Best supportive care for idiopathic pulmonary fibrosis: current gaps and future directions

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ABSTRACT Best supportive care (BSC) is generally defined as all the interventions and the multiprofessional approach aimed to improve and optimise quality of life (QoL) in patients affected by progressive diseases. In this sense, it excludes and might be complementary to other interventions directly targeting the disease. BSC improves survival in patients with different types of cancer. Patients with idiopathic pulmonary fibrosis (IPF) experience a vast range of symptoms during the natural history of the disease and might have a beneficial effect of BSC interventions. This review highlights the current evidence on interventions targeting QoL and gaps for the clinical assessment of BSC in the treatment of IPF patients. Very few interventions to improve QoL or improve symptom control are currently supported by well-designed studies. Sound methodology is paramount in evaluating BSC in IPF, as well as the use of validated tools to measure QoL and symptom control in this specific group of patients.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive respiratory disease characterised by a scarring process of the lung, bringing patients to respiratory failure and death in 3–5 years from diagnosis [1, 2]. New antifibrotic treatments are able to reduce the loss of respiratory function over time [3, 4], but their effect on symptom control and quality of life (QoL) is limited and needs further exploration [5–7]. A multidisciplinary approach for the diagnosis and treatment of IPF is recommended by current guidelines [1], as it has been shown to result in a more accurate diagnosis [8] and to positively affect survival in this group of patients [9].

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Best supportive care (BSC) is generally defined as all the interventions and the multiprofessional approach aimed to improve and to optimise QoL in patients affected by progressive diseases, taking into account physical, psychosocial, spiritual and cultural needs. Therapies targeting the disease, such as chemotherapy in cancer, are considered complementary but are not necessarily a part of BSC [10]. As such, it should be clearly distinguished from end-of-life care, adopted to reduce emotional and physical suffering in patients at the very last moments of their life, when active treatments and rehabilitation are no longer meaningful for patients [11, 12].

Most of the evidence about the efficacy of BSC in progressive diseases is derived from oncology, where it is recognised that BSC can influence survival [13]. Therefore, its role should be carefully considered when designing multicentre randomised trials [14, 15]. Unfortunately, an internationally accepted definition of BSC is not available, nor has it been possible to reach a consensus on a definition of BSC in oncology trials, due to the fact that the types of intervention vary greatly among different diseases. Therefore, a common definition of BSC and shared tools for its evaluation are simply not available [16]. Furthermore, the quality of BSC depends on the availability of resources to allocate to such interventions, and local differences play a major role in access to BSC.

Four domains are considered essential for the planning and evaluation of BSC strategies: multidisciplinary care, supportive care documentation, symptom assessment and symptom management (figure 1) [16]. The National Institute for Health and Care Excellence (UK) has identified BSC as a very important component of the management of patients with IPF, and has identified 13 components (varying from an accurate diagnosis to spiritual support) that should be addressed by caregivers, although no or very limited evidence is available to support their role or effect in improving QoL in this group of patients [17]. Relatively simple questions, such as the role of long-term oxygen treatment, are still not systematically explored with well-designed, targeted studies, so most of the recommendations in guidelines today are based on expert opinion or experiences from other fields, such as chronic obstructive pulmonary disease (COPD) and lung cancer [3]. In this review article, we will discuss what may be acknowledged as the state of the art for BSC for patients with IPF, based on the four aforementioned domains, with special emphasis on unanswered questions for future research.

Multidisciplinary care for patients with IPF

A multidisciplinary approach is strongly recommended by international guidelines on the diagnosis and treatment of IPF. Multidisciplinary conferences have rapidly become the main way to ensure quality and consistency in the diagnostic process, especially in university hospitals, and are recommended as the best possible "gold standard" for diagnosis in difficult cases [1, 18]. Highly specialised centres for the diagnosis and treatment of interstitial lung diseases (ILDs) have been developed and have been recommended by expert panels for the UK National Health Service on the model of current cancer services [19].

There is, however, no clear definition of multidisciplinary care of IPF, and it is unclear which professions should be involved in the care of this group of patients. Furthermore, the possibility to build a multidisciplinary team is strictly dependent on local resources, so great variability can be expected across the same healthcare system and especially among different countries and cultures/continents [20]. Although based on expert opinion with very few studies supporting this approach, it is recommended that access to specialised healthcare professionals should be regulated *via* referrals from primary care to specialists and thereafter to specialised centres [19]. At the tertiary level, a very important role is played by nurses specialising in the care of patients with ILDs [21, 22]. Indeed, as the main patient contacts in the healthcare system, they play a pivotal role in addressing a patient's needs and in coordinating a multidisciplinary team of other professionals around the patient. An example of the composition of such a team is shown in figure 1. It includes specialists with expertise in the care of ILDs, physiotherapists, occupational medicine professionals and professionals with expertise in the delivery of oxygen therapy, while psychologists, medical counsellors and professionals with expertise in providing palliative care are also very important for patients with progressive forms of ILDs. One of the main advantages of such organisation is the possibility to optimise the flow of patients, minimising delays in access to treatments and interventions, and at the same time giving a clear reference to patients, who often feel alone with their disease [13].

A very important task of the multidisciplinary team is the coordination of all the procedures/interventions to shortlist potential candidates for lung transplantation, thus avoiding unnecessary delays.

Supportive care documentation

A major problem is that BSC interventions are poorly reported, both in clinical trials and in real-life patient cohorts [16]. As discussed, there is no consensus on what is generally considered supportive care, and this is even less defined for rare diseases, such as ILDs in general and IPF in particular.

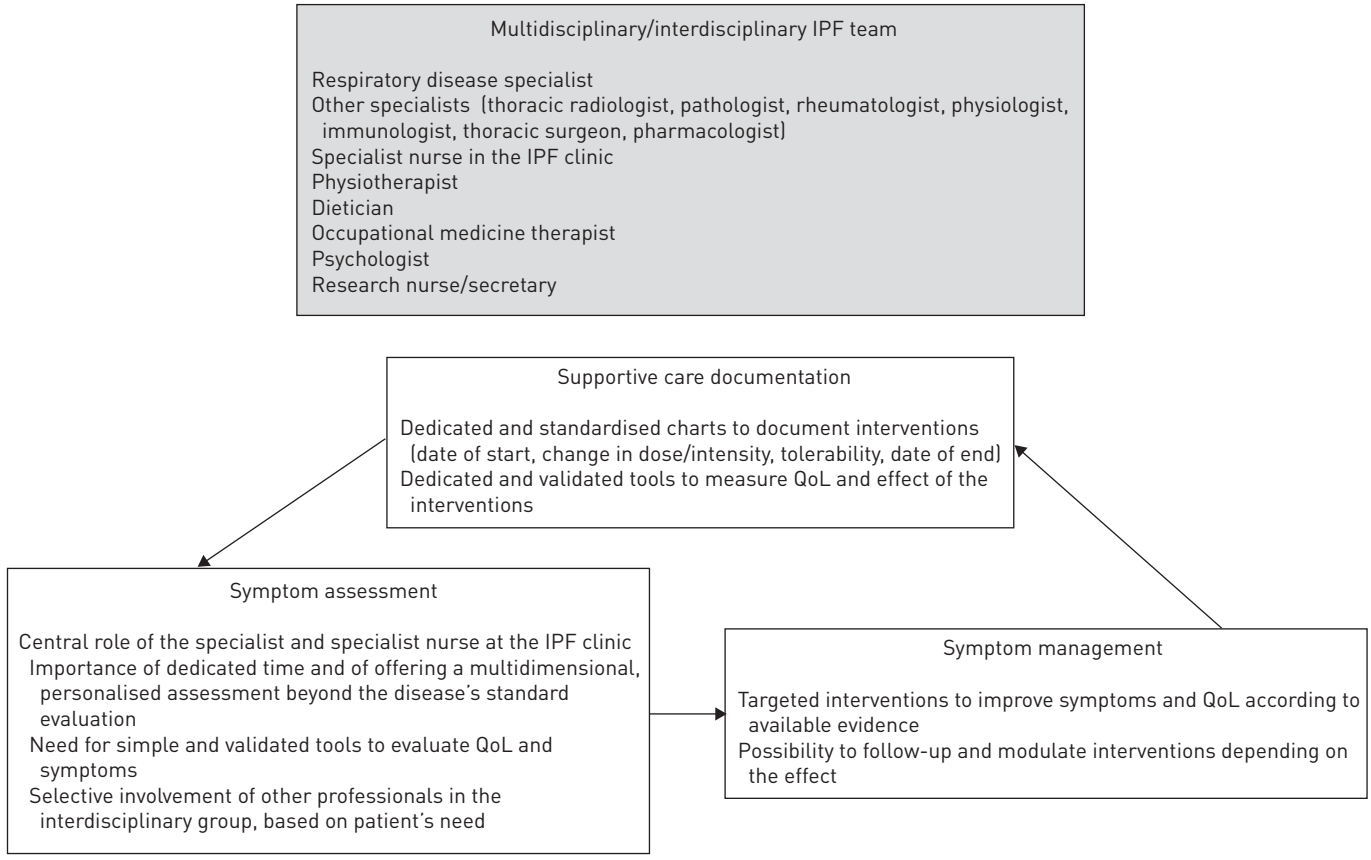

FIGURE 1 Flowchart showing the requirement for starting, documenting and evaluating the effect on quality of life (QoL) of interdisciplinary best supportive care in patients with idiopathic pulmonary fibrosis (IPF).

Trials targeted to slow down the progression of the disease [5, 6] have not reported data on BSC, and QoL was only a secondary outcome. Very poor attention has been paid to additional interventions (*e.g.* nutritional support, cough management and psychological support), even in studies targeted to assess the effect of new treatments or pulmonary rehabilitation on symptom control and the exercise capacity of IPF patients [23, 24].

It is thus paramount to define which complementary interventions are considered BSC in IPF patients and to implement specific ways of reporting how these interventions are used and their effect on the clinical history of the patients, both in randomised controlled trials (RCTs) and in real-life cohorts. The time of start, duration, intensity, follow-up and termination of an intervention should be documented with the same accuracy as for treatment interventions in RCTs, and their potential detrimental effect should also be carefully documented.

Symptom assessment

The major problem with the evaluation of QoL in IPF is that it has never been systematically and rigorously explored. Most data are collected by so-called "big RCTs" on new treatments [5, 6], but there are several limitations to this approach. First, exactly as in oncology, BSC interventions in control groups have never been clearly defined, and most results on QoL have been targeted to describe the effect of the intervention in the treatment arm in comparison to the control group. Secondly, most studies with primary outcomes strictly related to QoL (*e.g.* studies on the effect of drugs for pulmonary hypertension on dyspnoea and exercise capacity [23, 25–27]) have not shown positive results, and the duration of all RCTs has always been limited and often powered on surrogate outcomes. Last, but not least, there is a huge variability in the tools used to measure QoL in different studies, which often use questionnaires validated for other diseases (and not for IPF) or adjusted with poor methodology to fit the scope of the clinical trials.

Common tools to explore QoL are the EQ-5D (EuroQoL 5 dimension questionnaire) [28] and SF-36/RAND (36-item Short-Form Health Survey, developed by RAND, Santa Monica, CA, USA) [29], and their

use is encouraged by regulatory authorities when collecting data for national quality registries [30]. Unfortunately, they were developed to measure QoL in diseases with high prevalence in the population, and to explore domains (like physical pain) not really of primary interest when treating IPF and ILDs.

Recently, there has been a shift in assessing QoL in IPF and other fibrotic disorders. New tools offer a detailed assessment of major symptoms such breathlessness, but, unlike breathlessness scales, they also assess the impact of symptoms on activities, social interactions and mental health. The most widely used tool to assess QoL has been the St George's Respiratory Questionnaire (SGRQ) [31]. The validity of the SGRQ in IPF has been evaluated and is good [32]. When assessed with the SGRQ, QoL is severely impaired in IPF and comparable to other chronic disorders such as COPD [32, 33]. Although the SGRQ has been useful for gaining an early insight into the QoL of patients with IPF since it became readily available, it has some drawbacks. First, it was developed for COPD and not for IPF; as a consequence, it contains items that are not relevant to IPF. This potentially has a negative impact on the responsiveness of a tool, *i.e.* the ability to detect change. The SGRQ is also lengthy, containing 50 items. Recently, Yorke *et al.* [34] conducted a study to reduce the SGRQ to 34 items using well-established psychometric methodologies such as Rasch analysis. The SGRQ-IPF has good validity. It has, however, not been used widely, perhaps because of its length or because the initial pool of questions used to construct the questionnaire were for COPD and not IPF patients, so concerns regarding disease specificity remain. Swigris *et al.* [35] have developed an IPF-specific questionnaire (A Tool to Assess Quality of Life in IPF (ATAQ-IPF)) using validated methods. The ATAQ-IPF has good validity characteristics. The main limitation of the ATAQ-IPF is its length; 75 items are too many to be practical for routine clinical use or in clinical trials. Recently, Yorke *et al.* [36] have significantly reduced the number of items to 43, while retaining its validity in a USA–UK version called the cross-Atlantic ATAQ-IPF. The most recent QoL tool developed for IPF is the King's Brief Interstitial Lung Disease (K-BILD) questionnaire, which is composed of 15 questions exploring three domains (psychological, breathlessness and activity, chest symptoms), developed with modern item response theory methods, such as Rasch analysis [37]. The K-BILD has been well validated and its performance in fibrosing lung disorders has been as good as that in IPF [38, 39]. An advantage of the K-BILD is that it is brief and therefore practical. Its limitation is that it is relatively new and therefore few studies reporting its use are available. It also does not include any item to evaluate cough. Cough items were removed by Rasch analysis during development, because they did not conform to a unidimensional scale. This may have been because, while cough is a common symptom, the prevalence of severe and bothersome cough in IPF is poorly characterised and reported, due to different the methodologies and definitions used in the available studies [40]. Tools for the assessment of common symptoms (*e.g.* the Leicester Cough Questionnaire [41] or the modified Medical Research Council dyspnoea score (mMRC) [42]) have been developed and validated for other medical conditions (mainly COPD, refractory chronic cough) and only a few studies have been performed to assess their validity in patients with IPF/ILDs [43, 44].

Furthermore, it must be considered that all the available tools require time for the patient and caregivers to fill in the questionnaires and for evaluation of the results. Digital solutions offer the possibility to simplify this process by sending the questionnaires *via* email or by completion on a tablet in the waiting room before clinical evaluation [45].

Symptom management

Cough and exertional dyspnoea are the main symptoms reported by patients with IPF, with onset 2–5 years before diagnosis [1, 40]. In this section we will describe the main data on symptom control for the main medical problems in IPF patients, with special consideration of the effect of intervention on QoL. Table 1 offers an overview of the most common symptoms, tools and interventions to improve QoL in IPF patients.

Dyspnoea and exercise capacity

Shortness of breath is one of the main symptoms affecting QoL in patients with IPF [48], presenting more often as effort dyspnoea at the time of diagnosis, worsening during the natural history of the disease, until being manifest at rest in the terminal phases [2]. So far, no intervention has been proved to reverse the natural history of the disease and therefore to improve shortness of breath, acting on the causative mechanisms of the disease. Antifibrotic therapies such as pirfenidone and nintedanib have not shown any effect on dyspnoea, nor was this a primary outcome of published RCTs [5, 6]. Common interventions used in clinical practice to reduce shortness of breath include treatment of comorbidities, physical rehabilitation, supplemental oxygen and opioids/benzodiazepines [49].

Sildenafil has improved dyspnoea and QoL in a subgroup of IPF patients with pulmonary hypertension [23, 50] and, although it is currently not recommended as a treatment for IPF by international guidelines,

TABLE 1 Assessment and management of the most frequent problems in the best supportive care of patients with idiopathic pulmonary fibrosis (IPF)

Symptom/factors limiting QoL	Tool for assessment	Interventions
General well-being	EQ-5D	Management of symptoms influencing QoL
	SF-36/RAND	Mindfulness/meditation
	SGRQ-IPF#	Physical rehabilitation¶
	K-BILD#	Nutritional support
	ATAQ-IPF#	
Dyspnoea	mMRC	Physical rehabilitation¶
	SGRQ-IPF#	Supplemental oxygen
	K-BILD#	Treatment of PH with sildenafil¶
	ATAQ-IPF-cA#	Pharmacological interventions (morphine/benzodiazepines)¶
	UCSD SOB#	
Cough	LCQ#	Poor effect of usual anti-tussive drugs
	VAS#	Systemic steroids
	CQLQ#	Thalidomide¶
		Gabapentin
		Opiates
		PSALTI
Anxiety/depression	EQ-5D	Counselling/cognitive behavioural therapy
	SF-36/RAND	Antidepressants
	K-BILD#	Physical rehabilitation
	SGRQ-IPF#	Nutritional support (loss of appetite)
	ATAQ-IPF-cA#	
Weight loss	NA	Nutritional support
Comorbidities	NA	Treatment of PH with sildenafil¶
		Anti-reflux measures in patients with GORD

QoL: quality of life; EQ-5D: EuroQoL 5 dimension questionnaire [28]; SF-36/RAND: 36-item Short-Form Health Survey, developed by RAND (Santa Monica, CA, USA) [29]; SGRQ-IPF: St George's Respiratory Questionnaire, IPF-specific version [34]; K-BILD: King's Brief Interstitial Lung Disease questionnaire [38]; ATAQ-IPF: A Tool to Assess Quality of Life in IPF [35]; mMRC: modified Medical Research Council Dyspnoea Questionnaire [42]; ATAQ-IPF-cA: cross-Atlantic ATAQ-IPF [36]; UCSD SOB: University California San Diego Shortness of Breath Questionnaire [46]; LCQ: Leicester Cough Questionnaire [41]; VAS: visual analogue scale cough [47]; CQLQ: Cough Quality-of-Life Questionnaire; NA: not applicable; PH: pulmonary hypertension; PSALTI: physiotherapy, and speech and language intervention; GORD: gastro-oesophageal reflux disease. #: validated for use in IPF patients; ¶: efficacy somehow proved by randomised controlled trials involving patients with IPF.

its use can be considered in patients with concomitant pulmonary hypertension and low diffusing capacity for carbon monoxide, to improve effort dyspnoea and QoL [4]. No studies are available on the role of bronchodilators in patients with IPF and signs of airflow obstruction at spirometry.

Physical rehabilitation can improve exercise tolerance, dyspnoea and QoL in patients with ILDs [24], and its effect is proven in patients with IPF [51–53]. Despite differences in the programmes, outcomes and scales used in the available studies and the open questions about the long-term effect of the intervention and on how to maximise its effect [54], physical rehabilitation is probably the safest and most effective treatment of dyspnoea, and is widely recommended for all patients with IPF [1].

The use of supplemental oxygen during exertion to relieve dyspnoea in patients who are normoxic at rest but desaturating with exercise is still controversial: a recent meta-analysis, including 98 patients with IPF, failed to show any evidence to support or refuse the use of supplemental oxygen on exertion [55]. A recent study has shown that oxygen at a fraction of inspired oxygen of 0.50 improved tolerance, saturation and dyspnoea during exercise in patients with IPF [56], and it is possible that differences in methodology, oxygen dose and outcomes are behind the current uncertainty about this intervention and further studies are needed to clarify its impact on health and QoL of patients with IPF.

Opioids are often used in the latest stages of the disease to reduce refractory dyspnoea and, as such, their use should not really be contemplated for BSC. Their safety up to a dose of 30 $mg \cdot day^{-1}$ is based mainly on data from other chronic respiratory diseases [57]. A recent systematic review showed some effect on dyspnoea and exercise tolerance of systemic opioids in patients with IPF, but no effect at all of inhaled morphine, and constipation was a significant adverse event [58]. A recent systematic review/meta-analysis on the role of benzodiazepines for improving dyspnoea in patients with chronic respiratory diseases (including IPF) showed that this class of drugs could have a better tolerability profile compared to morphine, but not a better clinical effect [59]. Further studies are needed to better assess the value of

opioids and benzodiazepines in the treatment of dyspnoea in IPF patients, but side-effects such as drowsiness seem to reduce their clinical utility in patients at an early disease stage.

Cough

One symptom with a marked impact on daily life in IPF patients is cough [40]. It is usually refractory and considered an independent predictor of disease progression [60]. In the majority of patients, cough is among the first symptoms, often preceding dyspnoea on exertion, sometimes by years [61]. Cough in IPF patients is more common during the day and rarely wakens the patients from sleep, consistent with the diurnal variation reported in many chronic respiratory disorders [62]. Cough may coexist or be exacerbated by comorbid illnesses such as gastro-oesophageal reflux, despite its treatment [63], and is generally refractory to medical therapy [48]. In fact, symptomatic anti-tussive treatment is usually not effective [64].

Oral corticosteroids have been shown to be effective in improving cough in some IPF patients [64], and low doses of prednisone are sometimes prescribed in daily practice for this purpose and are then slowly tapered if they are beneficial [40]. However, no effect on QoL and survival has been shown, and possible side-effects should be taken into consideration [40]. Although opiates are recommended in palliative care, their effect has not been demonstrated in IPF [1]. Furthermore, administration of opiates might be effective for palliation of severe cough in patients with advanced IPF.

Horton *et al.* [65] studied the efficacy of thalidomide in suppressing cough in IPF patients. Using the Cough Quality-of-Life Questionnaire [66], they showed that thalidomide significantly improved cough in IPF patients. However, adverse events (mainly constipation, dizziness and malaise) occurred with high prevalence in patients receiving thalidomide. Evaluating the need to calculate a cost-effective benefit in administering thalidomide, only 20% of the screened subjects completed the study, with potentially severe side-effects. The mechanism of action of thalidomide is not known but is thought to be anti-inflammatory. Its side-effect profile, including dizziness and neuropathy, suggests that it might also have effects on sensory nerves, potentially explaining the effect of thalidomide on chronic cough. Although these results suggest the need for further investigations, thalidomide should not be considered a routine treatment for cough in IPF patients.

Although there are no specific trials performed in IPF, a meta-analysis focusing also on gabapentin has shown promising results in relieving sensory neuropathic cough and therefore in the treatment of cough for select cases of refractory chronic cough [67].

Mild to moderate IPF patients are usually treated with one of the two new antifibrotic drugs, pirfenidone or nintedanib [3]. Although the impact of these drugs on cough has not been extensively studied, there are some indications of a potential effect. Some effect has been shown, at least for pirfenidone, both in animal models [68] and in humans [69]. Currently, no data are available on the effect of nintedanib on cough, and the recommendation of these drugs in the guidelines concerns only their effect on lung function [3]. Recently, an RCT showed the efficacy of a combination of nonpharmacological interventions, grouped under the term "physiotherapy, and speech and language intervention" (PSALTI), in patients with refractory chronic cough [70]; this approach remains to be proven in IPF, but highlights the potential benefit of physiotherapy and nonpharmacological interventions.

Anxiety/depression and weight loss

IPF is a chronic condition with significant morbidity and mortality and, as with other chronic diseases, is frequently associated with anxiety and depression. Anxiety and depression are known to occur frequently in patients with dyspnoea [71, 72]. In COPD, reported breathlessness severity is linked both with depression and functional impairment [73]. Qualitative studies in COPD reported the patient-described perception of acute dyspnoea as "an experience inextricably related to anxiety and emotional functioning" [74]. Depression and anxiety should not be considered unrelated to breathlessness, or cough and other symptom increase, and require particular attention in IPF patients. Clinically significant symptoms of depression and anxiety are present in up to 50% and 30% of IPF patients [75–77], respectively, as well as in COPD, and are associated with dyspnoea and disease severity [78]. The presence of these symptoms deeply affects IPF patients' QoL [78]. All patients with IPF should be investigated regarding these symptoms at the time of diagnosis and when disease progresses and becomes severe [79, 80]. The close relationship between depression and anxiety and IPF severity suggests that these symptoms may improve with treatment of the IPF itself, such as with antifibrotic treatments, supplemental oxygen and pulmonary rehabilitation [79–81]. There are few data about the treatment results of clinically significant depression in IPF patients (there are more data for COPD, and most treatment recommendations are extrapolated from studies of non-IPF patients) [82, 83], but symptom persistence suggests that antidepressant and cognitive behavioural therapy should not be delayed in order to improve QoL [84]. Pulmonary rehabilitation may be

a useful treatment to improve psychological health in IPF through improvements in dyspnoea, fatigue and exercise tolerance [79]. Poor appetite is a common symptom of depression, and this is one of the possible causes of the weight loss observed in many people with severe IPF. Right heart failure, medications used for cough control, increased energy consumption due to increased work of breathing, and "difficulty" in eating can all contribute to weight loss. Lastly, the two drugs approved for IPF treatment, pirfenidone and nintedanib, may cause nausea [5, 6], reduction of appetite and contribute to weight loss. Nutrition is one of the less investigated aspects and unmet needs in IPF.

Treatment of comorbidities

As in many elderly populations, comorbid conditions are frequent in patients with IPF, affecting symptom burden and perhaps prognosis [80]. Many comorbidities have been stated to be more common in IPF than in the general population, including cardiovascular and thromboembolic diseases, depression, reflux disease, emphysema, lung cancer, sleep disorders and diabetes [85]. Furthermore, a significant association between the frequency of comorbidities and impaired health-related QoL has been described recently [86]. One may thus hypothesise that active screening for and treatment of comorbid conditions may ameliorate the burden of disease, increase QoL and perhaps improve the prognosis in IPF. However, this is currently under debate and has yet to be established. One example in this debate is gastro-oesophageal reflux disease, which has been reported to be frequent in IPF patients and affects symptom burden [87]. This has led to a discussion of a potential treatment effect of antireflux measures against IPF. *Post hoc* and retrospective data that reported on positive effects of antacid therapies with regard to lung function decline and acute exacerbations [88, 89] have led to a conditional recommendation for the use of antacid drugs in all IPF patients [3]. However, more recent data could not support these findings and even hypothesised a higher pulmonary infection rate in patients taking antacid drugs [90–92]. Therefore, future research must aim to prospectively assess the impact of comorbidities on symptoms and outcome as well as respective treatment measures. Currently, comorbidities in IPF should be treated as in non-IPF patients.

Conclusions

This review has explored the role of BSC in the clinical management of patients with IPF. As for other fields, like oncology, defining BSC for ILDs and IPF is particularly difficult due to differences in the methodologies of studies, scales to measure QoL and symptoms, and very often because BSC interventions and their results are not or are only poorly documented, in both real life and RCTs.

A systematic approach, based on four pillars (multidisciplinary care, supportive care documentation, symptom assessment and symptom management) [16] seems to offer the best framework to organise the available published data and to address gaps and needs for further clinical research.

The multidisciplinary/interdisciplinary workup around IPF patients is paramount to address the complex and multidimensional assessment of patients' needs. As discussed in the introductory section, it has not been demonstrated that this approach results in improved survival or QoL for IPF patients; nevertheless, experts recommend this approach for IPF patients in tertiary reference centres for ILDs, mainly based on the experience derived from cancer and other progressive diseases [19]. A very important task for the multidisciplinary/interdisciplinary teams will be to show how this approach is beneficial for IPF patients and eventually to explore the possibility of delegating some of its components to healthcare players in the field. One example of a multidisciplinary/interdisciplinary team is the Outpatient Clinic for IPF at the New Karolinska University Hospital in Stockholm, Sweden, where three respiratory disease specialists, two specialised nurses, two physiotherapists, one dietician, one occupational medicine therapist, one medical counsellor, two research nurses and a secretary work together to address all the supportive interventions needed to optimise the condition of the patients. QoL is evaluated at every medical visit thanks to digital solutions where the patient fills in QoL questionnaires on a tablet and scores are directly available to the team. In addition, three radiologists, one pathologist and one physiologist work closely with the team, taking regular part in monthly multidisciplinary conferences. The costs of this approach are high, and policies and guidelines recommend it only in tertiary, specialised reference centres [19], where patients with relatively rare diseases should be referred.

Documentation and analysis of the results of supportive interventions are also crucial to fill current gaps. Digital solutions are slowly entering clinical practice and their implementation can enable patients to self-report QoL and symptom scale measurements without absorbing resources from the staff. Simplified, validated disease-specific questionnaires will also contribute to simplifying this task in the near future, but at present it is important to devote time and resources to quality data reporting and analysis: this is crucial to evaluate and improve the impact of supportive care strategies.

The effect of pharmacological and nonpharmacological interventions must be systematically documented and evaluated in both clinical trials and real life (*e.g.* with a quality registry for IPF). This will contribute

to improving evidence about the use of these interventions in the treatment of patients with IPF and other ILDs and will contribute to highlighting areas of uncertainty and new research questions. It is thus very important that BSC is taken into account when designing new trials and in real-life studies.

As discussed in the section on symptom management, very few BSC interventions are supported by well-designed RCTs, so most approaches are based on experience and tradition at a single reference centre. The authors of this review believe that more attention should be devoted to symptom control and QoL of patients with IPF and that the current lack of studies on BSC should not limit the access of patients to potentially beneficial interventions.

Physical rehabilitation has documented positive effects on general well-being and dyspnoea [51–53]. A precise assessment of the symptoms should be offered to all IPF patients and should be performed by an experienced physiotherapist with a 6-min walk test (6MWT) and validated tools; the same tools should be used to document the effect of rehabilitation. Although the available studies are not conclusive on its effect [55, 56], supplemental oxygen can be beneficial in patients showing desaturation during the 6MWT; this need should be carefully assessed by a registered nurse with good experience in oxygen therapy, performing a 6MWT without and with oxygen, registering arterial oxygen saturation (S_aO_2) and intensity of dyspnoea during effort and trying to titrate the oxygen flow to maintain the S_aO_2 over 92%. Severe cough can be an important clinical problem in patients with IPF. A combined approach with pharmacological (including gabapentin [67] or thalidomide [65] in the severest cases) and nonpharmacological (*e.g.* mucus mobilisation/physical rehabilitation or PSALTI [70]) interventions is preferred in patients with severe cough, due to the limited effect of common anti-tussive drugs. Again, it is paramount that experienced staff performs a precise assessment of the symptom and of the effect of the interventions with validated tools. We do recommend nutritional support in patients reporting weight loss and poor appetite, with assessment and follow-up performed by a dedicated dietician. In our experience, psychological support is also very important to support IPF patients during their journey: a psychologist is of great added value in the interdisciplinary team and the possibility to establish contact with such an individual should be offered to all patients, at diagnosis and later on during the course of the disease. Patients also appreciate the possibility to meet and discuss their disease with other patients and in information meetings with all the professionals involved: such initiatives should be encouraged. Finally, pharmacological treatment of anxiety/depression has to be considered as soon as such problems arise. Optimal treatment of comorbidities is also important, as they can result in additional symptoms and added short- and long-term complications.

Despite all the methodological and practical limitations and despite the lack of solid evidence on the efficacy of the available interventions, a systematic collection of QoL measurements with validated tools and large cohorts is urgently needed to obtain reliable data and to evaluate the potential impact of all the available interventions on patient life.

National registries are a potential source of long-term, real-life data on QoL; the development and validation of patient-reported outcome measures is considered one of the main goals for quality registries, to ease resource allocation in the framework of value-based healthcare [30]. Although the same methodological problems are present with real-life data, national registries are already implementing the measurement of QoL in patients with IPF [45, 86, 93–95], and this approach will allow the collection of prospective data on the clinical history of the disease and will offer the possibility to explore the long-term effect of several interventions on QoL. One example is the recent report on QoL in the German INSIGHTS-IPF registry [86]. Statistically significant associations of QoL with clinical symptoms, number of comorbidities, hospitalisation rate and disease severity (including functional data) have been reported [86]. The life of a patient with IPF is influenced by respiratory (dyspnoea, cough, limited exercise capacity) and systemic (weight loss, anxiety/depression) symptoms/conditions [80] that must be properly recorded and evaluated over time to assess the effect of different interventions on their severity and impact on QoL. Furthermore, the role of comorbidities and of their respective treatments must be taken into account and properly evaluated, as they influence QoL and prognosis in IPF patients [80, 96, 97].

New clinical trials will need to precisely record all BSC interventions and measure QoL with appropriate tools. The potential confounding factor of side-effects will be of relevance, especially in the case of combination therapy [98, 99], and it is likely that supportive interventions will have a major role in increasing tolerance to new treatments.

Our review highlights the need for a wider consensus to standardise definitions and methodologies about BSC in IPF. We hope that this review will raise awareness for this important issue and boost the discussion for inclusion of BSC as an important part of the clinical management of IPF patients.

References

1 Raghu G, Collard HR, Egan JJ, *et al.* An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011; 183: 788–824.
2 Richeldi L, Collard HR, Jones MG. Idiopathic pulmonary fibrosis. *Lancet* 2017; 389: 1941–1952.
3 Raghu G, Rochwerg B, Zhang Y, *et al.* An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis. An update of the 2011 clinical practice guideline. *Am J Respir Crit Care Med* 2015; 192: e3–e19.
4 Sköld CM, Bendstrup E, Myllärniemi M, *et al.* Treatment of idiopathic pulmonary fibrosis: a position paper from a Nordic expert group. *J Intern Med* 2017; 281: 149–166.
5 Richeldi L, du Bois RM, Raghu G, *et al.* Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med* 2014; 370: 2071–2082.
6 King TE, Bradford WZ, Castro-Bernardini S, *et al.* A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 2014; 370: 2083–2092.
7 Richeldi L, Cottin V, du Bois RM, *et al.* Nintedanib in patients with idiopathic pulmonary fibrosis: combined evidence from the TOMORROW and INPULSIS trials. *Respir Med* 2016; 113: 74–79.
8 Flaherty KR, King TE, Raghu G, *et al.* Idiopathic interstitial pneumonia: what is the effect of a multidisciplinary approach to diagnosis? *Am J Respir Crit Care Med* 2004; 170: 904–910.
9 Lok SS. Interstitial lung disease clinics for the management of idiopathic pulmonary fibrosis: a potential advantage to patients. Greater Manchester Lung Fibrosis Consortium. *J Heart Lung Transplant* 1999; 18: 884–890.
10 Ahmed N, Ahmedzai S, Vora V, *et al.* Supportive care for patients with gastrointestinal cancer. *Cochrane Database Syst Rev* 2004; 3: CD003445.
11 Lindell KO, Liang Z, Hoffman LA, *et al.* Palliative care and location of death in decedents with idiopathic pulmonary fibrosis. *Chest* 2015; 147: 423–429.
12 Rajala K, Lehto JT, Saarinen M, *et al.* End-of-life care of patients with idiopathic pulmonary fibrosis. *BMC Palliat Care* 2016; 15: 85.
13 Prades J, Remue E, van Hoof E, *et al.* Is it worth reorganising cancer services on the basis of multidisciplinary teams (MDTs)? A systematic review of the objectives and organisation of MDTs and their impact on patient outcomes. *Health Policy* 2015; 119: 464–474.
14 Cherny NI, Abernethy AP, Strasser F, *et al.* Improving the methodologic and ethical validity of best supportive care studies in oncology: lessons from a systematic review. *J Clin Oncol* 2009; 27: 5476–5486.
15 Nipp RD, Currow DC, Cherny NI, *et al.* Best supportive care in clinical trials: review of the inconsistency in control arm design. *Br J Cancer* 2015; 113: 6–11.
16 Zafar SY, Currow DC, Cherny N, *et al.* Consensus-based standards for best supportive care in clinical trials in advanced cancer. *Lancet Oncol* 2012; 13: e77–e82.
17 National Clinical Guideline Centre. Diagnosis and Management of Suspected Idiopathic Pulmonary Fibrosis: Idiopathic Pulmonary Fibrosis. London, National Clinical Guideline Centre, 2013. www.ncbi.nlm.nih.gov/pubmedhealth/PMH0068972/pdf/PubMedHealth_PMH0068972.pdf
18 Walsh SL, Wells AU, Desai SR, *et al.* Multicentre evaluation of multidisciplinary team meeting agreement on diagnosis in diffuse parenchymal lung disease: a case–cohort study. *Lancet Respir Med* 2016; 4: 557–565.
19 Thickett DR, Kendall C, Spencer LG, *et al.* Improving care for patients with idiopathic pulmonary fibrosis (IPF) in the UK: a round table discussion. *Thorax* 2014; 69: 1136–1140.
20 Bendstrup E, Hyldgaard C, Altraja A, *et al.* Organisation of diagnosis and treatment of idiopathic pulmonary fibrosis and other interstitial lung diseases in the Nordic countries. *Eur Clin Respir J* 2015; 2: 28348.
21 Russell AM, Ripamonti E, Vancheri C. Qualitative European survey of patients with idiopathic pulmonary fibrosis: patients' perspectives of the disease and treatment. *BMC Pulm Med* 2016; 16: 10.
22 Russell AM, Sprangers MAG, Wibberley S, *et al.* The need for patient-centred clinical research in idiopathic pulmonary fibrosis. *BMC Med* 2015; 13: 240.
23 Idiopathic Pulmonary Fibrosis Clinical Research Network, Zisman DA, Schwarz M, *et al.* A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. *N Engl J Med* 2010; 363: 620–628.
24 Dowman L, Hill CJ, Holland AE. Pulmonary rehabilitation for interstitial lung disease. *Cochrane Database Syst Rev* 2014; 10: CD006322.
25 King TE, Behr J, Brown KK, *et al.* BUILD-1: a randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2008; 177: 75–81.
26 King TE, Brown KK, Raghu G, *et al.* BUILD-3: a randomized, controlled trial of bosentan in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011; 184: 92–99.
27 Raghu G, Behr J, Brown KK, *et al.* Treatment of idiopathic pulmonary fibrosis with ambrisentan: a parallel, randomized trial. *Ann Intern Med* 2013; 158: 641–649.
28 Devlin NJ, Parkin D, Browne J. Patient-reported outcome measures in the NHS: new methods for analysing and reporting EQ-5D data. *Health Econ* 2010; 19: 886–905.
29 Hays RD, Morales LS. The RAND-36 measure of health-related quality of life. *Ann Med* 2001; 33: 350–357.
30 Nilsson E, Orwelius L, Kristenson M. Patient-reported outcomes in the Swedish National Quality Registers. *J Intern Med* 2016; 279: 141–153.
31 Jones PW, Quirk FH, Baveystock CM, *et al.* A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. *Am Rev Respir Dis* 1992; 145: 1321–1327.
32 Swigris JJ, Esser D, Wilson H, *et al.* Psychometric properties of the St George's Respiratory Questionnaire in patients with idiopathic pulmonary fibrosis. *Eur Respir J* 2017; 49: 1601788.
33 Swigris JJ, Esser D, Conoscenti CS, *et al.* The psychometric properties of the St George's Respiratory Questionnaire (SGRQ) in patients with idiopathic pulmonary fibrosis: a literature review. *Health Qual Life Outcomes* 2014; 12: 124.
34 Yorke J, Jones PW, Swigris JJ. Development and validity testing of an IPF-specific version of the St George's Respiratory Questionnaire. *Thorax* 2010; 65: 921–926.
35 Swigris JJ, Wilson SR, Green KE, *et al.* Development of the ATAQ-IPF: a tool to assess quality of life in IPF. *Health Qual Life Outcomes* 2010; 8: 77.

36 Yorke J, Spencer LG, Duck A, *et al.* Cross-Atlantic modification and validation of the A Tool to Assess Quality of Life in Idiopathic Pulmonary Fibrosis (ATAQ-IPF-cA). *BMJ Open Respir Res* 2014; 1: e000024.
37 Patel AS, Siegert RJ, Bajwah S, *et al.* Rasch analysis and impact factor methods both yield valid and comparable measures of health status in interstitial lung disease. *J Clin Epidemiol* 2015; 68: 1019–1027.
38 Patel AS, Siegert RJ, Brignall K, *et al.* The development and validation of the King's Brief Interstitial Lung Disease (K-BILD) health status questionnaire. *Thorax* 2012; 67: 804–810.
39 Patel AS, Siegert RJ, Keir GJ, *et al.* The minimal important difference of the King's Brief Interstitial Lung Disease Questionnaire (K-BILD) and forced vital capacity in interstitial lung disease. *Respir Med* 2013; 107: 1438–1443.
40 van Manen MJ, Birring SS, Vancheri C, *et al.* Cough in idiopathic pulmonary fibrosis. *Eur Respir Rev* 2016; 25: 278–286.
41 Birring SS, Prudon B, Carr AJ, *et al.* Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). *Thorax* 2003; 58: 339–343.
42 Bestall JC, Paul EA, Garrod R, *et al.* Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax* 1999; 54: 581–586.
43 Tashkin DP, Volkmann ER, Tseng CH, *et al.* Improved cough and cough-specific quality of life in patients treated for scleroderma-related interstitial lung disease: results of Scleroderma Lung Study II. *Chest* 2017; 151: 813–820.
44 Yorke J, Swigris J, Russell AM, *et al.* Dyspnea-12 is a valid and reliable measure of breathlessness in patients with interstitial lung disease. *Chest* 2011; 139: 159–164.
45 Ferrara G, Carlson L, Palm A, *et al.* Idiopathic pulmonary fibrosis in Sweden: report from the first year of activity of the Swedish IPF-Registry. *Eur Clin Respir J* 2016; 3: 31090.
46 Swigris JJ, Han M, Vij R, *et al.* The UCSD shortness of breath questionnaire has longitudinal construct validity in idiopathic pulmonary fibrosis. *Respir Med* 2012; 106: 1447–1455.
47 Key AL, Holt K, Hamilton A, *et al.* Objective cough frequency in Idiopathic Pulmonary Fibrosis. *Cough* 2010; 6: 4.
48 Swigris JJ, Kuschner WG, Jacobs SS, *et al.* Health-related quality of life in patients with idiopathic pulmonary fibrosis: a systematic review. *Thorax* 2005; 60: 588–594.
49 Ryerson CJ, Donesky D, Pantilat SZ, *et al.* Dyspnea in idiopathic pulmonary fibrosis: a systematic review. *J Pain Symptom Manage* 2012; 43: 771–782.
50 Collard HR, Anstrom KJ, Schwarz MI, *et al.* Sildenafil improves walk distance in idiopathic pulmonary fibrosis. *Chest* 2007; 131: 897–899.
51 Dowman LM, McDonald CF, Hill CJ, *et al.* The evidence of benefits of exercise training in interstitial lung disease: a randomised controlled trial. *Thorax* 2017; 72: 610–619.
52 Nishiyama O, Kondoh Y, Kimura T, *et al.* Effects of pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. *Respirology* 2008; 13: 394–399.
53 Ozalevli S, Karaali HK, Ilgin D, *et al.* Effect of home-based pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. *Multidiscip Respir Med* 2010; 5: 31–37.
54 Curtis K, Hopkinson NS. Exercise training in interstitial lung disease: lumping or splitting? *Thorax* 2017; 72: 589–590.
55 Sharp C, Adamali H, Millar AB. Ambulatory and short-burst oxygen for interstitial lung disease. *Cochrane Database Syst Rev* 2016; 7: CD011716.
56 Dowman LM, McDonald CF, Bozinovski S, *et al.* Greater endurance capacity and improved dyspnoea with acute oxygen supplementation in idiopathic pulmonary fibrosis patients without resting hypoxaemia. *Respirology* 2017; 22: 957–964.
57 Ekström MP, Bornefalk-Hermansson A, Abernethy AP, *et al.* Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study. *BMJ* 2014; 348: g445.
58 Kohberg C, Andersen CU, Bendstrup E. Opioids: an unexplored option for treatment of dyspnea in IPF. *Eur Clin Respir J* 2016; 3: 30629.
59 Simon ST, Higginson IJ, Booth S, *et al.* Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults. *Cochrane Database Syst Rev* 2016; 10: CD007354.
60 Ryerson CJ, Abbritti M, Ley B, *et al.* Cough predicts prognosis in idiopathic pulmonary fibrosis. *Respirology* 2011; 16: 969–975.
61 Crystal RG, Fulmer JD, Roberts WC, *et al.* Idiopathic pulmonary fibrosis. Clinical, histologic, radiographic, physiologic, scintigraphic, cytologic, and biochemical aspects. *Ann Intern Med* 1976; 85: 769–788.
62 Vigeland CL, Hughes AH, Horton MR. Etiology and treatment of cough in idiopathic pulmonary fibrosis. *Respir Med* 2017; 123: 98–104.
63 Kilduff CE, Counter MJ, Thomas GA, *et al.* Effect of acid suppression therapy on gastroesophageal reflux and cough in idiopathic pulmonary fibrosis: an intervention study. *Cough* 2014; 10: 4.
64 Hope-Gill BD, Hilldrup S, Davies C, *et al.* A study of the cough reflex in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2003; 168: 995–1002.
65 Horton MR, Santopietro V, Mathew L, *et al.* Thalidomide for the treatment of cough in idiopathic pulmonary fibrosis: a randomized trial. *Ann Intern Med* 2012; 157: 398–406.
66 Lechtzin N, Hilliard ME, Horton MR. Validation of the Cough Quality-of-Life Questionnaire in patients with idiopathic pulmonary fibrosis. *Chest* 2013; 143: 1745–1749.
67 Wei W, Liu R, ZhangTong Y, *et al.* The efficacy of specific neuromodulators on human refractory chronic cough: a systematic review and meta-analysis. *J Thorac Dis* 2016; 8: 2942–2951.
68 Okazaki A, Ohkura N, Fujimura M, *et al.* Effects of pirfenidone on increased cough reflex sensitivity in guinea pigs. *Pulm Pharmacol Ther* 2013; 26: 603–608.
69 Azuma A, Taguchi Y, Ogura T, *et al.* Exploratory analysis of a phase III trial of pirfenidone identifies a subpopulation of patients with idiopathic pulmonary fibrosis as benefiting from treatment. *Respir Res* 2011; 12: 143.
70 Chamberlain Mitchell SA, Garrod R, Clark L, *et al.* Physiotherapy, and speech and language therapy intervention for patients with refractory chronic cough: a multicentre randomised control trial. *Thorax* 2017; 72: 129–136.
71 Bausewein C, Farquhar M, Booth S, *et al.* Measurement of breathlessness in advanced disease: a systematic review. *Respir Med* 2007; 101: 399–410.
72 Bausewein C, Booth S, Gysels M, *et al.* Understanding breathlessness: cross-sectional comparison of symptom burden and palliative care needs in chronic obstructive pulmonary disease and cancer. *J Palliat Med* 2010; 13: 1109–1118.

73 Funk GC, Kirchheiner K, Burghuber OC, *et al.* BODE index *versus* GOLD classification for explaining anxious and depressive symptoms in patients with COPD – a cross-sectional study. *Respir Res* 2009; 10: 1.
74 Bailey PH. The dyspnea-anxiety-dyspnea cycle – COPD patients' stories of breathlessness: "It's scary/when you can't breathe". *Qual Health Res* 2004; 14: 760–778.
75 Ryerson CJ, Berkeley J, Carrieri-Kohlman VL, *et al.* Depression and functional status are strongly associated with dyspnea in interstitial lung disease. *Chest* 2011; 139: 609–616.
76 Akhtar AA, Ali MA, Smith RP. Depression in patients with idiopathic pulmonary fibrosis. *Chron Respir Dis* 2013; 10: 127–133.
77 Holland AE, Fiore JF Jr, Bell EC, *et al.* Dyspnoea and comorbidity contribute to anxiety and depression in interstitial lung disease. *Respirology* 2014; 19: 1215–1221.
78 De Vries J, Kessels BL, Drent M. Quality of life of idiopathic pulmonary fibrosis patients. *Eur Respir J* 2001; 17: 954–961.
79 Fulton BG, Ryerson CJ. Managing comorbidities in idiopathic pulmonary fibrosis. *Int J Gen Med* 2015; 8: 309–318.
80 King CS, Nathan SD. Idiopathic pulmonary fibrosis: effects and optimal management of comorbidities. *Lancet Respir Med* 2017; 5: 72–84.
81 Ryerson CJ, Cayou C, Topp F, *et al.* Pulmonary rehabilitation improves long-term outcomes in interstitial lung disease: a prospective cohort study. *Respir Med* 2014; 108: 203–210.
82 Kunik ME, Veazey C, Cully JA, *et al.* COPD education and cognitive behavioral therapy group treatment for clinically significant symptoms of depression and anxiety in COPD patients: a randomized controlled trial. *Psychol Med* 2008; 38: 385–396.
83 Rayner L, Price A, Evans A, *et al.* Antidepressants for depression in physically ill people. *Cochrane Database Syst Rev* 2010; 3: CD007503.
84 Ryerson CJ, Arean PA, Berkeley J, *et al.* Depression is a common and chronic comorbidity in patients with interstitial lung disease. *Respirology* 2012; 17: 525–532.
85 Collard HR, Ward AJ, Lanes S, *et al.* Burden of illness in idiopathic pulmonary fibrosis. *J Med Econ* 2012; 15: 829–835.
86 Kreuter M, Swigris J, Pittrow D, *et al.* Health related quality of life in patients with idiopathic pulmonary fibrosis in clinical practice: INSIGHTS-IPF registry. *Respir Res* 2017; 18: 139.
87 Raghu G, Amatto VC, Behr J, *et al.* Comorbidities in idiopathic pulmonary fibrosis patients: a systematic literature review. *Eur Respir J* 2015; 46: 1113–1130.
88 Lee JS, Collard HR, Anstrom KJ, *et al.* Anti-acid treatment and disease progression in idiopathic pulmonary fibrosis: an analysis of data from three randomised controlled trials. *Lancet Respir Med* 2013; 1: 369–376.
89 Lee JS, Ryu JH, Elicker BM, *et al.* Gastroesophageal reflux therapy is associated with longer survival in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011; 184: 1390–1394.
90 Kreuter M, Spagnolo P, Wuyts W, *et al.* Antacid therapy and disease progression in patients with idiopathic pulmonary fibrosis who received pirfenidone. *Respiration* 2017; 93: 415–423.
91 Kreuter M, Wuyts W, Renzoni E, *et al.* Anti-acid treatment in patients with IPF: interpret results from post-hoc, subgroup, and exploratory analyses with great caution – authors' reply. *Lancet Respir Med* 2016; 4: e48.
92 Kreuter M, Wuyts W, Renzoni E, *et al.* Antacid therapy and disease outcomes in idiopathic pulmonary fibrosis: a pooled analysis. *Lancet Respir Med* 2016; 4: 381–389.
93 Behr J, Hoeper MM, Kreuter M, *et al.* Investigating significant health trends in idiopathic pulmonary fibrosis (INSIGHTS-IPF): rationale, aims and design of a nationwide prospective registry. *BMJ Open Respir Res* 2014; 1: e000010.
94 Moodley Y, Goh N, Glaspole I, *et al.* Australian Idiopathic Pulmonary Fibrosis Registry: vital lessons from a national prospective collaborative project. *Respirology* 2014; 19: 1088–1091.
95 Glaspole I, Goh N, Hopkins P, *et al.* Quality of life of patients with idiopathic pulmonary fibrosis (IPF) – What can the Australian IPF registry tell us? *Eur Respir J* 2015; 46: Suppl. 59, OA4964.
96 Kreuter M, Bonella F, Maher TM, *et al.* Effect of statins on disease-related outcomes in patients with idiopathic pulmonary fibrosis. *Thorax* 2017; 72: 148–153.
97 Kreuter M, Ehlers-Tenenbaum S, Palmowski K, *et al.* Impact of comorbidities on mortality in patients with idiopathic pulmonary fibrosis. *PLoS One* 2016; 11: e0151425.
98 Vancheri C, Kreuter M, Richeldi L, *et al.* Nintedanib with add-on pirfenidone in idiopathic pulmonary fibrosis: results of the INJOURNEY trial. *Am J Respir Crit Care Med* 2017; in press [https://doi.org/10.1164/rccm.201706-1301OC].
99 Wuyts WA, Antoniou KM, Borensztajn K, *et al.* Combination therapy: the future of management for idiopathic pulmonary fibrosis? *Lancet Respir Med* 2014; 2: 933–942.