	0.20	-0.65	27	0.13	-0.80	1.20	-0.50	0.50	0.00	27	0.00	-0.80	0.80	-0.60	0.50	0.04
Emotional Functioning	33	0.14	-0.43	0.86	-0.14	0.57	1.28	26	0.50	-0.32	1.18	0.07	1.17	2.18	27	0.29	-0.43	1.29	0.00	1.07	1.96
IPOS																					
Total Score	33	0.00	-5.67	3.31	-3.31	0.94	-1.11	27	-2.00	-6.70	2.83	-5.67	0.00	-1.92	27	-1.89	-7.56	0.00	-7.06	-0.75	-2.56
Physical Symptoms	33	1.00	-4.00	4.28	-1.50	2.00	0.42	27	-3.00	-5.00	4.00	-3.50	0.50	-1.21	27	-2.00	-5.00	1.00	-4.00	0.50	-1.64
Emotional Symptoms	33	0.00	-2.67	2.00	-1.50	1.00	-0.19	26	-0.50	-2.08	1.25	-1.83	1.00	-0.82	27	0.00	-5.00	2.00	-2.50	1.00	-1.14
Communication/ Practical Issues	33	-1.00	-2.50	0.00	-2.00	0.00	-2.58	26	-1.00	-3.00	0.25	-2.50	0.00	-1.89	27	-1.00	-2.00	0.00	-2.00	-0.50	-2.43
HADS																					
Anxiety	33	1.00	-1.00	2.00	-1.00	1.50	0.37	25	-2.00	-4.00	-0.50	-3.00	-0.50	-2.58	25	0.00	-5.00	1.50	-3.17	0.50	-1.39
Depression	33	0.00	-1.00	2.50	-0.83	1.50	0.64	25	0.00	-1.00	1.50	-1.00	1.50	0.20	25	0.00	-1.00	1.00	-1.00	0.50	-0.44
Episodic breathlessness																					
Intensity	33	0.00	-3.00	1.00	-1.50	0.00	-1.49	27	-1.00	-2.00	1.00	-2.00	0.50	-1.28	27	0.00	-2.00	1.00	-1.00	0.50	-0.87
Impairment	33	0.00	-1.00	1.00	-1.00	0.50	-0.78	27	-1.00	-2.00	0.00	-1.50	-0.50	-2.57	27	0.00	-1.00	1.00	-1.00	0.50	-0.95

Effect size *r* can be calutated as z/sqrt(2*n).

higher expectations of the intervention (in terms of novelty), however, they still described a positive change due to it. Eleven patients expressed negative opinions about the surveys, and said the constantly repeated questions were particularly annoying, and one person (of 22) described the assessments as exhausting.

Potential Effects

The main outcome of the potential effects *mastery* increased, with a maximum at week four (*change between median in week 4 and baseline:* 0.25) and a decrease after six weeks (Supplement 1, Fig. 1). The latter was still a higher score compared to the baseline (not statistically significant; see Table 2 for all Wilcoxon Signed Rank Tests). *Dyspnea* (CRQ) increased slightly at week four compared to the baseline. Patients rated the intensity of the breathlessness episodes as lower in weeks two, four, and six after intervention than at baseline. Patients' impairment rating was statistically significantly lower at week four than at baseline. The IPOS score assessing the patients' symptom burden and palliative care needs decreased at week two, at week four, and statistically significant at week six after the intervention compared to the baseline. The subscale *Communication/Practical Issues* showed lower values in week two, week four, and week six after the intervention than at baseline assessment. The CRQ total score reflecting the patients' quality of life increased at all assessments compared to the baseline, but only the changes from baseline to week four were statistically significant. Compared to the baseline, patients showed significantly increased values in emotional functioning in week four and week six. All CRQ scales increased at week four, with a decrease at week six. The reported *anxiety* (HADS) was statistically significantly lower in week four after the intervention than at baseline assessment and increased slightly from week four to week six. Depression scores decreased from baseline to week two, week four, and week six. Please see Supplement 1 for the descriptive statistics of the questionnaires (median/ IQR, Table 4; means/*SD*s, Table 5) and the changes in the median of the questionnaires between baseline and weeks two, four, and six (supplement 1, Figs. 2-5).

Exploratory sensitivity analysis of age (high vs. low), disease (cancer vs. COPD) and distress due to a breathlessness episode did not show statistically significant differences in *mastery*.

The main change due to the intervention described by the patients in the in-depth interviews was an improved competency in managing episodic breathlessness. They noted that fears/ anxieties concerning episodic breathlessness had been reduced and knowledge had been consolidated through the intervention. This facilitated the management of breathlessness episodes, e.g., it reduced the duration and frequency of the episodes. In addition, patients said that the

Table 3
Patients' Experiences with the Intervention

Category	Sample Quotation
Improved feeling of competency in managing episodic breathlessness	*Only I know now, of course, how to deal with it, or BETTER to deal with it, let me put it this way (. . .).* (COPD-218) *. . . I am no longer so afraid of it (breathlessness episode). This from the head, that also stirs up fear and that makes it worse, that has already changed; I can handle it better, yes.* (COPD-418)
Reduction of panic	*. . . I no longer have this, this unspeakable fear if I will survive that I had in the beginning.* (COPD-481)
Decrease of the episodes' frequency due to the use of strategies	*Yes, they (breathlessness episodes) come less. Well, because, as I said, I try to distract myself as well and as often as possible. And then they come less, actually VERY much less, than usual, than before.* (COPD-135)
Communication with relatives	*That I can say if I can't do something (e.g. activity), because it causes air problems for me, that I can say NO, I won't do it, I can't do it. In the past, I could NOT do that or I found it hard to do that ...* (COPD-120)

intervention helped them to reflect on and confirm their ways of managing episodic breathlessness and that the learned strategies provided security of action and thus reduced panic. Four interviewees described changes regarding their relatives. One person reported that the carer received valuable tips on how to take care of the patient and that it was also helpful to discuss the patient's impairments caused by episodic breathlessness together with the carer. Improved communication with relatives and the feeling that it was ok to say *no* (if they did not feel confident in doing something) was described.

Evaluation by the Carers Regarding Feasibility, Safety, and Acceptability of the Intervention

The 49 included patients were asked if they wished to nominate a carer to be invited to participate in the study. 16 carers were named by the patients and all carers (16/16) agreed to take part in the study. All carers (9/14 female; mean age 63.5; *SD* = 8.7) were married/in a relationship with the patients, and 14/16 lived with the patient. No carer reported any burdens due to the intervention/study procedure. The great majority of the carers were very satisfied with the intervention and the study procedure (≥ 8/10). For carers' data, see Supplement 3.

Discussion

The present phase II study demonstrated that the brief, one-time, cognitive-behavioral intervention to improve patients' management of episodic breathlessness is feasible, safe, and well-accepted with a positive change. Results are promising for the development and evaluation of an intervention to inform and educate patients about how to improve their management of episodic breathlessness (often triggered by exertion or emotion). The study procedure was feasible and accepted. The next step is to assess the intervention's effectiveness within an RCT.

Intervention

The intervention was safe, feasible, and well accepted. The feasibility derived from the short duration, which promoted the intervention's flexible use, was not too demanding for patients, and sufficient to deliver the intervention tailored to the patients' needs. Still, two patients considered it too long. Providing intervention deliverers with an easy-to-follow, individualizable intervention structure allowed health care employees with different professional backgrounds to deliver the intervention. The flexible delivery for in- /out hospital patients increased the feasibility. Adapting the intervention to the patient's individual needs was well accepted. The cognitive and behavioral strategies were discussed in a patient-oriented manner with patients trying different strategies, adapting them to their needs, and combining them. This aligned with recommendations on how interventions for breathlessness patients should be designed/conducted.[21,29,38,39] Using individual strategies for managing episodic breathlessness corresponded to findings showing that patients help themselves with different, highly individual strategies.[20] Overall, the acceptability of the intervention was very good but participants suggested addressing patients at an earlier stage of the disease.

In addition to the primary objective of the phase II study (feasibility, safety, and acceptability), we reported interesting changes in some outcome parameters. The outcome *mastery* showed a positive but statistically non-significant change. The changes in the *mastery* reached the threshold of the minimum clinically important difference of 0.5 at all outcome assessments,[40] underpinning the improved feeling of competency in managing breathlessness. The reported change in the *mastery* corresponds to trials evaluating breathlessness services.[21–23] However, as we chose mastery linked to breathlessness in general (for comparability with other studies) instead of a specific

episodic breathlessness-measure, we cannot say if the reported change was breathless-episodic specific. The *Dyspnea* subscale (CRQ) showed no changes but the episodic breathlessness-related parameters indicated a reduced intensity of the breathlessness episodes and decreased impairment.This touches a discussion about the relation between episodic breathlessness (or acute/severe/attack/dyspnea-crisis/acute-on-chronic) and breathlessness in general.[5,7,41,9,42,43] In our understanding, episodic breathlessness is one form of breathlessness, and can not be seen separately from breathlessness in general. It is useful to assess whether a patient experiences episodic breathlessness allowing the teaching of strategies to cope with these episodes. Following this, we expected changes on a general outcome (e.g,. *mastery*) by an intervention focused on episodic breathlessness. Following the intervention, patients described a reduction of panic during an episode. Patients' anxiety ratings decreased from baseline to week four with a large effect size (r = -.51; CI [-3.0, − 0.5]). Given the importance of understanding the interaction between episodic breathlessness and panic, this required further assessments (independent from the intervention), which will be reported separately. The CRQ subscales increased at week four and decreased in week six, possibly indicating that changes associated with the intervention persist until week four but then diminish. In the future, it should be considered that patients might benefit from a refresher between weeks four and six to prevent the intervention's effect from diminishing.

Study Procedure

The study procedure was feasible: the targeted enrolment rate of 49 patients (34%) within 13 months and a study completion rate of 65% were reached. However, the lengthy recruitment period should be considered for the RCT. The study completion rate of ≥ 50% which was considered as a lower bound to subsequently implement an RCT, was met. The aimed diversity regarding patients' diagnoses to allow conclusions for different patient groups was not achieved. Even though seven cancer patients completed the study, most patients suffered from COPD. Adapting recruitment strategies to the different diseases could increase diagnostic diversity. The attrition of 35% was mainly caused by the progress of the underlying illness (53%), and 11 patients discontinued even before the intervention. Another reason for discontinuing could have been the questionnaires, as some patients described their dissatisfaction with the repeated questions. However, this problem would be solved in the RCT as the repeated measurement was due to the pilot design aiming to find out the best time point for assessment (week four). Four patients criticized that they expected more (e.g., novelties) from the intervention, this should be considered when planning the intervention for the RCT. The uptake rate was relatively low with 146 patients screened of whom 49 signed informed consent. This might be explained by 20 patients who were eligible but declined to participate due to a lack of interest and a further 9 who were afraid that participation could be too exhausting.

Strength and Limitations

The patient population with a majority of patients with COPD limits the generalizability of the findings for other patient groups than COPD. Recruitment of cancer patients was difficult, as they either did not suffer from episodic breathlessness or their health condition no longer allowed study participation.

Due to the lack of a control group, conclusions about whether the intervention led to changes in the outcomes are limited and no conclusions about the feasibility and acceptability of randomization can be drawn. However, using a single-group design allowed us to realize a pilot study with limited resources.

The mixed-methods approach, with qualitative data recorded, allowed interpretation of the results in-depth and helped achieve a better understanding of the pros/cons of the phase II study. This approach is common when investigating interventions for breathlessness and breathlessness services.[21,22] Additionally, service providers' and referrers' views are missing in the present study. The phase II study benefited from using the MRC framework for complex interventions, leading to a robust and evidence-based development and evaluation.

Conclusion

The brief cognitive and behavioral intervention is safe, feasible, and well accepted. The phase II study shows a potentially positive change for better management of episodic breathlessness in patients with life-limiting diseases, enabling them to reduce symptom burden and increase their quality of life. Patients did not experience severe disadvantages of the intervention or the study procedure. However, suggestions for modification included inviting patients at an earlier stage of the disease. Given the short duration, the possible delivery from different professional groups, and the one-time appointment, this intervention seems to be feasible for the clinical practice and should be evaluated in a Phase III trial before being considered as part of a broad approach for the management of breathlessness in general, e.g., by a breathlessness service.

Disclosures and Acknowledgments

The authors have nothing to disclose. The work was supported by the Federal Ministry of Education and Research (funding code: 01GY1716). The funding source had no impact on the study design, on the data

collection, analysis, and interpretation of the data nor the writing of the manuscript. The study group would like to thank all participants for their time and interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jpainsymman.2021.11.003.

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6. Discussion

6.1 Key findings of the dissertation

The aim of this dissertation was the development and evaluation of a brief cognitive and behavioral intervention for the management of episodic breathlessness. This intervention is intended to support patients with life-limiting diseases with their symptom management. The aims have been successfully and entirely achieved and implemented within the dissertation as reported in DP1 (145) and DP2 (146).

Fifteen cognitive and behavioral strategies specifically for managing breathlessness episodes have been consented to by the experts (e.g., breathing techniques, body positions, or distraction). Critical aspects for the management of episodic breathlessness should be discussed within the intervention as part of patient education (e.g., identifying triggers, how to pace daily activities). The developed intervention is flexibly adaptable to each patient and allows for tailoring the intervention to the individual's needs. It also incorporates a high amount of communication between the person delivering the intervention and the patient to assure a patient-centered approach. The use of the BTF model (77) is implemented in the intervention to explain the vicious cycles that maintain and worsen the patient's breathlessness episodes, together with strategies on how to interrupt the escalation caused by the vicious cycles. The recommendation of involving carers in the brief intervention is followed by asking patients to name a close person caring for them to participate with them in the intervention; the carers are addressed during patient education. As proposed by the experts, the duration of the intervention is short, lasting 1–2 hours (all findings of DP1, (145). The newly developed brief intervention is the first to focus specifically on the management of **episodic breathlessness** (as a particular form of chronic breathlessness). The results of the subsequent single-arm phase II study evaluating the intervention are promising. After the intervention, patients reported a positive change regarding symptom management: They described a reduction in panic and anxiety and felt more competent in managing breathlessness episodes. The single-appointment intervention delivered by healthcare professionals with different professional backgrounds and at different settings (at home/in care facility) was demonstrated to be feasible, well accepted by the patients, and safe, just as the research procedure. Given the positive results of the single-arm phase II study, an RCT is recommended to evaluate the effectiveness of this intervention (findings of DP2, (146).

6.2 Relation to the current state of research

6.2.1 Characteristics of the intervention

An individualized but standardized approach. A vital characteristic of the newly developed intervention was the individualized but standardized approach. Experts suggested this approach to guarantee an individually tailored treatment within a given structure. Accordingly, this individualizable, patient-centered approach formed the basis of the intervention evaluated in the subsequent single-arm phase II study and was reflected in its various components. To meet this requirement, the intervention featured a high amount of conversation between the patient and the deliverer, characterized by empathic listening by the latter and a comprehensive recording of the individual problems of the patient. The purpose was to gather the most precise possible impression of the patient; the characteristics, management strategies, and trigger for their breathlessness episodes; their associated impairments; and their hopes for improvement. In this way, the intervention components aimed to meet the needs of each patient (145). Tailoring the intervention to each patient's needs instead of a one-size-fits-all model corresponds to recommendations on how interventions for the management of chronic breathlessness should be designed (147) and had been conducted previously (148). This also aligns with how interventions in breathlessness services are delivered (39–41) and meets the demand for patient-centered communication as a foundation for discussing breathlessness (147). Patients valued the communication and contact with the healthcare professionals in the present intervention, as reported in the in-depth interviews (146).

Cognitive and behavioral strategies. Fulfilling the experts' request for an intervention tailored to individual needs, the cognitive and behavioral strategies were discussed in a patient-oriented manner, and different strategies were tried, adapted, and combined (145). Selecting the cognitive and behavioral strategies according to the patient's needs corresponds to the finding that patients use unique strategies to manage their breathlessness episodes (23, 29). Given the complexity and the subjective experience of chronic breathlessness in general (47, 149) and breathlessness episodes in particular (22, 23, 29), an individual approach and a combination of different cognitive and behavioral strategies are necessary (39). The expert-consented cognitive and behavioral strategies are already used for managing chronic breathlessness (30, 34, 35, 150) and as components of breathlessness services (39–41). Clinical studies and reviews have demonstrated their positive effect (30–32, 34–36, 133, 150).

Use of the BTF model. In addition to the individualized approach, experts recommended the use of the BTF model (77) to explain episodic breathlessness within the patient education component of the intervention (145). The BTF model was initially developed to explain chronic breathlessness as a multimodal experience to patients. It works as an educational tool in clinical practice and demonstrates good methodological evidence. The BTF model postulates

three vicious cycles as cognitive and behavioral reactions to breathlessness, which maintain or worsen the symptom (77). Besides the *breathing domain* and the *functioning domain*, the *thinking domain* is essential for discussing the close interaction between episodic breathlessness and anxiety/panic (see Section 2.3.4 Impact of episodic breathlessness on patients, Fig. 1). According to the experts, the BTF model is considered helpful for patient education and to identify the domain (e.g., breathing, thinking, functioning) of the patient's central impairments (145). Therefore, we discussed the BTF model, particularly the *thinking domain*, with every patient in an attempt to understand the individual vicious cycles. It was helpful to gain a better understanding of the individual interactions impairing the patient's quality of life in different aspects and to select appropriate cognitive and behavioral strategies matching the patient's needs (146).

Involvement of carers. The experts recommended and consented to, as a critical intervention component, involving carers (145). Supporting carers of breathless patients corresponds to the literature describing their crucial role in healthcare management for breathless patients (151). Support for carers of breathless patients in regular care is lacking (152). However, supporting patients and carers can improve breathlessness management, increase the quality of life of patients and carers, and lower healthcare costs (39). The Delphi experts' call to involve carers in the intervention (145) coincides with affected carers who describe that they would benefit from, for example, more information about breathlessness and education on anxiety management (153). Thus, in accordance with the experts' recommendation, carers were invited to participate in the intervention and to discuss relevant topics with the patient during patient education *(*e.g., their role in a breathlessness episode) (145). In the qualitative interviews, patients described that the intervention led to positive changes in the communication with their carer (146).

6.2.2 Potential effects of the intervention

A positive change in the mastery of breathlessness was reported (non-significant) (146). The *mastery* subscale reached the threshold of the minimum clinically important difference (0.5; 154) in all outcome assessments (146). It underpinned the feeling of improved competency in managing episodic breathlessness that patients described in the interviews (146). This finding corresponds to trials evaluating breathlessness services (39–41), revealing a positive impact of the use of a breathlessness service on the patients' confidence in managing breathlessness. Still, this effect was only found for chronic breathlessness, and an evaluation focusing on episodic breathlessness was lacking. The present evaluation reported changes on the NRS assessing episodic breathlessness-specific impairment and intensity, but the *Dyspnea* subscale developed for the assessment of chronic breathlessness failed to show changes (146). Thus, a RCT should consider developing an appropriate questionnaire to assess all

aspects of episodic breathlessness to test the intervention's effectiveness. Further CRQ subscales to assess potential changes resulting from the brief cognitive and behavioral intervention increased at week four and decreased in week six (146). This suggests that intervention-associated changes may persist until week four and then diminish. This is interesting, as two similar studies with interventions focusing on breathlessness management among COPD (148) resp. lung cancer patients (36) reported improvement in breathlessness severity (36, 148), quality of life, anxiety, and depression (36) six weeks after the intervention. But both studies had a single-arm design lacking a control group, thus conclusions about the intervention's effect on the patient-rated outcomes are limited. Furthermore, both studies had just one post-intervention outcome assessment after six weeks, so maybe, the intervention's effect also diminished, but the change not assessed.

Furthermore, patients described reduced panic in a breathlessness episode following the intervention. The patients' anxiety ratings consistently decreased from baseline to week four with a large effect size (146). This corresponds to findings of an RCT evaluating the BIS, which showed that participation in the BIS reduced fear and worries (39). As the interaction between episodic breathlessness and panic is critical, the results of further assessments focusing on the interaction between panic and episodic breathlessness (independent from the intervention) will be reported in another paper that is separate from this dissertation.

6.2.3 Feasibility, safety, and acceptability of the intervention

The brief cognitive and behavioral intervention is feasible, safe, and well accepted. The short duration contributes to the intervention's feasibility and follows the experts' recommendation from the preceding Delphi survey (145). Experts suggested the short duration (max. 90 minutes) to prevent it from being too strenuous for the seriously ill target group (145), still, two patients felt the time commitment as a disadvantage (146). While the short course also corresponds to the duration of the interventions in breathlessness services (39–41) and cognitive and behavioral therapy sessions addressing the management of chronic breathlessness (38), the intervention should be kept as short as possible to limit the temporal strain for the patient.

In contrast to breathlessness services, the intervention has been designed as a one-time appointment. On the one hand, this increases the intervention's feasibility due to its brevity (146). On the other hand, it creates the risk of not having enough meetings to produce changes in cognitive and behavioral patterns, as usually these need some time (155). Nevertheless, Johnson et al. (119) demonstrated that one session of breathing training (compared to three) appears appropriate to minimize a patient's burden. The 65% completion rate of the present single-arm phase II study exceeded the required 50% as the lower bound for implementing the following RCT (146). The enrollment rate of 49 patients (34%) within the planned recruitment

period of 13 months was achieved, but the uptake rate was relatively low, with 146 patients screened and just 49 signing informed consent (146). Of the eligible patients, 44 declined to participate. The main reasons were a lack of interest and the fear that participating could be too exhausting. Reasons for discontinuing study participation (attrition of 35% in the phase II study) mainly involved progression of the underlying illness (53%), and 11 patients discontinued even before the intervention (146). Another reason for discontinuing the study could have been the questionnaires, as some patients described their dissatisfaction with the repeated questions (146). However, this problem would not be present in the future trial RCT, as the repeated measurement was due to the pilot design aiming to identify the best time point for the central assessment (week four). The study completion rate, the enrolment rate and the uptake rate was lower than in similar feasibility studies (36, 38, 148), whereby Greer et al. (36) was the only research team reporting all feasibility parameters. A reason for the lower rates might be the inclusion criteria of „more than one breathlessness episode per week“ due to any life-limiting and progressive disease of the present single-arm phase II study (146). Given the fact that breathlessness increases towards the end of life (71) and that episodic breathlessness is characterized by increased breathlessness intensity (21), the present study could have adressed patients in more advanced stages of disease progression, resulting in lower complition, enrolment and uptake rates. The single-arm phase II study aimed at diverse patient diagnoses to enable conclusions for different patient groups. Nevertheless, most participants had been diagnosed with COPD, and only seven cancer patients completed the study. Therefore, based on the findings, conclusions can mainly be drawn for COPD patients (146). Adapting recruitment strategies to the various diseases could increase diagnostic diversity.

While most participants rated the intervention and the accompanying research as acceptable, some patients suggested contacting patients at an earlier stage of disease progression (146). This seems reasonable, as patients in previous qualitative studies have described suffering from intense fear in a breathlessness episode and, once having suffered from a breathlessness episode, being afraid of experiencing it again (23, 29). This fear of suffering from a breathlessness episode can trigger a cascade of behaviors and emotions that promote subsequent breathlessness episodes (e.g., reduction of physical activities, anxiety, paying attention to breathing) (Simon, Weingärtner, et al., 2016). Thus, educating patients with life-limiting diseases about episodic breathlessness and possible management options at an early stage could positively impact the vicious cycle, preventing the patients from becoming trapped in such cycles and possibly establishing dysfunctional behaviors (e.g., reduction of physical activity to avoid becoming breathless; 23, 29). Inviting patients at an earlier stage of their disease would also address participants’ criticism that they would have expected more (e.g., novelties) from the intervention.

6.3 Implications for clinical practice

The newly developed brief cognitive and behavioral intervention provides clinicians with information on how to support patients in managing breathlessness episodes. Support should be patient centered and tailored to individual needs, and healthcare professionals should listen empathically to understand the patient's concerns. Whenever possible, relatives should be included in conversations or support offers. Using the BTF model to discuss the patient's breathlessness episodes can be helpful. While the experts recommended these characteristics for a brief cognitive and behavioral intervention, they can also be helpful for a "daily" clinical conversation with patients suffering from episodic breathlessness. Of 31 non-pharmacological strategies for chronic breathlessness, 15 had been consented to particularly for managing episodic breathlessness by the international experts and were positively evaluated as part of the intervention.

6.4 Implications for research

6.4.1 Implications for a following RCT

There was a positive change in the patients' mastery of breathlessness after the intervention. Patients described improved competences in managing breathlessness episodes and decreased anxiety in the episodes following the intervention. The single arm-phase II study successfully demonstrated the intervention's safety and feasibility and patients' satisfaction with the intervention and the research methods (146). The next step, following the MRC framework for the evaluation of complex interventions (156), would be to conduct an RCT to gain information about the intervention's effectiveness.

The RCT to evaluate the intervention's effectiveness would benefit from the findings of the present dissertation: The intervention was developed using a solid and widely acknowledged approach (145, 157–159), and the evaluation already showed the intervention's feasibility, safety, acceptability, and positive changes after the intervention regarding the patients' management with episodic breathlessness (146). Therefor, the planned RCT should consider the following findings of the present dissertation (145, 146):

- The intervention's content and delivery were well-accepted, so the RCT would not require further adaption.
- There are no significant reasons for changes for the RCT regarding the intervention's safety and acceptability. As two patients felt the time commitment of the intervention as a disadvantage, possibilities to shorten the intervention could be considered. Furthermore, as previously described, the participants suggested inviting patients to participate in the intervention earlier in disease progression, which should also be considered in an RCT.
- The intervention's feasibility resulted from three factors that should be maintained: (1) the flexible delivery for in-/out-hospital patients; (2) the short duration, not being too demanding

for the patients, promoted the intervention's flexible use, and the timeframe was still sufficient to deliver the individually tailored intervention; and (3) the easy-to-follow, individualizable intervention structure allowed healthcare professionals from different backgrounds to deliver the intervention.

- The recruitment of the single-arm phase II study was feasible. However, the RCT should be conducted with a lengthy recruitment period and a relatively low uptake rate. The main reasons that eligible participants declined to participate were a lack of interest and fear that participating would be too exhausting. Thus, the RCT should develop strategies to approach the patients' concerns, motivating them to participate.
- The single-arm phase II study was mainly conducted with patients diagnosed with COPD. This limits the generalizability of the findings to patient groups other than COPD, so the RCT might only focus on COPD patients.
- It should be considered that patients might benefit from a further refresher between weeks four and six to prevent the intervention's effect from diminishing.
- Outcome measures especially for the assessment of episodic breathlessness and associated aspects (e.g., panic) are needed and should be developed to evaluate the intervention's effect in an RCT. Thus far, aside from episodic breathlessness-specific NRS (intensity/impairment), questionnaires for chronic breathlessness have been used in the single-arm phase II study.

Based on these findings, an RCT evaluating the intervention's effectiveness can be designed and conducted.

6.4.2 Pending research questions

Various research questions concerning episodic breathlessness among patients suffering from different life-limiting diseases offer implications for clinical practice. They need to be addressed to ensure the best possible care for patients and their carers.

1. There is a close interaction between episodic breathlessness and panic experiences among patients. Panic does not only trigger breathlessness episodes (48) but is also a consequence of the patient's episodic breathlessness, often resulting in a vicious cycle of escalating fear leading, in the worst case, to hospital admission (29). At present, the interaction between episodic breathlessness and panic is poorly understood, even though patient descriptions have strongly emphasized the panic component in breathlessness episodes (23, 29). The phase II study also assessed the patients' panic experience in breathlessness episodes (independent from the intervention), including possible moderating factors (such as anxiety sensitivity or catastrophizing thought when breathless). The results of this analysis, focusing on the interaction between panic experiences and episodic breathlessness, should provide important clues as to what

appropriate, urgent, necessary approaches that also take the patients‘ panic experiences into account look like. A first paper reporting on patients’ panic experience in breathlessness episodes is in preparation, but questions about the mechanisms remain unanswered and require further investigation.

2. Carers of breathless patients suffer from high burden due to their vital role in the patient’s care. While initial studies have demonstrated that the carer’s burden negatively impacts their mental and physical health, it also impacts the care for the breathless patient (160, 161). Given the unique character of breathlessness episodes (e.g., accompanied by intense fear), a focus should be set on the carer’s experiences with the patient’s breathlessness episodes. Improved understanding of the carer‘s experiences, in turn, enables support options tailored to the carer’s needs. These could benefit both carers and patients. In a separate dissertation, our research group conducted qualitative interviews with carers of patients participating in the single-arm phase II study to evaluate the intervention. The corresponding paper has been accepted and is soon to be published (01/2022). Here again, research concerning appropriate support for carers of breathlessness patients is just at its beginnings and requires further investigation.
3. A screening tool for episodic breathlessness should be developed to identify whether someone is suffering from episodic breathlessness and to provide appropriate treatment options accordingly. At present, the screening is based on clinical assessment by healthcare professionals, takes some time, and is highly subjective. On the other hand, episodic breathlessness is a subjective experience, so a standardized screening tool may not do it justice.
4. Breathlessness services support patients and their carers in the management of breathlessness. Breathlessness services combine pharmacological and non-pharmacological strategies and expertise from healthcare professionals with various backgrounds to provide comprehensive support for the patients and their carers (39–41). The brief cognitive and behavioral intervention described in this dissertation focused on episodic breathlessness, while the breathlessness services address chronic breathlessness. This touches on an important aspect of the relation between episodic breathlessness and chronic breathlessness. According to our understanding, episodic breathlessness is one distinct form of chronic breathlessness that occurs with and without continuous breathlessness. Therefore, assessing whether a patient suffers from breathlessness episodes is helpful to better manage breathlessness in general. This allows for teaching/discussing management options to cope with breathlessness episodes, improving the overall management of symptoms. For this reason, the brief cognitive and behavioral intervention can be an essential component of a breathlessness service, addressing episodic breathlessness. We are currently preparing a proposal for the

evaluation of a breathlessness service from the perspective of health services research (to be submitted to the *Deutsche Krebshilfe*).

5. Episodic breathlessness was defined in 2014 (21), but, to date, no assessment tools have focused on the experience of episodic breathlessness and its impairments. The S3 Leitlinie Palliativmedizin recommends assessing the episodes' intensity, unpleasantness, and resulting impairment in daily life using NRS (105). To evaluate the potential effects of the intervention, the recommended NRS was applied together with outcome parameters for chronic breathlessness. Interestingly, the episodic breathlessness-related parameters demonstrated significant changes in the assessments after the intervention, indicating reduced intensity of the breathlessness episodes and decreased impairment. In contrast, the "general" parameter, the *Dyspnea* subscale of the Chronic Respiratory Questionnaire, did not indicate any change after the intervention (146). This may suggest that episodic breathlessness requires specific outcome parameters.

6.5 Methodological strengths and limitations

The methods applied to develop and evaluate the brief intervention must be viewed in the light of different strengths and limitations. A Delphi survey with international, multi-professional experts is a widely acknowledged procedure to gain consensus (159). This well-funded approach strengthened the project and built a solid foundation for the following single-arm phase II study. The various methods applied are well suited to obtain the best possible and valid information to address the respective research objective.

For the development of the brief cognitive and behavioral intervention, an online Delphi survey was used (145). It is a valid and successfully used method in health care research (157, 158) to achieve a consensus when there is no known gold standard. The consensus criterion of 70% was defined a priori, which corresponds to the consensus criteria of comparable studies (21, 49, 158) and fulfills the requirements of Delphi procedures (137). While the response rate was acceptable and comparable to similar Delphi surveys (21, 147), still only half of the experts participated (round 1/2/3: 47%/53%/42%). Experts with various professional backgrounds participated in the Delphi survey, but we used a predefined eligibility criterion for the expert recruitment; thus, relevant aspects from a much wider pool of experts who did not meet our eligibility criterion may not have been captured. Even though the opinions of psychologists, nurses, physiotherapists, and health and social scientists were captured in the Delphi survey, most of the experts identified as clinicians or researchers. This left healthcare professionals with other professions underrepresented (145). As a consequence, the characteristics of the cognitive and behavioral intervention may have been more strongly determined by clinicians and researchers, while the perspectives of other professionals were less salient. The development of the intervention could have benefited from interviewing patients and relatives

regarding the aspects they considered relevant for this kind of intervention. While we did not invite patients for participation, the strategies presented in round one and the characteristics of the first draft of the intervention were identified based on (qualitative) studies with patients (23).

The subsequent phase II study benefited from using the MRC framework for complex interventions (Skivington et al., 2021). This led to a sound and evidence-based development and evaluation. The single group design allowed us to realize the phase II study with limited resources. Conducting feasibility studies is vital before planning and conducting RCTs, which are highly demanding. Particularly in palliative care, conducting RCTs can be challenging, as there may be difficulties in recruitment and study conduction due to a lack of interest in participation, as well as morbidity and mortality (140). The present single-arm phase II study provides the basis for an RCT to test the effectiveness of the brief cognitive and behavioral intervention in people with life-limiting diseases suffering from episodic breathlessness. While the phase II study contributes to a following RCT with important information about the intervention's feasibility, acceptability, safety, and changes due to the intervention (146), no conclusions about the effectiveness of the intervention can be drawn. Moreover, due to the lack of a control group, no conclusions concerning the feasibility and acceptability of randomization, necessary for an RCT, can be drawn.

Using the mixed-methods approach, which is common for the evaluation of interventions for breathlessness and breathlessness services (39, 40), an appropriate methodology was applied to capture as much of the patients' opinions as possible. Recording qualitative data in addition to questionnaires allowed for an in-depth interpretation of the results and promoted an understanding of the patients' pros and cons of the intervention (146).

As a recruitment strategy, the recruiting healthcare professionals actively approached patients that matched the inclusion criteria. This resulted in a patient selection limited to those patients who are currently attached to medical care. By actively approaching patients during their hospital visits, following a clinician's advice, or in patient support groups, we may have missed those patients who are underserved for the management of their episodic breathlessness, chronic breathlessness, or even their general health condition and, thus, do not appear in the hospital's support network.

We aimed to achieve diversity regarding the patients' diagnoses to enable conclusions for different patient groups. While some cancer patients completed the study, most participating patients suffered from COPD (146). The recruitment of cancer patients was difficult, as either their health condition did not permit study participation or they did not suffer from episodic breathlessness (146). As only few cancer patients participated in the single-arm phase II study, comparisons between the disease groups were not possible. This leaves unanswered the question regarding the different requirements for a brief intervention depending on the

underlying disease causing the breathlessness episodes. The majority of COPD patients in the patient population limits the generalizability of the study's results to other patient groups.

7. Conclusion

The current dissertation project aims to support patients with life-limiting diseases in managing their breathlessness episodes. Episodic breathlessness impacts patients' quality of life. Thus, appropriate management of episodic breathlessness can maintain or improve the patient's mastery of breathlessness and can improve their quality of life.

The aim of this dissertation was the development and evaluation of a brief cognitive and behavioral intervention for the management of episodic breathlessness. The intervention was developed by conducting an online Delphi survey with international, multidisciplinary experts working as researchers or clinicians in the field of breathlessness. After collecting and consenting non-pharmacological strategies for managing episodic breathlessness, the brief cognitive and behavioral intervention, comprising the consented strategies, was developed. The experts recommended balancing the intervention's individualization and standardization, involving carers, using the BTF model, and implementing a short duration. The development of the brief cognitive and behavioral intervention served as preparation for the subsequent single-arm phase II study, which evaluated the intervention's feasibility, safety, acceptability, and potential effects with patients suffering from episodic breathlessness due to a life-limiting disease. Patients and carers evaluated the intervention as safe, feasible, and acceptable. While patients did not experience any severe disadvantages due to the intervention, they suggested offering the intervention at an earlier stage of disease. Importantly, patients' mastery of breathlessness improved after the intervention. They described a positive change in their management of episodic breathlessness by reducing panic and anxiety and promoting a feeling of competence in managing their episodes. This enables them to mitigate symptom burden and increase their quality of life. The possible delivery from healthcare professionals with diverse backgrounds, the short duration, and the single appointment contribute to the feasibility of the intervention. It appears appropriate for clinical practice and should therefore be evaluated in a phase III trial to assess its effectiveness before considering it as part of a broad approach for managing breathlessness, for example, in a breathlessness service.

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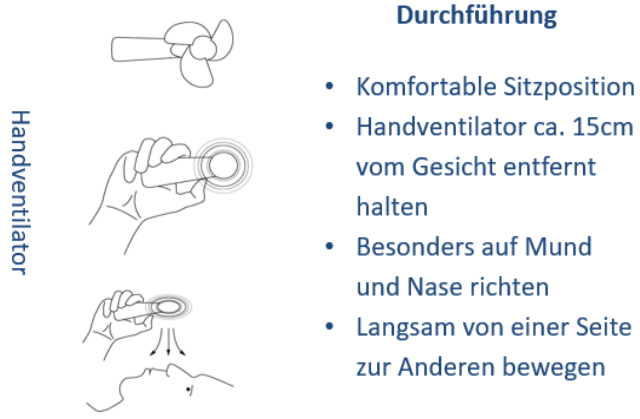
Appendix

Supplement 1

Key cards describing the selected strategies easily and briefly as support in breathlessness episodes. They were explained within the intervention and provided to the patients.

Front and backside of the key cards

1. The hand-held fan



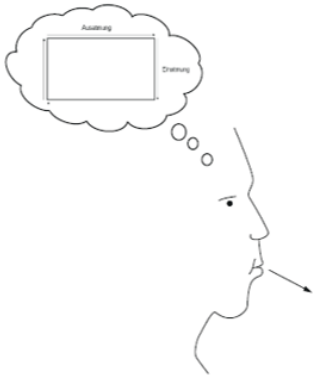
2. Pursed lips breathing

Lippenbremse

Durchführung

- Bei Ausatmung durch den Mund Lippen leicht aufeinander drücken
- Langsam gegen diesen Widerstand ausatmen
- Anschließende Einatmung ohne Lippenbremse

3. Long breaths out



Verlängerte Ausatmung

Durchführung

- Verschiedene Möglichkeiten
- Konzentrieren auf Ausatmung
- Bei Ausatmung bis 5 zählen
- Atemrythmus, der an Rechteck anpasst ist

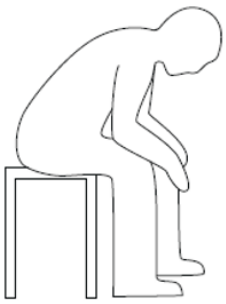
4. Diaphragmatic breathing

Tiefe Bauchatmung

Durchführung

- Konzentration auf die Atmung in den Bauch
- Zur Unterstützung: Hände auf Bauch legen und darauf achten, dass diese bei der Einatmung leicht vom Bauch angehoben werden

5. Forward lean I

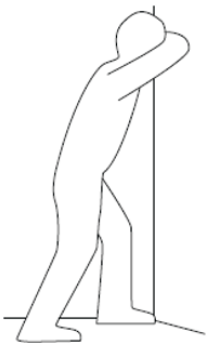


Kutschersitz

Durchführung

- Auf einem Stuhl/Sessel sitzen
- Beide Füße stehen fest auf dem Boden mit Abstand zwischen den Füßen
- Oberkörper nach vorn beugen und mit den Unterarmen auf den vorderen Oberschenkeln abstützen

6. Forward lean II



Stütze im Stehen

Durchführung

- Stehend
- Einen Ausfallschritt nach vorne
- Mit dem Oberkörper nach vorne beugen
- Mit den Armen auf einen stabilen Gegenstand stützen (z.B. Sessellehne, Wand etc.)

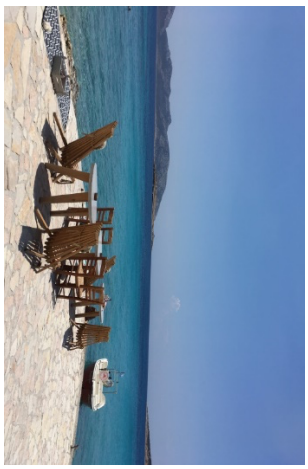
7. Forward lean III

Torwartstellung

Durchführung

- Stehend
- Beine schulterbreit, Knie leicht gebeugt
- Oberkörper nach vorne beugen
- Mit den Händen oberhalb der Knie abstützen
- Finger zeigen nach innen, Ellenbogen leicht gebeugt

8. Relaxation training

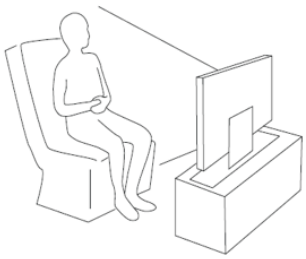


Entspannung

Gehen Sie in das Bild hinein:

- Was ist um Sie herum?
- Welche Formen und Farben gibt es?
- Was können Sie hören?
- Können Sie etwas riechen oder schmecken?
- Spüren Sie etwas auf Ihrer Haut oder unter Ihren Füßen?

9. Distraction



Ablenkung

Das lenkt mich ab:

10. Mantra

Atemnotgedicht

Die Attacke wird
vorübergehen,
ich werde wieder
normal atmen
können!

Mein Atemnotgedicht

Declaration of the contribution of the doctoral student

Dissertation project 1

Development of a Brief Cognitive and Behavioral Intervention for the Management of Episodic Breathlessness—A Delphi Survey With International Experts

Karlotta Schloesser, Yvonne Eisenmann, Anja Bergmann, Steffen T. Simon
Journal of Pain and Symptom Management, DOI: 10.1016/j.jpainsymman.2020.09.034

Contribution of the authors

Steffen Simon developed the study idea. Karlotta Schlösser developed the different rounds of the Delphi survey in collaboration with Yvonne Eisenmann and Steffen Simon. Karlotta Schlösser conducted the online Delphi survey and analyzed the results. Karlotta Schlösser wrote the manuscript and revised it in cooperation with Steffen Simon. All authors read the manuscript critically, revised it, and agreed to the final version of the manuscript for publication.

Dissertation project 2

“Only I know now, of course, how to deal with it, or better to deal with it”: A mixed methods phase II single-arm study of a cognitive and behavioral intervention for the management of episodic breathlessness

Karlotta Schloesser, Anja Bergmann, Yvonne Eisenmann, Berenike Pauli, Martin Hellmich, Max Oberste-Frielinghaus, Stefanie Hamacher, Armin Tuchscherer, Konrad F. Frank, Winfried Randerath, Simon Herkenrath, Steffen T. Simon

Journal of Pain and Symptom Management, DOI: 10.1016/j.jpainsymman.2021.11.003

Contribution of the authors

Steffen Simon developed the study idea. Karlotta Schlösser with support from Steffen Simon and Yvonne Eisenmann worked out the specific methods of the study. Karlotta Schlösser created the study material. Karlotta Schlösser conducted the interventions with the patients. Karlotta Schlösser, Berenike Pauli and Anja Bergmann conducted the quantitative data collection of the study. Karlotta Schlösser conducted the qualitative interviews. Karlotta Schlösser, Stefanie Hamacher and Max Oberste-Frielinghaus and Martin Hellmich analyzed the data. Karlotta Schlösser prepared the manuscript. All authors read the manuscript critically, revised it, and agreed to the final version of the manuscript for publication.

Declaration

Ich versichere, dass ich die von mir vorgelegte Dissertation selbstständig angefertigt, die benutzten Quellen und Hilfsmittel vollständig angegeben und die Stellen der Arbeit - einschließlich Tabellen, Karten und Abbildungen -, die anderen Werken im Wortlaut oder dem Sinn nach entnommen sind, in jedem Einzelfall als Entlehnung kenntlich gemacht habe; dass diese Dissertation noch keiner anderen Fakultät oder Universität zur Prüfung vorgelegen hat; dass sie - abgesehen von unten angegebenen Teilpublikationen - noch nicht veröffentlicht worden ist sowie, dass ich eine solche Veröffentlichung vor Abschluss des Promotionsverfahrens nicht ohne Genehmigung der Dekanin / dem Dekan vornehmen werde. Die Bestimmungen dieser Ordnung sind mir bekannt. Die von mir vorgelegte Dissertation ist von Prof. Dr. med. Steffen Simon, M.Sc. betreut worden.

Übersicht der Publikationen:

2. **Schloesser, K.,** Bergmann, A., Eisenmann, Y., Pauli, B., Hellmich, M., Oberste, M., Hamacher, S., Tuchscherer, A., Frank, K. F., Randerath, W., Herkenrath, S., Simon, S.T. (2022). “Only I know now, of course, how to deal with it, or better to deal with it”: A mixed methods phase II single-arm study of a cognitive and behavioral intervention for the management of episodic breathlessness. *Journal of Pain and Symptom Management*, *63*(5), 758-768. DOI: 10.1016/j.jpainsymman.2021.11.003.

3. **Schloesser, K.,** Eisenmann, Y., Bergmann, A., & Simon, S. T. (2021). Development of a Brief Cognitive and Behavioral Intervention for the Management of Episodic Breathlessness—A Delphi Survey With International Experts. *Journal of Pain and Symptom Management*, *61*(5), 963-973. DOI: 10.1016/j.jpainsymman.2020.09.034.

Ich versichere, dass ich alle Angaben wahrheitsgemäß nach bestem Wissen und Gewissen gemacht habe und verpflichte mich, jedmögliche, die obigen Angaben betreffenden Veränderungen, dem Promotionsausschuss unverzüglich mitzuteilen.

.....	.....
Datum	Unterschrift

Curriculum Vitae

Mein Lebenslauf wird aus Gründen des Datenschutzes in der elektronischen Fassung meiner Arbeit nicht veröffentlicht.