Interventions to improve symptoms and quality of life of patients with fibrotic interstitial lung disease: a systematic review of the literature

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ABSTRACT

Background Patients with fibrotic interstitial lung disease have symptom control and quality of life (QoL) needs. This review aims to evaluate the evidence for the use of interventions in improving dyspnoea, other symptoms and QoL.

Methods Eleven databases, relevant websites and key journals were hand-searched. Studies were assessed and data extracted independently by two researchers using standardised proformas. Meta-analyses were performed where possible with 95% CI.

Results 34 papers with 19 interventions in 3635 patients were included. Meta-analyses showed no significant effect of interferon γ-1b or sildenafil on 6-minute walking distance (6MWD) or dyspnoea. Pulmonary rehabilitation and pirfenidone had a positive effect on 6MWD (mean difference (95% CI) 27.4 (4.1 to 50.7)) and 24.0 (4.3 to 43.7), respectively), and pulmonary rehabilitation had a mixed effect on dyspnoea. Both pulmonary rehabilitation and sildenafil showed a trend towards significance in improving QoL. There was weak evidence for the improvement of 6MWD using oxygen; dyspnoea using prednisolone, diamorphine, D-pencillamine and colchicine; cough using interferon α and thalidomide; anxiety using diamorphine; fatigue using pulmonary rehabilitation; and QoL using thalidomide and doxycycline. A wide range of outcome scales was used and there were no studies with economic evaluation.

Conclusions There is strong evidence for the use of pulmonary rehabilitation and pirfenidone to improve 6MWD and moderate evidence for the use of sildenafil and pulmonary rehabilitation to improve QoL. Future recommendations for research would include careful consideration of the dichotomy of radical and palliative treatments when deciding on how symptom and QoL outcome measures are used and data presented.

Key messages

What is the key question?

- What is the overall outcome of trials assessing the use of pharmacological and non-pharmacological methods to improve symptom control and QoL in patients with progressive idiopathic fibrotic interstitial lung diseases?

What is the key point?

- There is strong evidence for the use of pulmonary rehabilitation and some evidence for sildenafil and pirfenidone. There is weak evidence for a number of other interventions which warrants further investigation.

Why read on?

- All patients with progressive idiopathic fibrotic interstitial lung diseases should receive best supportive care to improve symptom control and QoL and, where possible, this should be evidence-based.

INTRODUCTION

Patients with interstitial lung disease have a wide range of diagnoses and prognoses. Many patients can live many years with their diagnosis and some are responsive to treatments. However, a subset of patients with progressive idiopathic fibrotic interstitial lung diseases (PIF-ILD), such as idiopathic pulmonary fibrosis (IPF), have a short disease trajectory and a similar prognosis to patients with lung cancer.[1]

Only a small number of patients are suitable for lung transplantation and no other treatments have been shown to influence mortality. Evidenced-based palliation is seldom applied, despite the high symptom burden[2] and poor quality of life (QoL).[3]

In this systematic review of PIF-ILD, we evaluate (1) the evidence for the use of interventions to improve symptoms and QoL; (2) the evidence for the use of symptom scales for dyspnoea and other symptoms; and (3) the cost-effectiveness of interventions to improve symptoms and QoL. In addition, we aim to make a crucial distinction between radical (potentially disease-modifying) and palliative (non-disease-modifying) treatments, and consider this in appraising the evidence as interpretation of secondary outcome measures should differ between these contexts.

METHODS

Search strategy

We performed comprehensive searches of 11 electronic databases including MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) from 1966 to December 2010 using a combination of MESH headings and keywords (for full search strategy see online appendix 1). In addition, three key respiratory journals (*Thorax*, *American Journal of Respiratory and*

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Critical Care Medicine and *Chest*) were hand-searched for the last 3 years, with reference lists of all included papers. The search was updated to September 2011. Study authors were contacted to obtain full reports where abstracts only were available or further information was required (authors contacted twice in 1 month period). No language restrictions were imposed and translation was performed where needed.

Selection

Study populations

Published data for patients diagnosed with IPF, non-specific interstitial pneumonia (NSIP), cryptogenic fibrosing alveolitis (CFA) and idiopathic interstitial pneumonia (IIP) were evaluated. All stages of disease were included. Studies including subjects with other forms of ILD were acceptable if outcomes for PIF-ILD were reported separately. Where necessary, authors were contacted and, if no separate data was obtainable, the study was excluded but listed as potentially relevant.

Types of interventions

Any single or combined interventions for the treatment of PIF-ILD were reviewed including pharmacological and non-pharmacological treatments, with the exception of lung transplantation.

Types of comparison

Because of the paucity of evidence, all intervention comparisons were assessed but meta-analysis was only conducted for randomised controlled trials (RCTs) of placebo-controlled interventions.

Types of outcome measures

The outcomes included were effects on dyspnoea (at rest), QoL, all other symptoms, 6-minute walking distance (6MWD) and economic data.

Types of study included

A scoping search identified a paucity of controlled trials so all trials, including prospective and retrospective studies, were evaluated. Studies published only in abstract form were included if sufficient information was available to satisfy inclusion criteria. Higher weighting was given to randomised placebo-controlled studies. The quality of RCTs was assessed as described by Jadad *et al*.[4] Studies with qualitative enquiry or mixed method designs were also included. Studies with fewer than five patients were excluded. Paediatric studies were excluded due to radical differences in the PIF-ILD syndromes between childhood and adulthood.[5]

Data extraction

Details of data extraction can be found in online appendix 1.

Data analysis

Where data quantity and quality allowed, data were combined using fixed or random effects meta-analysis. The choice of model was determined by the degree of heterogeneity, as judged by the I^2 statistic and p value for the χ^2 test (a random effects model was used if $p<0.10$ and/or $I^2>50\%$). Results are presented as pooled mean differences between intervention and placebo groups with 95% CI. Forest plots are used to display the results from the individual studies and the pooled estimate. For single studies, the effect size and 95% CI were calculated using standard formulae when not reported in the original paper. A descriptive summary of other studies has been given.

RESULTS

Overview of included studies

Joint data extraction was conducted for 75 papers with interventional data (figure 1). Thirty-four papers were included (see online appendix 2) and 41 were excluded or listed as potentially relevant (see online appendix 3). Of the 34 papers included, these reported 35 studies (two papers each contained two studies[6 7] and one study was reported in two papers[8 9]). No health economic papers were identified.

Seventeen pharmacological interventions and two non-drug interventions were evaluated. In total, 3635 patients were used in the analysis (IPF, n=3419; CFA, n=153; IIP, n=54; usual interstitial pneumonia (UIP), n=9) with a range of 6–826. Interferon γ-1b (IFNγ-1b) was the intervention most tested, with the greatest number of patients analysed, the greatest number of RCTs and the largest individual RCT. Pulmonary rehabilitation had the largest number of studies (n=6).[10–15]

The 17 RCTs had an average Jadad score of 4 (range 2–5). There was a preponderance of placebo-controlled RCTs with few comparisons across classes (notably between pharmacological and non-pharmacological interventions). Twenty-six studies used American Thoracic Society/European Respiratory Society (ATS/ERS) diagnostic criteria.[16] Only two papers were not published in English.[13 17]

Studies were funded by industry (20%), industry and other sources (6%), government (6%), investigators (3%) and other sources such as charities (31%), with the funding source unclear in (34%).

Outcome measures

There were a wide range of outcome measures for dyspnoea and QoL (table 1, see appendix 4).

Interventions

Interventions are presented in order of weighted evidence by study design and subdivided into 6MWD, dyspnoea and other symptoms and QoL. Evidence supported by meta-analysis is listed as 'strong', if supported by single RCTs the evidence is listed as 'moderate'. All other evidence which is supported by non-RCT study designs has been listed as 'weak'. A summary of the results are presented in table 2 and effect sizes are shown in table 3 with full results in appendix 2.

Interventions trialled in RCTs

Interferon γ-1b (IFNγ-1b)

6MWD, dyspnoea and cough: Three RCTs[23 25 32] studied IFNγ-1b in 908 patients. There were no significant effects of IFNγ-1b on 6MWD (figure 2), dyspnoea (figure 3) or cough.

QoL: There was a significant difference in St George's Respiratory Questionnaire (SGRQ) symptom domain favouring IFN in one study (change in mean score from baseline: IFN −13.2 (95% CI −21.4 to 5.0) vs colchicine 7.5 (95% CI −4.5 to 19.5), p=0.01).[23] However, no other improvements in QoL were seen.

Sildenafil

Sildenafil was trialled in four studies, two RCTs[6 21] (one of which[6] which was followed by an open-label study) and an uncontrolled quasi-experimental study.[20] A total of 378 patients were used in the analysis.

6MWD: Collard *et al*[20] conducted an open-label uncontrolled quasi-experimental study which found a significant mean improvement in 6MWD of 49.0 m (95% CI 17.5 to 84.0).

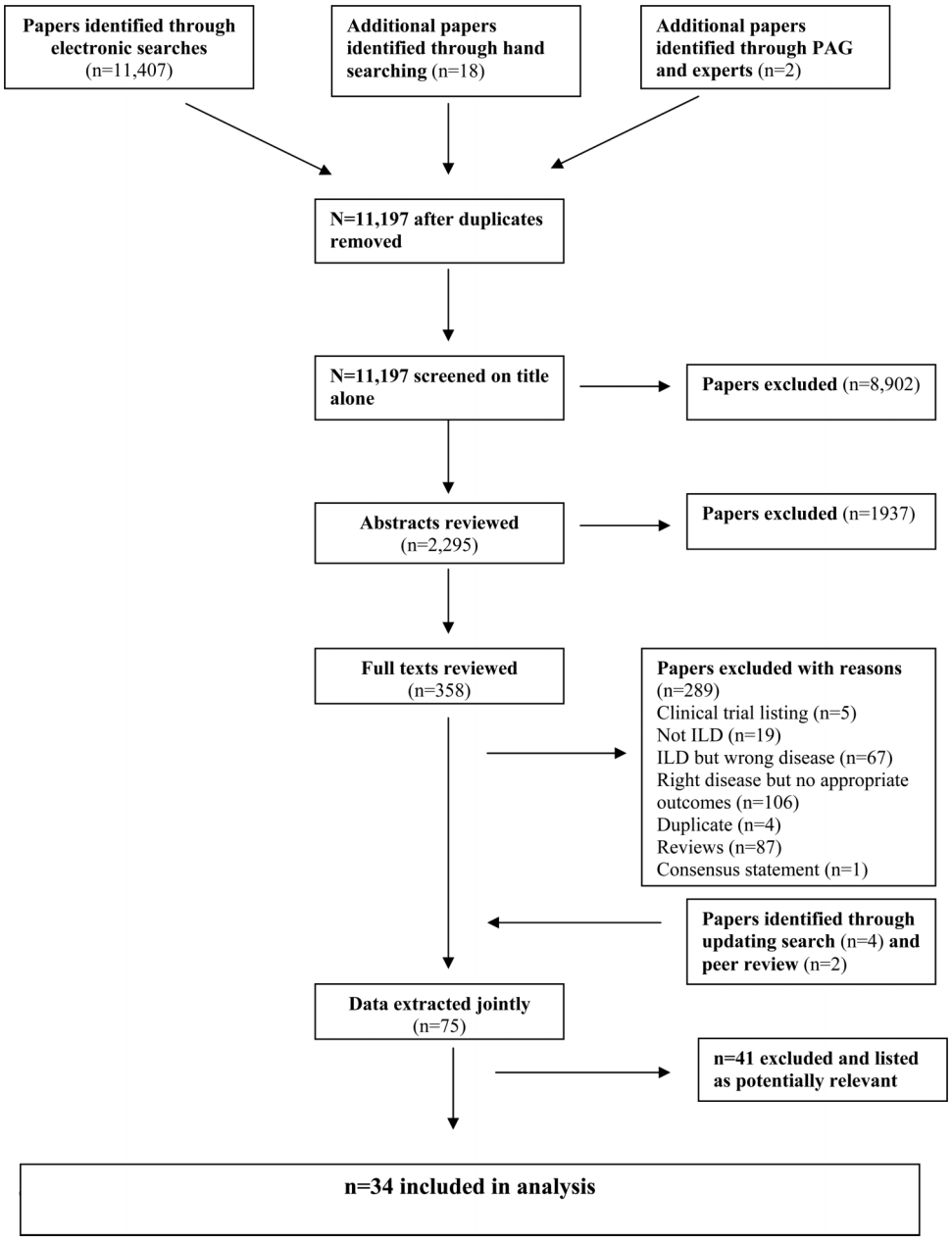

Figure 1 Flow of studies through review.

Eleven patients were used in the analysis. However, a meta-analysis of data from the two larger RCTs[6 21] did not support this finding (figure 4).

Dyspnoea: One RCT[6] showed less deterioration in dyspnoea but overall benefit was not supported by meta-analysis (figure 5).

QoL: Zisman *et al*[6] found that the SGRQ total score remained stable in the sildenafil group but worsened in the placebo group (mean difference −4.08 (95% CI −7.3 to −0.86)). The Short Form Health Survey (SF-36) general health subscore was better preserved in the sildenafil group than in the placebo group (mean difference 2.86 (95% CI 0.76 to 4.95)). This was not seen during the open-label phase.

Pulmonary rehabilitation

Six studies used pulmonary rehabilitation as the intervention. These included two RCTs[10 11] and four quasi-experimental open-label studies,[12 14 15] of which two had controls. A total of 194 patients were used in the analysis.

6MWD: Meta-analysis showed an overall significant benefit of pulmonary rehabilitation on 6MWD (figure 6). This was also supported by other non-randomised studies.[12 14 15]

Dyspnoea and other symptoms: Nishiyama *et al*[10] found no significant effects on dyspnoea. However, in a subset of patients in the paper by Holland *et al*,[11] even though improvements were not seen in the MRC scale, a positive effect was seen for the Chronic Respiratory Disease Questionnaire (CRDQ) dyspnoea score. Kozu *et al*[14] also found a significant improvement in dyspnoea in the IPF subgroup ($p<0.01$). Ozalevli *et al*[12] found a significant decrease in baseline MRC score after pulmonary rehabilitation ($p=0.003$) and Rammaert *et al*[13] found non-significant changes in the Borg and MRC scales. Swigris *et al*[15] found that there was a significant improvement in fatigue. There were no significant improvements in anxiety, depression or sleep quality.

QoL: Two RCTs[10 11] found positive effects on QoL in a number of domains of the SF-36, CRDQ and SGRQ, of which

Table 1 Outcome measures used in studies analysed

Type of outcome measure	Symptom	Outcome measure	Papers using outcome measure
Symptom control	Dyspnoea	Borg Dyspnoea Index	Krowka *et al*,[18] Ozalevli *et al*,[12] Zisman *et al*,[6] Hicks *et al*,[19] Collard *et al*,[20] King Jr *et al*,[8] Raghu *et al*,[9] Rammaert *et al*,[13] Jackson *et al*,[21] Visca *et al*[22]
		Medical Research Council Scale	Antoniou *et al*,[23] Holland *et al*,[11] Ozalevli *et al*,[12] Varney*et al*,[24] Rammaert*et al*,[13] Kozu *et al*,[14] Strieter *et al*[25]
		Baseline Dyspnoea Index	Nishiyama *et al*,[10] King *et al*,[26] King Jr *et al*,[8] Raghu *et al*,[9] Strieter *et al*,[25] Rammaert *et al*,[13] Kozu *et al*[14]
		Transition Dyspnoea Index	King *et al*,[26] King Jr *et al*,[8] Raghu *et al*,[9] Strieter *et al*,[25] Kozu *et al*[14]
		Visual Analogue Scale	Rammaert *et al*,[13] Allen *et al*[27]
		Four-step improvement in dyspnoea scale	Turner-Warwick *et al*[28]
		Five-point dyspnoea scale	Agusti *et al*[29]
		20-point dyspnoea scale	Fiorucci *et al*,[30] Demedts *et al*,[31] Undurraga *et al*[17]
		University of California San Diego Scale	Zisman *et al*,[6] King *et al*,[32] Lindell *et al*,[33] Strieter *et al*,[25] Noble *et al*[7]
		NYHA	Krowka *et al*[18] Hanania and Thomas[34]
		Mahler Dyspnoea Scale	Raghu *et al*[35]
	Cough	Visual Analogue Scale	Hope-Gill *et al*[36]
		Leicester Cough Questionnaire	Lutherer *et al*[37]
		Question 2 on St George's Respiratory Questionnaire	Horton *et al*[38]
		Dry, productive or absent	Antoniou *et al*[23]
	Depression	HADS	Rammaert *et al*[13]
		Beck Depression	Lindell *et al*[33]
		Patient Health Questionnaire-8	Swigris *et al*[15]
	Anxiety	Beck Anxiety	Lindell *et al*[33]
		General Anxiety Disorder-7	Swigris *et al*[15]
	Fatigue	Fatigue severity scale	Swigris *et al*[15]
	Sleep	Pittsburgh Sleep Quality Index	Swigris *et al*[15]
Quality of life		SF-36	Holland *et al*,[11] King *et al*,[26] Zisman *et al*,[6] King Jr *et al*,[8] Raghu *et al*,[9] Raghu *et al*,[35] Rammaert *et al*,[13] Swigris *et al*[15]
		SF-36 Japanese version	Kozu *et al*,[14] Tomioka *et al*[39]
		SF-36 Turkish version	Ozalevli *et al*[12]
		St George's Respiratory Questionnaire	Nishiyama *et al*,[10] Antoniou *et al*,[23] Varney *et al*,[24] Zisman *et al*,[6] King *et al*,[32] King Jr *et al*,[8] Raghu *et al*,[9] Demedts *et al*,[31] Raghu *et al*,[35] Rammaert *et al*,[13] Mishra *et al*[40]
		EQ5D	King *et al*,[26] Zisman *et al*[6]
		Chronic Respiratory Disease Questionnaire	Holland *et al*[11]

the SGRQ total score was also significant ($p<0.05$). This was supported by Ozalevli *et al*[12] and Rammaert *et al*[13] who found that, among other positive QoL results, SF-36 physical limitation scores decreased significantly post-intervention ($p=0.05$).[13] Other non-randomised studies did not find any positive effects on QoL.[14 15]

Bosentan

Two RCTs were reported in three papers trialling bosentan,[8 9 26] with 769 patients included in the analysis.

6MWD: BUILD-1 showed no benefit of bosentan compared with placebo for 6MWD.[8 9]

Dyspnoea: In BUILD-1 there was no significant effect of bosentan on dyspnoea in the total population or in the diagnostic biopsy subset at the primary endpoint of 12 months.[8 9] These findings were supported by a second larger RCT (BUILD-3).[26]

QoL: BUILD-1 found no difference for any domain of the SGRQ at 12 months.[8] Forty-two percent of bosentan-treated patients had an improved SF-36 health transition score compared with 28% of the placebo group ($p=0.084$). However, a subanalysis of patients who had undergone diagnostic biopsy favoured bosentan, showing a significant beneficial effect on QoL with mean total SGRQ scores favouring bosentan.[8] Significant treatment effects were observed at 12 months in the impact domain of the SGRQ (median treatment effect (MTE) −7.0, $p=0.03$) and the physical functioning (MTE 9.3, $p=0.04$), general health (MTE=9.4, $p=0.01$) and role emotional domains of the SF-36 (MTE 0.0, $p=0.04$).[9] However, none of these findings were supported in the larger BUILD-3 study.[26]

Pirfenidone

Two RCTs (CAPACITY) testing pirfenidone were presented in one paper.[7] A total of 692 patients were included in the analysis. Significant improvement was seen in 6MWD of pooled data for the intervention group compared with placebo (absolute difference 24.0 m (95% CI 4.3 to 43.7)). No significant change in dyspnoea score was seen (table 3) and there were no QoL data.

N-acetylcysteine (NAC)

Two RCTs[39 31] with 177 patients included in the analysis did not show any significant differences for aerosolised or oral NAC compared with control for 6MWD, dyspnoea or QoL.

Co-trimoxazole

A pilot RCT of 20 patients compared oral co-trimoxazole alone with a combination with oral prednisolone.[24]

Dyspnoea and other symptoms: The MRC dyspnoea score showed improvement with a median score of 3 (95% CI 2 to 4) before treatment compared with 2 (95% CI 1 to 3) 3 months after treatment for the active group ($p=0.05$) which was maintained at 12 months. The Borg breathlessness score and visual

Table 2 Summary of studies included and results (presented as radical or palliative treatments and in order of weighted evidence)

Intervention	Papers	Patients analysed	Disease group with diagnostic criteria	Type of trial with Jadad score if applicable	Control	Summary of results
			Radical treatments			
IFNγ-1b	King *et al*[32]	826	IPF: ATS/ERS	RCT (5)	Placebo	No significant effects of IFNγ-1b on 6MWD, dyspnoea and cough. Significant difference in SGRQ symptom domain in one study. No other improvement in QoL seen
	Antoniou *et al*[23]	50	IPF: ATS/ERS	RCT (3)	two-arm colchicine and IFN	
	Strieter *et al*[25]	32	IPF: ATS/ERS	RCT (3)	placebo	
Sildenafil	Four studies, three papers and three cohorts of patients;					
	Zisman *et al*[6]	180 161 cont	IPF: ATS/ERS	RCT (5) Quasi-experimental open-label	Placebo two-arm sildenafil	Improvement in smaller open-label uncontrolled study of 6MWD which is not supported by RCTs. Less deterioration of dyspnoea in intervention group compared with placebo of one RCT which is not supported by meta-analysis. Some preservation of QoL scores for sildenafil compared with placebo found in RCT
	Jackson *et al*[21]	26	IPF: ATS/ERS	RCT (5)	Placebo	
	Collard *et al*[20]	11	IPF: ATS/ERS	Quasi-experimental open-label	No control	
Bosentan	King Jr *et al* (BUILD-1)[8] Raghu *et al* (2nd paper BUILD-1)[9]	154	IPF: ATS/ERS	RCT (3)	Placebo	No effects on 6MWD or dyspnoea at rest seen. Minimal QoL changes in all treated population; some more marked benefits in subgroup with biopsies was seen in BUILD-1 but these were not supported by the larger BUILD-3 study
	King *et al*[26]	615	IPF: ATS/ERS	RCT (5)	Placebo	
Pirfenidone	Noble *et al*[7] (CAPACITY trial 004)	348	IPF: ATS/ERS	RCT (5)	Placebo	Positive effect on 6MWD. No significant effect on dyspnoea. No QoL data
	Noble *et al*[7] (CAPACITY trial 006)	344	IPF:ATS/ERS	RCT (5)	Placebo	
NAC	Tomioka *et al*[39]	22	IPF: ATS/ERS	RCT (3)	Bromohexine	No evidence for NAC improving 6MWD, dyspnoea or QoL
	Demedts *et al*[31]	155	IPF: ATS/ERS	RCT (4)	Placebo	
Co-trimoxazole	Varney *et al*[24]	20	IIP:ATS/ERS	RCT (5)	Placebo	Some improvements in dyspnoea and SGRQ symptom score but numbers small
Etanercept	Raghu *et al*[35]	87	IPF: ATS/ERS	RCT (3)	Placebo	No evidence for etanercept improving 6MWD, dyspnoea or QoL
Iloprost	Krowka *et al*[18]	51	IPF: no criteria given	RCT (3)	Matched placebo	No evidence for iloprost improving 6MWD, dyspnoea or QoL
D-pencillamine	Hanania *et al*[34]	10	IPF: no criteria given	Quasi-experimental, open-label	No control	Improvement in dyspnoea following administration of D-pencillamine but weak study design and numbers small
Interferon α	Lutherer *et al*[37]	6	IPF: ATS/ERS	Quasi-experimental, open-label	No control	Improvement in cough following administration of interferon α lozenges but weak study design and numbers small
Ribavarin	Agusti[29]	10	CFA: Turner Warwick	Quasi-experimental, open-label	No control	No improvement in dyspnoea following administration of aerosolised ribavirin
Colchicine	Undurraga *et al*[17]	17	IPF: Turner Warwick criteria	Quasi-experimental, open-label	No control	Improvement in dyspnoea following administration of colchicine but weak study design and numbers small
Doxycycline	Mishra *et al*[40]	6	IPF: ATS/ERS	Quasi-experimental, open-label	No control	No improvement in 6MWD following administration of doxycycline. Improvement in QoL but weak study design and numbers very small
Prednisolone*	Hope-Gill *et al*[36]	6	IPF: ATS/ERS	Quasi-experimental, open- label	No control	Some improvement in dyspnoea in prednisolone groups but numbers small and weak study design
	Turner-Warwick *et al*[28]	127	CFA: Turner-Warwick	Retrospective case note review	No control	
	Fiorucci *et al*[30]	30	IPF: ATS/ERS	Quasi-experimental, open-label	Three arms: colchicine, cyclophosphamide and prednisolone	

Continued

Table 2 Continued

Intervention	Papers	Patients analysed	Disease group with diagnostic criteria	Type of trial with Jadad score if applicable	Control	Summary of results
Palliative treatments						
Pulmonary rehabilitation	Holland *et al*[11]	34	IPF: ATS/ERS	RCT (3)	Telephone advice	6MWD improved immediately following pulmonary rehabilitation (however not as much as in COPD). Mixed results for dyspnoea. Positive effects on fatigue and QoL also seen
	Nishiyama *et al*[10]	28	IPF: ATS/ERS	RCT (3)	Usual care	
	Ozalevli *et al*[12]	15	IPF: ATS/ERS	Quasi-experimental, open-label	No control	
	Rammaert *et al*[13]	13	IPF:ATS/ERS	Quasi-experimental, open-label	No control	
	Kozu *et al*[14]	90	IPF: ATS/ERS	Quasi-experimental, open-label	COPD group	
	Swigris *et al*[15]	14	IPF:ATS/ERS	Quasi-experimental, open-label	COPD group	
Disease management programme	Lindell *et al*[33]	21	IPF: unclear	RCT (2) with qualitative interviews	Usual care	Mixed evidence on benefit of disease management programme in improving symptoms and QoL. Quantitative work suggested negative impact of intervention on perceptions of physical QoL and a tendency for greater anxiety. Qualitative work suggested patients felt less isolated and were able to put their disease into perspective
Oxygen	Hicks *et al*[19]	70	IPF: ATS/ERS	Retrospective case note study	Two-arm oxygen	Improvement in 6MWD and some improvements in dyspnoea in oxygen-treated groups, but weak study designs
	Visca *et al*[22]	34	IPF/NSIP: ATS/ERS	Retrospective case note study	No control	
Diamorphine	Allen *et al*[27]	11	IPF: characteristic changes on chest x-ray	Quasi-experimental, open-label	No control	Improvement in dyspnoea following administration of diamorphine. May improve anxiety. Weak study design and numbers small

analogue scale (VAS) score were significantly improved (data not presented in paper). Cough improved within 4 weeks of treatment (p=0.002) (data not presented in paper).

QoL: The SGRQ showed a significant reduction in symptom scores in the co-trimaxole group (p=0.05) but an improvement was also seen in the placebo group (p=0.02). Non-significant effect sizes were seen for other components of the SGRQ.

Etanercept

A RCT of etanercept in 87 patients with IPF showed no significant improvement in 6MWD (table 3), dyspnoea or QoL compared with placebo (data not presented in paper).[35]

Iloprost

A RCT of 51 patients treated with inhaled iloprost showed no significant differences between inhaled iloprost and placebo for change in 6MWD or Borg dyspnoea score (data not presented in paper).[18]

Disease management programme

Lindell *et al*[33] conducted a RCT of 21 patients which compared a disease management programme delivered using a format of support group for both patients with IPF and carers with a control group of best usual care. There was mixed evidence of benefit.

Quantitative work suggested a negative impact of this intervention on perceptions of physical QoL and a tendency for greater anxiety. The mean end Beck Anxiety Index scores approached statistical significance (intervention 15.13 (6.92) vs control 8.56 (6.95), p=0.077), reflecting increased anxiety in the intervention group. The mean (SD) end score for the SF-36 physical component showed a statistically significant difference (intervention 31.06 (4.61) vs control 36.04 (4.63), p=0.038), reflecting a negative impact on perceptions of physical health-related QoL. However, qualitative work in which 19 participants in the experimental group were interviewed found that patients did not feel isolated and felt that the intervention had enabled them to put the disease into perspective, gave comfort and provided an improved mental picture.

Interventions trialled more than once in non-randomised controlled studies

Prednisolone

Two quasi-experimental studies[30 36] and one retrospective review[28] were included. A total of 163 patients were used in the analysis.

Dyspnoea and other symptoms: Fiorucci *et al*[30] conducted a three-arm study of 30 patients using prednisolone alone (group 1), prednisolone and cyclophosphamide (group 2) and prednisolone and colchicine (group 3). There were significant improvements in dyspnoea in the prednisolone and colchicine group compared with the two other groups (mean (SD) baseline dyspnoea score 8.4 (2.5) vs 6.3 (2.2) at 18 months (p=0.001)). Two patients in group 1 (18%), one patient in group 2 (11%) and eight patients in group 3 (80%) showed a significant decrease in dyspnoea (p=0.001). However, the numbers were small and the study was conducted in a single centre. Turner Warwick *et al*[28] conducted a retrospective review which included 127 patients in the analysis. After 4–6 weeks of treatment, 55 (43%) were classified as non-responders and 72 (57%) as responders with improvement in dyspnoea on a 4-point scale. However, patients were classed as CFA using the criteria of Turner Warwick *et al*[41] without diagnostic biopsies.

Hope-Gill *et al*[36] conducted an open-label study of prednisolone on capsaicin-induced cough and found a significant

Table 3 Effect sizes and pooled estimates where applicable

Interventions ordered by evidence	Study	Outcome	Change from baseline, mean difference (95% CI)	Effect size, mean difference (95% CI)	Pooled estimate (95% CI), I^2 and p value if applicable
Interferon γ-1b	King *et al*[32]	6MWD		−7.80 (−31.8 to 15.9)	−7.45 (−30.26 to 15.36), I^2=0.0%, p=0.52
	Strieter *et al*[25]			−3.20 (−85.7 to 79.3)	
	King *et al*[32]	UCSD		0.40 (−4.1 to 4.87)	0.08 (−4.18 to 4.34), I^2=0.0%, p=0.97
	Strieter *et al*[25]			−3.1 (−17.19 to 11.01)	
	King *et al*[32]	SGRQ total score		−0.50 (−2.53 to 1.53)	
Sildenafil	Zisman *et al*[6]	6MWD		16.7 (−3.92 to 37.32)	5.25 (−8.90 to 19.40), I^2=56.6%, p=0.47
	Jackson *et al*[21]	6MWD		0.70 (−0.43 to 1.83)	
	Zisman *et al*[6]	Borg		−0.34 (−0.81 to 0.14)	−0.34 (−0.82 to 0.13), I^2=39.5%, p=0.16
	Jackson *et al*[21]	Borg		−31.0 (−77.73 to 15.73)	
	Zisman *et al*[6]	UCSD		−6.58 (−11.25 to −1.92)	
		SGRQ total score		−4.08 (−7.3 to −0.86)	
		SGRQ symptom score		−5.73(−10.61 to −0.85)	
		SGRQ activity score		−3.64 (−7.2 to −0.09)	
		SGRQ impact score		−3.7 (−7.76 to 0.37)	
		SF-36 aggregate physical score		−0.17 (−2.06 to 1.73)	
		SF-36 aggregate mental score		−1.72 (−4.38 to 0.94)	
		SF-36 aggregate bodily pain score		−2.17 (−4.86 to 0.52)	
		SF-36 general health score		2.86 (0.76 to 4.95)	
		SF-36 mental health score		1.15 (−1.15 to 3.46)	
		SF-36 physical functioning		0.53 (−1.31 to 2.37)	
		SF-36 role emotional score		2.1 (−1.9 to 6.1)	
		SF-36 role physical score		1.16 (−1.62 to 3.93)	
		SF-36 social functioning		1.99 (−1.22 to 5.21)	
		Vitality score difference		2.03 (−0.39 to 4.44)	
		EuroQol		0.02 (−0.04 to 0.08)	
		EuroQol thermometer		2.28 (−2.75 to 7.32)	
Pulmonary rehabilitation	Nishiyama *et al*[10]	6MWD		46.30 (8.30 to 84.40)	27.4 (4.1 to 50.7), I^2=33.9%, p=0.021
	Holland *et al*[11]			16.12 (−13.32 to 45.56)	
	Kozu *et al*[14]		16.2 (7.1 to 25.4)		
	Holland 2008	SF-36 functioning		1.83 (−1.19 to 4.85)	
	Kozu *et al*[14]		1.9 (−1.1 to 5)		
	Holland 2008	SF-36 role physical		1.01 (0.27 to 1.75)	
	Kozu *et al*[14]		1.0 (−1.6 to 3.6)		
	Holland 2008	SF-36 pain index		0.69 (−0.95 to 2.33)	
	Kozu *et al*[14]		−2.7 (−8.2 to 2.7)		
	Holland *et al*[11]	SF-36 general health perception		2.67 (0.23 to 5.09)	
	Kozu *et al*[14]		−0.2 (−2.8 to 2.4)		
	Holland *et al*[11]	SF-36 vitality		4.50 (2.24 to 6.76)	
	Kozu *et al*[14]		0.9 (−1.9 to 3.6)		
	Holland *et al*[11]	SF-36 social functioning		1.73 (−0.05 to 3.51)	
	Kozu *et al*[14]		−0.7 (−3.2 to 1.8)		
	Holland *et al*[11]	SF-36 role emotional		0.10 (−0.90 to 1.10)	
	Kozu *et al*[14]		−0.9 (−5.4 to 3.6)		
	Holland *et al*[11]	SF-36 mental health index		4.52 (1.10 to 7.94)	
	Kozu *et al*[14]		1.9 (−1.1 to 5)		

Continued

Table 3 Continued

Interventions ordered by evidence	Study	Outcome	Change from baseline, mean difference (95% CI)	Effect size, mean difference (95% CI)	Pooled estimate (95% CI), I^2 and p value if applicable
	Holland *et al*[11]	MRC scale		−0.84 (−1.73 to 0.05)	
	Kozu *et al*[14]		−0.4 (−0.6 to −0.3)		
	Nishiyama *et al*[10]	Baseline Dyspnoea Index		0.4 (−0.6 to 1.4)	
		SGRQ total score		−6.1 (−11.7 to −0.5)	
		SGRQ symptom score		−5.7 (−18.7 to 7.2)	
		SGRQ activity score		−5.8 (−14.7 to 3.1)	
		SGRQ impact score		−6.2 (−12.8 to 0.3)	
	Holland *et al*[11]	CRDQ dyspnoea		5.43 (1.34 to 9.52)	
		CRDQ fatigue		4.67 (1.76 to 7.58)	
		CRDQ mastery		3.33 (0.82 to 5.84)	
		CRDQ emotional		7.44 (0.87 to 14.01)	
	Swigris *et al*[15]	6MWD	61.6 (−19.08 to 142.22)		
		Fatigue Severity Scale	−1.5 (−2.48 to −0.52)		
		General Anxiety Disorder 7	−1.4 (−3.36 to 0.56)		
		Patients' Health Questionnaire 8	−0.9 (−2.27 to 0.47)		
		Pittsburgh Sleep Total	0.9 (−0.67 to 2.47)		
		SF-36 physical functioning	1.2 (−3.11 to 5.51)		
		Role physical	1.5 (−2.42 to 5.42)		
		Bodily pain	2.7 (−2.59 to 7.99)		
		General health	1.4 (−4.09 to 6.89)		
		Vitality	3.6 (−0.71 to 7.91)		
		Social functioning	1.9 (−2.41 to 6.21)		
		Role emotional	−1.9 (−10.33 to 6.53)		
		Mental health	1.6 (−1.73 to 4.93)		
		Physical component summary	3.0 (−1.12 to 7.12)		
		Mental component summary	0.3 (−5.19 to 5.79)		
Bosentan	King *et al*[26]	SF-36 physical functioning		0 (−3.9 to 3.9)	
		SF-36 role-physical		−2.80 (−7.70 to 2.20)	
		SF-36 pain index		0.70 (−4.20 to 5.70)	
		SF-36 general health perception		−2.90 (−6.50 to 0.60)	
		SF-36 vitality		−1.60 (−5.40 to 2.10)	
		SF-36 social functioning		−1.50 (−6.40 to 3.40)	
		SF-36 role-emotional		−3.20 (−8.60 to 2.20)	
		SF-36 mental health index		−1.60 (−5.30 to 2.20)	
		SF-36 health transition score		0 (−0.20 to 0.20)	
		EuroQol EQ-5D health state score		−0.04 (−0.10 to 0.03)	
		EuroQol EQ-5D visual analogue score		−1.50 (−5.40 to 2.40)	
		Transition dyspnoea Index		0.10 (−0.50 to 0.70)	
	King Jr *et al*[8]	6MWD		−18.00 (−57.23 to 21.23)	
		SGRQ total		−6.60 (−0.72 to −12.48)	
Pirfenidone	Noble *et al*[7]	6MWD			24.0 (4.3 to 43.7)
	CAPACITY 004			16.4 (−10.9 to 43.7)	
	CAPACITY 006			31.8 (3.2 to 60.4)	
	CAPACITY 004	UCSD		−3.1 (8.5 to 2.3)	−2.5 (−6.4 to 1.4)
	CAPACITY 006			−2.0 (−7.6 to 3.6)	

Continued

Table 3 Continued

Interventions ordered by evidence	Study	Outcome	Change from baseline, mean difference (95% CI)	Effect size, mean difference (95% CI)	Pooled estimate (95% CI), I^2 and p value if applicable
Co-trimoxazole	Varney *et al*[24]	SGRQ total score		−2.52 (−19.01 to 13.97)	
		SGRQ symptom score		−7.5 (−28.54 to 13.54)	
		SGRQ activity score		0.4 (−18.53 to 19.33)	
		SGRQ impact score		−5.9 (−24.21 to 12.41)	
Etanercept	Raghu *et al*[35]	6MWD		14.9 (−29.28 to 59.08)	
NAC	Tomioka *et al*[39]	6MWD		66.4 (−37.94 to 170.74)	
		SF-36 physical functioning		−0.7 (−18.18 to 16.78)	
		SF-36 bodily pain		−6.1 (−30.52 to 18.32)	
		SF-36 role physical		−6.7 (−42.77 to 29.38)	
		SF-36 general health		6.4 (−6.36 to 19.16)	
		SF-36 vitality		13.4 (−1.45 to 28.25)	
		SF-36 social functioning		8.7 (−11.27 to 28.68)	
		SF-36 role emotional		42.2 (−1.64 to 86.04)	
		SF-36 mental health		12.7 (0.76 to 26.16)	
	Demedts *et al*[31]	Dyspnoea score		−0.32 (−1.72 to 1.09)	
Interferon α	Lutherer *et al*[37]	Leicester cough questionnaire score	3.16 (1.58 to 4.74)		
Doxycycline	Mishra *et al*[40]	6MWD	43.0 (−36.05 to 122.01)		
		Total SGRQ score	−32.5 (22.91 to 42.09)		

Lower SGRQ score indicates better quality of life. Higher score on EQ-5D indicates a better quality of life and a negative value indicates a health state worse than death.
CRDQ, Chronic Respiratory Disease Questionnaire; 6MWD, 6-minute walking distance; NAC, N-acetylcysteine; SF-36, Short Form Health Survey; SGRQ, St George's Respiratory Questionnaire; UCSD, University of California San Diego shortness of breath questionnaire.

reduction in cough reflex sensitivity to capsaicin with a reduction in the mean (SE) VAS score from 7.2 (0.8) to 2.2 (2.5) at 4 weeks ($p<0.05$). However, the numbers were small (n=6) and only five of the six patients reported VAS data.

No 6MWD or QoL data were available for prednisolone.

Oxygen

6MWD: Hicks *et al*[19] conducted a retrospective review of 70 patients with IPF to assess the benefits of ambulatory oxygen. Patients not requiring regular oxygen before the study managed to walk further on optimal oxygen therapy (mean 81.2 m, $p<0.01$). Patients already on regular oxygen showed less benefit on optimal oxygen therapy, walking an extra 16.9 m ($p=0.02$). A second retrospective review[22] of 34 patients with IPF/NSIP showed that ambulatory oxygen (additional or increased) significantly improved 6MWD from baseline (mean (SE) 272.3 (19.8) m vs 304.7 (17.8) m, $p=0.0001$).

Dyspnoea: Visca *et al*[22] found that dyspnoea measured by the Borg scale improved with oxygen (median 4.25 (95% CI 3 to 5) at baseline vs 3.25 (95% CI 2.5 to 4) on oxygen, $p<0.00001$). Borg scores at the end of the study were not significantly different using optimal oxygen than baseline tests in the study by Hicks *et al*.[19]

There were no QoL studies for oxygen.

Interventions trialled only once in non-randomised open-label uncontrolled studies

Diamorphine

An uncontrolled quasi-experimental open-label study[27] of 11 patients on subcutaneous diamorphine showed no adverse effects on vital signs and oxygen saturation but a substantial fall in the dyspnoea analogue score from a mean (SD) of 83 (13) at baseline to 36 (11) at 15 min and 36 (12) at 30 min ($p<0.001$). The authors also reported decreased observed

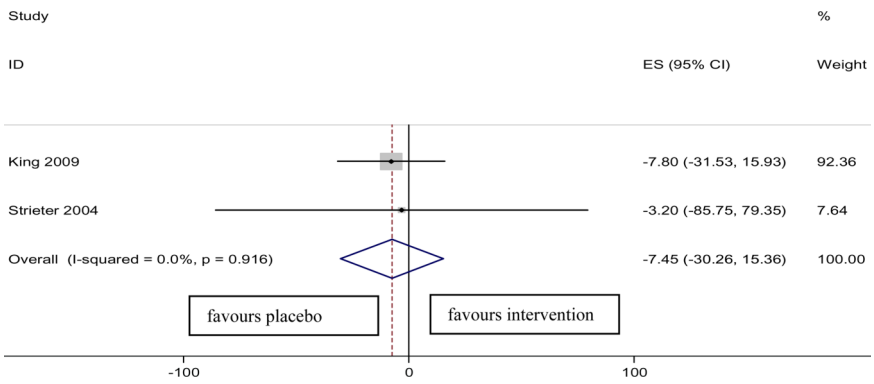

Figure 2 Forest plot showing comparison of effect of interferon γ-1b (IFNγ-1b) versus control on change in 6-minute walking distance (6MWD): effect size −7.45 (95% CI −30.26 to 15.36), p=0.52. Access the article online to view this figure in colour.

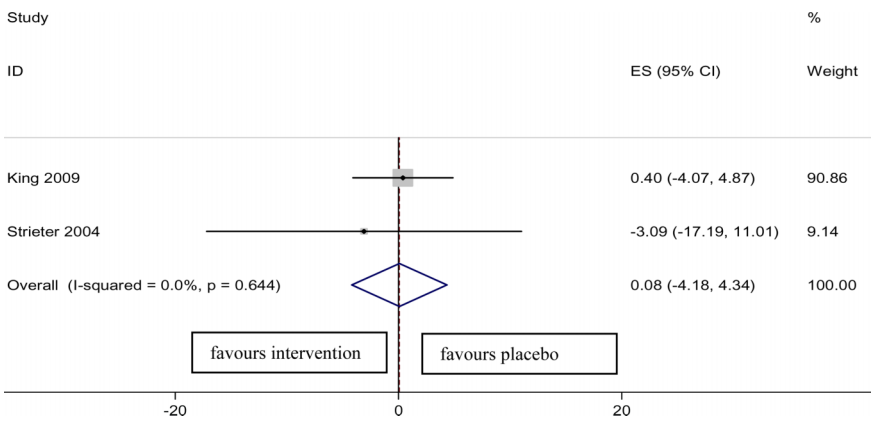

Figure 3 Forest plot showing comparison of effect of interferon γ-1b (IFNγ-1b) versus control on change in San Diego breathlessness scale: effect size 0.08 (95% CI −4.18 to 4.34), p=0.97. Access the article online to view this figure in colour.

anxiety (no details given). However, strict diagnostic criteria were not used.

D-pencillamine

An uncontrolled quasi-experimental open-label study of D-pencillamine in 10 patients with IPF showed improvement by one full grade on the New York Heart Association (NYHA) dyspnoea scale in 50% of patients.[34] No diagnostic criteria were given.

Interferon α

A quasi-experimental open-label study using interferon α lozenges showed improvements in frequency, duration, intensity of daytime cough and improvements in night-time cough.[37] Five of six subjects with chronic cough who completed the Leicester Cough Questionnaire improved with a mean change in total score from baseline of 3.16 (95% CI 1.58 to 4.74), where 1.3 is considered to exceed the minimal important difference.

Ribavarin

An uncontrolled quasi-experimental open-label study of 10 patients with ribavirin showed no significant change in dyspnoea.[29]

Thalidomide

Cough: A phase II trial of the effect of thalidomide on cough in 11 patients with IPF showed marked improvement/resolution of symptoms.[38] Three patients who stopped taking thalidomide all experienced return of cough within 2 weeks but, with reinstitution, all three patients again had resolution of the cough.

QoL: SGRQ data showed a significant decrease on question 2 (cough question) between baseline and 3 months (4.9 (0.3) vs 2.2 (1.6), p=0.03).

Colchicine

A quasi-experimental open-label uncontrolled study of 17 patients with IPF showed improvement in dyspnoea of 1.7 units (as part of a composite clinical score) in 10 patients (significance not stated).[17] The diagnostic criteria used were those of Turner Warwick *et al*[41] and therefore patients are likely to include a mixed group. Of note, improvement in dyspnoea was also noted in the study by Fiorucci *et al*[30] which compared colchicine with prednisolone and cyclophosphamide.

Doxycycline

6MWD: A quasi-experimental open-label uncontrolled trial of six patients with IPF showed no improvement in 6MWD.[40]

QoL: There was a significant improvement in QoL on the SGRQ total score after treatment with doxycycline (p<0.0001). However, other SGRQ scores were not presented or commented on in the paper.

DISCUSSION

Patients with PIF-ILD suffer a high symptom burden[2] and impaired QoL[3] in the terminal stages of their disease. This systematic review aimed to present the evidence for the use of interventions to improve dyspnoea, other symptoms and QoL in PIF-ILD. We reviewed the symptom scales used in these interventions and sought to perform an economic evaluation of them.

While a recent review examining the treatment of dyspnoea in IPF recommends that sildenafil should be considered,[42] we do not believe that there is sufficient evidence to support its use in improving dyspnoea. A Cochrane review of physical training for ILD[43] that involved meta-analyses of RCT evidence for 6MWD, dyspnoea and QoL (and included some unpublished data) supported the use of pulmonary rehabilitation. However,

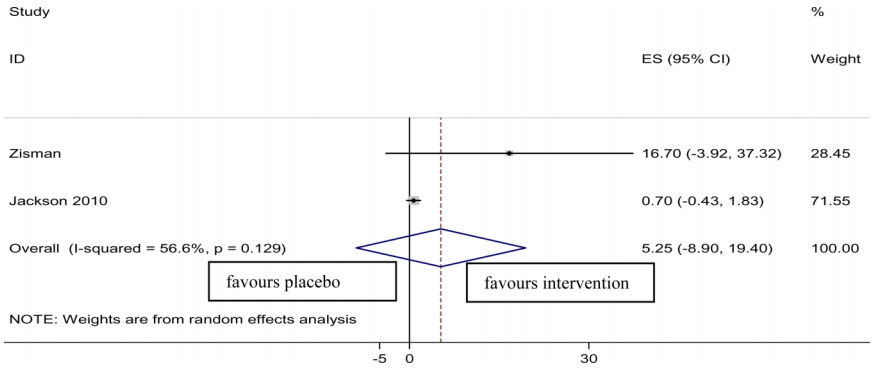

Figure 4 Forest plot showing comparison of effect of sildenafil versus control on change in 6-minute walking distance (6MWD): effect size 5.25 (95% CI −8.90 to 19.40), p=0.467. Access the article online to view this figure in colour.

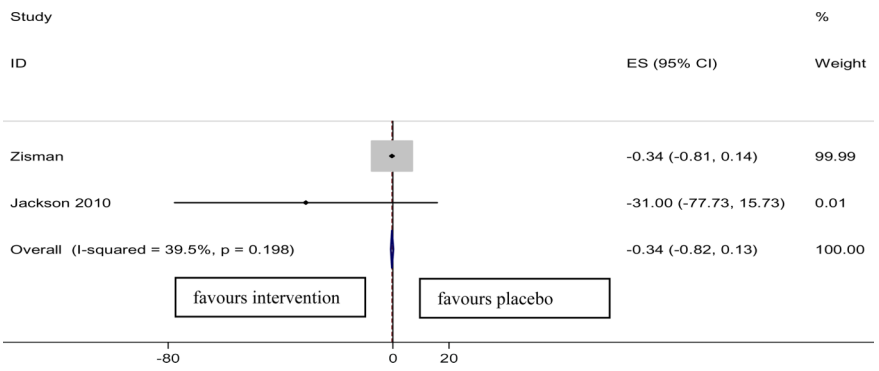

Figure 5 Forest plot showing comparison of effect of sildenafil versus control on change in Borg score at rest: effect size -0.34 (95% CI −0.82 to 0.13), p=0.157. Access the article online to view this figure in colour

our data, which include all types of studies, can only support the use of pulmonary rehabilitation in improving 6MWD and, to a lesser extent, QoL.

The minimum clinically important difference in 6MWD in patients with IPF has been reported as 24–45 m.[44–46] Our analysis show that pooled data for both pulmonary rehabilitation and pirfenidone are within that range. Even though pulmonary rehabilitation improved 6MWD, the effect on dyspnoea was mixed. In addition, pirfenidone improved 6MWD but not dyspnoea.[7] Interplay between functional capacity and dyspnoea at rest is complex and a clear correlation was not found. This may be because dyspnoea is a complex multifaceted problem[47] which is not necessarily linked to functional capacity, or it may be that appropriate dyspnoea outcome measures were not used.

Although there is weak evidence for ambulatory oxygen, it is worth taking into account that a feature of pulmonary rehabilitation itself is to optimise the use of oxygen prior to proceeding with the programme. Therefore, oxygen may have been an important element of the intervention which adds to its positive effects.

Despite their widespread use, we could find only weak evidence for the benefit of steroids in improving dyspnoea and cough and no extractable or appropriate data on QoL. However, a number of studies were excluded (see appendix 3 online), largely due to mixed patient groups and a paucity of extractable symptom control or QoL data. Individually, it is possible that patients may experience a subjective improvement from a short course of low-dose steroids due to the mood and appetite-enhancing effects. In deciding whether to continue treatment, the subjective symptomatic benefit should be balanced with recent data[48] and any potential side effect burden.

Our aim in this systematic review was to present the evidence for interventions which improved symptom control and QoL. However, the crucial distinction and essential dichotomy in considering these interventions is to classify them as radical or palliative. In using palliative interventions (eg, diamorphine), the only goal is to improve symptoms and QoL while, in using radical interventions (eg, pirfenidone), the primary goal is to slow disease progression with no adverse effect on symptoms or QoL. When considering the effect of radical treatments, the more important and currently realistic goal may be a stabilisation or slowing in the deterioration of symptoms and QoL. This in itself is important as stabilisation of disease may result in physiological and psychological adaptations which could result in improvement in symptom control and QoL over time.

For patients where radical treatments are being applied, a change in score within a patient group may not be a sensitive measure since the underlying efficacy of the treatment to slow or alter the rate of disease progression may be effective but mirrored by no change in symptom score which would otherwise have declined. For purely palliative interventions, an improvement in symptom experience is often the more meaningful outcome. For example, Zisman *et al*[6] reported a non-significant change in dyspnoea with sildenafil treatment but presented data showing that there was less deterioration in the intervention group than in the placebo group. Conversely, many other radical interventions do not present these data and a non-significant change cannot be interpreted further. We would encourage authors to present this information clearly to facilitate a true interpretation of the impact of radical interventions on symptoms and QoL.

Our review has highlighted a number of important issues which limit comparison across studies. There was a paucity of RCTs (all were published in the last 10 years), very few studies were powered for QoL or symptoms as the primary outcome, there was poor reporting of data and mixed group studies did not report outcome measures separately. Despite some work at developing outcome scales specifically related to this disease group,[49–51] we found poor use of validated outcome measures and a heterogeneity of measures used. Interestingly, in one study[33] the quantitative results were contradictory to the qualitative results. We would recommend international consensus regarding patient-

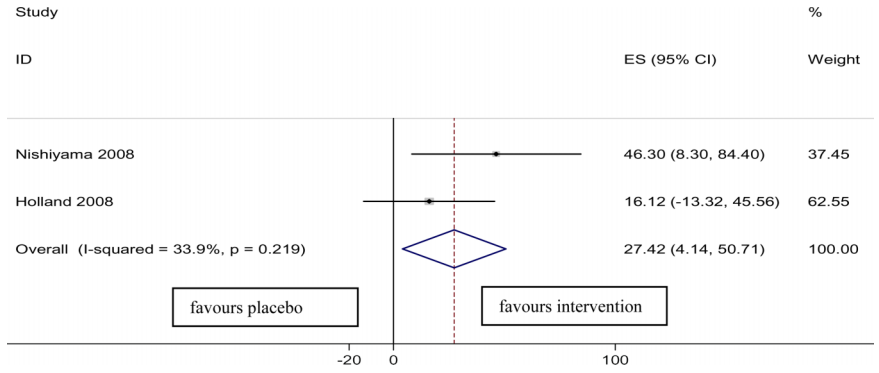

Figure 6 Forest plot showing comparison of effect of pulmonary rehabilitation versus control on change in 6-minute walking distance (6MWD): effect size 27.4 (95% CI 4.1 to 50.7), p=0.021. Access the article online to view this figure in colour.

reported outcome measures and study methodology to ensure that future trials capture accurate symptom control and QoL data. In addition, future trials looking at symptoms and QoL outcomes should include a priori subgroup analysis of patients with severe symptoms and longitudinal analysis of subgroups in which radical interventions result in stable disease.

Patients with IPF experience increased healthcare resource utilisation and direct medical costs.[52] As the population gets older, we can expect that the burden on healthcare will increase.[52] We believe that timely and adequate symptom control may prevent unnecessary hospital admissions and therefore contain some expenditure. Interestingly, government funding provided only 6% of support for trials and over a quarter of studies had some source of industry funding. Studies which are funded by industry are unlikely to have symptoms and QoL as primary outcome measures, so the design of these studies may not be best to assess these outcome measures. In the absence of economic analysis of interventions, recommendations about future directions of government spending and conclusions about the resultant potential savings cannot be made.

Study limitations

Only one reviewer retrieved and chose papers. However, a number of sources including a multidisciplinary panel of experts in the ILD and palliative care fields were consulted to ensure that no known studies were missing. We included all study types and all studies regardless of whether PIF-ILD was diagnosed using ATS/ERS criteria.[16] There were only a few studies for each outcome. However, we have only used high-quality studies in the meta-analyses and presented studies clearly to allow readers to draw their own conclusions.

This review presents respiratory physicians with the evidence for interventions in improving 6MWD, dyspnoea, other symptoms and QoL in patients with PIF-ILD.

CONCLUSIONS

There is strong evidence for the use of pulmonary rehabilitation and pirfenidone to improve 6MWD and moderate evidence for the use of sildenafil and pulmonary rehabilitation to improve QoL. The evidence for pulmonary rehabilitation in improving dyspnoea is mixed. There is weak evidence for oxygen, prednisolone, diamorphine, D-pencillamine, colchicine, interferon α, thalidomide and doxycycline which warrants further investigation. Future recommendations for research include consensus on the use of validated outcome scales, primary endpoints related to symptom control and QoL and economic evaluation of interventions. In addition, careful consideration should be given to how symptom control and QoL outcome measures are used and the presentation of data in radical versus palliative treatment contexts.

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Contributors All authors were involved in conceiving the review. SB conducted the review. SB and JRR jointly extracted data. SB and JLP conducted analysis. SB, JRR, JLP and AUW drafted the paper. All authors reviewed a copy of the paper and had intellectual input into the final version.

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Competing interests AUW is a member of the UK Intermune advisory board.

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Search strategy

We performed comprehensive searches of the following electronic databases: MEDLINE, EMBASE, Science Citation Index Expanded, pre-MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL) and Database for Abstracts of Reviews of Effectiveness, Health Economic Evaluations Database, LILACS, National Health Service Economic Evaluations Database, AMED and CINAHL from 1966-December 2010 using a combination of MESH headings and keywords. Ongoing trials registers- www.ClinicalTrials.gov and www.whoint/trialsearch were also searched. Furthermore the following websites were also searched: www.cam.org.nz, www.controlledtrials.com, www.rccm.org.uk/ciscom/ CISCOM_intro.aspx and the US food and Drug administration website. Hand searching of journals and conference proceedings for the last 3 years and searching BIOSIS Previews and the Conference Papers Index was conducted. In addition, hand searching of the 3 key respiratory journals THORAX, American Journal of Respiratory and Critical Care Medicine, CHEST for the last 3 years was conducted and of the reference lists of all included papers. The search was updated to September 2011 after all analysis was completed. Study authors were contacted to obtain full reports where abstracts only were available or when further information was required (authors were contacted twice in a month period). No language restrictions were imposed during the searches and translation obtained where needed.

- MEDLINE searched using Ovid interface

Interventions

1. exp idiopathic interstitial pneumonias/ or exp pulmonary fibrosis/
2. (((fibrotic NSIP) or (fibrotic lung disease) or (fibrotic non-specific interstitial pneumonia) or (fibrotic non specific interstitial pneumonia) or (pulmonary fibrosis) or IPF or (cryptogenic fibrosing alveolitis) or (interstitial pneumonia) or UIP or IIP) not cystic fibrosis).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
3. 1 or 2
4. animal/
5. human/
6. 4 not (4 and 5)
7. 3 not 6

Appendix 1 Search strategy

8. (Prednisolone or Methylprednisolone or steroid$ or corticosteroid$).mp. or exp prednisolone/ or N-acetylcysteine.mp. or NAC.mp. or acetylcysteine.mp. or exp acetylcysteine/ or azathioprine.mp. or exp azathioprine/ or cyclophosphamide.mp. or exp cyclophosphamide/ or pirfenidone.mp. or exp pyridines/ or interferon gamma 1 b.mp. or IFN.mp. or Interferon-gamma-Ib.mp. or IFN-1b.mp. or exp interferon/ or colchicine.mp. or exp colchicine/ or penicillamine.mp. or exp penicillamine/ or exp cyclosporins/ or cyclosporin$.mp. or Etanercept.mp. or tumo#r necrosis factor$.mp. or tumo#r necrosis factor alpha.mp. or TNF$.mp. or endothelin-1 antagonist$.mp. or endothelin 1 antagonist$.mp. or endothelin antagonist$.mp. or ET-1 antagonist$.mp. or ET 1 antagonist$.mp. or ET receptor antagonist$.mp. or endothelin receptor antagonist$.mp. or Bosentan.mp. or exp warfarin/ or Warfarin.mp. or low molecular weight heparin.mp. or LMWH.mp. or exp Heparin/ or exp Heparin, Low-Molecular-Weight/ or Heparin.mp. or lansoprazole.mp. or omeprazole.mp. or exp omeprazole/ or Ranitidine.mp. or histamine H2 receptor antagonist.mp. or exp ranitidine/ or exp proton pump inhibitor/ or proton pump inhibitor.mp. or exp oxygen/ or exp oxygen inhalation therapy/ or O2.mp. or exp oxygen consumption/ or oxygen.mp. or oxygen therapy.mp. or oxygen inhalation therapy.mp. or oxygen consumption.mp. or pharmacological intervention$.mp. or intervention.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

9. ((exp nursing/ or exp nursing care/ or nursing.mp. or nursing care.mp. or nursing intervention$.mp. or exp Physical Therapy Techniques/ or physical therap$.mp. or exp "Physical Therapy (Specialty)"/ or exp exercise therapy/ or kinesiotherapy.mp. or exp Exercise movement techniques/ or exercise movement technique$.mp. or exercise technique.mp. or exercise therapy.mp. or breathing technique$.mp. or exp respiratory therapy/ or pulmonary rehabilitation.mp. or breathing exercise$.mp. or exp breathing exercises/ or physiotherapy.mp. or physiotherap$.mp. or fan.mp. or exp complementary therapies/ or Complementary therap$.mp. or complementary medicin$.mp. or Alternative medicin$.mp. or Alternative therap$.mp. or yoga.mp. or meditation.mp. or acupuncture.mp. or acupressure.mp. or massage.mp. or exp musculoskeletal manipulations/ or musculoskeletal manipulation$.mp. or exp Mind-Body/ or mind.mp.) and body.mp.) or mind-body.mp. or exp relaxation therapy/ or relaxation therapy.mp. or Relaxation Techniques.mp. or reflexology.mp. or relaxation.mp. or hypnosis.mp. or exp nutrition/ or nutrition.mp. or exp self-care/ or self care.mp. or self-help.mp. or self help.mp. or self-care.mp. or self-management.mp. or self management.mp. or exp

counselling/ or counsel#ing.mp. or exp psychotherapy/ or psychotherapy.mp. or Non-pharmacological intervention$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

10. exp antidepressive agents/ or antidepressive agent$.mp. or antidepressant$.mp.

11. (amesergide or amineptine or amitriptyline or amoxapine or benactyzine or brofaromine or bupropion or butriptyline or cianopramine or citalopram or clomipramine or clorgyline or clovoxamine or demexiptiline or desipramine or dibenzepin or dimetacrin$ or dosulepin or dothiepin or doxepin or etoperidone or femoxetine or fezolamine or fluoxetine or flupenthixol or fluphenazine or fluvoxamine or ifoxetine or imipramine or iprindole or iproniazid or phosphate or isocarboxazid or levoprotiline or lofepramine or l-tryptophan or maprotiline or medifoxamide or melitracen or metapramine or mianserin or milnacipran or minaprine or mirtazepine or moclobemide or nefazodone or nialamide or nomifensine or nortriptyline or opipramo or oxaflozane or oxaprotiline or oxitriptan or paroxetine or phenelzine or pirlindole or propizepine or protriptyline or quinupramine or reboxetine or rolipram or rubidium or sertraline or setiptiline or sibutramine or sulpiride or teniloxazine or tianeptine or tofenacin or toloxatone or tranylcypromine or trazodone or trimipramine or tryptophan or venlafaxine or viloxazine or viqualine or zimeldine).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

12. exp benzodiazepines/ or anxiolytic$.mp. or benzodiazepine$.mp. or adinazolam.mp. or alprazolam.mp. or bentazepam.mp. or bromazepam.mp. or brotizolam.mp. or chlordiazepoxide.mp. or cinolazepam.mp. or clobazam.mp. or clonazepam.mp. or clorazepate.mp. or clotiazepam.mp. or cloxazolam.mp. or delorazepam.mp. or demoxepam.mp. or desmethyldiazepam.mp. or diazepam.mp. or estazolam.mp. or etizolam.mp. or etozolam.mp. or fludiazepam.mp. or flunitrazepam.mp. or flurazepam.mp. or flutoprazepam.mp. or halazepam.mp. or haloxazolam.mp. or ketazolam.mp. or loprazolam.mp. or lorazepam.mp. or lormetazepam.mp. or medazepam.mp. or metaclazepam.mp. or mexazolam.mp. or midazolam.mp. or nimetazepam.mp. or nitrazepam.mp. or nordazepam.mp. or oxazepam.mp. or oxazolam.mp. or pinazepam.mp. or prazepam.mp. or quazepam.mp. or temazepam.mp. or tetrazepam.mp. or tofisopam.mp. or triazolam.mp. or abecarnil.mp. or alpha hydroxymidazolam.mp. or alpidem.mp. or bretazenil.mp. or camazepam.mp. or chlorazepam.mp. or dealkylflurazepam.mp. or eszopiclone.mp. or ethyl loflazepate.mp. or imidazenil.mp. or ketazolam.mp. or loflazeplate.mp. or norchlordiazepoxide.mp. or

norclobazam.mp. or paglone.mp. or persumbran.mp. or phenazepam.mp. or premazepam.mp. or suproclone.mp. or suriclone.mp. or tuclazepam.mp. or zaleplon.mp. or zapizolam.mp. or zolazepam.mp. or zolpidem.mp. or zopiclone.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

13. exp Analgesics, Opioid/

14. (morphine or fentanyl or hydromorphone, or oxycodone, or pentazocine or methadone or opioid or opiate or opioids or opiates or codeine or dextromoramide or OTFC or diamorphine or dihydrocodeine or dextropropoxyphene or meptazinol or sufentanil or alfentanil or remifentanil or nalbuphine or meptazinol or dipipanone or pethidine or tramadol or buprenorphine).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

15. or/8-14

16. 7 and 15

17. Lung Diseases, Interstitial/dt, nu, rh, su, th, pc, dh, px or idiopathic interstitial pneumonias/dt, nu, rh, su, th, pc, dh, px or idiopathic pulmonary fibrosis/dt, nu, rh, su, th, pc, dh, px or pulmonary fibrosis/dt, nu, rh, su, th, pc, dh, px

18. 16 or 17

19. exp Evaluation Studies as Topic/

20. evaluation.mp.

21. 19 or 20

22. 18 and 21

Economic

1. exp idiopathic interstitial pneumonias/ or exp pulmonary fibrosis/

2. ((fibrotic NSIP or fibrotic lung disease or fibrotic non-specific interstitial pneumonia or fibrotic non specific interstitial pneumonia or pulmonary fibrosis or IPF or cryptogenic fibrosing alveolitis or interstitial pneumonia or UIP or IIP) not cystic fibrosis).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

3. 1 or 2

4. animal/

5. human/

6. 4 not (4 and 5)

7. 3 not 6

Appendix 1 Search strategy

8. Economics/ or "costs and cost analysis"/ or cost allocation/ or cost-benefit analysis/ or cost control/ or cost savings/ or cost of illness/ or cost sharing/ or "deductibles and coinsurance"/ or medical savings accounts/ or health care costs/ or direct service costs/ or drug costs/ or employer health costs/ or hospital costs/ or health expenditures/ or capital expenditures/ or value of life/ or exp economics, hospital/ or exp economics, medical/ or economics, nursing/ or economics, pharmaceutical/ or exp "fees and charges"/ or exp budgets/ or (low cost).mp. or (high adj cost).mp. or (health?care cost$).mp. or (fiscal or funding or financial or finance).tw. or (cost estimate$).mp. or (cost variable).mp. or (unit cost$).mp. or (economic$ or pharmacoeconomic$ or price$ or pricing).tw.
9. 7 and 8

Data extraction

One author (SB) screened all titles and abstracts. When multiple reports of a study were identified, they were treated as a single study and reference made to the full text if available. A Project Advisory Group and other experts in the field were asked to check the list to identify any known missing studies. A selection of papers were piloted using a data extraction sheet by applying the inclusion criteria to a sample of papers in order to check that they could be reliably interpreted and that they classified the studies appropriately. A data extraction sheet was completed for each paper passing the inclusion/exclusion stage. 2 authors (SB and JRR) extracted the data from all the full papers identified by SB except for the non-English papers for which data was extracted by SB in conjunction with translators. Disagreements for all papers were resolved by iteration and consensus. Data collected included study design, subject characteristics and study results as they pertained to the prespecified endpoints. Data for primary endpoints as stated by the authors has been extracted and presented.

Appendix 1 Search strategy

Author and year of publication	Methods including design of study and	Quality (percentage of withdrawals, number used in analysis)	JADAD score	Primary objective Secondary objective	Participants Number Diagnosis and how diagnosed (with ref)	Intervention Control	Results	Notes including conclusions
King 2009[1]	Randomised double blind, placebo controlled, multi-centre trial	N=826 enrolled, N=132 died (N=93 in IFN group, N=39 in placebo group)	5	Primary: To assess whether IFN gamma 1b SC improves survival in IPF patients. Secondary: To assess effect on symptoms, QOL and disease progression	ATS/ERS[2, 3] guidelines used- N=456 N=305 (55%) IFN, N=151 (55%) placebo biopsy confirmed	IFN gamma 1b SC 200mcg three times a week- half the dose for first 2 weeks and then full dose	No significant difference between IFN and placebo in effect on 6MWD, dyspnoea or quality of life.	Early termination of the trial occurred as secondary interim analysis did not show any improvement in survival. QOL, 6MWD and dyspnoea were secondary outcomes
Antoniou 2006[4]	Randomised, open label multicentre trial	Run in total N=68, N=50 underwent randomisation, N=12 died during study, N=21 completing study, N=50 included in analysis (ITT)	3	Primary: To assess the clinical effect of IFN gamma 1b and colchicine at 6,12 and 24 months of therapy Secondary: To assess adverse events	N=50 Histologically proven IPF (N=42 UIP on surgical biopsy) or fulfilled ATS/ERS criteria[3]	IFN gamma 1b SC 200mcg three times a week or colchicine 1mg/day orally in combination with low dose prednisolone	No significant difference in dyspnoea assessed by MRC scale, nor cough at each time-point. SGRQ QOL symptoms were significantly better after 12 months of treatment in interferon group- change in scores from baseline IFN -13.2 (-21.4, 5.0) mean (95% CI)and colchicine 7.5 (-4.5, 19.5) p=0.01	Improvement in SGRQ QOL symptoms with interferon gamma-1b compared to colchicine but not supported by other outcome measures, no power calculation undertaken for sample size
Strieter 2004[5]	Randomised double-blinded placebo controlled, multi-centre trial	N=32 enrolled, N=17 IFN group- N=17 completed. N=15 placebo group, N=1 discontinued N=1 died, N=13 completed. N=32 included in analysis	3	Primary: To assess the effects of IFN gamma 1b on biological markers of fibrosis in IPF. Secondary: To explore the effect on clinical measures such as dyspnoea, oxygen use and 6MWD	N=32 IPF- diagnosed using HRCT and tissue confirmation on all. ATS/ERS diagnostic criteria.	IFN gamma 1b SC 100mcg for first 2 weeks then 200mcg 3 times/week for 6 months, matched placebo	No significant difference in dyspnoea or 6MWD between intervention and control group	No significant difference in dyspnoea or 6MWD seen between intervention and placebo group

Appendix 2 Included studies

Author and year of publication	Methods including design of study and	Quality (percentage of withdrawals, number used in analysis)	JADAD score	Primary objective Secondary objective	Participants Number Diagnosis and how diagnosed (with ref)	Intervention Control	Results	Notes including conclusions
Zisman 2010[6]	Randomised double blind placebo controlled trial (multicentre) with open label following- data from open label presented separately below	N=180 randomised, N=89 sildenafil, N=79 completed sildenafil group, N=180 used in analysis	5	Primary: To demonstrate improved 6MWD in subjects with advanced IPF treated for 12 weeks with sildenafil compared to placebo. Secondary: To demonstrate improved dyspnoea and quality of life in patients with advanced IPF treated for 12 weeks with sildenafil compared to placebo	IPF ATS and ERS guidelines[3]	Oral sildenafil 20mg TDS or placebo	No significant improvement in 6MWD compared to placebo. Scores remained stable in the sildenafil group but worsened in placebo group on the SOB questionnaire (estimated difference, -6.58 p=0.006) and total score on St George's respiratory questionnaire (estimated difference, -4.08;p=0.01). SF36 there was no between group differences in the aggregate physical or mental sub scores however the general health sub score was better preserved in sildenafil group than placebo (absolute difference, 2.86;p=0.008). No significant difference in Borg Dyspnoea Index or EQ-5D scores.	No benefit of sildenafil compared to placebo for primary outcome of improving 6MWD. Improved dyspnoea and QOL in sildenafil group.
Zisman 2010[6]	Open label study following RCT to compare two arms receiving sildenafil. One arm has previously received sildenafil in the RCT, one has received placebo.	N=161, N=78 previously received sildenafil in RCT, N=83 previously received placebo in RCT	N/A	As primary study. In addition, second study used to estimate the 24 week safety and efficacy profile of sildenafil therapy.	As above	Oral sildenafil 20mg TDS	Among patients who were initially assigned to the placebo group but who received sildenafil during period 2, the 6MWD did not change significantly in the open label phase. There was also no significant change in the score on the SOB questionnaire, the activity score on SGRQ and the SF-36 general health and vitality scores.	No significant difference in 6MWD, dyspnoea or QOL scores between RCT and open label.

Appendix 2 Included studies

Author and year of publication	Methods including design of study and	Quality (percentage of withdrawals, number used in analysis)	JADAD score	Primary objective Secondary objective	Participants Number Diagnosis and how diagnosed (with ref)	Intervention Control	Results	Notes including conclusions
Jackson 2010[7]	Randomised double blind placebo controlled single centre trial	N=29 included, N=14 sildenafil, N=15 placebo, N=3 withdrawn sildenafil, N=1 withdrawn placebo, N=26 included in analysis	5	Primary: To examine the effects of sildenafil on exercise tolerance. To compare changes from baseline in pre and post exercise dyspnoea	ATS and ERS clinical diagnostic criteria with exception of bronchoscopy[3] >30% had lung biopsies confirming UIP	Sildenafil citrate titrated: 20mg OD for 3 days, 20mg BD 3 days, 20mg TDS or placebo	No significant difference between placebo and sildenafil groups regarding 6MWD. No difference in secondary endpoint of dyspnoea at rest and after each 6MWT as measured by Borg scale.	Sildenafil did not significantly increase 6MWD or decrease the Borg dyspnoea index at rest or after 6MWT.
Collard 2007[8]	Quasi-experimental Open label study with no control	N=14 enrolled, N=0 died, N=11 completed study and included in analysis	N/A	Primary: To assess whether treatment with sildenafil would improve 6MWD in patients with IPF and PAH Secondary: To assess clinically meaningful response to sildenafil (defined as a >20% improvement in 6MWD and incidence of adverse events	N=14 IPF ATS/ERS guidelines[2], N=6 biopsy proven	Sildenafil 20-50 mg TDS	Mean improvement in 6MWD was 49.0m (90% CI, 17.5, 84.0m). 57% of patients classified as responders.	Significant improvement in 6MWD in patients with IPF and PAH but numbers small. Not clear why a 90% CI was used
Holland 2008[9]	Randomised single blinded 2 site trial	N=57 randomised, N=34 IPF patients. N=20 intervention group, N=14 placebo. ITT	3	Primary: To assess functional exercise capacity before and after intervention using 6MWT Secondary: To	N=34 had diagnosis of IPF including 12 with biopsy confirmed UIP and remainder had typical findings of	Twice weekly exercise programme-completed programme if attended 12/16 sessions, control	Proportion of improved participants were similar in the subgroup of patients with IPF (73% in intervention group, 20% in control group). Mean difference [95%CI] in 6MWD of 16.12 [-13.32, 45.56]. No positive effect on MRC score but CRDQ scores improved in all domains (please see main paper)	Study powered to detect changes in 6MWD and all domains in CRDQ. Non-sustained improvement in 6MWD.

Appendix 2 Included studies

Author and year of publication	Methods including design of study and	Quality (percentage of withdrawals, number used in analysis)	JADAD score	Primary objective Secondary objective	Participants Number Diagnosis and how diagnosed (with ref)	Intervention Control	Results	Notes including conclusions
		analysis used, missing data replaced with last observation carried forward		evaluate the safety of a standard exercise programme in ILD, to evaluate the effects of exercise training on exercise capacity, dyspnoea and QOL and whether there is a difference in response to exercise training in IPF compared to other ILDs	UIP on HRCT	group did not receive supervised exercise programme but were contacted once a week by telephone to provide support and general health advice		Improvements shown in exercise group for two dyspnoea scores and all of CRDQ QOL score.
Nishiyama 2008[10]	Randomised open label controlled trial	N=30, N=15 intervention, N=15 control. N=2 withdrew from intervention group	3	To assess the effects of pulmonary rehabilitation programme compared to usual care on pulmonary function, functional exercise capacity and health related quality of life	N=30 IPF diagnosed using ATS/ERS 2002 criteria[3] Unclear how many biopsy confirmed	10 week exercise programme with education lectures or control of usual care	After the programme, 6MWD and the total SGRQ score the mean difference [95%CI] for SGRQ total score of -6.1 [-11.7, -0.5] was found to be significant ($p<0.05$)	Improvement in 6MWD and health related quality of life seen
Ozalevli 2010 [11]	Quasi-experimental open label uncontrolled study	N=17, N=2 withdrew due to infectious disease, N=15 completed and	N/A	To investigate the effects of a home-based pulmonary rehabilitation	N=17 with IPF diagnosed using ATS/ERS consensus statement[2]	Home based pulmonary rehabilitation program for 12 weeks.	There was an increase in the 6MWD from baseline 390.3m to 430.5m (not clear whether mean value) post intervention ($p=0.04$) There was a significant decrease in perceived dyspnoea	Improvement in dyspnoea, and increase in 6MWD and general health related quality of life

Appendix 2 Included studies

Author and year of publication	Methods including design of study and	Quality (percentage of withdrawals, number used in analysis)	JADAD score	Primary objective Secondary objective	Participants Number Diagnosis and how diagnosed (with ref)	Intervention Control	Results	Notes including conclusions
		used in analysis		program on functional outcome parameters in IPF			baseline MRCS score 2.3 (1.2) (mean (SD)) and after pulmonary rehabilitation 1.4 (1.3) (p=0.003). There was a found an improvement in general health related quality of life scores on SF36 mean (SD) (general health pre 57.0 (-4.6) post 74.0 (-4.7) p=0.04, physical role pre 25.0 (1.7) post 68.3 (1.6) p=0.01, and emotional role pre 29.0 (1.3) post 65.0 (1.4) p=0.02)	scores
Rammaert 2009[12]	Quasi-esperimental open label uncontrolled study	N=17, N=2 died, N=13 completed study. N=13 included in analysis	N/A	To assess the impact of a pulmonary rehabilitation program on exercise capacity, pulmonary function, dyspnoea and quality of life	N=17 IPF ATS/ERS criteria[2]	8 week home base pulmonary rehabilitation program- if O_2 saturations less than 90% when baseline 6MWT carried out then O_2 titrated	Improvement in quality of life VAS scales looking at impact of treatment on daily life(p=0.002), dyspnea (p=0.025), quality of sleep (0.035), physical capacity (0.028). SF36 physical limitation score decreased significantly post intervention (p=0.047) No details of other SF36 scores given. SGRQ/HADs no significant changes post intervention. Non-significant changes in Borg (median (range) pre 4 (2-8) and post 3 (2-9) p=0.78 and MRC scales (pre 1.5 (1-3) and post intervention 2 (1-3) p=0.18.	O_2 given to all patients and titrated therefore may have interfered in assessing effect of intervention. Little effect on QOL and SOB validated measures. Some VAS scores showed improvement post intervention (not validated in this group)
Kozu 2011[13]	Quasi-experimental open label study	N=90 enrolled. N=45 IPF, N=45 COPD, N=4 died in IPF group, N=36, N=30 completed at 8 weeks and 6 months for IPF group respectively, N=40 and N=37 completed at 6 months for COPD group	N/A	Primary: To evaluate the effects of pulmonary rehabilitation on dyspnoea, exercise capacity and health status in IPF patients compared to COPD control group	ATS/ERS n=9 had biopsies	8 week outpatient program of pulmonary rehabilitation with 2 classes each week including exercise training, breathing retraining and education. Completed if attended 75% of the 16 supervised sessions.	Significant improvements in 6MWD and dyspnoea occurred in both groups at 8 weeks compared to baseline. Baseline 6MWD IPF group 323m (109) and at 8 weeks 340 (122) p<0.01, baseline 6MWD COPD group 325m (107) and 8 weeks 378m (99) p<0.01. However these benefits were maintained at the 6 month follow up for the COPD group but not for the IPF group: 6 month 6MWD IPF group 320m (106) (not significant- value not given) 6 month 6MWD COPD score 367m (95) p<0.01. Baseline MRC grade IPF 3.0 (0.8) and at 8 weeks 2.5 (1.1) p<0.01, baseline MRC grade COPD group 3.0 (0.8) and at 8 weeks 2.3 (0.9) p<0.01. 6 month MRC scores were not significant. No improvement in QOL scores in the IPF group but all domains with the exception of social function improved in	Significant improvements in dyspnoea and 6MWD at 8 weeks but this effect lost by 6 months. The magnitude of improvements in all outcomes was less in IPF group than in COPD group.

Appendix 2 Included studies

Author and year of publication	Methods including design of study and	Quality (percentage of withdrawals, number used in analysis)	JADAD score	Primary objective Secondary objective	Participants Number Diagnosis and how diagnosed (with ref)	Intervention Control	Results	Notes including conclusions
							the COPD group. The magnitude of improvements in all outcomes was less in IPF group than in COPD group.	
Swigris 2011[14]	Quasi experimental open label multicentre pilot study	N=21 patients enrolled in IPF group, N=2 died, N=14 completed, N=14 used in analysis	N/A	Primary: to investigate if a 6 week rehabilitation program improves functional capacity, fatigue, anxiety, depression, sleep and quality of life in IPF patients	N=21 IPF ATS/ERS criteria, N=14 had surgical biopsy	Pulmonary rehabilitation-exercise and education component. 18 sessions over 6-8 weeks. During PR SpO2 monitored and oxygen titrated to ensure that saturations remain >89%	6MWD Follow up data available for 8 IPF patients. 6MWD improved a mean (SE) 61.6m (41) (p=0.01). There was no significant improvement difference between the IPF and COPD groups. There was a significant improvement in Fatigue with mean change from baseline (95% CI) -1.5 (-2.48, -0.52) p=0.01 (no data available for COPD group). However there were no significant improvements in anxiety, depression, sleep quality or quality of life.	Sample size small and high dropout rate, comparison group were 56 COPD in another study.
King 2008[15]	Randomised double blind multicentre controlled trial - BUILD 1 trial	N=158 enrolled, N=74 bosentan, N=84 placebo, last observation carried forward or imputation, N=109 completed study N=154 used in analysis	3	To assess the effects of bosentan on exercise capacity and time to progression in patients with IPF.	N=158 IPF ATS/ERS criteria.[2] 68% of treatment and 60% of placebo group biopsy proven.	62.5mg bosentan orally twice daily for 4 weeks titrated to 125mg twice daily thereafter or matching placebo for at least 12 months.	Dyspnoea at the end of 6MWD using Borg Dyspnoea Index was more pronounced in placebo group compared with bosentan group up to 12 month (median treatment effect, -0.5;p=0.071). From similar baseline BDI, worsening TDI was significantly smaller for patients treated with bosentan than for patients treated with placebo TDI -0.6 bosentan and -1.9 placebo (p=0.016) at 6 months but not at the primary endpoint of 12 months -1.7 and -2.6 respectively (p=0.292). 42.4% of bosentan treated patients had an improved SF-36 health transition score compared with 28.4% of placebo-relative risk of improvement in favour of bosentan of 1.49 (95% CI, 0.96-2.33;p=0.084). Changes in seven of the eight domains of SF-36 up to 12 months were in favour of bosentan treatment, with a significant treatment effect in favour of bosentan observed in the domain role emotional (p=0.032) Total SGRQ score at baseline in bosentan group (mean, 45.7 (18.1)) was similar to that in placebo group (mean (SD), 45.2 (19)). Up to 6 months, the total score in bosentan	Bosentan showed no benefit compared to placebo for 6MWD. Changes from baseline up to 12 months in dyspnoea and QOL were seen for bosentan. Separate subanalysis completed for patients who had undergone surgical lung biopsy which favoured and showed a more pronounced effect on QOL.

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							group remained almost unchanged (mean (SD), 45.0 (21.3)) but worsened in placebo group (mean (SD), 47.8 (21.7)), representing a mean (SEM) treatment effect of -3.3 (2.6) (p=0.034). Mean treatment differences up to 12 months continued to favour bosentan but were smaller (data not provided). Subset analysis of surgical biopsy proven IPF treatment effects observed at 12 months in favour of Bosentan group in 3 domains of SF-36: "physical functioning" (p=0.041), "general health" (p=0.012), and "role emotional" (p=0.037). Up to 6 months, the mean total SGRQ score in the bosentan treated sub-group remained similar to baseline (mean (SD), 43.6 (18.2)) but worsened in the placebo-treated subgroup (mean (SD) , 49.2 (-21.3)) a mean (SEM) treatment effect of -7.3 (2.8) (p=0.010) in favour of bosentan. Up to 12 months the mean total SGRQ scores favoured treatment with bosentan (mean (SD), 46.1 (19.9)) versus placebo (mean (SD), 51.1 (23.7))- a mean (SEM) treatment effect of -6.6 (3.0) (p=0.058).	
Raghu 2010[16]	Second paper published from BUILD 1	As above	As above	To examine longitudinal changes in HRQOL and dyspnoea in IPF on patients on bosentan compared to placebo	As above	As above	At 6 months, a change from baseline in SGRQ total score indicated improvement in bosentan patients; however, up to 12 months no differences were observed between treatment groups in any domain of SGRQ. SF-36 showed no difference at 6 months but at 12 months there was a change from baseline in role emotional domain of placebo-treated patients suggesting improvement in bosentan-treated patients. (data not given) SLB subset- In addition, treatment effects were observed at 12 months in the impact domain of the SGRQ (median treatment effect -7.0 p=0.03) and the physical functioning (MTE 9.3 p=0.04, general health (MTE=9.4 p=0.01) and role emotional domains of the SF-36 (MTE 0.0 p=0.04). AT 6 months, the number of subjects with improved dyspnoea identified by TDI of greater than or equal to 1 was 18 (26.9%) in bosentan group and 10 (12.2%) in the	As above

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							placebo group, corresponding to a relative risk of 2.2 (95% CI 1.1-4.5). This effect is not apparent up to 12 months (relative risk 1.0;95% CI 0.5-2.0). In SLB subset, upto 12 months, the Borg score was unchanged in the bosentan group and had changed from 0.0 (95% CI 0.0-0.0) to 1.0 (0.0-1.0) in the placebo group, a treatment effect of bosentan of 1.3 (95% CI 0.0-2.9;p=0.03). At 6 months, the number of subjects in SLB subset with improved dyspnoea identified by a TDI of greater than or equal to 1 was 12 (25.0%) in the bosentan group and 4 (8.2%) in placebo group, corresponding to a relative risk of 3.1 (95% CI 1.1-8.8). This effect was not apparent upto 12 months (relative risk 0.9;95% CI 0.4-2.1).	
King 2011[17]	Randomised double blind placebo controlled trial with parallel group	N=616 enrolled, N=407 bosentan, N=209 placebo, N=17 (N=11 bosentan) died during study, N=615 included in analysis- ITT and N=1 not treated	5	Primary: To demonstrate the effect of bosentan on delaying IPF progression/survival Secondary: To assess the effect of on HRQOL, dyspnoea and pulmonary function	IPF by ATS/ERS[2] with all participants having confirmed surgical biopsy.	Bosentan 62.5mg BD for 4 weeks and then titrated to 125mg BD if weight equal or greater than 40kg or matched placebo until 202 primary endpoints acheived	No treatment effects were observed on health related quality of life or dyspnoea.	No benefit of bosentan shown on QOL or symptoms compared to placebo.
Noble 2011[18] CAPACITY 004	Double blind randomised placebo controlled trial- multi-centre	N=435 enrolled, N=18 deaths, N=348 included in efficacy analysis. The group assigned to pirfenidone 1197mg/day was summarised descriptively.	5	Primary: To assess whether pirfenidone reduces deterioration in lung function in patients with IPF Secondary: include categorical FVC,	Patients younger than 50 y and those not meeting protocol criteria for definite IPF by HRCT were required to have lung biopsy showing UIP	Patients assigned in a 2:1:2 ratio to pirfenidone 2403mg/day, pirfenidone 1197mg/day or placebo for a minimum of 72 weeks	Mean change in USCD not significant. Pirfenidone did not significantly reduced decline in 6MWD- Absolute difference (95% CI) 16.4 m (-10.9 to 43.7). No Qol data	No change in dyspnoea or 6MWD. No efficacy data for lower dose of pirfenidone.

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				progression free survival, dyspnoea and 6MWD	surgical biopsy pirfenidone 1197mg/day 32 (37%), pirfenidone 2403mg/day 86 (49%), placebo 85 (49%)			
Noble 2011[18] CAPACITY 006	Double blind randomised placebo controlled trial- multi-centre	N=344 enrolled,N=12 died, N=344 included in analysis	5	Primary: To assess whether pirfenidone reduces deterioration in lung function in patients with IPF Secondary: include categorical FVC, progression free survival, dyspnea and 6MWD	Patients younger than 50y and those not meeting protocol criteria for definite IPF by HRCT were required to have lung biopsy showing UIP surgical biopsy pirfenidone 94 (55%), placebo 94 (54%)	Patients assigned in a 1:1 ratio to pirfenidone 2403mg/day or placebo for a minimum of 72 weeks	Mean change in USCD not significant. Pirfenidone significantly reduced decline in 6MWD- Absolute difference (95% CI) 31.8m (3.2 to 60.4). No Qol data	No change in dyspnoea but improvement in 6MWD. Pooled data from study 004 and 006: absolute difference (95% CI) 24.0 m(4.3 to 43.7)
Tomioka 2005[19]	Open, non-blinded RCT (pilot study)	N=30 enrolled, N=15 both arms, N=10 completing NAC arm, N=12 completing bromhexine arm, N=22 included in analysis	3	Primary: To assess the effectiveness of NAC in altering the decline in lung function, 6MWT and HRCT progression. Secondary: Effects on serum KL-6 and HRQOL	N=4 diagnosis based on presence of UIP by surgical biopsy, N=26 based on ATS and ERS 2000 consensus[2]	NAC 325mg/day inhaled, control-bromhexine hydrochloride 4mg/day inhaled for 12 months	No significant differences observed for 6MWD or HRQOL	No significant treatment effect observed for 6MWD or HRQOL. Steroids were started in 3 patients due to disease progression (control N=2 and NAC N=1)
Demedts 2005[20]	Double blind randomised placebo	N=182 enrolled, N=15 died, N=108	4	Primary: To assess the effect of NAC on	Mandatory biopsy in patients <50 years of age.	NAC- 600mg TDS or matched placebo, Both	No significant difference in dyspnoea or QOL	No significant differences in dyspnoea or QOL

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	controlled trial-multi-centre	completed, N=155 included in analysis		pulmonary function. Secondary: To assess the effect on dyspnoea, quality of life and disease progression, SE profile of intervention	ATS/ERS diagnosis criteria. [2, 3]	groups received prednisolone and azathioprine (2mg/kg/day)		
Varney 2008[21]	Randomised double blind placebo controlled pilot study	N=20, N=10 active treatment, N=10 placebo, no withdrawals	5	To assess the benefit of oral co-trimoxazole alone or in combination with oral prednisolone on exercise capacity, lung function and quality of life	N=20 with progressive fibrotic lung disease (IIP) with physical examination, HRCT scan and pulmonary function tests compatible with advanced fibrotic lung disease (UIP or NSIP or mixed +/-histological diagnosis). N=4 co-trimoxazole and N=3 placebo HRCT pattern of UIP, N=5 co-trimoxazole, N=4 placebo HRCT pattern UIP/fibrotic NSIP, N=1 co-trimoxazole and N=3 unclassifiable	Co-trimoxazole or identical placebo with dosage according to body weight (upto 70kg received 960mg BD, greater than 70 kg received 3 times 480mg BD). Folic acid was given 3 times a week and ranitidine 150mg BD was supplied but optional) Total duration of treatment 5months- 3 months active/placebo treatment, followed by 6 weeks pulmonary rehabilitation with decode 2 weeks post rehabilitation	MRC dyspnoea score showed improvement with a median score (95% CI) of 3(2.0,4.0) pretreatment 2 (1.0-3.0) post-treatment at 3 months for the active group (p=0.05) which was maintained at 12 months. SGHRQ showed significant reduction in symptom scores (pre-treatment 64.2 (21.7) mean (SD) and at 12 months (44.5 (20.7) (p=0.05)). Borg breathlessness score and VAS were significantly improved (data not presented in paper). Improvement in cough within 4 weeks of treatment (p=0.002) data not presented in paper. Treatment effect data analysed at 12 months.	Co-trimoxazole may be helpful in improving SOB and cough. QOL and Prednisolone was taken by 55% of patients- difficult to assess contribution of this. No power calculation and small numbers.

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					HRCT fibrotic (mixed)			
Raghu 2008[22]	Randomised prospective double blind placebo controlled multicentre phase II trial	N=88, N=46 randomised to Etanercept with N=34 completing. N=41 randomised to placebo with N=31 completing, N=87 included in analysis	3	Primary: To investigate the efficacy and safety of etanercept as therapy for IPF Secondary: to assess its effects on quality of life and mortality	N=88 IPF as diagnosed by ATS/ERS consensus statement[2]	Etanercept SC 25mg twice weekly for 48 weeks or placebo	No significant improvements in QOL, dyspnoea or 6MWD.	No improvement in QOL, dyspnoea or 6MWD.
Krowka 2007[23]	Randomised double blind placebo controlled multi-centre trial	N=51 enrolled N=26 Iloprost N=25 placebo N=6 dropped out of iloprost group and N= 9 out of Placebo group	3	Primary: To assess safety of inhaled iloprost Secondary: to assess efficacy and effect on exercise, symptoms, exercise induced O_2 sats and clinical status	N=51 IPF patients- no details on how diagnosed	Inhaled Iloprost (2.5mcg or 5mcg per dose:6-9 doses/day) for 12 weeks or matched placebo	No significant differences between intervention and placebo from baseline in 6MWD (-31m vs 9.8m for iloprost and placebo respectively), NYHA class (16% vs 13% improved) or Borg Dyspnoea Score.	No evidence of clinical benefit. Poster therefore limited information- unclear how many patients included in analysis. Patients randomised to Iloprost were less severely impaired than those randomised to placebo. Secondary efficacy endpoints were not met.
Lindell 2010[24]	Randomised controlled trial with control	N=42 enrolled but included patients and	2	Primary: to assess the impact of a disease	14% of intervention and 43% of control	Intervention- program delivered using format of	There was no statistically significant difference in end mean (SD) scores in the Shortness of Breath Questionnaire for intervention 49.51 (22.64) or control 49.88 (22.64) p=0.972,	Quantitative outcome measures showed greater anxiety in

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	group, concurrent mixed method design.	carers. Only N=21 patients, N=1 patient died during study, N=19 patients completing.		management program on symptom management and health related quality of life Secondary: to assess the impact on carers	group had biopsy	support group with 6 weekly group sessions attended by patients and carers. Control-usual care consisted of being seen by members of clinical care team at interviews of 3-6 months	Perceived Stress Scale for intervention 19.32 (3.64) and control 18.20 (3.65) p=0.531 and Beck Depression Index for intervention 9.71 (4.34) and control 9.44 (4.35) p=0.894. The mean end Beck Anxiety Index scores approached statistical significance intervention 15.13 (6.92) and control 8.56 (6.95) p=0.077 reflecting increased anxiety in the intervention group. Intervention had negative impact on patients (experimental group rated their HRQOL less positively after intervention p=0.038 and tended to report more anxiety p=0.077 than controls) . This is contradictory to what found in qualitative work which consisted of 19 interviews of experimental group participants who didn't feel isolated and felt the intervention had enabled them to put the disease into perspective, gave comfort and provided an improved mental picture.	patients receiving the intervention and a negative impact on some quality of life scores. Contradictory to what was found in qualitative work.
Hope-Gill 2003[25]	Open label-no control	N=6 No withdrawals	N/A	To assess the effect of prednisolone on capsaicin induced cough	N=6 IPF diagnosed using ATS/ERS 2000 criteria[3] with VAS cough score greater than 5	Oral prednisolone 40-60mg/day+ omeprazole 20mg/day for 4 weeks	Significant reduction in cough reflex sensitivity to capsaicin ($p<0.05$). Reduction in mean VAS score from 7.2+/-0.8 to 2.2+/-2.5 ($p<0.05$) at 4 weeks. Only 5/6 patients data reported as one patient unable to reliably indicate cough severity using VAS	Subset of main study- Not clear whether inclusion /exclusion criteria listed in main study apply to these 6 patients- no age/male, female data. Reduction in artificially induced cough. Intervention included omeprazole to be given for 1/12 before start of study which may have improved GORD related cough.

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Turner-Warwick[26]	Retrospective review of case notes	N=220 but only N=143 received steroids, outcome data available for N=127	N/A	To distinguish factors influencing an early response to treatment. To assess influence of steroid treatment on survival	N=143 CFA-diagnosed by using Turner Warwick criteria[27]	Prednisolone various doses	After 4-6 weeks of treatment 55 (43%) classified as non-responders and 72 (57%) as responders from dyspnoea.	Majority classed as dyspnoea responders. N=143 given steroids but outcome data only available on N=127- difficult to elicit information from paper.
Fiorucci 2008[28]	Open label single centre, 3 arm study	N=30, N=11 group 1 of which N=4 died, N=9 group 2 of which N=4 died, N=10 group 3 of which N=3 died. N=30 included in analysis	N/A	To evaluate the role of colchicine, cyclophosphamide and prednisolone on efficacy, tolerability and impact on survival	N=30 IPF on ATS ERS[2, 3] criteria, N=8 had VATS biopsy, N=25 had transbronchial biopsy	Group 1: Prednisolone alone- 1mg/kg/day for 4/52 then 0.5mg/kg/day for 2 months followed by gradual reduction to 20mg/day. Group 2: Prednisolone 0.5mg/kg/day for 1 month, 0.25mg/kg/day for 2 months following reduction + oral cyclophosphamide 100mg/day. Group3: Prednisolone 0.5mg/kg/day then reduced+ colchicine1mg/day	Significant improvement in dyspnoea in colchicine and prednisolone group. Baseline dyspnoea 8.4 +/-2.5 and at 18 months 6.3 +/-2.2 P=0.001. Two patients of group 1 (18%), one patient of group 2 (11%) and eight patients of group 3 (80%) showed a decrease of dyspnoea (p=0.001). Analysis of score variations from baseline to follow up showed a significant difference in group 3 (average -2.1+/-1.3, 95% confidence interval -5.4 and 0.7) as compared with group 1 (average 3.1 +/-1.5, 95% confidence interval -0.2 and 6.5) and group2 (average 4.1 +/-1.9, 95% confidence interval -0.3 and 8.5) p=0.03	Single centre study and small numbers but some improvement in dyspnoea in colchicine and prednisolone treated group compared to other groups

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Hicks 2007[29]	Retrospective case note study	N=70 N=41 already using O_2 prior and performed baseline test with O_2 , N=29 not using O_2 prior and performed baseline without O_2	N/A	To assess the benefits of ambulatory oxygen on 6MWD and dyspnoea in patients with IPF comparing patients who were on O_2 prestudy with those who were not	N=70 IPF diagnosis using ATS/ERS criteria[3]	Ambulatory oxygen- may be increased during test (at 2L increments) – all patients required to have PaO_2 levels >8kPa to commence test	Patients not on O_2 pretest managed to walk a statistically significant 81.2m (mean) p<0.01 further using optimal O_2 therapy. Patients already on O_2 walked an extra 16.9m (mean) p=0.02. Borg scores at test end were not significantly different using optimum O_2 compared to baseline tests	IPF patients receive benefit from ambulatory oxygen in terms of distance walked. This is more marked in those not on O_2 pre-therapy. Retrospective case note analysis and poster therefore limited information.
Visca 2011[30]	Retrospective case note study	N=52 in total study, N=34 IPF/NSIP patients	N/A	Primary: To assess the effect of ambulatory O_2 on 6MWD for ILD patients. Secondary: To assess the effect on dyspnoea	N=34 IPF/NSIP, N=8 ILD associated with connective tissue disease. N=10 fibrotic granulomatous disease using ATS/ERS criteria but unclear how many biopsy proven	Ambulatory O_2 - dose decided on individual oxygen requirements based on desaturation on baseline test, patients BMI, gender and whether cylinder to be carried by patient or others.	In subgroup of IPF and NSIP patients ambulatory O_2 significantly improved 6MWD from baseline 272.3m +/-19.8 mean +/- SE to 304.7 +/-17.8 at endpoint (p=0.0001) and Borg score recovery time from 167.1 +/-28.2 sec at baseline to 120.7 +/-15.5 sec on oxygen (additional or increased) (p=0.008) . Dyspnoea as measured by Borg scale also improved with O_2 4.25(3-5) (median and 95% CI) at baseline compared to 3.25 +/- (2.5-4) on O_2 (<0.00001).	Improved 6MWD, dyspnoea and Borg recovery time in patients using ambulatory oxygen. Retrospective case note analysis with no control.
Allen 2005[31]	Quasi-experimental, open label study	N=11	N/A	Primary: To assess effectiveness of diamorphine on breathlessness Secondary: To assess side effects	Characteristic changes on CXR, N=6 had previous CT supporting diagnosis and 8 had restrictive pattern on spirometry	Diamorphine sc 2.5mg (< or 60kg), 5mg (>60kg)	No adverse effects on vital signs and oxygen saturation but substantial fall in dyspnoea analogue score from mean baseline (SD) 83(13) to 36 (11) at 15min and 36 (12) at 30min p<0.001 after administration of diamorphine. In addition there was a fall in observed anxiety (no details given).	Improvement in SOB with diamorphine without significant adverse effects. No details of objective improvements in anxiety and no subjective measurements. Poor diagnostic criteria for IPF.

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Hanania 1993[32]	Quasi-experimental open label uncontrolled study	N=10, N=3 died, N=10 included in analysis	N/A	To assess the effects of D-pencillamine	N=10 IPF- no criteria given	D-pencillamine- initially dose of 250mg/day which is then increased by increments of 250mg/week up to a maximum of 4000mg/day	N=5 improved by at least one full grade of NYHA criteria. N=1 had no change, N=3 deteriorated	50% showed improvement but numbers small and no diagnostic criteria given- limited data as abstract only
Lutherer 2010 [33]	Quasi-experimental Open label single arm study	N=20, N=3 died during study, N=12 completing, N=12 included in overall analysis but only N=6 completed Leicester Cough Questionnaire (LCQ)	N/A	Primary: To assess the efficacy of oral interferon alpha on the progression of IPF. Seconday: to assess the effect on symptoms	N=20 IPF diagnosed using ATS/ERS consensus statement , N=3 had lung biopsies unclear which patients, N=20 had HRCT	Interferon alpha lozenge, 150IU TDS	Five of the six subjects with chronic cough on entry reported an overall improvement within two to three weeks after starting treatment. Three reported decreases in the frequency, the duration, and the intensity of their cough, and two reported decreases in at least one of these categories. Night-time coughing was eliminated in four subjects. Five of six subjects with a chronic cough who completed the Leicester Cough Questionnaire had an improvement in their total score.	Improvement in cough but numbers were small
Agusti 1993[34]	Quasi-experimental Open label- no control	N=10 No withdrawals	N/A	Evaluate efficacy of ribavarin in patients with CFA	N=10 CFA-diagnosis by lung biopsy in 2 patients. In remaining by Turner-Warwick criteria. [35]	6g of ribavarin dissolved in water delivered via aerosol generator delivered for seven hours daily for 14 days	No significant change in dyspnoea on a 5 point scale after treatment with aerosolized ribavirin baseline dyspnea 2.4 (1), 3 month 2.3 (1.1) and 12 month 2.7 (0.1). We have assumed these to be mean (SD) as not clear from paper.	No significant change in dyspnoea.
Horton 2008[36]	Quasi-experimental open label study with no control	N=11, N=11 completed and analysed but only N=6 data available for SGRQ and cough	N/A	Primary: To assess the effect of thalidomide on cough in IPF patients	N=IPF, no diagnostic criteria given	Thalidomide 100-400mg	10/11 experienced marked or complete resolution of cough. SGRQ data only available for N=6- showed significant decrease in score from baseline 4.9 (0.3) to 2.2 (1.6)(p=0.03 after 3 months). N=3 who stopped taking thalidomide all experienced return of cough within 2 weeks but with reinstitution, all three patients again had resolution of cough.	Improvement of cough with thalidomide but small numbers
Undurraga	Quasi-	N=17, N=7	N/A	Primary: To	N=17 IPF as	Colchicine 0.5-	Improvement in dyspnoea in 10/17 patients of an average	Some improvement in

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Author and year of publication	Methods including design of study and	Quality (percentage of withdrawals, number used in analysis)	JADAD score	Primary objective Secondary objective	Participants Number Diagnosis and how diagnosed (with ref)	Intervention Control	Results	Notes including conclusions
1998[37]	experimental open label, no control	completing study, N=17 included in anlalysis		evaluate the clinical, radiological and physiological effect of colchicine Secondary: To assess possible side effects of treatment	diagnosed using Turner Warwick criteria. [27] N=4 had biopsies of which N=1 was transbronchial	1mg/day, N=14 had 1mg/day, N=3 had 0.5mg/day. N=7 completing trial had treatment for a mean of 21 months	of 1.7 units (significance unclear). 7 patients did not notice any change.	breathlessness but unclear whether this is significant. Likely to be mixed group of patients.
Mishra 2011[38]	Quasi-experimental Open label uncontrolled trial	N=6, N=5 completing, N=6 included in analysis	N/A	Primary: Effect of doxycycline on matrix metalloproteinase (MMPs) activity and clinical outcomes	N=6 IPF diagnosed using ATS/ERS. No biopsies done.	Doxycycline 100mg OD if weight less than 50kg, 200mg BD if greater	SGRQ improved significantly Mean (SD) Before 50.90 (8.38), after 18.40 (6.39) p<0.001but no significant improvement in 6MWD	Improvement in QOL but numbers small.

Appendix 2 Included studies

1. King Jr TE, Albera C, Bradford WZ, et al. Effect of interferon gamma-1b on survival in patients with idiopathic pulmonary fibrosis (INSPIRE): a multicentre, randomised, placebo-controlled trial. The Lancet. 2009;374 (9685):222-8.
2. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). American Journal of Respiratory & Critical Care Medicine. 2000 Feb;161(2 Pt 1):646-64.
3. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. American Journal of Respiratory & Critical Care Medicine. 2002 Jan 15;165(2):277-304.
4. Antoniou KM, Nicholson AG, Dimadi M, et al. Long-term clinical effects of interferon gamma-1b and colchicine in idiopathic pulmonary fibrosis. European Respiratory Journal. 2006 Sep;28 (3):496-504.
5. Strieter RM, Starko KM, Enelow RI, et al. Effects of interferon-gamma 1b on biomarker expression in patients with idiopathic pulmonary fibrosis. American Journal of Respiratory & Critical Care Medicine. 2004 Jul 15;170(2):133-40.
6. Zisman DA, Schwarz M, Anstrom KJ, et al. A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. New England Journal of Medicine. 2010 12 Aug;363 (7):620-8.
7. Jackson RM, Glassberg MK, Ramos CF, et al. Sildenafil therapy and exercise tolerance in idiopathic pulmonary fibrosis. Lung. [Randomized Controlled Trial Research Support, U.S. Gov't, Non-P.H.S.]. 2010 Apr;188(2):115-23.

8. Collard HR, Anstrom KJ, Schwarz MI, et al. Sildenafil improves walk distance in idiopathic pulmonary fibrosis. Chest. 2007;131(3):897-900.
9. Holland AE, Hill CJ, Conron M, et al. Short term improvement in exercise capacity and symptoms following exercise training in interstitial lung disease. Thorax [serial on the Internet]. 2008; (6): Available from: http://www.mrw.interscience.wiley.com/cochrane/clcentral/articles/697/CN-00637697/frame.html.
10. Nishiyama O, Kondoh Y, Kimura T, et al. Effects of pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. Respirology. 2008 May;13 (3):394-9.
11. Ozalevli S, Karaali HK, Ilgin D, et al. Effect of home-based pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. Multidisciplinary Respiratory Medicine. 2010 February;5 (1):31-7.
12. Rammaert B, Leroy S, Cavestri B, et al. Home-based pulmonary rehabilitation in idiopathic pulmonary fibrosis. [French]. Revue des Maladies Respiratoires. 2009;26 (3):275-82.
13. Kozu R, Senjyu H, Jenkins SC, et al. Differences in response to pulmonary rehabilitation in idiopathic pulmonary fibrosis and chronic obstructive pulmonary disease. Respiration. 2011;81(3):196-205.
14. Swigris JJ, Fairclough DL, Morrison M, et al. Benefits of pulmonary rehabilitation in idiopathic pulmonary fibrosis. Respir Care. 2011 Jun;56(6):783-9.

15. King Jr TE, Behr J, Brown KK, et al. BUILD-1: A randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis. American Journal of Respiratory and Critical Care Medicine. 2008 01 Jan;177 (1):75-81.
16. Raghu G, King Jr TE, Behr J, et al. Quality of life and dyspnoea in patients treated with bosentan for idiopathic pulmonary fibrosis (BUILD-1). European Respiratory Journal. 2010 January;35 (1):118-23.
17. King TE, Jr., Brown KK, Raghu G, et al. The BUILD-3 Trial: A Prospective, Randomized, Double-Blind, Placebo-Controlled Study Of Bosentan In Idiopathic Pulmonary Fibrosis [Abstract]. American Journal of Respiratory and Critical Care Medicine [serial on the Internet]. 2010; (Meeting Abstracts): Available from: http://www.mrw.interscience.wiley.com/cochrane/clcentral/articles/179/CN-00758179/frame.html.
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22. Raghu G, Brown KK, Costabel U, et al. Treatment of idiopathic pulmonary fibrosis with etanercept: an exploratory, placebo-controlled trial. American Journal of Respiratory & Critical Care Medicine. 2008;178(9):948-56.
23. Krowka MJ, Ahmad S, de Andrade JA, et al. A randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of iloprost inhalation in adults with abnormal pulmonary arterial pressure and exercise limitation associated with idiopathic pulmonary fibrosis. Chest [serial on the Internet]. 2007; (4): Available from: http://www.mrw.interscience.wiley.com/cochrane/clcentral/articles/705/CN-00642705/frame.html.
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26. Turner-Warwick M, Burrows B, Johnson A. Cryptogenic fibrosing alveolitis: response to corticosteroid treatment and its effect on survival. Thorax. 1980 Aug;35(8):593-9.
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29. Hicks S, Spencer LG, Duck A, et al. Ambulatory oxygen in idiopathic pulmonary fibrosis: Of what benefit? Thorax. 2007 Dec;62:A45-A6.

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31. Allen S, Raut S, Woollard J, et al. Low dose diamorphine reduces breathlessness without causing a fall in oxygen saturation in elderly patients with end-stage idiopathic pulmonary fibrosis. Palliative Medicine. 2005;19(2):128-30.
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37. Undurraga Pereira A, Meneses Ciuffardi M, Sabbagh P E, et al. Tratamiento de la fibrosis pulmonar idiopática con colchicina. Rev méd Chile. 1998;126(11):1345-53.
38. Mishra A, Bhattacharya P, Paul S, et al. An alternative therapy for idiopathic pulmonary fibrosis by doxycycline through matrix metalloproteinase inhibition. Lung India. 2011 Jul;28(3):174-9.

Study	Reason for exclusion
Abernethy 2010[1]	Unable to separate PIF-ILD data
Abernethy 2003[2]	Unable to separate PIF-ILD data
Addrizzo-Harris 2002[3]	Unable to separate PIF-ILD data
Azuma 2005[4]	No extractable data
Behera 1998[5]	Subjective improvement, no outcome measurements used
Behr 1997[6]	Unable to separate PIF-ILD data. No outcome measures used.
Bhattacharyya 2009[7]	No appropriate outcome measures
Chapela 1986[8]	No extractable data
Dimadi 2003[9]	No appropriate outcome measures
Douglas 1998[10]	No extractable data
Fasciolo 1994[11]	Unable to separate PIF-ILD data
Ferreira 2006[12]	Unable to separate PIF-ILD data
Ferreira 2009[13]	Unable to separate PIF-ILD data
Flaherty 2001[14]	Unable to separate out dyspnoea data
Glockl 2009[15]	No extractable data
Gomez 2007[16]	Incomplete study
Gross 1995[17]	Unable to separate PIF-ILD data
Gunella 1991[18]	Unable to separate PIF-ILD data
Janssen 2010[19]	No extractable data
Jastrzebski 2006[20]	Unable to separate out PIF-ILD data
Johnson 1989[21]	Unable to extract dyspnoea data from paper
Kalra 2003[22]	No appropriate outcome measures
Lanuza 2000[23]	Unable to separate PIF-ILD data
Leung 1996[24]	Unable to separate PIF-ILD data
Naji 2006[25]	Unable to separate PIF-ILD data
Peters 1993[26]	No appropriate outcome measures.
Raghu 2004[27]	No extractable data
Rodrigue 2005 [28]	Unable to separate PIF-ILD data
Salhi 2010[29]	Unable to separate PIF-ILD data
Scano 1981[30]	Unable to separate PIF-ILD data
Selman 1998[31]	No extractable data
Sharifabad 2010[32]	Unable to separate PIF-ILD data
Stack 1972[33]	No appropriate outcome measures
Sturani 1988[34]	No appropriate outcome measures
Swinburn 1991[35]	Unable to separate PIF-ILD data
Taniguchi 2010[36]	No extractable data
TenVergert 1998[37]	Unable to separate PIF-ILD data
Webb 2000[38]	Not clear that any IPF patients are included.
Young 1989[39]	No appropriate outcome measures
Ziesche 1999[40]	No appropriate outcome measures
Zisman 2000[41]	No extractable data

Appendix 3 Potentially relevant excluded studies

1. Abernethy AP, McDonald CF, Frith PA, Clark K, Herndon JE, 2nd, Marcello J, et al. Effect of palliative oxygen versus room air in relief of breathlessness in patients with refractory dyspnoea: a double-blind, randomised controlled trial. *Lancet* 2010;376(9743):784-93.
2. Abernethy AP, Currow DC, Frith P, Fazekas BS, McHugh A, Bui C. Randomised, double blind, placebo controlled crossover trial of sustained release morphine for the management of refractory dyspnoea. *BMJ* 2003;327(7414):523-8.
3. Addrizzo-Harris DJ, Harkin TJ, Tchou-Wong KM, McGuinness G, Goldring R, Cheng D, et al. Mechanisms of colchicine effect in the treatment of asbestosis and idiopathic pulmonary fibrosis. *Lung* 2002;180(2):61-72.
4. Azuma A, Nukiwa T, Tsuboi E, Suga M, Abe S, Nakata K, et al. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *American Journal of Respiratory & Critical Care Medicine* 2005;171(9):1040-7.
5. Behera D, Gupta D, Jindal SK. Response to steroid therapy in patients of idiopathic pulmonary fibrosis: a retrospective analysis. *The Indian journal of chest diseases & allied sciences* 1998;40 (3):163-69.
6. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *American Journal of Respiratory & Critical Care Medicine* 2011;183(6):788-824.
7. Bhattacharyya P, Nag S, Bardhan S, Acharya D, Paul R, Ghosh M, et al. The role of long-term doxycycline in patients of idiopathic pulmonaryfibrosis: The results of an open prospective trial. *Lung India* 2009;26 (3):81-85.
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9. Dimadi MA, Rapti A, Latsi P, Antoniou KM, Birba G, Trigidou R, et al. Preliminary results of a prospective, multicentre randomised study comparing interferon Gamma-1b (IFN-y) and Colchicane in the treatment of idiopathic pulmonary fibrosis (IPF) [Abstract]. *European Respiratory Journal*, 2003.
10. Douglas WW, Ryu JH, Swensen SJ, Offord KP, Schroeder DR, Caron GM, et al. Colchicine versus prednisone in the treatment of idiopathic pulmonary fibrosis. A randomized prospective study. Members of the Lung Study Group. *American Journal of Respiratory & Critical Care Medicine* 1998;158(1):220-5.
11. Fasciolo G, Nicolini A, Vacca N, Viglierchio P. Efficacy and safety of moguisteine in comparison with levodropropizine in patients with cough assoclated with chronic obstructive pulmonary disease, lung cancer, or pulmonary fibrosis. *Curr Ther Res Clin Exp*, 1994:251-61.
12. Ferreira G, Feuerman M, Spiegler P. Results of an 8-week, outpatient pulmonary rehabilitation program on patients with and without chronic obstructive pulmonary disease. *Journal of Cardiopulmonary Rehabilitation* 2006;26(1):54-60.
13. Ferreira A, Garvey C, Connors GL, Hilling L, Rigler J, Farrell S, et al. Pulmonary rehabilitation in interstitial lung disease: benefits and predictors of response. *Chest* 2009;135(2):442-7.
14. Flaherty KR, Toews GB, Lynch JP, 3rd, Kazerooni EA, Gross BH, Strawderman RL, et al. Steroids in idiopathic pulmonary fibrosis: a prospective assessment of adverse reactions, response to therapy, and survival. *American Journal of Medicine* 2001;110(4):278-82.
15. Glockl R, Weber-Lange B, Halle M, Kenn K. Interval versus continuous training in patient with end stage lung disease before lung transplantation [Abstract]. *European Respiratory Society Annual Congress, Vienna, Austria, September 12-16*, 2009:[E1715].
16. Gomez O, Ramos C, LaPerriere A, Glassberg M, Jackson R. Vasodilator therapy exercise tolerance and oxidant stress in IPF patients [Abstract]. *European Respiratory Journal*, 2007:111s [P779].

Appendix 3 Potentially relevant excluded studies

17. Gross CR, Savik K, Bolman RM, 3rd, Hertz MI. Long-term health status and quality of life outcomes of lung transplant recipients. *Chest* 1995;108(6):1587-93.
18. Gunella G, Zanasi A, Massimo Vanasia CB. [Efficacy and safety of the use of levodropropizine in patients with chronic interstitial lung diseases]. *Clin Ter* 1991;136(4):261-6.
19. Janssen DJ, Spruit MA, Alsemgeest TP, Does JD, Schols JM, Wouters EF. A patient-centred interdisciplinary palliative care programme for end-stage chronic respiratory diseases. *International Journal of Palliative Nursing* 2010;16(4):189-94.
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21. Johnson MA, Kwan S, Snell NJ, Nunn AJ, Darbyshire JH, Turner-Warwick M. Randomised controlled trial comparing prednisolone alone with cyclophosphamide and low dose prednisolone in combination in cryptogenic fibrosing alveolitis. *Thorax*, 1989:280-8.
22. Kalra S, Utz JP, Ryu JH. Interferon gamma-1b therapy for advanced idiopathic pulmonary fibrosis. *Mayo Clinic Proceedings* 2003;78(9):1082-88.
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24. Raghu G. Idiopathic pulmonary fibrosis: guidelines for diagnosis and clinical management have advanced from consensus-based in 2000 to evidence-based in 2011. *European Respiratory Journal* 2011;37(4):743-6.
25. Naji NA, Connor MC, Donnelly SC, McDonnell TJ. Effectiveness of pulmonary rehabilitation in restrictive lung disease. *Journal of Cardiopulmonary Rehabilitation* 2006;26(4):237-43.
26. Peters SG, McDougall JC, Douglas WW, Coles DT, DeRemee RA. Colchicine in the treatment of pulmonary fibrosis. *Chest* 1993;103 (1):101-04.
27. Raghu G, Brown KK, Bradford WZ, Starko K, Noble PW, Schwartz DA, et al. A Placebo-Controlled Trial of Interferon Gamma-1b in Patients with Idiopathic Pulmonary Fibrosis. *New England Journal of Medicine* 2004;350 (2):125-33.
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31. Selman M, Carrillo G, Salas J, Padilla RP, Pérez-Chavira R, Sansores R, et al. Colchicine, D-penicillamine, and prednisone in the treatment of idiopathic pulmonary fibrosis: a controlled clinical trial. *Chest*, 1998:507-12.
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34. Sturani C, Galavotti V, Fabbri M, del Bufalo C, Galleri C, Ravaglia C, et al. Preliminary results of a single-blind, randomized trial of cyclosporine and corticosteroids in idiopathic pulmonary fibrosis (IPF) [abstract]. *European Respiratory Journal*, 1988:247s.
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36. Taniguchi H, Ebina M, Kondoh Y, Ogura T, Azuma A, Suga M, et al. Pirfenidone in idiopathic pulmonary fibrosis. *European Respiratory Journal* 2010;35(4):821-9.

Appendix 3 Potentially relevant excluded studies

37. TenVergert EM, Essink-Bot ML, Geertsma A, van Enckevort PJ, de Boer WJ, van der Bij W. The effect of lung transplantation on health-related quality of life: a longitudinal study. *Chest* 1998;113(2):358-64.
38. Webb M, Moody LE, Mason LA. Dyspnea assessment and management in hospice patients with pulmonary disorders. *The American journal of hospice & palliative care* 2000;17 (4):259-64.
39. Young IH, Daviskas E, Keena VA. Effect of low dose nebulised morphine on exercise endurance in patients with chronic lung disease. *Thorax*, 1989:387-90.
40. Ziesche R, Hofbauer E, Wittmann K, Petkov V, Block LH. A preliminary study of long-term treatment with interferon gamma-1b and low-dose prednisolone in patients with idiopathic pulmonary fibrosis. *The New England journal of medicine*, 1999:1264-9.
41. Zisman DA, Lynch JP, 3rd, Toews GB, Kazerooni EA, Flint A, Martinez FJ. Cyclophosphamide in the treatment of idiopathic pulmonary fibrosis: a prospective study in patients who failed to respond to corticosteroids. *Chest* 2000;117(6):1619-26.

Appendix 3 Potentially relevant excluded studies

Study	Outcome measure with original reference where given in paper
Antoniou 2006[1]	Medical Research Council (MRC) dyspnoea scale[2] Cough- Dry, productive, absent (no reference) St George's Respiratory Questionnaire (SGRQ) [3, 4]
King 2009[5]	University of California San Diego shortness of breath questionnaire (UCSD)[6] SGRQ[7]
Strieter 2004[8]	Modified MRC scale (no ref) Baseline Dyspnoea Index (BDI) and Transition (endpoint) dyspnoea index (TDI) (no ref) UCSD (no ref)
Jackson 2010[9]	Borg dyspnoea scale (modified 10 point)[10]
Zisman 2010[11]	UCSD [12] Borg dyspnoea index [13] SGRQ [14] SF-36 [14] EQ-5D [15]
Collard 2007[16]	Borg Dyspnoea Index (no ref)
Nishiyama 2008[17]	BDI [18] SGRQ [19]
Holland 2008[20]	MRC scale (modified)[2] SF-36[7] Chronic Respiratory Disease Questionnaire (CRDQ)[7]
Ozalevli 2010[21]	MRC scale [22] Borg dyspnoea Index (modified) [2] SF-36 (Turkish version) [23]
Rammaert 2009[24]	Baseline Dyspnoea Index [25] Borg Dyspneoa Index [26] MRC scale [27] SF-36 [28] SGRQ [29] Hospital Anxiety and Depression scale [30] 7 questions in Visual Analogue Scale looking at symptoms and quality of life
Kozu 2011[31]	MRC scale [32] BDI & TDI [18] SF-36 version 2 (Japanese version)[33]
Swigris 2011[34]	Fatigue Severity Scale[35] General Anxiety Disorder-7 scale[36] Patient Health Questionnaire-8 [37] Pittsburgh Sleep Quality Index [38] SF-36 [37]
King 2011[39]	Baseline Dyspnoea Index Transition Dyspnoea Index [18] SF-36[40] EQ5D[41]
King Jr 2008 (BUILD 1)[42] **Raghu 2010 (2nd paper BUILD 1)[43]**	Borg Dyspnoea Index [26] Baseline Dyspnoea Index Transition Dyspnoea Index [18] SF-36[44] SGRQ[3]
Noble 2011[45]	UCSD[6]
Tomioka 2005[46]	SF-36 (Japanese version) [33, 47]
Demedts 2005[48]	Dyspnoea Score[49] SGRQ [3]
Varney 2008[50]	MRC scale (no ref) SGRQ (no ref)
Raghu 2008[51]	Mahler dyspnoea scale (no ref) SF-36 (no ref) SGRQ[52]
Krowka 2007[53]	Borg Dyspnoea Index (no ref) NYHA class (no ref)
Lindell 2010[54]	UCSD[6] Beck Anxiety Inventory[55] Beck Depression Inventory-II[56] Perceived Stress Scale[57] SF-36[58]
Hope-Gill 2003[59]	Visual Analogue Scale for cough (no ref)
Turner-Warwick 1980[60]	4 step improvement in dyspnoea scale (no ref)
Fiorucci 2008[61]	20 point dypsnoea scale (as part of clinical radiologic physiologic-CRP scoring system) [49, 62]
Hicks 2007[63]	Borg dyspnoea index (no ref)
Visca 2011[64]	Borg dyspnoea index [26]
Allen 2005[65]	Visual Analogue Scale for dyspnoea (no ref)
Hanania 1993[66]	NYHA criteria (no ref)
Lutherer 2011[67]	Leicester Cough Questionnaire[68]
Agusti 1993[69]	5 point dyspnoea scale[70]
Horton 2008[71]	Question 2 on SGRQ (no ref) for assessment of cough
Undurraga 1998[72]	20 point dypsnoea scale (as part of clinical radiologic physiologic-CRP scoring system) [49]
Mishra 2011[73]	SGRQ (no ref)

Appendix 4 Outcome measures

1. Antoniou KM, Nicholson AG, Dimadi M, et al. Long-term clinical effects of interferon gamma-1b and colchicine in idiopathic pulmonary fibrosis. European Respiratory Journal. 2006 Sep;28 (3):496-504.
2. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. Chest. 1988 Mar;93(3):580-6.
3. Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. Respiratory Medicine. 1991 Sep;85 Suppl B:25-31; discussion 3-7.
4. Bouros D, Psathakis K, Siafakas NM. Quality of life in interstitial lung disease. Eur Respir Rev. 1997;7:66-70.
5. King Jr TE, Albera C, Bradford WZ, et al. Effect of interferon gamma-1b on survival in patients with idiopathic pulmonary fibrosis (INSPIRE): a multicentre, randomised, placebo-controlled trial. The Lancet. 2009;374 (9685):222-8.
6. Eakin EG, Resnikoff PM, Prewitt LM, et al. Validation of a new dyspnea measure: the UCSD Shortness of Breath Questionnaire. University of California, San Diego. Chest. 1998 Mar;113(3):619-24.
7. Chang JA, Curtis JR, Patrick DL, et al. Assessment of health-related quality of life in patients with interstitial lung disease. Chest. 1999 Nov;116(5):1175-82.
8. Strieter RM, Starko KM, Enelow RI, et al. Effects of interferon-gamma 1b on biomarker expression in patients with idiopathic pulmonary fibrosis. American Journal of Respiratory & Critical Care Medicine. 2004 Jul 15;170(2):133-40.
9. Jackson RM, Glassberg MK, Ramos CF, et al. Sildenafil therapy and exercise tolerance in idiopathic pulmonary fibrosis. Lung. [Randomized Controlled Trial
Research Support, U.S. Gov't, Non-P.H.S.]. 2010 Apr;188(2):115-23.
10. ATS statement: guidelines for the six-minute walk test. American Journal of Respiratory & Critical Care Medicine. 2002 Jul 1;166(1):111-7.
11. Zisman DA, Schwarz M, Anstrom KJ, et al. A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. New England Journal of Medicine. 2010 12 Aug;363 (7):620-8.
12. Kupferberg DH, Kaplan RM, Slymen DJ, et al. Minimal clinically important difference for the UCSD Shortness of Breath Questionnaire. Journal of Cardiopulmonary Rehabilitation. 2005 Nov-Dec;25(6):370-7.
13. Ries AL. Minimally clinically important difference for the UCSD Shortness of Breath Questionnaire, Borg Scale, and Visual Analog Scale. COPD. 2005 Mar;2(1):105-10.
14. Swigris JJ, Brown KK, Behr J, et al. The SF-36 and SGRQ: validity and first look at minimum important differences in IPF. Respiratory Medicine. 2010 Feb;104(2):296-304.
15. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. . Health QualLife Outcomes. 2007;5:70.
16. Collard HR, Anstrom KJ, Schwarz MI, et al. Sildenafil improves walk distance in idiopathic pulmonary fibrosis. Chest. 2007;131(3):897-900.
17. Nishiyama O, Kondoh Y, Kimura T, et al. Effects of pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. Respirology. 2008 May;13 (3):394-9.
18. Mahler DA, Weinberg DH, Wells CK, et al. The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. Chest. 1984 Jun;85(6):751-8.
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