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

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		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

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		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

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							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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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
							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.

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
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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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
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.

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
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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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

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