CHEST Online Supplement

Pharmacologic Therapy for Pulmonary Arterial Hypertension in Adults

CHEST Guideline and Expert Panel Report

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e-Table 1 - COI Information by Recommendation

Recommendation #'s	Panelists with Conflicts	Description of Conflicts
1-9	No panelists with conflicts	
10-74	David Badesch, MD	Dr. Badesch has received honoraria for service on steering committees or advisory boards (or as a consultant) to the following companies working in the area of pulmonary hypertension: Actelion/CoTherix, Gilead/Myogen, Encysive, Pfizer, Mondo-Biotech/Mondogen, Biogen IDEC, United Therapeutics/Lung Rx, GlaxoSmithKline, Lilly/ICOS, Bayer, Ikaria, and Arena. He has received grant support for clinical studies from GlaxoSmithKline, Actelion/CoTHerix, Gilead/Myogen, Pfizer/Encysive, United Therapeutics/Lung Rx, Lilly/ICOS, Bayer, and Novartis. He has provided expert legal assistance to Actelion.
75-79	No panelists with conflicts	

 DOI: 10.1378/chest.14-0793

e-Table 2 – Evidence Profile by Recommendation

Rec. #	# of Studies (Subjects)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Effect Estimate (95% CI)	Strength of Evidence (SOE)	Downgrades
10	2 (393)	Not Serious (-0)	Not Serious (-0)	Very Serious (-2)	Not Serious (-0)	Undetected	MD -42.86 (-60.24, -25.49)	**Low - C**	Downgraded two levels due to indirectness. Patient population from pooled studies is not specific to functional class. Also, the dosing of Ambrisentan was different between the two studies.
14	2 (542)	Not Serious (-0)	Not Serious (-0)	Very Serious (-2)	Not Serious (-0)	Undetected	MD -36.34 (-53.91, -18.77)	**Low - C**	Downgraded two levels due to indirectness because of the patient population from pooled studies is not specific to functional class, and the intervention from the PACES study included an intervention with Sildenafil plus Epoprostenol.

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21	2 (245)	Not Serious (-0)	Not Serious (-0)	Not Serious (-0)	Serious (-1)	Undetected	MD -47.66 (-69.29, -21.01)	**Moderate - B**	Downgraded one level due to indirectness because of the patient population from pooled studies is not specific to functional class.
22	2 (398)	Not Serious (-0)	Not Serious (-0)	Serious (-1)	Serious (-1)	Undetected	OR 0.30 (0.11, 0.78)	**Low - C**	Downgraded one level due to indirectness because of the patient population from pooled studies is not specific to functional class, nor is the outcome specific to the short-term. Downgraded only level due to imprecision because of low sample size.

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24	2 (393)	Not Serious (-0)	Not Serious (-0)	Very Serious (-2)	Not Serious (-0)	Undetected	MD -42.86 (-60.24, -25.49)	**Moderate - C**	Downgraded two levels due to indirectness because of the patient population from pooled studies is not specific to functional class and the dosages of Ambrisentan is different between the two studies.
27	2 (542)	Not Serious (-0)	Not Serious (-0)	Very Serious (-2)	Not Serious (-0)	Undetected	MD -36.34 (-53.91, -18.77)	**Low - C**	Downgraded two levels due to indirectness because of the patient population from pooled studies is not specific to functional class, and the intervention from the PACES study included an intervention with Sildenafil plus Epoprostenol.
39	2 (130)	Not Serious (-0)	Not Serious (-0)	Very Serious (-2)	Serious (-1)	Undetected	MD -86.95 (-143.67, -30.23)	**Insufficient**	Downgraded two levels due to indirectness because of the patient population from pooled studies is not specific to functional class and epoporstnol was tested as a combination therapy in the two studies. Downgraded one level due to imprecision because combines sample size was low.

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41	2 (493)	Not Serious (-0)	Not Serious (-0)	Very Serious (-2)	Serious (-1)	Undetected	MD -16.77 (-28.2, -5.33)	**Insufficient**	Downgraded two levels due to indirectness because of the patient population from pooled studies is not specific to functional class and the Simmeneau 2002 study tested treprostinil plus conventional therapy. Downgraded one level for imprecision because McLaughlin 2003 study has wide confidence intervals
42	2 (493)	Not Serious (-0)	Not Serious (-0)	Very Serious (-2)	Serious (-1)	Undetected	MD -16.77 (-28.2, -5.33)	**Insufficient**	Downgraded two levels due to indirectness because of the patient population from pooled studies is not specific to functional class and the Simmeneau 2002 study tested treprostinil plus conventional therapy. Downgraded one level for imprecision because McLaughlin 2003 study has wide confidence intervals

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45	2 (130)	Not Serious (-0)	Not Serious (-0)	Very Serious (-2)	Serious (-1)	Undetected	MD -86.95 (-143.67, -30.23)	**Insufficient**	Downgraded two levels due to indirectness because of the patient population from pooled studies is not specific to functional class and epoporstnol was tested as a combination therapy in the two studies. Downgraded one level due to imprecision because combines sample size was low.
47	2 (493)	Not Serious (-0)	Not Serious (-0)	Very Serious (-2)	Serious (-1)	Undetected	MD -16.77 (-28.2, -5.33)	**Insufficient**	Downgraded two levels due to indirectness because of the patient population from pooled studies is not specific to functional class and the Simmeneau 2002 study tested treprostinil plus conventional therapy. Downgraded one level for imprecision because McLaughlin 2003 study has wide confidence intervals

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49	2 (705)	Not Serious (-0)	Not Serious (-0)	Very Serious (-2)	Not Serious (-0)	Undetected	MD -17.93 (-26.27 to -9.59)	**Low - C**	Downgraded two levels due to indirectness because of the patient population from pooled studies is not specific to functional class and differences in dosages between the two studies.
53	2 (130)	Not Serious (-0)	Not Serious (-0)	Very Serious (-2)	Serious (-1)	Undetected	MD -86.95 (-143.67, -30.23)	**Insufficient**	Downgraded two levels due to indirectness because of the patient population from pooled studies is not specific to functional class and epoporstnol was tested as a combination therapy in the two studies. Downgraded one level due to imprecision because combines sample size was low.

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55	2 (493)	Not Serious (-0)	Not Serious (-0)	Very Serious (-2)	Serious (-1)	Undetected	MD -16.77 (-28.2, -5.33)	**Insufficient**	Downgraded two levels due to indirectness because of the patient population from pooled studies is not specific to functional class and the Simmeneau 2002 study tested treprostinil plus conventional therapy. Downgraded one level for imprecision because McLaughlin 2003 study has wide confidence intervals
56	2 (493)	Not Serious (-0)	Not Serious (-0)	Very Serious (-2)	Serious (-1)	Undetected	MD -16.77 (-28.2, -5.33)	**Insufficient**	Downgraded two levels due to indirectness because of the patient population from pooled studies is not specific to functional class and the Simmeneau 2002 study tested treprostinil plus conventional therapy. Downgraded one level for imprecision because McLaughlin 2003 study has wide confidence intervals
58	2 (245)	Not Serious (-0)	Not Serious (-0)	Serious (-1)	Not Serious (-0)	Undetected	MD -47.66 (-69.29, -21.01)	**Moderate - B**	Downgraded one level due to indirectness because of the patient population from pooled studies is not specific to functional class.

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62	2 (493)	Not Serious (-0)	Serious (-1)	Serious (-1)	Serious (-1)	Undetected	MD -16.77 (-28.2, -5.33)	**Insufficient**	Downgraded two levels due to indirectness because of the patient population from pooled studies is not specific to functional class and the Simmeneau 2002 study tested treprostinil plus conventional therapy. Downgraded one level for imprecision because McLaughlin 2003 study has wide confidence intervals
65	2 (493)	Not Serious (-0)	Not Serious (-0)	Serious (-1)	Serious (-1)	Undetected	MD -16.77 (-28.2, -5.33)	**Low - C**	Downgraded one level due to indirectness because of the patient population from pooled studies is not specific to functional class. Downgraded one level for imprecision because McLaughlin 2003 study has wide confidence intervals

Recommendations not listed have no pooled data available

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e-Table 3 – Evidence Table

RCT Study	Sample size	Sample Description	Setting Description	Intervention Name	Intervention Dose	Outcomes	Quality Appraisal
Badesch 2000[1]	111	Patients with NYHA functional class III (98%) or IV symptoms and a 6-min walk distance (6MWD) of 200 to 450 m while treated with bosentan (70%) or sildenafil	12 weeks	Epoprosteno IV plus conventional therapy vs. convention therapy alone	Gradual increase in infustion rate to week 12	6MWD - Epo Group: 270 baseline, 316 at week 12, +46 difference. Conventional Group: 240.0 baseline, 192 at week 12, -48 difference. Difference week 12: -108 m (95% CI, 55.2 m to 180.0 m), SE=26.94. Mortality - 4/56 treatment, 5/55 control	Fair
Barst 1996[2]	81	Patients with NYHA functional class III or IV, despite optimal medical therapy which consisted of the administration of anticoagulants, oral vasodilators, diuretic agents, cardiac glycosides, and supplemental oxygen.	12 weeks	Epoprosteno IV plus conventional therapy vs. convention therapy alone	Infused at an initial rate of 2 ng per kilogram of body weight per minute, with increments of 2 ng per kilogram per minute every 15 minutes	Mortality - 0/41 treatment, 8/40 control	Good
Channick 2001[3]	32	Patients with WHO functional classes III–IV, despite previous treatment with vasodilators, anticoagulants, diuretics, cardiac glycosides, or	12 weeks, five centres in the USA and one in France	Bosentan	62.5 mg twice daily for the first 4 weeks, followed by the target dose of 125 mg twice daily	6MWD - increased by 51 m in patients given bosentan and decreased by 6 m in those given placebo; the mean change was 76 m (95% CI 12–139, p=0·021) further for patients given	Good

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		supplemental oxygen. Patients were included if they had a baseline 6-min walking distance of between 150 m and 500 m, a mean pulmonary artery pressure of greater than 25 mm Hg, a pulmonary capillary wedge pressure of less than 15 mm Hg, and a pulmonary vascular resistance of greater than 240 dyn s cm-5.				bosentan than those given placebo.	
Galie 2005 SUPER[4]	278	Patients were included if they had PAH (idiopathic, associated with connective-tissue disease, or occurring after surgical repair of congenital systemic-to-pulmonary shunts that had been performed at least five years previously). PAH defined as a mean pulmonary-artery pressure of 25 mm Hg or more and a	12-week, double-blind, placebo-controlled trial conducted in 53 centers in the United States, Mexico, South America, Europe, Asia, Australia, South Africa, and Israel between	Sildenafil	20mg, 40mg, 80mg	6MWD - Placebo: 344 baseline. 20mg 347 baseline, +45 at 12 weeks (p<0.001). 40mg 345 baseline, +46 at 12 weeks (p<0.001). 80mg 339 baseline, +50 at 12 weeks (p<0.001). Functional Class - Proportions of patients with an improvement of at least one WHO functional class: Placebo 7% 5/70, 20mg 28% P=0.003 19/69, 40mg 36% P<0.001 24/67, 80% 42% P<0.001 30/71; 73/207 sildenafil (all)	Good

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		pulmonary-capillary wedge pressure of 15 mm Hg or less at rest. Patients with a six-minute walking distance of less than 100 m or more than 450 m were excluded.	October 2002 and November 2003				
Galie 2008 AIRES 1[5]	201	Patients who had PAH (idiopathic or associated with connective tissue disease, HIV infection, or anorexigen use). Treatment with bosentan, sitaxsentan, sildenafil, epoprostenol, iloprost, or treprostinil was prohibited. Patients with a 6-minute walk distance <150 or >450 m were excluded.	46 centers in the United States, Mexico, South America, Australia, and Europe; conducted between December 2003 and February 2006,	Ambrisentan	5mg, 10mg	6MWD - Increase observed in ambrisentan dose group at week 4, and this effect was maintained at weeks 8 and 12, deterioration observed in the placebo group by week 12. Mean placebo-corrected treatment effects at week 12: 31 m (95% confidence interval [CI], 3 to 59; P=0.008) for ambrisentan 5 mg; 51 m (95% CI, 27 to 76; P=0.001) for ambrisentan 10 mg; 41 average. Mortality - 5mg: 1, 10mg: 1, Placebo: 2. Hospitalizatoin - 5mg: 2, 10mg: 2, Placebo: 2	Good
Galie 2008 AIRES 2[5]	192	Patients who had PAH (idiopathic or associated with connective tissue disease, HIV infection, or anorexigen use).	41 centers in Europe, Israel, and South America: conducted between	Ambrisentan	2.5mg, 5mg	6MWD - 32 m (95% CI, 2 to 63; P=0.022) for ambrisentan 2.5 mg; 59 m (95% CI, 30 to 89; P=0.001) for ambrisentan 5 mg; 45.5 average. Mortality -	Good

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		Treatment with bosentan, sitaxsentan, sildenafil, epoprostenol, iloprost, or treprostinil was prohibited. Patients with a 6-minute walk distance <150 or >450 m were excluded.	December 2003 and February 2006			2.5mg: 2, 5mg: 0, Placebo: 3. Hospitalizatoin - 2.5mg: 3, 5mg: 2, Placebo: 9	
Galie 2008 EARLY[6]	185	Patients with WHO FC II PAH, aged 12 years or over with 6-min walk distance of less than 80% of the normal predicted value or less than 500 m associated with a Borg dyspnoea index of 2 or greater	52 sites in 21 countries. 32 weeks	Bosentan	62·5 mg twice daily, up-titrating to 125 mg twice daily after 4 weeks (or remaining at 62·5 mg twice daily if bodyweight <40 kg)	Mortality - Bosentan 1, Placebo 1. Hospitalizatoin - Bosentan: 1/93; Placebo 3/92	Good
McLaughlin 2003[7]	24	Patients with NYHA functional class III or IV despite conventional therapy, a mean pulmonary artery pressure greater than or equal to 25 mm Hg, a pulmonary capillary wedge pressure or left ventricular end diastolic pressure of less than or equal	10 tertiary care academic institutions, 8 weeks	Treprostinil	administered intravenously beginning at 2 ng/kg/min and increased every 15 to 30 minutes in 2-ng/kg/min increments to a maximum tolerated dose	6MWD - Difference 43.0 (-24.9, 110.9)	Good

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		to 15 mm Hg, and a pulmonary vascular resistance of greater than 3 Wood units.					
McLaughlin 2010 TRIUMPH 1[8]	235	Patients with NYHA functional class III (98%) or IV symptoms and a 6-min walk distance (6MWD) of 200 to 450 m while treated with bosentan (70%) or sildenafil	12 weeks	inhaled treprostinil + either bosentan (70%) or sildenafil (30%) vs. inhaled placebo + either bosentan (70%) or sildenafil (30%)	up to 54 g, 4x daily	6MWD - Background sildenafil: +9 at 12 weeks. Background bosentan: +25 at 12 weeks. Mean difference at 12 weeks was 16 in favor of background bosentan. At 12 weeks, there was a placebo-corrected improvement of -20 m (8.0 to 32.8) at 12 weeks, SE calculated = 6.12. Hodges-Lehmann between-treatment median difference in change from baseline in peak 6MWD +19m at week 6 (p=0.0001) and +20m at week 12 (p=0.0004). Baseline 346	Good

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Rubin 2002 BREATHE[9]	213	Patients with symptomatic, severe PAH (WHO functional class III or IV) despite treatment with anticoagulant drugs, vasodilators, diuretics, cardiac glycosides, or supplemental oxygen. Pulmonary arterial hypertension was either primary or associated with connective-tissue disease (scleroderma or systemic lupus erythematosus). 6MWD between 150 and 450 m, a resting mean pulmonary-artery pressure greater than 25 mm Hg, a pulmonarycapillary wedge pressure of less than 15 mm Hg, and pulmonary vascular resistance greater than 240 dyn·sec·cm. Patients were excluded if they had started or stopped any therapy for PAH	27 centers in Europe, North America, Israel, and Australia. 28 weeks	Bosentan	62.5 mg of bosentan twice daily for 4 weeks followed by either of two doses of bosentan (125 or 250 mg twice daily)	6MWD - combined bosentan groups = +36 placebo group = -8, mean difference of 44 m (95 percent confidence interval, 21 to 67; P<0.001). The placebo-corrected improvement was more pronounced for the dose of 250 mg twice daily than for the dose of 125 mg twice daily (54 m and 35 m, respectively). Mortality - 250mg: 0, 125mg: 1, Placebo: 2. Hospitalization - 250mg: 3; 125mg: 3, Placebo: 9	Good

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		within one month before screening or if they had received or had been scheduled to receive long-term treatment with epoprostenol within three months before screening. To avoid potential drug interactions, patients were also excluded if they were receiving glyburide (glibenclamide) or cyclosporine.					
Rubin 1990[10]	24 (19 completed)	Patients with primary pulmonary hypertension	8 weeks	Epoprosteno IV plus conventional therapy vs. convention therapy alone	Doses determined by acute responses during baseline catheterization	Mortality - Epo: 246m at baseline, 378m at 2 months (p=0.011), 132 difference (49.8 to 212.6) Conventional Therapy: 205m at baseline, 292m at 2 months (p=0.022) 87 difference (21.7 to 135.8). Mean difference at 8 weeks (2 months) 45 in favor of epo. 6MWD - Epo: 246m at baseline, 378m at 2 months (p=0.011), 132 difference (49.8 to 212.6). Conventional Therapy: 205m at baseline, 292m at 2 months (p=0.022) 87	Good

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						difference (21.7 to 135.8). Mean difference at 8 weeks (2 months): 45 in favor of epo	
Simmonneau, 2002[11]	469	Patients with primary pulmonary hypertension or pulmonary hypertension associated with connective tissue diseases or associated with congenital systemic to pulmonary shunts, Age between 8 and 75 yr, NYHA functional class II, III, or IV. Mean pulmonary arterial pressure 25 mm Hg at rest, mean pulmonary capillary wedge pressure15 mm Hg, Pulmonary vascular resistance 3 mm Hg/L/min, Ventilation perfusion lung scan or pulmonary angiography not indicative of thromboembolic disease.	12 weeks, 24 centers in North America (Canada, Mexico, and the United States), and from 16 centers in the rest of the world (Australia, Austria, Belgium, France, Germany, Israel, Italy, Poland, Spain, UK).	treprostinil plus conventional therapy vs. continuous infusion of placebo plus conventional therapy	maximum allowable dose was 22.5 ng/kg/min	6MWD - At Week 12, treprostinil group by a median change of 10 m (-24 to 47 m; 25th–75th percentile) placebo group with a median change of 0 m(-44 to 32 m; 25th–75th percentile). The difference in median distance walked between the two groups. At Week 12, -16 m (95% CI, 4.4 m to 27.6 m), SE calculated = 5.92	Good

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Simonneau 2008 PACES[12]	267	Patients at least 18 years of age (16 years of age in the United States) and had received a diagnosis of PAH, (idiopathic, familial, associated with anorexigen use or connective tissue disease, or occurring after surgical repair of congenital systemic-to-pulmonary shunts done at least 5 years earlier). Patients had to have received longterm intravenous epoprostenol (Flolan, GlaxoSmithKline, Research Triangle Park, North Carolina) therapy for at least 3 months, with a stable dose for at least 4 weeks before randomization. We excluded patients with a 6-minute walk distance less than 100 meters or	46 centers in 11 countries were involved in this study (United States, 26; Canada, 6; France, 3; Netherlands, 2; Spain, 2; United Kingdom, 2; Belgium, 1; Czech Republic, 1; Denmark, 1; Israel, 1; and Italy, 1). All sites were academic centers or hospitals, and specialists cared for all patients.	Sildenafil + Epo	20 mg three times daily, titrated to 40 mg and 80 mg three times daily, as tolerated, at 4-week intervals.	6MWD - Placebo: 341.6 baseline, +1 at week 16. Sildenafil 348.9 baseline, +29.8 at week 16. (p<0.001)	Good

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		greater than 450 meters or those whose 6-minute walk distance was affected by conditions other than pulmonary arterial hypertension.					

1. Badesch DB, Tapson VF, McGoon MD, et al. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. *Ann Intern Med.* Mar 21 2000;132(6):425-434.
2. Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. *The New England journal of medicine.* Feb 1 1996;334(5):296-301.
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8. McLaughlin VV, Benza RL, Rubin LJ, et al. Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: a randomized controlled clinical trial. *J Am Coll Cardiol.* May 4 2010;55(18):1915-1922.
9. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *The New England journal of medicine.* Mar 21 2002;346(12):896-903.
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11. Simonneau G, Barst RJ, Galie N, et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. *American journal of respiratory and critical care medicine.* Mar 15 2002;165(6):800-804.
12. Simonneau G, Rubin LJ, Galie N, et al. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial. *Ann Intern Med.* Oct 21 2008;149(8):521-530.

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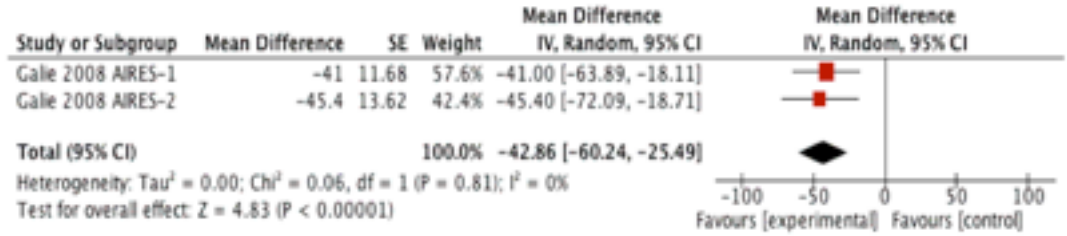
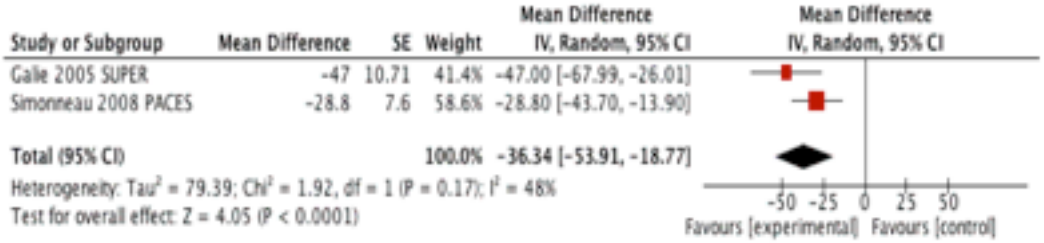
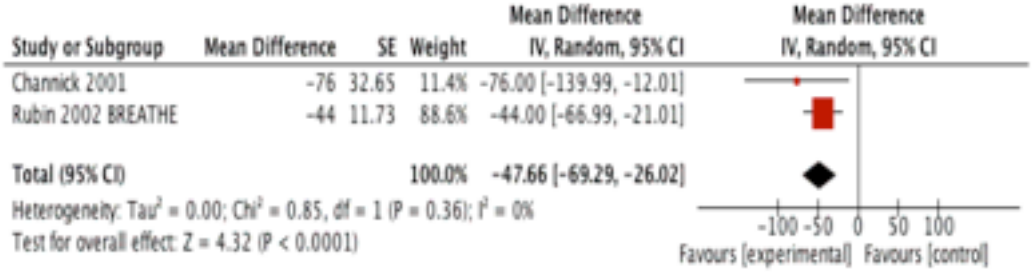
e-Figure 1 – Forest Plots by Recommendation

Recommendation #	Forest Plot
10	
14	
21	

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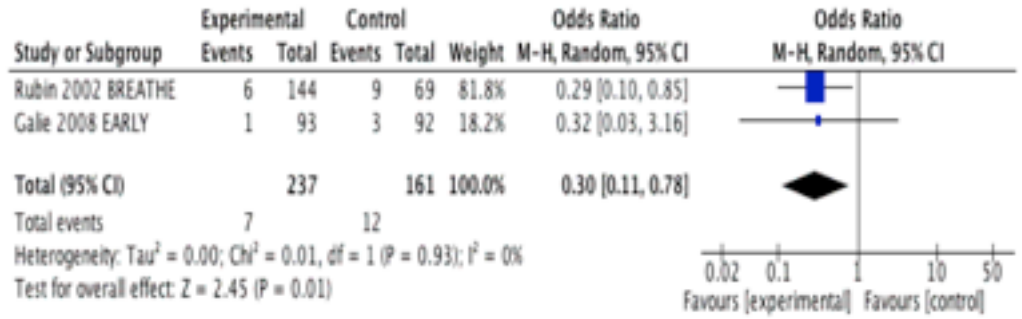
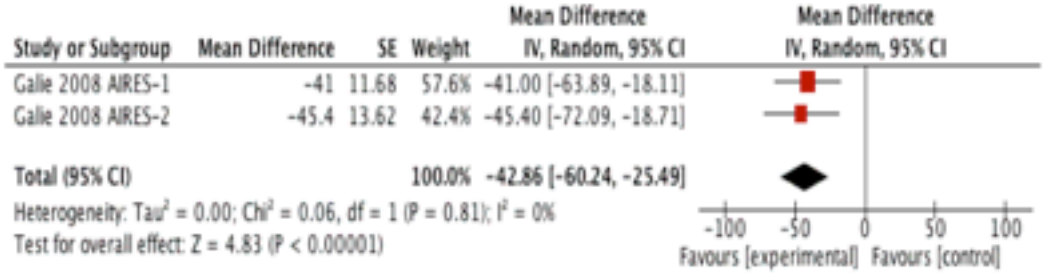
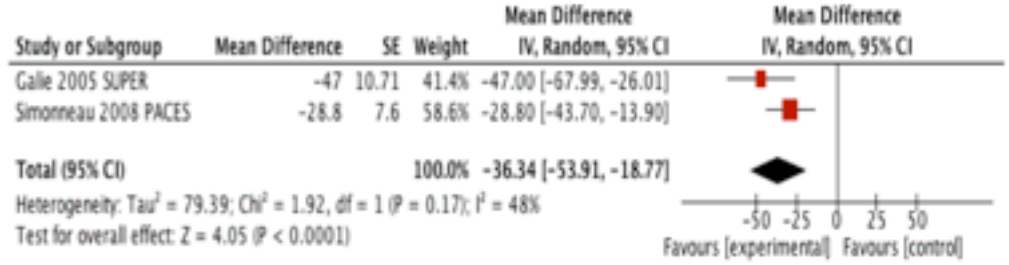
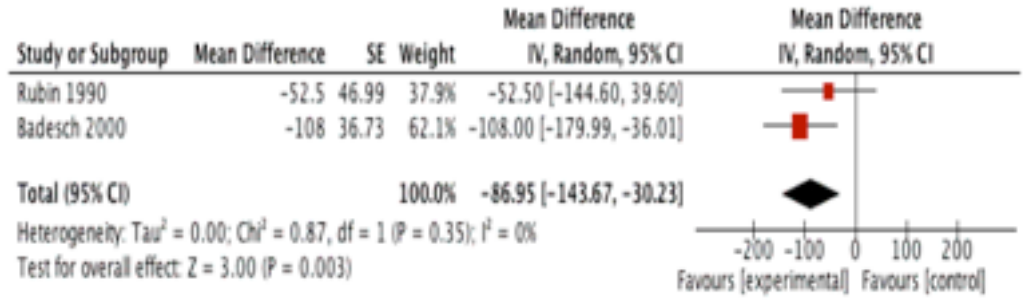
22	
24	
27	
39	

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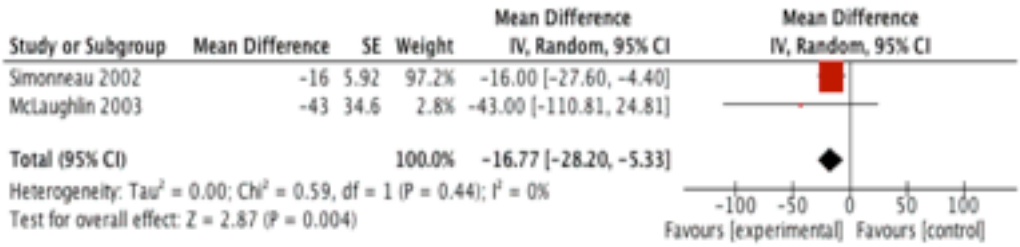
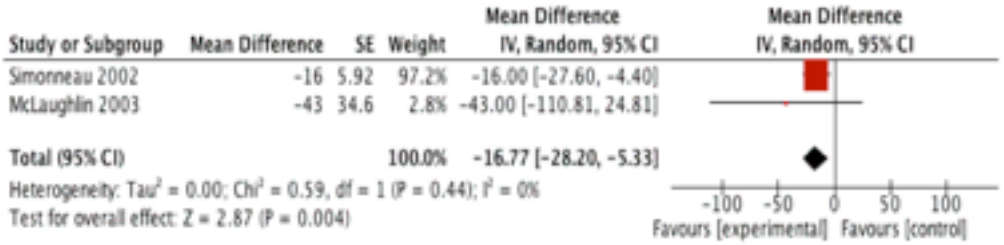
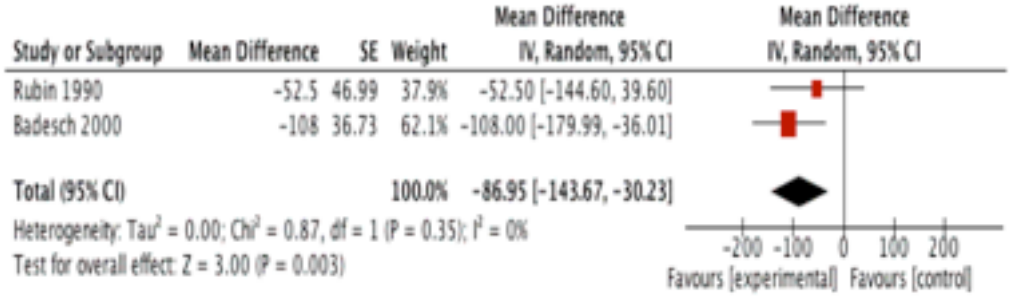
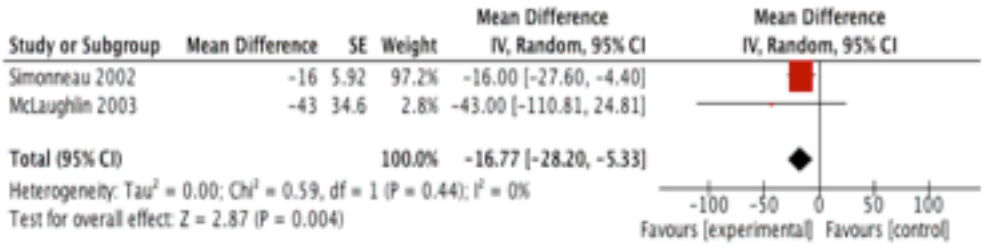
41	
42	
45	
47	

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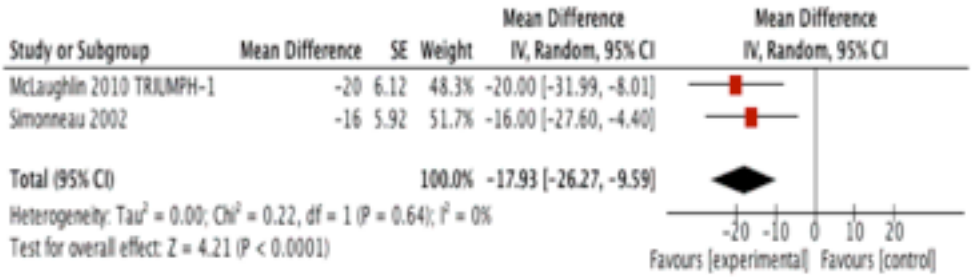
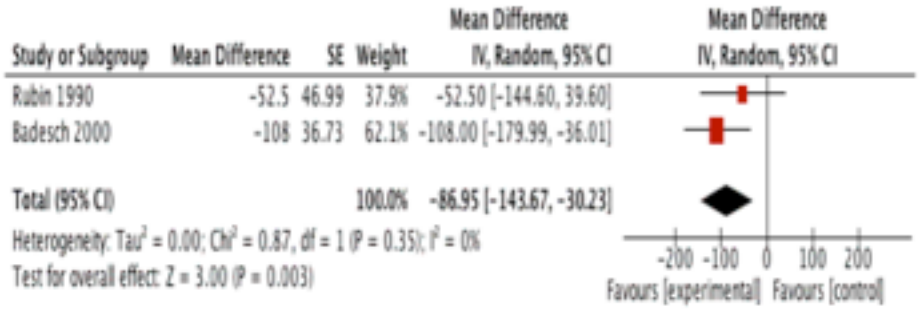
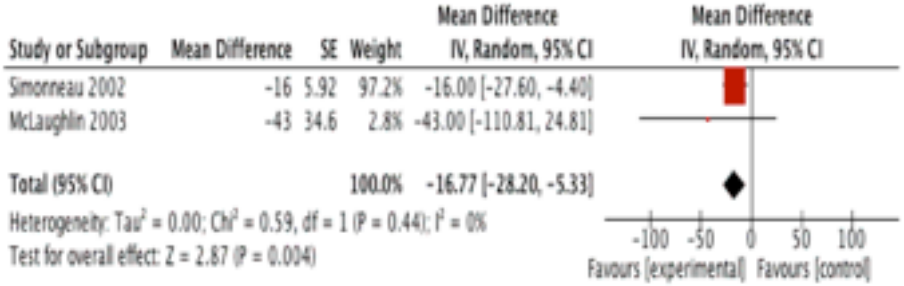
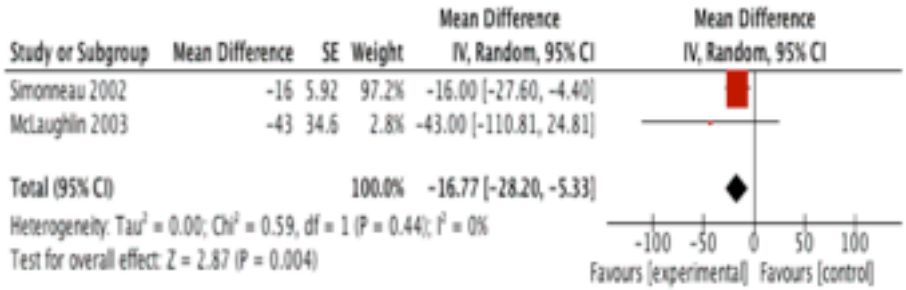
49	
53	
55	
56	

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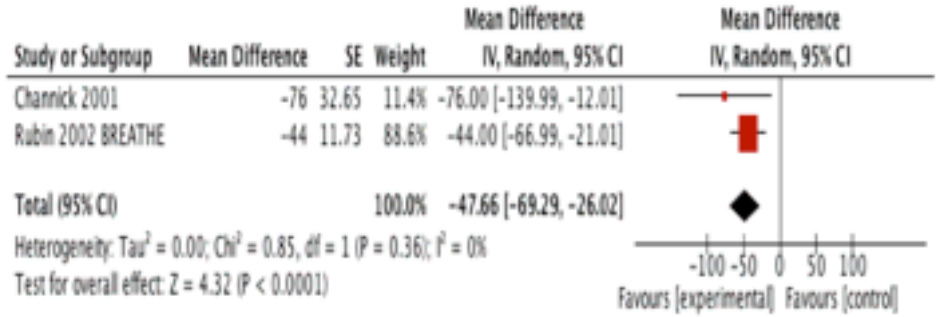
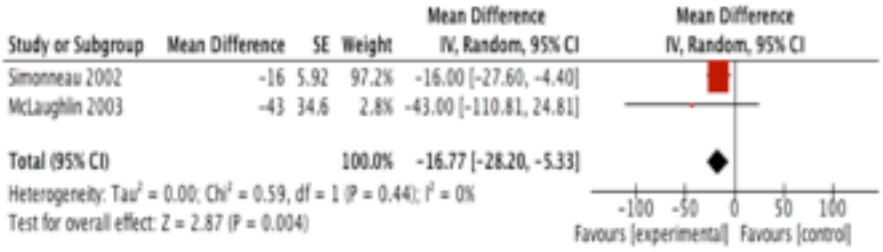
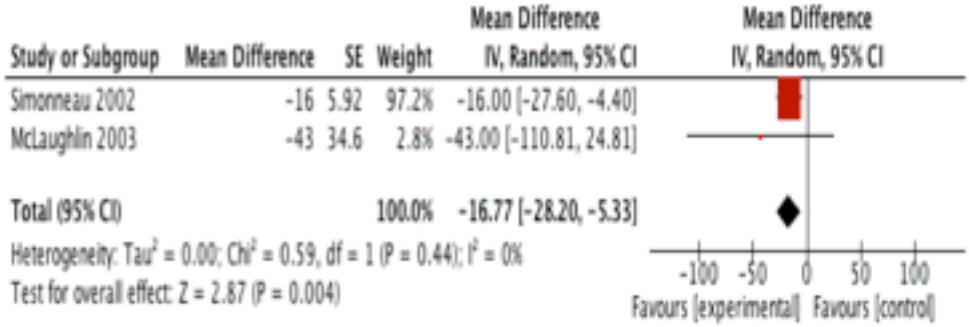
58	
62	
65	

Recommendations not listed have no pooled data available

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e-Appendix 1: Grading

Grade of Recommendation	Benefit vs Risk and Burdens	Methodological Strength of Supporting Evidence	Implications
Strong recommendation, High-quality evidence (1 A)	Benefits clearly outweigh risk and burdens, or vice versa	Consistent evidence from randomized controlled trials without important limitations or exceptionally strong evidence from observational studies.	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change our confidence in the estimate of effect.
Strong recommendation, Moderate-quality evidence (1 B)	Benefits clearly outweigh risk and burdens, or vice versa	Evidence from randomized, controlled trials with important limitations (inconsistent results, methodological flaws, indirect or imprecise), or very strong evidence from observational studies.	Recommendation can apply to most patients in most circumstances. Higher quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.
Strong recommendation, Low or very low-quality evidence (1 C)	Benefits clearly outweigh risk and burdens, or vice versa	Evidence for at least one critical outcome from observational studies, case series, or from randomized, controlled trials with serious flaws or indirect evidence.	Recommendation can apply to most patients in many circumstances. Higher quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.
Weak recommendation, High-quality evidence (2 A)	Benefits closely balanced with risks and burden	Consistent evidence from randomized controlled trials without important limitations or exceptionally strong evidence from observational studies.	The best action may differ depending on circumstances or patients' or societal values. Further research is very unlikely to change our confidence in the estimate of effect. Best action may differ depending on circumstances or patients' or societal values. Higher quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.
Weak recommendation, Moderate-quality evidence (2 B)	Benefits closely balanced with risks and burden	Evidence from randomized, controlled trials with important limitations (inconsistent results, methodological flaws, indirect or imprecise), or very strong evidence from observational studies.	
Weak recommendation, Low or very low-quality evidence (2 C)	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk and burden may be closely balanced	Evidence for at least one critical outcome from observational studies, case series, or from randomized, controlled trials with serious flaws or indirect evidence.	Other alternatives may be equally reasonable. Higher quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.
Non-Graded Consensus-based Suggestions			
Consensus-based (CB)	Uncertainty due to lack of evidence but expert opinion that benefits outweigh risk and burdens or vice versa	Insufficient evidence for a graded recommendation	Future research may well have an important impact on our confidence in the estimate of effect and may change the estimate.

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