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REVIEW

Understanding the impact of breathing pattern disorders in difficult-to-treat asthma

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ABSTRACT

Introduction: Difficult-to-treat asthma is defined as asthma that is uncontrolled despite high-level treatment or requires such treatment to maintain good control and reduce exacerbations. Breathing pattern disorders (BPD) have been reported as a comorbidity in ~ 24–42% % of patients with difficult-to-treat asthma. This narrative review will assess the association, impact, and management of BPD in difficult-to-treat asthma.

Areas covered: We outline current understandings of the nature of difficult-to-treat asthma and BPD. We then review the impact of BPD on difficult-to-treat asthma and Multidisciplinary Team (MDT) approaches to assessing and managing BPD in this patient group. A comprehensive literature search was performed by an asthma specialist MDT including physiotherapists, psychologists, and physicians to create a holistic perspective on this subject.

Expert opinion: BPD exerts significant negative impacts across multiple domains in patients with difficult-to treat asthma. There is a need for further observational, interventional, qualitative and quantitative research to develop better diagnosis, treatment, and awareness of the impacts of BPD including health economic analysis. Studies should develop multimodal approaches that better treat both BPD and associated comorbidities within the multimorbidity framework of difficult-to-treat asthma. Recognizing and addressing BPD should be key elements in future difficult-to-treat asthma management guidelines and clinical practice.

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KEYWORDS
Breathing pattern disorder*; breathing exercises; difficult-to-treat asthma; dysfunctional breathing; multimorbidity; physiotherapy

1. Introduction

Difficult-to-treat asthma has been defined by the Global Initiative for Asthma (GINA) as asthma that is uncontrolled despite GINA Step 4 or 5 treatment or requires such treatment to maintain good control and reduce exacerbations [1] The prevalence of Breathing Pattern Disorders (BPD) in people with asthma is between 29–42% [2] and has been reported to be consistently raised in patients with difficult-to-treat asthma. This narrative review will assess the association, impact, and management of BPD in difficult-to-treat asthma.

2. Review methods

A narrative review for the literature was performed. Electronic searches included MEDLINE, EMBASE, CINAHL, AMED, PsychINFO, Cochrane Airways Group Centralised Register, EMCARE, PubMed, PsychARTICLES, Francis and Taylor online, Elsevier, ScienceDirect, Sage, Google Scholar and EBSCOhost. Search terms included 'difficult to treat asthma,' 'breathing pattern disorder*'|, 'dysfunctional breathing,' 'physiotherapy,' 'breathing exercises,' 'trauma' and 'multimorbidity.' All reviewed articles were published in English and no limitations on publication date were applied.

3. Difficult-to-treat asthma as a multimorbidity disease model

Difficult-to-treat asthma has been defined by the Global Initiative for Asthma (GINA) as asthma that is uncontrolled despite GINA Step 4 or 5 treatment or requires such treatment to maintain good control and reduce exacerbations [1]. This GINA definition of difficult-to-treat asthma also recognizes that in many cases asthma may be 'difficult-to-treat' because of modifiable factors including poor inhaler technique, suboptimal treatment adherence, behaviors like smoking, aggravating comorbidities or because of incorrect diagnosis. It is estimated that difficult-to-treat asthma affects 3–10% of people with asthma in whom it is associated with greater disease morbidity, healthcare dependency, treatment needs and potential

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Article highlights

- BPD is highly prevalent in difficult-to-treat Asthma. BPD treatment has been shown to be effective in improving quality of life in patients with difficult-to-treat asthma.
- BPD is associated with multiple comorbidities.
- BPD is associated with worse health outcomes.
- BPD's can be treated with a variety of different treatment techniques.

mortality risk [3]. Studies have indicated that most patients with complex or severe asthma fall into this category of 'difficult-to-treat' disease [4,5]. Importantly, while comprising a small fraction of the asthma population, difficult-to-asthma accounts for a significant proportion of the burden associated with asthma and is responsible for more than 50% of asthma-associated healthcare costs [3].

Understanding of the airway pathophysiology of more severe asthma has matured considerably in recent decades, crystallizing around the concept of a dominant Type 2 (T2) inflammation/eosinophil associated airway disease [6–10]. However, it is becoming clear that a substantial proportion of patients with difficult-to-treat asthma achieve limited clinical improvement despite full optimization of asthma medications to address such patterns of airway disease. In parallel, there is also growing recognition that problematic asthma is typically part of a wider complex web of adverse health issues rather than an isolated severe airway disease (Figure 1).

It is increasingly recognized that comorbidities are highly prevalent in difficult-to-treat asthma and detrimentally impact patient outcomes [11–14]. These comorbidities may be both physical (rhinitis, gastro-esophageal reflux disease (GORD), obesity and obstructive sleep apnea (OSA) [15–17] and psycho-physiological (depression, anxiety, BPD and ILO) [18–20]. In turn, amassing evidence suggests that comorbidities are 'treatable traits' and specifically addressing those can significantly improve patient outcomes in difficult-to-treat asthma [9,13,21–23].

Multimorbidity is defined by the World Health Organization (WHO) as co-existence of 2 or more long-term health conditions [24]. That framework is very pertinent to a model of difficult-to-treat asthma. As illustrated in Figure 1, difficult-to-treat asthma often comprises a multimorbidity network of adverse health conditions that in turn has recently been proposed to constitute a 'Difficult Breathing Syndrome' rather than an 'asthma-centric' state [25]. Studies have demonstrated that most difficult-to-treat asthma patients meet the criteria for multimorbidity [26] with a median of 3 additional comorbidities reported by an Australian specialist referral difficult asthma clinic [11]. Attempts to model multimorbidity have defined both airway centric and non-airway -centric profiles of treatable traits/comorbidities [27]. Of note, non-airway-centric profiles may be associated with worse measures of asthma control and quality of life but may be amenable to interventions as part of a structured assessment and treatment approach [27].

One comorbidity that is attracting particular interest in difficult-to-treat asthma is BPD, previously known as dysfunctional breathing. This review will assess the association, impact, and management of BPD in difficult-to-treat asthma.

4. Defining breathing pattern disorders

BPD is an umbrella term (Figure 2) and diagnosis that has been 'characterized as multidimensional, involving biomechanical, biochemical, breathing related symptoms, and breathing

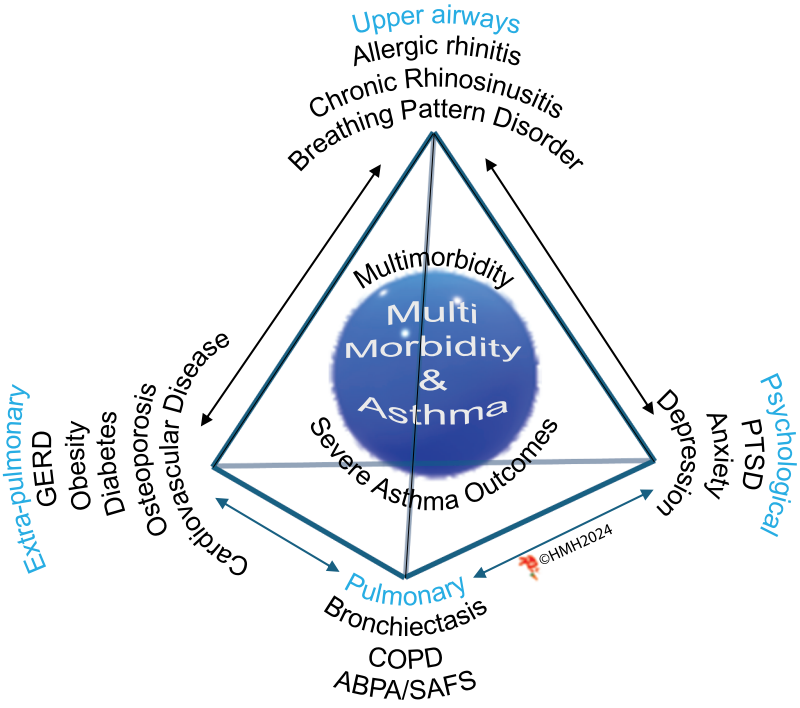

Figure 1. Multimorbidity associated breathing pattern disorder and severe asthma outcomes.

Gastroesophageal Reflux Disease (GERD), Chronic Obstructive Pulmonary Disease (COPD, Allergic Bronchopulmonary Aspergillosis (ABPA), Severe Asthma with Fungal Sensitization (SAFS), Post-Traumatic Stress Syndrome (PTSD).

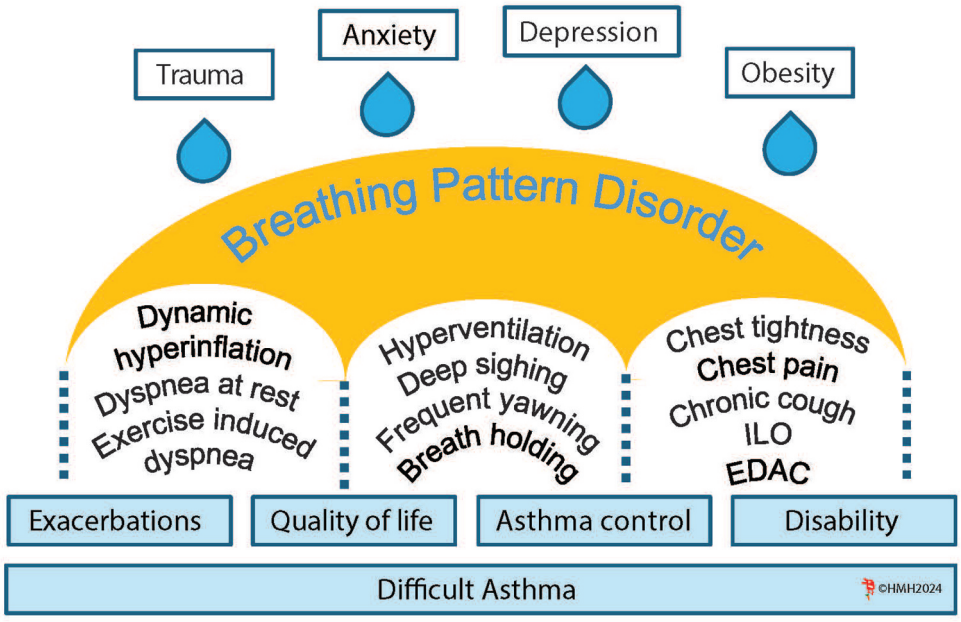

Figure 2. "Umbrella" of Breathing Pattern Disorders and Dicult Asthma.
Inducible Laryngeal Obstruction (ILO), Excessive Dynamic-Airway-Collapse (EDAC).

function which may or may not co-exist' [28]. Figure 2 shows the clusters of common presentation and symptoms in BPD patients, on the left are a cluster of symptoms often described by patients with biomechanical dysfunction, seen in conditions like chronic obstructive pulmonary disease (COPD). The central column represents some of the most common clinical features of hyperventilation and often result in biochemical changes. Finally, the right-hand column represents functional respiratory complaints and a combination of clinical features and diagnoses of upper airway dysfunction. All can be treated with breathing pattern retraining supported by the MDT. Although these clinical features can be clustered, presentation is often more complex and patients may present with multiple aspects of dysfunction that can be treated with breathing pattern retraining supported by the MDT.

BPD can be a primary or secondary diagnosis, and in difficult-to-treat asthma, is commonly seen as part of a multimorbidity picture, presenting with many possible causes or characteristics (Figure 1). There is no gold standard diagnostic test for BPD which should be regarded as a predominantly clinical diagnosis relying on both clinician subjective assessment of the reported clinical features and objective assessment including a physical examination and objective measures [28]. Therefore diagnosis is based on a combination of evidence from the patient history (subjective) and most commonly using reported outcome measures such as the Nijmegen questionnaire (NQ) [29]. Other physiological objective tests such as the voluntary hyperpnea test, Cardiopulmonary Exercise Test (CPET), or End Tidal Carbon Dioxide ($EtCO_2$) can be used, often in specialist settings. The term 'function' within 'dysfunction' relates to the physical changes that manifest often habitually through repetitive conditioning in response to particular triggers and associated perceptual changes to breathing. A rigorous subjective and objective assessment involves using the senses to appreciate changes in someone's breathing mechanics, through observation, hearing and tactile feedback, and this performance is both an art and science, considering the person being assessed also knows their breathing is under observation. This may trigger some conscious control of the breathing pattern during the assessment. Assessment of breathing pattern requires further expertise, particularly when someone also has asthma, is experiencing breathlessness (which is not BPD), and no gold standard to refer to. Dysfunction within BPD impacts on multiple body symptoms, particularly if changes in blood biochemistry result, in the case of hyperventilation syndrome, and which may lead to reduced CO_2 levels. Breath hold time, was thought to predict $EtCO_2$ but has been shown to relate to the breathing pattern in patients with altered spirometry [30]. This is reflected in the symptoms and signs scored on the NQ diagnostic tool which itself is a measure of functional respiratory complaints [31] to complicate matters, not all breathing pattern disorders manifest from over breathing and can be more about changes in flow, rhythm, and movement pattern of the chest wall and abdominal compartments [32].

Breathing pattern is further complicated by the fact that normal breathing is deliberately variable. We can highlight different aspects of breathing pattern using the Breathing Pattern Assessment Tool (BPAT) [33].The BPAT is an objective assessment involving scoring each aspect of the breathing pattern including rate, rhythm, flow, thoracic and abdominal movement plus additional features such as sighing, coughing, deep breathing or volume change. A normal breathing pattern is considered when someone breathes at rest through their nose. There is little debate here and the protective functions, humidification and filtration provided by the nasal anatomy, provides better air quality to the lungs than

mouth breathing [34]. If there is no obstruction to breathing it should also be quiet with a regular rate and rhythm at rest. However, the BPAT scores a breathing pattern as negative (and therefore disordered to some extent) if someone has a combined thoracic and abdominal breathing pattern. A combination pattern could be considered normal and initiated with lateral movement with some synchrony between upper chest and abdominal components which has been confirmed via optoelectric plethysmography [35]. Sighing too is scored as negatively impactful. Sighing is normal every 6 minutes or so to reset essential respiratory variability [36] and prevent alveolar collapse [37] so if a clinician observes a sigh this could be normal. Having a respiratory rate of 13–25 is scored negatively but the normal range could be around 14 [38] and healthy individuals have been shown to have respiratory rates into this threshold at 16 [36] and 18 [39] breaths per minute. Others suggest that a respiratory rate of up to 28 May be normal [40]. Breathing can either be scored as regular or erratic. However, normal breathing should have a level of random and non-random variability in its rhythm to be flexible to environmental demands and maintain system stability [41]. Too much rigidity in breathing pattern, like very little heart rate variability, is not healthy.

Differentiating between each aspect of the breathing pattern using the NQ and BPAT does not fully account for dysfunction of the upper airway in the cases of Inducible Laryngeal Obstruction (ILO) (previously known as vocal cord dysfunction) or Excessive Dynamic Airway Collapse. These both arguably disrupt a 'normal' breathing pattern and may mask and present similarly to difficult-to-treat asthma. No assessment tool to date addresses upper and lower airway dysfunction in a holistic manner and batteries of tests are performed to differentiate the cause of a patient's symptoms. Tools such as the Pittsburgh Vocal Cord Dysfunction Index can be of use and help differentiate symptoms [42]. Upper airway dysfunction is often considered separately [43] but often present in difficult asthma as per Figure 2.

There is some difficulty doing interventional studies for people living with a breathing pattern disorder. Although it is a highly prevalent condition for people with difficult-to-treat asthma (1) people often do not recognize that they have BPD themselves, and it is often misdiagnosed by clinicians, and asthma or medical management escalated as a consequence [43].

Qualitative research has shown that people who have comorbid BPD and difficult-to-treat asthma often report frustration and acknowledge that asthma treatments such as inhaled medications don't fully resolve symptoms of 'breathing difficulty.' This can result in considerable ongoing symptom burden and unmet need for care [12]. This itself impacts on other aspects of multimorbidity that may be present such as anxiety, depression and mental health in general.

It is not possible to simply define BPD and clinical coding for BPD is not always clear. Various terminology is used in the literature, making it difficult to establish consensus, clear definitions, and comparison within this area of research [44]. With difficult-to-treat-asthma, BPD often presents in clinical practice as shown in Figure 2. In conclusion, currently there is no single test or definitive assessment for BPD and further research in this field is warranted. For now, BPD diagnosis remains a pragmatic clinical diagnosis supported by multiple objective assessments.

5. The association and impact of BPD in difficult-to-treat asthma

Difficult-to-treat asthma is increasingly recognized as a multidimensional condition associated with numerous comorbidities that merit targeted treatment approaches [45]. These 'treatable traits' frequently combine into a multimorbidity disease framework (defined as coexistence of ≥ 2 long-term health conditions) that collectively imposes significant patient burden (Figure 1). In turn, not all symptoms of breathing difficulty in patients with difficult-to-treat asthma may be driven by their asthma. In a not insignificant proportion of cases, a state of 'symptom high, biomarker low' pertains. Consistent with that concept, unbiased cluster analysis of the US Severe Asthma Research Program (SARP) demonstrated a cluster of older mostly obese women with late-onset non atopic asthma, relatively preserved lung function but high OCS needs for acute exacerbations [46]. A similar obese older non-eosinophilic female predominant cluster was demonstrated in a UK population [47]. That cluster notably had highest NQ scores among the identified clusters in that study which included a further symptom predominant, inflammation low early-onset cluster. BPD is one highly prevalent comorbidity in difficult-to-treat asthma, occurring in 24–47% patients [12,18,48,49]. The associations with, and impact of, BPD in patients with difficult-to-treat asthma has only been reported in a small number of studies to date. The consensus findings from these studies is that BPD is associated with a spectrum of characteristic clinical features and adverse patient outcomes in difficult-to-treat asthma. In a study of 157 patients seen at a tertiary referral difficult-to-treat asthma service in Melbourne, Australia, BPD was diagnosed in 47% of patients using an NQ cutoff >23 to make the diagnosis [18]. Patients with BPD were more often female and had higher prevalence of comorbidities including anxiety, depression, sleep apnea, GORD, and sinonasal symptoms. Patients with BPD in this study also demonstrated worse ACQ, AQLQ, greater asthma exacerbation frequency and greater unemployment. BPD wasn't associated with lung function in this study. In a further study on a subset of 29 BPD patients, this group showed that a breathing retraining intervention could deliver significant improvements across multiple patient domains. These included improvements in asthma control, asthma exacerbations, asthma related quality of life as well as NQ scores [50]. In a study of 117 Danish asthma clinic patients, BPD was diagnosed in 30% of patients using an NQ cutoff >23 to make the diagnosis [48]. As with the Australian study, BPD patients in this study had worse ACQ and AQLQ. Objective signs of BPD were further assessed using BPAT. Patients with higher BPAT also showed worse asthma control. Another Danish study of BPD in the difficult-to-treat asthma population was conducted in the MAPout II study within an outpatient clinic setting in Copenhagen. In this study of 127 patients, 24% were diagnosed with BPD using an NQ cutoff >23 to make the diagnosis. In this study, BPD was significantly associated with

worse asthma control (ACQ), asthma related quality of life (AQLQ) and self-estimated asthma severity status. In contrast to the other described study this study also found associations of BPD with worse lung function (FEV_1; Forced Expiratory Volume in 1 Second and FVC; Forced Vital Capacity). Regression analysis showed that the impact of BPD on asthma control in this study was independent of airway inflammation or airway hyper-responsiveness status [49].

The Wessex AsThma CoHort of difficult asthma (WATCH), based in Southampton, United Kingdom, recently presented the largest published characterization, outlining the associations and impact of BPD in difficult-to-treat asthma from our well characterized real-world cohort [51,52]. This study explored the relationship between BPD and difficult asthma outcomes, in the context of differing diagnostic strategies [51,52]. As already described, there is no gold standard for the diagnosis of BPD; in clinical practice, a combination of clinical diagnosis and NQ score are used to arrive at a pragmatic diagnosis.

This study demonstrated that a clinical diagnosis of BPD in difficult-to-treat asthma patients, was significantly independently associated with female sex, multiple comorbidities (rhinitis, GORD, ILO, and any psychological comorbidity) and measures of high health care usage (asthma exacerbations and previous intensive care unit (ICU) asthma admissions) [52]. Abnormal NQ-based BPD diagnosis was also assessed using an NQ cutoff of > 23 to define BPD diagnosis as utilized in the previous studies reported above. Using this NQ-based approach, BPD was significantly independently associated with multiple comorbidities including psychological comorbidity, GORD, salicylate sensitivity and eczema. A noteworthy finding from this study was that NQ based diagnoses and clinical diagnoses of BPD were not always concordant, suggesting that they may identify differing BPD-related phenotypes of difficult-to-treat asthma. Among the 357 participants who had data for both NQ scores and a clinical diagnosis of BPD, 58.5% showed concordance of BPD status for clinical and NQ-based definitions. One-fifth (22.7%) had a clinical diagnosis of BPD but NQ ≤ 23, while a similar proportion (18.8%) had NQ > 23 but no clinical diagnosis of BPD. Numerous driving mechanisms may lead to the same superficial symptom of breathlessness and a tool like the NQ may detect influence of other conditions on expression of that symptom and not just the presence of BPD. Thus, the NQ could detect signals from states including asthma, cardiovascular disease, obesity and physical deconditioning. That 'wider radar' could in turn account for some of the discordance between NQ- and clinically-diagnosed BPD. An element of this discordance may also reflect perceptual distortion whereby some individuals do not recognize their BPD symptoms as particularly abnormal or burdensome and therefore register a lower NQ which does not align with a clinician assessment of the presence of BPD. Conversely, a clinician diagnosis also bears an inherent degree of subjectivity which may at times overestimate or underestimate the presence and severity of BPD. What this study indicates is that neither diagnostic approach can provide a comprehensive means to detect or assess BPD, and additional diagnostic methods need to be developed in the future. Nevertheless, regardless of diagnostic terminology, this study demonstrated that BPD was associated with multiple adverse impacts on patients with difficult-to-treat asthma. These included associations with significantly worse ACQ, quality of life (St George's Respiratory Questionnaire [SGRQ]), measures of psychological distress (Hospital Anxiety & Depression Scores [HADS]) and asthma exacerbations needing OCS as well as greater degrees of multimorbidity. Additionally, a clinical (but not NQ)-based diagnosis of BPD was significantly associated with asthma hospitalizations and lost working days further illustrating patient level impacts of BPD in difficult-to-treat asthma.

As evident from previous literature [48–50] an NQ-based definition of BPD using a dichotomous cutoff of > 23 is widely used. However, there is little understanding of the utility of a continuous measure NQ in difficult-to-treat asthma. The recent WATCH study further explored the relevance of a gradient understanding to the NQ, both as a continuous variable and as a quartile-based interpretation of that value [52]. It was found that rising NQ as a continuous measure was associated with multiple detrimental impacts on domains such as asthma control (reflected by ACQ6 score), psychological distress (reflected by HADS score), quality of life (reflected by SGRQ) and level of multimorbidity. Multivariable linear regression analysis identified independently significant associations of continuous measure NQ with female sex, ever smoking, GORD, psychological comorbidity, sleep apnea and ever needing ICU admission for asthma. NQ was categorized in terms of quartiles (low: ≤ 12, moderate: 13–21, high: 22–31, very high: >31). Rising NQ quartile was consistently associated with greater symptom burden (higher ACQ), higher HADS scores, worse quality of life (SGRQ scores), and greater levels of multimorbidity. Of note, the increases in ACQ across the moderate, high and very high quartiles were each associated with a greater than minimal clinically importance difference (>0.5) increase in symptom burden. These results demonstrating increasing adverse outcome gradient with increasing NQ have potentially quickly applicable clinical utility. For example, following validation in other cohorts, NQ as a continuous measure could be used as a triage for referrals to physiotherapy services.

This recent study highlights the need for nuanced assessment for BPD in difficult-to-treat asthma, and along with previous publications emphasizes the much poorer asthma outcomes associated with a diagnosis of BPD in this patient group [52]. The observed lack of association of more objective markers such as FeNO, spirometry and peripheral blood eosinophil count have been variably reported in the literature [18,49]. This study also highlights the difficulties in diagnosing BPD using currently available diagnostic approaches and suggests the need to be alert to this diagnostic possibility. It also emphasizes the utility of a comprehensive assessment process to support BPD diagnosis and augments the case for early treatment of BPD in difficult-to-treat asthma management. Indeed, holistic patient management which includes BPD treatment can significantly benefit patients with difficult-to-treat asthma. An Australian group demonstrated that systematic assessment and management of treatable traits in difficult-to-treat asthma could reduce oral corticosteroid burden by half and improve at least 1 asthma outcome measure in over

90% of patients. These results were comparable to outcomes with biological treatments, with BPD one of the treatable traits that responded well to intervention [53]. Targeting treatable traits should involve not only targeting of biological treatable traits, but a shift in focus to include other traits which are both modifiable and have evidence for association with detrimental outcomes in asthma.

Collectively, the emerging literature on BPD in difficult-to-treat asthma clearly demonstrates that impacts of BPD on this patient population are of high clinical relevance and that addressing BPD in patients with difficult-to-treat asthma could have clinical and health economic benefits.

6. Physiotherapy and breathing retraining for BPD in difficult-to-treat asthma

From here we will focus on reviewing evidence for interventions and the concepts supporting treatment for patients with BPD and difficult-to-treat asthma. This will be undertaken within the setting of multimorbidity, as there are often multiple aspects of dysfunction affecting and impacting on the perceived symptoms and severity in such patients.

Understanding the complex interventions to treat BPD is challenging when considered in the context of asthma. Breathing pattern retraining focuses on restoring effective ventilation with minimal effort and maximal protective function, and patients will require the tools to self-monitor and continue ongoing management independently. However varying descriptions of 'breathing exercises' are demonstrated in the literature [32]. Common terminology and breathing exercises used to help people 'correct' their breathing pattern and 'control' their breathing are 'breathing control,' 'diaphragmatic,' 'abdominal,' or 'belly breathing,' but these are poorly defined and challenging to compare [32]. The intention is to stop people breathing apically, using accessory muscles of the neck, shoulders and back to increase ribcage volumes, and gain more inspiratory movement from the abdomen, but also the lower rib cage. The theory is that movement from the abdomen indicates that the diaphragm is working more efficiently and effectively. However, this is not necessarily the case, neither do experts agree that this occurs in practice (13). Furthermore, sole abdominal breathing is not always described in studies of normal breathing (5). Breathing control or controlled pauses aims to reduced hyperventilation, restore a normal rest respiratory rate and increase end tidal carbon dioxide [30].

Three specific methods of breathing pattern retraining have been studied in asthmatic patients, the Buteyko method, [54–57], the Papworth method [58], and BrEX [59]. Studies of these specific breathing retraining methods have shown improvement in quality of life, with varying intervention length and follow up period. In a single study of the Papworth method, they reported significant improvements in quality of life (SGRQ) sustained over 12 months [58]. Similar findings for the Buteyko method are found with statistically significant improvements in the AQLQ [54,56] and the Mini AQLQ) [55]. Statistical improvements in asthma control have been reported with use of the Buteyko method but with varying methods of outcome assessment. In a Canadian study, asthma control was defined as the composite score based on the Canadian asthma consensus [55]. Other studies using the Buteyko method measured asthma control using the more commonly utilized ACQ meeting statistical significance [56,57] and reaching the MCID of > 0.5. [57]. Although promising, these results represent small single center or geographical locations, in patients predominantly with mild to moderate asthma. BrEx has shown improvements in mini AQLQ in a large multicenter RCT in moderate to severe asthma regardless of asthma severity [59].

Although results suggest improvement in quality of life, the presence of BPD remains unconfirmed in many studies in this patient population. The NQ is used as an outcome [57,58] but is not an inclusion criteria and diagnosis is unsupported by objective assessment in those that do [60]. Treatment with breathing pattern retraining methods, is studied based on the hypothesis it will improve asthma control or symptoms rather than treat comorbid BPD specifically and the exact mechanisms of the improvement shown are not well understood [61].

Other emerging methods such as The Bradcliff breathing method are also used in clinical practice but there is no specific evidence to support this in asthma. Each methods includes various aspects of education, breathing exercises, lifestyle, postural and upper airway management. In clinical practice clinicians may use one or parts in combination of these technique to treat patients.

A single study of people with difficult-to-treat asthma and coexisting BPD, suggests that the NQ, asthma control and AQLQ scores improve following breathing retraining [50]. The approach used in this non-randomized controlled study was to focus on a complex intervention combining advice on nose and abdomen breathing, postural training, relaxation, and conscious feedback of reducing respiratory rate. The slight variation from specific methods of breathing retraining, also showed similar results in a single center RCT in asthmatic patients with mild to moderate asthma and BPD diagnosed by NQ alone. This research showed statistically significant improvement in the AQLQ at 1 month and NQ at 6 months [60]. Ascertaining a confirmed diagnosis of both BPD and Asthma in these studies appeared difficult. Further large, multicenter, randomized controlled trials, with a multimodal approach, in patients with a confirmed diagnosis of coexistent BPD and difficult-to-treat asthma are warranted.

The delivery of breathing pattern retraining in asthma has also been studied and face to face delivery by a physiotherapist has been shown to be preferred in a quantitative process analysis [62]. However it has also been shown in a large RCT within a primary care asthma population that it can be effectively delivered via self-guided digital resources [63]. This study, like others, showed improvement in quality-of-life measures (AQLQ) but minimal change in pulmonary markers, spirometry or FeNO. Interestingly NQ was not significantly different between the digital support, face to face support or usual care group who did not receive breathing pattern retraining. However, inclusion to the study did not require a positive NQ or clinical diagnosis of a breathing pattern disorder but shows the impact of the breathing retraining on the asthma population more broadly.

The most recent systematic review of breathing exercises in asthma indicates that in a meta-analysis of different breathing exercises, both AQLQ and NQ scores can be improved with breathing pattern retraining in asthma patients (23). The impact of BPD and multimorbidity in difficult-to-treat asthma suggests worse outcomes for those with higher NQ and greater multimorbidity [18].

The clinical presentation of BPD and multiple morbidity in difficult-to-treat asthma increase the likelihood of physical deconditioning due to the fear of breathlessness leading to reduced physical capacity [64]. The most recent Cochrane review of Pulmonary Rehabilitation (PR) for adults for asthma, has shown PR to be effective in improving functional capacity beyond the Minimal Clinical Important Difference (MCID) for the 6-minute walk test and in wellbeing measured by the SGRQ [65]. PR may improve cardiovascular fitness, muscle strength and respiratory health but the specifics of this and the long-term effects, 12 months and beyond is not fully understood in asthma or difficult-to-treat asthma and warrants further RCTs. The most recent study of effect of PR on BPD in uncontrolled asthma reports significant improvement in NQ, highlighting physical exercise to have a positive impact on BPD specifically [66]. Studies of the effects of exercise on BPD in difficult-to-treat asthma are most certainly warranted as well as the interaction of these in the context of multimorbidity.

7. The complex neuropsychological framework for BPD in difficult-to-treat asthma

Psychological conditions such as anxiety and depression, and physiological conditions (such as obesity) will likely impact on psychological/cognitive appraisal of changes to breathing alongside physical breathing pattern changes. Often such symptoms of breathing difficulty are solely attributed to asthma and are perceived to be related to small airways disease rather than considering the bigger picture of multimorbidity [67]. Breathing is a complex sensorimotor process, involving both unconscious and conscious cognitive/perceptive processes as well as well as neurocognitive functioning.

In asthmatic patients, neuroimaging and clinical findings have shown alterations in brain areas notably in the anterior cingulate cortex and the insula [68] with evidence that deleterious neurocognitive function is associated with increased asthma severity [69]. These structures receive afferent information from the lungs and alter the breathing rhythm in response through connection with the brainstem and prefrontal cortex. The anterior cingulate cortex is involved in processing bottom-up and top-down sensory information as well as attention and is also part of emotional processing alongside the insula. These structures are also implicated in threat processing either directly or through their connection with surrounding brain areas, the prefrontal cortex and the amygdala [70] The prefrontal cortex processes past learnings and, based on these, sets anticipation. When these brain regions are hypersensitized, sensory processing, cognitive interpretation of internal information, and anticipation are inaccurate [71]. Consequently, body signals might be misinterpreted leading to inappropriate command to brain structures that regulate breathing. Recent cognitive models have demonstrated that, in people with asthma, low mood was associated with less accurate interpretation of breath-related bodily sensation, [72]. Similarly, a connection between negative emotions and breathing experience led to worse breathing control in patients with dysfunctional breathing [73].

More broadly, in stress and depression, changes in the brain may also drive systemic inflammation and any consequent increase in proinflammatory cytokine levels. This can negatively impact asthma, alongside bronchoconstriction that has been shown to occur in response to negative emotions through activation of the cingulate cortex [68].

8. Psychological treatment to support BPD in difficult-to-treat asthma

Considering the breadth of evidence from a wide range of scientific disciplines on the multiple structures and physiological processes involved, it follows that treatments should similarly be addressed with an interdisciplinary, holistic approach – matching and providing tailored support for the diversity of the experience of dysfunctional breathing patterns and breathlessness [74].

Alongside the holistic benefits of dedicated physiotherapy-focused interventions such as breathing pattern retraining (which studies have indicated can benefit subjective perceptions of wellbeing [75], several psychoneurological approaches have demonstrated promise in addressing BPD. Mindfulness-based training has demonstrated a range of improvements for people with respiratory disease, both functionally [76,77] and physiologically [78]. Mindfulness has a large focus on increased attention to (and acceptance of) sensations focused on breathing, and as such has been suggested as a mechanism through which benefits of breathing retraining are conferred [79]. Similarly, controlled breath practices such as yoga and meditative breathing techniques have demonstrated improvements to both autonomic and psychological breathing mechanisms [80].

Whilst the benefits of therapies with a distinct breathing-related component are likely to have a direct effect on putative mechanisms, it is also likely that standard psychological therapies (such as cognitive behavioral therapy) but also any therapy that influences mood, calmness and cognition, such as exercise [81] may impact neurocognitive mechanisms important for breathing patterns [e.g. [82]– although this needs to be evaluated in relevant patient groups. Furthermore, some physiotherapy-led interventions (such as singing, [83] are often delivered with a focus on physiological outcomes such as lung function but may provide important psychological benefits via psychological and social interactions.

The Multi-Disciplinary Team (MDT) plays an important role of managing difficult-to-treat asthma and a wide variety of professionals may provide treatment for different presentations of BPD in difficult-to-treat asthma. Speech and language therapist (SLT), for example, may focus on 'rescue techniques' isolating and addressing upper airway dysfunction [84] but this can also used by physiotherapist and services vary in the

professional providing these treatments across different health care settings. Psychologists may focus on the perceived shortness of breath, and normalizing breathlessness. Therefore SLT, physiotherapist and psychologist may utilize 'breathing control' or 'diaphragmatic breathing,' but the definition of these may be vastly different. Therefore, the true effects of singular interventions are poorly understood, and variation of interventions makes comparison challenging.

9. Pharmacotherapy for BPD in difficult-to-treat asthma

While there is some data to support use of pharmacotherapy to treat general breathlessness associated with COPD, particularly toward the palliative end of the spectrum, there are little data to suggest pharmacotherapy is effective for BPD. As a result, there are no specific evidence-based medical treatments directly indicated in BPD. One interesting paper studying rats suggested that earlier treatment with inhaled corticosteroids in a rat model of asthma has a protective effect in reduction of breathing pattern complexity whereas late treatment only had a partial impact on asthma induced respiratory pattern changes [85,86]. While direct BPD-specific pharmacotherapy is not available, there is interest in adjunctive treatments that address other comorbidities that potentially facilitate BPD. One feature of BPD is obligate mouth breathing that is often driven by comorbid sinonasal disease. In that context, BPD was reported in 53% of patients with chronic rhinosinusitis and severe asthma in one UK clinic series [87]. Furthermore, BPD was shown to be significantly associated with severity of sinonasal symptoms in an Australian difficult-to-treat asthma population [18]. In turn, sinonasal disease is a highly prevalent comorbidity in difficult-to-treat asthma and was observed in 67% of our WATCH cohort [12]. Restoring a nasal breathing pattern through treatment of sinonasal breathing can be considered a potentially important indirect pharmacological approach in BPD. Such treatments may include guideline advocated approaches for sinonasal disease like nasal corticosteroids and saline nasal sinus rinses [88,89] In some cases, additional surgical approaches to improve nasal patency may offer additional benefits to addressing sinonasal disease [89]. A small study of patients assessed at a tertiary center for refractory breathlessness examined the effect of identifying and treating rhinitis in patients referred for assessment of BPD/ILO [88]. Treatments comprised a combination of patient education, nasal corticosteroids, saline nasal rinses, and antihistamines. Treating rhinitis in this patient group significantly improved nasal symptom severity and improved asthma control among those patients with asthma.

10. Conclusions

The multimorbidity framework is very pertinent to a model of difficult-to-treat asthma. Difficult-to-treat asthma often comprises a multimorbidity network of adverse health conditions of which BPD is one of the most common. BPD presentations are complex and with no single assessment that holistically identifies BPD and diagnosis remains challenging. For now, diagnosis is a pragmatic clinical diagnosis supported by multiple objective assessments. The NQ as a continuous measure has demonstrated an increasing adverse outcome gradient and has potential clinical utility, following validation in other cohorts. This could be easily implemented into clinical practice, for example, to triage referrals to physiotherapy services.

Collectively, the emerging literature on BPD in difficult-to-treat asthma clearly demonstrates the significant impact of BPD on patient outcomes and is of high clinical relevance. Addressing BPD in patients with difficult-to-treat asthma could have clinical and health economic benefits. Specific interventions to treat BPD in difficult-to-treat asthma are not well established. Although positive effects on ACQ, and AQLQ have been demonstrated with breathing retraining and reductions in NQ have been shown with physical exercise, the underlying mechanism of improvement in patient outcomes are not well understood.

The literature presented suggest multimodal interventions are likely of benefit including, breathing pattern retraining, physical exercise and psychosocial interventions. There is a need for further research to develop better recognition and awareness of BPD as well as multimorbidity and the interactions of interventions to better manage patients with difficult-to treat-asthma.

11. Expert opinion summary

11.1. Relevance to impacting real-world outcomes

This review paper demonstrates that Breathing Pattern Disorder (BPD) is a very common comorbidity in patients with difficult-to-treat asthma. It also highlights that when BPD is present it exerts significant detrimental impacts on patients with difficult-to-treat asthma. These include negative impacts on asthma control, psychological well-being, and quality of life plus increased healthcare dependency for events such as exacerbations and hospital admissions. The research reviewed in this paper also provides guidance to support better identification of BPD in clinical practice and collectively should improve the ability of healthcare professionals to promptly diagnose BPD and to address it. Diagnostic tools like the Nijmegen Questionnaire should be readily implementable as low-cost measures that can be easily adopted in clinical practice in combination with other objective assessments to improve a more rigorous approach to BPD diagnosis. Asthma management guidelines could benefit from incorporating the enhanced understanding of BPD described in this review into clinical practice recommendations. Given the negative impacts of BPD outlined in this review, treating it is likely to deliver significant benefits at individual patient levels and in terms of wider health economic impacts. One barrier to clinical implementation of the treatment approaches described in this review may be lack of access to specialist physiotherapy. However, this review could be considered as a driver to developing such resources.

11.2. Key areas to address

This review highlights that one key limitation to addressing BPD more effectively in patients with difficult-to-treat asthma is a lack of clarity in diagnosis. Developing accurate and easy to use diagnostic tools that aid healthcare professionals to

make a prompt BPD diagnosis needs to be a core focus of future research. A shortcoming of current research on BPD and difficult-to-treat asthma is that it has been conducted in ethnically very similar populations in Europe, the UK and Australia. There is therefore a need to undertake future research on the associations of BPD with difficult-to-treat asthma in different ethnic populations to determine if they experience the same burden and impacts.

11.3. Potential future research in the field

Future research should focus on the impacts of treating BPD within difficult-to-treat asthma management to establish individual patient level benefits and parallel health-economic benefits. A definitive endpoint would be an intervention that is shown to be effective at reducing BPD significantly and further research is required to establish a MCID for the NQ in difficult to treat asthma. Although in a non-asthmatic population, it has been suggested that a reduction of 10 points on the NQ is clinically relevant [90] an acceptance of a score below the diagnostic threshold (<23) may also be appropriate in the asthmatic population. Future studies must be large in sample size and representative of the population being treated in international healthcare systems. Future research should also focus on understanding how BPD sits within the complex multimorbidity model of difficult-to-treat asthma and how holistic treatment approaches based on that model may address both BPD and difficult-to-treat asthma. This should utilize both qualitative and quantitative research. Further BPD research in these areas could significantly impact asthma management guidelines and clinical practice.

11.4. Future research focus in this field

A key area that future research should focus on is the development and assessment of multimodal non-pharmacological approaches that better support the wider needs of patients with difficult-to-treat asthma. The aim of such approaches would be to not only address BPD as an individual comorbidity in difficult-to-treat asthma, but to address its interactions with the many other comorbidities that often coexist with it such as obesity and psychological comorbidity.

11.5. Predicting evolution in this field

Asthma management has evolved dramatically in the past 10 years and will continue to do so in terms of airway focused pharmacological treatments. However, there is increasing recognition of the wider model of ill-health that envelopes patients with difficult-to-treat asthma. In the coming years, research will need to increasingly focus on the incorporation of multimodal interventions to holistically address this model of difficult-to-treat asthma into mainstream practice. We propose that such strategies must centrally address BPD assessment, diagnosis, and management. Based on the evidence we have presented, we would consider that BPD recognition, assessment, and management should become a standard of care alongside asthma pharmacotherapy in this high morbidity difficult to-treat asthma patient group.

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Abbreviations

Global Initiative for Asthma (GINA)short-acting beta-2 agonists (SABA), corticosteroids (OCS) inhaled corticosteroids (ICS), maintenance and reliever therapy (MART), Fractional Exhaled Nitric Oxide (FeNO), Body Mass Index (BMI), Asthma Quality of Life Questionnaire; (AQLQ), Breathing Pattern Disorder (BPD), Inducible Laryngeal Obstruction (ILO), gastro-esophageal reflux disease (GORD), obstructive sleep apnea (OSA) World Health Organisation (WHO), Nijmegen questionnaire (NQ), Cardiopulmonary Exercise Test (CPET), End Tidal Carbon Dioxide (EtCO2), Breathing Pattern Assessment, Tool (BPAT), Multi-disciplinary team (MDT)

Declarations of interest

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