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Pressurised metered dose inhalers versus all other hand-held inhaler devices to deliver beta-2 agonist bronchodilators for non-acute asthma (Review)

Ram FSF, Brocklebank DDM, White J, Wright JJ, Jones P

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Cochrane Database of Systematic Reviews 2002, Issue 2. Art. No.: CD002158.

DOI: [10.1002/14651858.CD002158](https://doi.org/10.1002/14651858.CD002158).

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	3
OBJECTIVES	3
METHODS	3
RESULTS	6
DISCUSSION	8
AUTHORS' CONCLUSIONS	10
ACKNOWLEDGEMENTS	10
REFERENCES	12
CHARACTERISTICS OF STUDIES	22
DATA AND ANALYSES	69
Analysis 1.1. Comparison 1 Adults - Crossover design: Turbuhaler vs pMDI (mean absolute value), Outcome 1 FEV1 (L).	70
Analysis 1.2. Comparison 1 Adults - Crossover design: Turbuhaler vs pMDI (mean absolute value), Outcome 2 FVC (L).	71
Analysis 1.3. Comparison 1 Adults - Crossover design: Turbuhaler vs pMDI (mean absolute value), Outcome 3 PEFR - Daily (L/min).	71
Analysis 1.4. Comparison 1 Adults - Crossover design: Turbuhaler vs pMDI (mean absolute value), Outcome 4 PEFR (morning). .	72
Analysis 1.5. Comparison 1 Adults - Crossover design: Turbuhaler vs pMDI (mean absolute value), Outcome 5 PEFR (evening). .	72
Analysis 1.6. Comparison 1 Adults - Crossover design: Turbuhaler vs pMDI (mean absolute value), Outcome 6 AUC-FEV1 (L x min).	72
Analysis 1.7. Comparison 1 Adults - Crossover design: Turbuhaler vs pMDI (mean absolute value), Outcome 7 Heart Rate (bpm).	73
Analysis 1.8. Comparison 1 Adults - Crossover design: Turbuhaler vs pMDI (mean absolute value), Outcome 8 Systolic Pressure (mmHg).	73
Analysis 1.9. Comparison 1 Adults - Crossover design: Turbuhaler vs pMDI (mean absolute value), Outcome 9 Diastolic Pressure (mmHg).	73
Analysis 1.10. Comparison 1 Adults - Crossover design: Turbuhaler vs pMDI (mean absolute value), Outcome 10 Serum K+ (mmol/L).	74
Analysis 1.11. Comparison 1 Adults - Crossover design: Turbuhaler vs pMDI (mean absolute value), Outcome 11 Adverse Events.	74
Analysis 1.12. Comparison 1 Adults - Crossover design: Turbuhaler vs pMDI (mean absolute value), Outcome 12 Treatment Failures/Dropouts.	75
Analysis 1.13. Comparison 1 Adults - Crossover design: Turbuhaler vs pMDI (mean absolute value), Outcome 13 Preference for inhaler.	75
Analysis 2.1. Comparison 2 Adults - Crossover design: Turbuhaler vs pMDI (absolute change from baseline), Outcome 1 FEV1 (L).	76
Analysis 2.2. Comparison 2 Adults - Crossover design: Turbuhaler vs pMDI (absolute change from baseline), Outcome 2 FVC (L).	76
Analysis 2.3. Comparison 2 Adults - Crossover design: Turbuhaler vs pMDI (absolute change from baseline), Outcome 3 Heart Rate (bpm).	77
Analysis 3.1. Comparison 3 Adults - Crossover design: Turbuhaler vs pMDI (% change from baseline), Outcome 1 FEV1.	77
Analysis 4.1. Comparison 4 Adults - Crossover design: Turbuhaler vs pMDI (combined using SMD), Outcome 1 FEV1.	78
Analysis 4.2. Comparison 4 Adults - Crossover design: Turbuhaler vs pMDI (combined using SMD), Outcome 2 FVC.	78
Analysis 4.3. Comparison 4 Adults - Crossover design: Turbuhaler vs pMDI (combined using SMD), Outcome 3 Heart Rate.	79
Analysis 5.1. Comparison 5 Adults - Crossover design: Diskhaler vs pMDI (mean absolute value), Outcome 1 FEV1 (L).	80
Analysis 5.2. Comparison 5 Adults - Crossover design: Diskhaler vs pMDI (mean absolute value), Outcome 2 PEFR - Daily (L/min).	80
Analysis 5.3. Comparison 5 Adults - Crossover design: Diskhaler vs pMDI (mean absolute value), Outcome 3 Adverse Events. ...	80
Analysis 6.1. Comparison 6 Adults - Crossover design: HFA-pMDI vs pMDI (mean absolute value), Outcome 1 FEV1 (L).	81
Analysis 6.2. Comparison 6 Adults - Crossover design: HFA-pMDI vs pMDI (mean absolute value), Outcome 2 FVC (L).	81
Analysis 7.1. Comparison 7 Adults - Crossover design: HFA-pMDI vs pMDI (absolute change from baseline), Outcome 1 FEV1 (L).	82
Analysis 7.2. Comparison 7 Adults - Crossover design: HFA-pMDI vs pMDI (absolute change from baseline), Outcome 2 FVC (L). .	83
Analysis 7.3. Comparison 7 Adults - Crossover design: HFA-pMDI vs pMDI (absolute change from baseline), Outcome 3 Heart Rate (bpm).	83

Analysis 7.4. Comparison 7 Adults - Crossover design: HFA-pMDI vs pMDI (absolute change from baseline), Outcome 4 Systolic Pressure (mmHg).	84
Analysis 7.5. Comparison 7 Adults - Crossover design: HFA-pMDI vs pMDI (absolute change from baseline), Outcome 5 Diastolic Pressure (mmHg).	84
Analysis 7.6. Comparison 7 Adults - Crossover design: HFA-pMDI vs pMDI (absolute change from baseline), Outcome 6 Serum K ⁺ (mmol/L).	84
Analysis 7.7. Comparison 7 Adults - Crossover design: HFA-pMDI vs pMDI (absolute change from baseline), Outcome 7 Adverse Events.	85
Analysis 7.8. Comparison 7 Adults - Crossover design: HFA-pMDI vs pMDI (absolute change from baseline), Outcome 8 AUC-FEV1 (L x min).	85
Analysis 8.1. Comparison 8 Adults - Crossover design: HFA-pMDI vs pMDI (% change from baseline), Outcome 1 FEV1.	86
Analysis 8.2. Comparison 8 Adults - Crossover design: HFA-pMDI vs pMDI (% change from baseline), Outcome 2 FVC.	86
Analysis 8.3. Comparison 8 Adults - Crossover design: HFA-pMDI vs pMDI (% change from baseline), Outcome 3 AUC-FEV1.	87
Analysis 8.4. Comparison 8 Adults - Crossover design: HFA-pMDI vs pMDI (% change from baseline), Outcome 4 Adverse Events.	87
Analysis 9.1. Comparison 9 Adults - Crossover design: HFA-pMDI vs pMDI (combined using SMD), Outcome 1 FEV1.	88
Analysis 9.2. Comparison 9 Adults - Crossover design: HFA-pMDI vs pMDI (combined using SMD), Outcome 2 AUC-FEV1.	88
Analysis 10.1. Comparison 10 Adults - Crossover design: Rotahaler vs pMDI (mean absolute value), Outcome 1 FEV1 (L).	90
Analysis 10.2. Comparison 10 Adults - Crossover design: Rotahaler vs pMDI (mean absolute value), Outcome 2 PEFR (morning).	90
Analysis 10.3. Comparison 10 Adults - Crossover design: Rotahaler vs pMDI (mean absolute value), Outcome 3 PEFR (evening).	90
Analysis 10.4. Comparison 10 Adults - Crossover design: Rotahaler vs pMDI (mean absolute value), Outcome 4 AUC-FEV1 (L x min).	91
Analysis 10.5. Comparison 10 Adults - Crossover design: Rotahaler vs pMDI (mean absolute value), Outcome 5 Heart Rate (bpm).	91
Analysis 10.6. Comparison 10 Adults - Crossover design: Rotahaler vs pMDI (mean absolute value), Outcome 6 Preference for inhaler.	91
Analysis 10.7. Comparison 10 Adults - Crossover design: Rotahaler vs pMDI (mean absolute value), Outcome 7 Adverse Events.	92
Analysis 11.1. Comparison 11 Adults - Crossover design: Rotahaler vs pMDI (absolute change from baseline), Outcome 1 FEV1 (L).	93
Analysis 11.2. Comparison 11 Adults - Crossover design: Rotahaler vs pMDI (absolute change from baseline), Outcome 2 FVC (L).	93
Analysis 11.3. Comparison 11 Adults - Crossover design: Rotahaler vs pMDI (absolute change from baseline), Outcome 3 Heart Rate (bpm).	93
Analysis 12.1. Comparison 12 Adults - Crossover design: Rotahaler vs pMDI (% change from baseline), Outcome 1 FEV1.	94
Analysis 12.2. Comparison 12 Adults - Crossover design: Rotahaler vs pMDI (% change from baseline), Outcome 2 FVC.	95
Analysis 12.3. Comparison 12 Adults - Crossover design: Rotahaler vs pMDI (% change from baseline), Outcome 3 PEFR - Daily.	95
Analysis 12.4. Comparison 12 Adults - Crossover design: Rotahaler vs pMDI (% change from baseline), Outcome 4 AUC-FEV1.	96
Analysis 12.5. Comparison 12 Adults - Crossover design: Rotahaler vs pMDI (% change from baseline), Outcome 5 Acute Exacerbations.	96
Analysis 12.6. Comparison 12 Adults - Crossover design: Rotahaler vs pMDI (% change from baseline), Outcome 6 Preference for inhaler.	96
Analysis 12.7. Comparison 12 Adults - Crossover design: Rotahaler vs pMDI (% change from baseline), Outcome 7 Adverse Events.	97
Analysis 13.1. Comparison 13 Adults - Crossover design: Rotahaler vs pMDI (combined using SMD), Outcome 1 FEV1.	98
Analysis 13.2. Comparison 13 Adults - Crossover design: Rotahaler vs pMDI (combined using SMD), Outcome 2 FVC.	98
Analysis 13.3. Comparison 13 Adults - Crossover design: Rotahaler vs pMDI (combined using SMD), Outcome 3 AUC-FEV1.	99
Analysis 13.4. Comparison 13 Adults - Crossover design: Rotahaler vs pMDI (combined using SMD), Outcome 4 Preference for inhaler.	99
Analysis 14.1. Comparison 14 Adults - Crossover design: Spiros vs pMDI (mean absolute value), Outcome 1 FEV1 (L).	100
Analysis 14.2. Comparison 14 Adults - Crossover design: Spiros vs pMDI (mean absolute value), Outcome 2 FVC (L).	101
Analysis 14.3. Comparison 14 Adults - Crossover design: Spiros vs pMDI (mean absolute value), Outcome 3 PEFR - Daily (L/min).	101
Analysis 14.4. Comparison 14 Adults - Crossover design: Spiros vs pMDI (mean absolute value), Outcome 4 AUC-FEV1 (L x min).	102
Analysis 14.5. Comparison 14 Adults - Crossover design: Spiros vs pMDI (mean absolute value), Outcome 5 Heart Rate (bpm).	102
Analysis 14.6. Comparison 14 Adults - Crossover design: Spiros vs pMDI (mean absolute value), Outcome 6 Systolic Pressure (mmHg).	102

Analysis 14.7. Comparison 14 Adults - Crossover design: Spiros vs pMDI (mean absolute value), Outcome 7 Diastolic Pressure (mmHg).	103
Analysis 14.8. Comparison 14 Adults - Crossover design: Spiros vs pMDI (mean absolute value), Outcome 8 Serum K+ (mmol/L).	103
Analysis 15.1. Comparison 15 Adults - Crossover design: Spinhaler vs pMDI (absolute change from baseline), Outcome 1 FEV1 (L).	104
Analysis 15.2. Comparison 15 Adults - Crossover design: Spinhaler vs pMDI (absolute change from baseline), Outcome 2 FVC (L).	104
Analysis 16.1. Comparison 16 Adults - Crossover design: Easyhaler vs pMDI (mean absolute value), Outcome 1 FEV1 (L).	106
Analysis 16.2. Comparison 16 Adults - Crossover design: Easyhaler vs pMDI (mean absolute value), Outcome 2 FVC (L).	106
Analysis 16.3. Comparison 16 Adults - Crossover design: Easyhaler vs pMDI (mean absolute value), Outcome 3 PEFR - Daily (L/min).	106
Analysis 16.4. Comparison 16 Adults - Crossover design: Easyhaler vs pMDI (mean absolute value), Outcome 4 PEFR - Morning (L/min).	107
Analysis 16.5. Comparison 16 Adults - Crossover design: Easyhaler vs pMDI (mean absolute value), Outcome 5 AUC-FEV1 (L x min).	107
Analysis 16.6. Comparison 16 Adults - Crossover design: Easyhaler vs pMDI (mean absolute value), Outcome 6 Heart Rate (bpm).	108
Analysis 16.7. Comparison 16 Adults - Crossover design: Easyhaler vs pMDI (mean absolute value), Outcome 7 Systolic Pressure (mmHg).	108
Analysis 16.8. Comparison 16 Adults - Crossover design: Easyhaler vs pMDI (mean absolute value), Outcome 8 Diastolic Pressure (mmHg).	108
Analysis 16.9. Comparison 16 Adults - Crossover design: Easyhaler vs pMDI (mean absolute value), Outcome 9 Adverse Events.	109
Analysis 17.1. Comparison 17 Adults - Crossover design: Easyhaler vs pMDI (% change from baseline), Outcome 1 FEV1 (L).	109
Analysis 18.1. Comparison 18 Adults - Crossover design: Easyhaler vs pMDI (combined using SMD), Outcome 1 FEV1 (L).	110
Analysis 19.1. Comparison 19 Adults - Crossover design: Multi Dose Powder Inhaler vs pMDI (mean absolute value), Outcome 1 FEV1 (L).	111
Analysis 19.2. Comparison 19 Adults - Crossover design: Multi Dose Powder Inhaler vs pMDI (mean absolute value), Outcome 2 AUC-FEV1 (L x min).	111
Analysis 19.3. Comparison 19 Adults - Crossover design: Multi Dose Powder Inhaler vs pMDI (mean absolute value), Outcome 3 Preference for inhaler.	111
Analysis 19.4. Comparison 19 Adults - Crossover design: Multi Dose Powder Inhaler vs pMDI (mean absolute value), Outcome 4 Adverse Events.	112
Analysis 20.1. Comparison 20 Adults - Crossover design: Clickhaler vs pMDI (absolute change from baseline), Outcome 1 FEV1 (L).	112
Analysis 20.2. Comparison 20 Adults - Crossover design: Clickhaler vs pMDI (absolute change from baseline), Outcome 2 Adverse Events.	113
Analysis 21.1. Comparison 21 Adults - Crossover design: Gentlehaler vs pMDI (% change from baseline), Outcome 1 FEV1.	114
Analysis 21.2. Comparison 21 Adults - Crossover design: Gentlehaler vs pMDI (% change from baseline), Outcome 2 FVC.	114
Analysis 21.3. Comparison 21 Adults - Crossover design: Gentlehaler vs pMDI (% change from baseline), Outcome 3 PEFR - Daily.	114
Analysis 22.1. Comparison 22 Adults - Crossover design: Autohaler vs pMDI (absolute change from baseline), Outcome 1 FEV1 (L).	115
Analysis 22.2. Comparison 22 Adults - Crossover design: Autohaler vs pMDI (absolute change from baseline), Outcome 2 FVC (L).	115
Analysis 22.3. Comparison 22 Adults - Crossover design: Autohaler vs pMDI (absolute change from baseline), Outcome 3 PEFR - Daily (L/min).	116
Analysis 23.1. Comparison 23 Adults - Crossover design: All other inhaler devices vs pMDI (combined using SMD), Outcome 1 FEV1.	118
Analysis 23.2. Comparison 23 Adults - Crossover design: All other inhaler devices vs pMDI (combined using SMD), Outcome 2 FVC.	119
Analysis 23.3. Comparison 23 Adults - Crossover design: All other inhaler devices vs pMDI (combined using SMD), Outcome 3 PEFR - Daily.	119
Analysis 23.4. Comparison 23 Adults - Crossover design: All other inhaler devices vs pMDI (combined using SMD), Outcome 4 PEFR (morning).	120

Analysis 23.5. Comparison 23 Adults - Crossover design: All other inhaler devices vs pMDI (combined using SMD), Outcome 5 PEFR (evening).	120
Analysis 23.6. Comparison 23 Adults - Crossover design: All other inhaler devices vs pMDI (combined using SMD), Outcome 6 AUC-FEV1.	121
Analysis 23.7. Comparison 23 Adults - Crossover design: All other inhaler devices vs pMDI (combined using SMD), Outcome 7 Heart Rate.	121
Analysis 23.8. Comparison 23 Adults - Crossover design: All other inhaler devices vs pMDI (combined using SMD), Outcome 8 Preference for inhaler.	122
Analysis 23.9. Comparison 23 Adults - Crossover design: All other inhaler devices vs pMDI (combined using SMD), Outcome 9 Adverse Events.	122
Analysis 23.10. Comparison 23 Adults - Crossover design: All other inhaler devices vs pMDI (combined using SMD), Outcome 10 Serum K+.	123
Analysis 24.1. Comparison 24 Adults - Crossover design: All other inhalers vs pMDI (for outcomes measured 15-45 mins post-dose, using SMD), Outcome 1 FEV1.	125
Analysis 24.2. Comparison 24 Adults - Crossover design: All other inhalers vs pMDI (for outcomes measured 15-45 mins post-dose, using SMD), Outcome 2 FVC.	125
Analysis 24.3. Comparison 24 Adults - Crossover design: All other inhalers vs pMDI (for outcomes measured 15-45 mins post-dose, using SMD), Outcome 3 AUC-FEV1.	126
Analysis 24.4. Comparison 24 Adults - Crossover design: All other inhalers vs pMDI (for outcomes measured 15-45 mins post-dose, using SMD), Outcome 4 Heart Rate.	126
Analysis 24.5. Comparison 24 Adults - Crossover design: All other inhalers vs pMDI (for outcomes measured 15-45 mins post-dose, using SMD), Outcome 5 PEFR - Daily.	127
Analysis 24.6. Comparison 24 Adults - Crossover design: All other inhalers vs pMDI (for outcomes measured 15-45 mins post-dose, using SMD), Outcome 6 PEFR - Morning.	128
Analysis 24.7. Comparison 24 Adults - Crossover design: All other inhalers vs pMDI (for outcomes measured 15-45 mins post-dose, using SMD), Outcome 7 PEFR - Evening.	128
Analysis 25.1. Comparison 25 Adults - Crossover design - Challenge testing: Turbuhaler vs pMDI (mean absolute values), Outcome 1 FEV1 (L) - Adults: Increase post Mch challenge and bronchodilator.	129
Analysis 25.2. Comparison 25 Adults - Crossover design - Challenge testing: Turbuhaler vs pMDI (mean absolute values), Outcome 2 FEV1 (L) - Children: Increase post exercise challenge and bronchodilator.	129
Analysis 26.1. Comparison 26 Adults - Crossover design - Challenge testing: Diskhaler vs pMDI (mean absolute values), Outcome 1 FEV1 (L).	130
Analysis 26.2. Comparison 26 Adults - Crossover design - Challenge testing: Diskhaler vs pMDI (mean absolute values), Outcome 2 FVC (L).	130
Analysis 27.1. Comparison 27 Adults - Crossover design - Challenge testing: Multi Dose Powder Inhaler vs pMDI (mean absolute values), Outcome 1 Methacholine Challenge (mg Mch) (PD20-FEV1).	131
Analysis 28.1. Comparison 28 Adults - Crossover design - Challenge testing: Autohaler vs pMDI (mean absolute values), Outcome 1 Methacholine Challenge (mg Mch) (PD20-FEV1).	131
Analysis 29.1. Comparison 29 Adults - Crossover design - Challenge testing: HFA vs pMDI (% fall in outcome), Outcome 1 FEV1 - adults.	132
Analysis 29.2. Comparison 29 Adults - Crossover design - Challenge testing: HFA vs pMDI (% fall in outcome), Outcome 2 FEV1 - children.	132
Analysis 30.1. Comparison 30 Adults - Crossover design - Different doses in inhalers: Turbuhaler vs pMDI (mean absolute value), Outcome 1 FEV1 (L).	133
Analysis 30.2. Comparison 30 Adults - Crossover design - Different doses in inhalers: Turbuhaler vs pMDI (mean absolute value), Outcome 2 PEFR - Morning (L/min).	134
Analysis 30.3. Comparison 30 Adults - Crossover design - Different doses in inhalers: Turbuhaler vs pMDI (mean absolute value), Outcome 3 PEFR - Evening (L/min).	134
Analysis 30.4. Comparison 30 Adults - Crossover design - Different doses in inhalers: Turbuhaler vs pMDI (mean absolute value), Outcome 4 Preference.	135
Analysis 31.1. Comparison 31 Adults - Crossover design - Different doses in inhalers: Diskhaler vs pMDI (mean absolute value), Outcome 1 FEV1 (L).	135
Analysis 32.1. Comparison 32 Adults - Crossover design - Different doses in inhalers: HFA vs pMDI (absolute change from baseline), Outcome 1 FEV1 (L).	136
Analysis 33.1. Comparison 33 Adults - Crossover design - Different doses in inhalers: Rotahaler vs pMDI (absolute change from baseline), Outcome 1 PEFR - Daily (L/min).	136

Analysis 34.1. Comparison 34 Adults - Crossover design - Different doses in inhalers: Rotahaler vs pMDI (% change from baseline), Outcome 1 FEV1.	137
Analysis 34.2. Comparison 34 Adults - Crossover design - Different doses in inhalers: Rotahaler vs pMDI (% change from baseline), Outcome 2 Symptom Scores - Daily (higher score worse).	137
Analysis 35.1. Comparison 35 Adults - Crossover design - Different doses in inhalers: All other inhaler devices vs pMDI (combined using SMD, Outcome 1 FEV1.	138
Analysis 36.1. Comparison 36 Adults - Parallel design: Turbuhaler vs pMDI (mean absolute value), Outcome 1 Treatment Failures/Dropouts.	139
Analysis 36.2. Comparison 36 Adults - Parallel design: Turbuhaler vs pMDI (mean absolute value), Outcome 2 Preference for inhaler.	140
Analysis 37.1. Comparison 37 Adults - Parallel design: HFA-pMDI vs pMDI (mean absolute values), Outcome 1 FEV1 (L).	141
Analysis 37.2. Comparison 37 Adults - Parallel design: HFA-pMDI vs pMDI (mean absolute values), Outcome 2 PEFR - Daily (L/min).	141
Analysis 37.3. Comparison 37 Adults - Parallel design: HFA-pMDI vs pMDI (mean absolute values), Outcome 3 PEFR (morning). .	142
Analysis 37.4. Comparison 37 Adults - Parallel design: HFA-pMDI vs pMDI (mean absolute values), Outcome 4 Beta-2 usage (doses per week).	142
Analysis 37.5. Comparison 37 Adults - Parallel design: HFA-pMDI vs pMDI (mean absolute values), Outcome 5 Serum K+ (mmol/L).	142
Analysis 37.6. Comparison 37 Adults - Parallel design: HFA-pMDI vs pMDI (mean absolute values), Outcome 6 Treatment Failures/Dropouts.	143
Analysis 37.7. Comparison 37 Adults - Parallel design: HFA-pMDI vs pMDI (mean absolute values), Outcome 7 Acute Exacerbations.	143
Analysis 37.8. Comparison 37 Adults - Parallel design: HFA-pMDI vs pMDI (mean absolute values), Outcome 8 Adverse Events. ..	143
Analysis 37.9. Comparison 37 Adults - Parallel design: HFA-pMDI vs pMDI (mean absolute values), Outcome 9 Inhaled steroid requirement.	144
Analysis 38.1. Comparison 38 Adults - Parallel design: HFA-pMDI vs pMDI (absolute change from baseline), Outcome 1 Heart Rate (bpm).	145
Analysis 38.2. Comparison 38 Adults - Parallel design: HFA-pMDI vs pMDI (absolute change from baseline), Outcome 2 Adverse Events.	145
Analysis 38.3. Comparison 38 Adults - Parallel design: HFA-pMDI vs pMDI (absolute change from baseline), Outcome 3 Acute Exacerbations.	146
Analysis 39.1. Comparison 39 Adults - Parallel design: pMDI vs HFA-pMDI (% change from baseline), Outcome 1 FEV1.	147
Analysis 39.2. Comparison 39 Adults - Parallel design: pMDI vs HFA-pMDI (% change from baseline), Outcome 2 AUC-FEV1.	147
Analysis 39.3. Comparison 39 Adults - Parallel design: pMDI vs HFA-pMDI (% change from baseline), Outcome 3 Treatment Failures/Dropouts.	147
Analysis 39.4. Comparison 39 Adults - Parallel design: pMDI vs HFA-pMDI (% change from baseline), Outcome 4 Oral corticosteroid requirement for treatment of acute exacerbations.	148
Analysis 39.5. Comparison 39 Adults - Parallel design: pMDI vs HFA-pMDI (% change from baseline), Outcome 5 Acute Exacerbations.	148
Analysis 39.6. Comparison 39 Adults - Parallel design: pMDI vs HFA-pMDI (% change from baseline), Outcome 6 Adverse Events.	149
Analysis 40.1. Comparison 40 Adults - Parallel design: HFA-pMDI vs pMDI (combined using SMD), Outcome 1 FEV1.	150
Analysis 40.2. Comparison 40 Adults - Parallel design: HFA-pMDI vs pMDI (combined using SMD), Outcome 2 Treatment Failures/Dropouts.	150
Analysis 40.3. Comparison 40 Adults - Parallel design: HFA-pMDI vs pMDI (combined using SMD), Outcome 3 Acute Exacerbations.	150
Analysis 40.4. Comparison 40 Adults - Parallel design: HFA-pMDI vs pMDI (combined using SMD), Outcome 4 Adverse Events. ..	151
Analysis 41.1. Comparison 41 Adults - Parallel design: Rotahaler vs pMDI (absolute change from baseline), Outcome 1 Treatment Failures/Dropouts.	152
Analysis 41.2. Comparison 41 Adults - Parallel design: Rotahaler vs pMDI (absolute change from baseline), Outcome 2 Acute Exacerbations.	152
Analysis 41.3. Comparison 41 Adults - Parallel design: Rotahaler vs pMDI (absolute change from baseline), Outcome 3 Adverse Events.	153
Analysis 42.1. Comparison 42 Adults - Parallel design: Spiros vs pMDI (mean absolute value), Outcome 1 AUC-FEV1 (L x min). ..	153
Analysis 42.2. Comparison 42 Adults - Parallel design: Spiros vs pMDI (mean absolute value), Outcome 2 Treatment Failures/Dropouts.	154
Analysis 42.3. Comparison 42 Adults - Parallel design: Spiros vs pMDI (mean absolute value), Outcome 3 Acute Exacerbations. .	154

Analysis 42.4. Comparison 42 Adults - Parallel design: Spiros vs pMDI (mean absolute value), Outcome 4 Adverse Events.	155
Analysis 43.1. Comparison 43 Adults - Parallel design: Multi Dose Powder Inhaler vs pMDI (mean absolute value), Outcome 1 FEV1 (L).	156
Analysis 43.2. Comparison 43 Adults - Parallel design: Multi Dose Powder Inhaler vs pMDI (mean absolute value), Outcome 2 FVC (L).	156
Analysis 43.3. Comparison 43 Adults - Parallel design: Multi Dose Powder Inhaler vs pMDI (mean absolute value), Outcome 3 PEFR - Daily (L/min).	157
Analysis 43.4. Comparison 43 Adults - Parallel design: Multi Dose Powder Inhaler vs pMDI (mean absolute value), Outcome 4 Beta-2 usage (doses per week).	157
Analysis 43.5. Comparison 43 Adults - Parallel design: Multi Dose Powder Inhaler vs pMDI (mean absolute value), Outcome 5 Symptom Scores - Day time (higher score worse).	157
Analysis 43.6. Comparison 43 Adults - Parallel design: Multi Dose Powder Inhaler vs pMDI (mean absolute value), Outcome 6 Symptom Scores - Night time (higher score worse).	158
Analysis 43.7. Comparison 43 Adults - Parallel design: Multi Dose Powder Inhaler vs pMDI (mean absolute value), Outcome 7 Treatment Failures/Dropouts.	158
Analysis 43.8. Comparison 43 Adults - Parallel design: Multi Dose Powder Inhaler vs pMDI (mean absolute value), Outcome 8 Adverse Events.	158
Analysis 44.1. Comparison 44 Adults - Parallel design: All other inhaler devices vs pMDI (combined using SMD), Outcome 1 Treatment Failures/Dropouts.	160
Analysis 44.2. Comparison 44 Adults - Parallel design: All other inhaler devices vs pMDI (combined using SMD), Outcome 2 FEV1 (L).	160
Analysis 44.3. Comparison 44 Adults - Parallel design: All other inhaler devices vs pMDI (combined using SMD), Outcome 3 PEFR - Daily (L/min).	161
Analysis 44.4. Comparison 44 Adults - Parallel design: All other inhaler devices vs pMDI (combined using SMD), Outcome 4 Beta-2 usage (doses per week).	161
Analysis 44.5. Comparison 44 Adults - Parallel design: All other inhaler devices vs pMDI (combined using SMD), Outcome 5 Acute Exacerbations.	161
Analysis 44.6. Comparison 44 Adults - Parallel design: All other inhaler devices vs pMDI (combined using SMD), Outcome 6 Adverse Events.	162
Analysis 44.7. Comparison 44 Adults - Parallel design: All other inhaler devices vs pMDI (combined using SMD), Outcome 7 AUC-FEV1.	162
Analysis 45.1. Comparison 45 Children - Crossover design: Turbuhaler vs pMDI (mean absolute value), Outcome 1 FEV1 (L).	163
Analysis 45.2. Comparison 45 Children - Crossover design: Turbuhaler vs pMDI (mean absolute value), Outcome 2 PEFR (morning) L/min.	164
Analysis 45.3. Comparison 45 Children - Crossover design: Turbuhaler vs pMDI (mean absolute value), Outcome 3 PEFR (evening) L/min.	164
Analysis 45.4. Comparison 45 Children - Crossover design: Turbuhaler vs pMDI (mean absolute value), Outcome 4 Preference for inhaler.	164
Analysis 46.1. Comparison 46 Children - Crossover design: Turbuhaler vs pMDI (absolute change from baseline), Outcome 1 Symptom Scores - Day time (higher score worse).	165
Analysis 46.2. Comparison 46 Children - Crossover design: Turbuhaler vs pMDI (absolute change from baseline), Outcome 2 Symptom Scores - Night time (higher score worse).	165
Analysis 46.3. Comparison 46 Children - Crossover design: Turbuhaler vs pMDI (absolute change from baseline), Outcome 3 Adverse Events.	166
Analysis 47.1. Comparison 47 Children - Crossover design: Turbuhaler vs pMDI (% change from baseline), Outcome 1 FEV1.	167
Analysis 47.2. Comparison 47 Children - Crossover design: Turbuhaler vs pMDI (% change from baseline), Outcome 2 Adverse Events.	167
Analysis 48.1. Comparison 48 Children - Crossover design: Turbuhaler vs pMDI (combined using SMD), Outcome 1 FEV1.	168
Analysis 48.2. Comparison 48 Children - Crossover design: Turbuhaler vs pMDI (combined using SMD), Outcome 2 Adverse Events.	168
Analysis 49.1. Comparison 49 Children - Crossover design: HFA-pMDI vs pMDI (mean absolute value), Outcome 1 FEV1 (L).	169
Analysis 50.1. Comparison 50 Children - Crossover design: pMDI vs Rotahaler (mean absolute value), Outcome 1 FEV1 (L).	170
Analysis 50.2. Comparison 50 Children - Crossover design: pMDI vs Rotahaler (mean absolute value), Outcome 2 PEFR - Daily (L/min).	171
Analysis 50.3. Comparison 50 Children - Crossover design: pMDI vs Rotahaler (mean absolute value), Outcome 3 Beta-2 usage.	171

Analysis 50.4. Comparison 50 Children - Crossover design: pMDI vs Rotahaler (mean absolute value), Outcome 4 Symptom Scores - Day time (higher score worse).	171
Analysis 50.5. Comparison 50 Children - Crossover design: pMDI vs Rotahaler (mean absolute value), Outcome 5 Symptom Scores - Night time (higher score worse).	172
Analysis 50.6. Comparison 50 Children - Crossover design: pMDI vs Rotahaler (mean absolute value), Outcome 6 Inhaled steroid requirement.	172
Analysis 50.7. Comparison 50 Children - Crossover design: pMDI vs Rotahaler (mean absolute value), Outcome 7 Preference. ..	172
Analysis 51.1. Comparison 51 Children - Crossover design: pMDI vs All other inhaler devices (combined using SMD), Outcome 1 FEV1.	173
Analysis 52.1. Comparison 52 Children - Parallel design: pMDI vs Turbuhaler (mean absolute value), Outcome 1 FEV1 (L).	174
Analysis 52.2. Comparison 52 Children - Parallel design: pMDI vs Turbuhaler (mean absolute value), Outcome 2 FVC (L).	174
Analysis 53.1. Comparison 53 Children - Parallel design: pMDI vs HFA-pMDI (mean absolute value), Outcome 1 PEFR - morning (L/min).	175
Analysis 53.2. Comparison 53 Children - Parallel design: pMDI vs HFA-pMDI (mean absolute value), Outcome 2 PEFR - evening (L/min).	175
Analysis 53.3. Comparison 53 Children - Parallel design: pMDI vs HFA-pMDI (mean absolute value), Outcome 3 Beta-2 usage (daily mean).	176
Analysis 54.1. Comparison 54 Children - Parallel design: pMDI vs HFA-pMDI (absolute change from baseline), Outcome 1 AUC-FEV1 (L x min).	176
Analysis 55.1. Comparison 55 Children - Parallel design: pMDI vs Rotahaler (% change from baseline), Outcome 1 FEV1.	177
Analysis 55.2. Comparison 55 Children - Parallel design: pMDI vs Rotahaler (% change from baseline), Outcome 2 Treatment Failures.	177
Analysis 55.3. Comparison 55 Children - Parallel design: pMDI vs Rotahaler (% change from baseline), Outcome 3 Acute Exacerbations.	178
Analysis 55.4. Comparison 55 Children - Parallel design: pMDI vs Rotahaler (% change from baseline), Outcome 4 Preference. ..	178
ADDITIONAL TABLES	180
WHAT'S NEW	186
HISTORY	186
CONTRIBUTIONS OF AUTHORS	186
DECLARATIONS OF INTEREST	186
SOURCES OF SUPPORT	186
INDEX TERMS	186

[Intervention Review]

Pressurised metered dose inhalers versus all other hand-held inhaler devices to deliver beta-2 agonist bronchodilators for non-acute asthma

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Editorial group: Cochrane Airways Group.

Publication status and date: Edited (no change to conclusions), published in Issue 1, 2010.

Citation: Ram FSF, Brocklebank DDM, White J, Wright JJ, Jones P. Pressurised metered dose inhalers versus all other hand-held inhaler devices to deliver beta-2 agonist bronchodilators for non-acute asthma. *Cochrane Database of Systematic Reviews* 2002, Issue 2. Art. No.: CD002158. DOI: [10.1002/14651858.CD002158](https://doi.org/10.1002/14651858.CD002158).

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ABSTRACT

Background

A number of different inhaler devices are available to deliver beta2-agonist bronchodilators in asthma. These include hydrofluoroalkane (HFA) or chlorofluorocarbon (CFC)-free propelled pressurised metered dose inhalers (pMDIs) and dry powder devices.

Objectives

To determine the clinical effectiveness of pMDI compared with any other available handheld inhaler device for the delivery of short-acting beta-2 agonist bronchodilators in non-acute asthma in children and adults.

Search methods

The Cochrane Collaboration Clinical Trials register was searched for studies as well as separate additional searches carried out on MEDLINE, EMBASE, CINAHL and also on the Current Contents Index as well as the Science Citation Index. In addition, 17 individual online respiratory journals and 12 electronically available clinical trial databases were also searched. The UK pharmaceutical companies who manufacture inhaled asthma medication were contacted in order to obtain details of any published or unpublished studies.

Selection criteria

The full texts of all potentially relevant articles were reviewed independently by two reviewers.

Data collection and analysis

Fixed and random effect models were used. Dichotomous outcomes were assessed using Odds Ratios or Relative Risks (RR) with 95% Confidence Intervals (95% CI).

Main results

Eighty-four randomised controlled trials were included in this review, but few could be combined to assess a specific outcome for a given delivery device comparison. Only two studies required demonstration of adequate pMDI technique as an entry requirement. There were no difference between a standard CFC containing pMDI and any other device for most outcomes. Regular use of HFA-pMDI containing salbutamol reduced the requirement for short courses of oral corticosteroids (3 trials, 519 patients: RR 0.67; 95% CI 0.49, 0.91); however the total number of exacerbations were unchanged (3 trials, 1271 patients: RR 1.0; 95% CI 0.75, 1.33).

Authors' conclusions

In patients with stable asthma, short-acting beta-2 bronchodilators in standard CFC-pMDI's are as effective as any other devices. The effect of HFA-pMDI on requirement for oral corticosteroid courses to treat acute exacerbations should be confirmed. Effectiveness studies that use an intention-to-treat analysis are required.

PLAIN LANGUAGE SUMMARY**Pressurised metered dose inhalers versus all other hand-held inhaler devices to deliver beta-2 agonist bronchodilators for non-acute asthma**

This review determined to look at whether fast acting relievers performed better when they were delivered via different inhalers in people with asthma. The authors did not find differences between the devices in lung function measurements that exceeded what would be expected with the play of chance. HFA-metered dose inhalers reduced the requirement for oral steroids. However, the studies reported data in ways that prevented formal statistical combination. More research is required to establish more reliably whether the devices commonly used to deliver reliever medication provide similar efficacy and safety.

BACKGROUND

Inhaled therapy has become accepted as the mainstay of asthma treatment. It allows low doses of medication to be delivered directly to the site of action in the airways, significantly reducing systemic side effects compared with oral therapy (BTS 1997). An ever-increasing number of drugs are available to treat asthma, which can be divided broadly into two categories. Bronchodilators, which are, used for symptom relief and corticosteroids that are mainly used to control the inflammatory activity that is the underlying pathological process in asthma. A number of different inhalation devices are available including the pressurised metered dose inhaler (pMDI) which is the most commonly used and cheapest inhaler device to be used with or without a spacer device. Other device types include the breath-actuated pMDIs (e.g. Autohaler, Easibreathe) and the dry powder inhalers (e.g. Turbuhaler, Diskhaler, Accuhaler, Rotahaler). This is now further complicated by the introduction of hydrofluoroalkane (HFA) or chlorofluorocarbon (CFC)-free propelled pMDIs with properties that may be different from the current CFC propelled pMDIs.

In clinical practice, the fundamental principle of prescribing is to use the most clinically and cost effective drug. Pressurised MDIs are usually regarded as first choice but their use is to a large degree dependent upon an individual's ability to co-ordinate their breathing to the actuation of the device. Greater than 50 to 80% of adults have difficulty using a pMDI (Crompton 1990, Larsen 1994, van Beerendonk 1998). This is a particular issue in the very young and old, particularly during acute exacerbations of their condition. In this circumstance, it is believed that the addition of a large volume spacer may be the cheapest effective alternative (North England 1999).

Due to the bulkiness of large volume spacers, they are not very portable and this means that they are rarely used with "reliever medication" by young mobile asthma sufferers irrespective of clinical efficacy. For these reasons other devices are often prescribed in order to optimise compliance. This often determines which particular drug is prescribed as pharmaceutical companies usually limit inhaler use to their own products and some spacers do not fit other manufacturers inhaler devices.

OBJECTIVES

To determine the clinical effectiveness of pMDI (with or without spacer device) compared with any other handheld inhaler device for the delivery of short-acting beta-2 agonist bronchodilators in non-acute asthma.

METHODS

Criteria for considering studies for this review

Types of studies

Due to the varying differences in pharmacokinetic and pharmacodynamic parameters of the short-acting beta-2 agonists (e.g. salbutamol, terbutaline, fenoterol) compared with longer-acting beta-2 agonists (e.g. formoterol, salmeterol) and anticholinergic bronchodilators (e.g. ipratropium, oxitropium) only the short-acting beta-2 bronchodilators were considered in this review. Salbutamol and terbutaline are the most widely used short acting beta-2 agonists bronchodilators with CFC-based MDIs, accounting

for greater than 80% of all bronchodilator delivery devices sold in the UK.

Therefore, a study was considered for inclusion if it compared a single short-acting bronchodilator drug delivered using a standard pMDI (with or without spacer device) versus any other hand-held inhaler device (e.g. CFC-free pMDI, breath-actuated pMDI or a DPI).

Only randomised controlled trials were considered for inclusion. Studies were either laboratory or community based, of any duration and conducted in patients with non-acute (stable) asthma.

Types of participants

Children and adults with any degree of asthma severity were included. Asthma needed to be diagnosed by a physician or according to internationally accepted criteria (e.g. ATS 1993, BTS 1997) in order to be considered for inclusion in the review.

Types of interventions

Trials were considered that compared clinical or patient oriented outcomes for a single short-acting beta-2 agonist bronchodilator delivered by a standard pMDI versus the same drug delivered by any other available hand-held inhaler device in non-acute asthma. Co-intervention and/or contamination (e.g. from crossover designs) which may have occurred were recorded where possible.

Types of outcome measures

Primary outcomes

1. Physiological lung function measurements (e.g. FEV1, FVC, PEFR, FRC, TLC)
2. Quality of life measures

Secondary outcomes

1. Symptom scores
2. Additional relief medication
3. Inhaled or oral steroid requirement
4. Nocturnal awakening
5. Acute exacerbation (worsening asthma requiring medical intervention)
6. Days off work/school
7. Treatment failure (study dropouts)
8. Compliance
9. Patient preference
10. Adverse effects and safety measurements (e.g. heart rate, blood pressure)
11. Bronchial hyperreactivity
12. Systemic bioavailability

Search methods for identification of studies

The Cochrane Airways Group Specialised Asthma and Wheeze Randomised Controlled Trials register was searched for studies as well as separate additional searches carried out on MEDLINE (1966-Jan 2001), EMBASE (1980-Jan 2001), CINAHL (1982-Jan 2001) and also on the CURRENT CONTENTS INDEX (1995-Jan 2001) as well as the SCIENCE CITATION INDEX (1995-Jan 2001). In addition 17 individual online journals known to publish respiratory articles were searched (American Journal of Respiratory & Critical Care Medicine; American Medical Association; Allergy, Asthma &

Immunology; Archives of Disease in Childhood; Archives of Allergy & Immunology; Applied Physiology; Allergy & Clinical Immunology; Chest; Current Opinion in Pulmonary Medicine; Lung; New England Journal of Medicine; Pediatrics; Pediatric Research; Pulmonary Pharmacology & Therapeutics; Respiration; Respiratory; Thorax). Twelve electronically available clinical trials databases were also searched (USA databases include: CenterWatch Clinical Trials; Controlled Clinical Trials; Current Controlled Trials; Society for Clinical Trials; Clinical Trials; National Jewish Medical & Research Centre and the UK databases include: Center for Evidence-Based Medicine; Clinical Evidence; Clinical Trial Finder; NHS Centre for Reviews & Dissemination; NHS National Research Register; GlaxoWellcome Clinical Trials). All citations were reviewed without language restriction.

All searches were conducted using the following search terms:

a) inhaler OR spacer* OR holding chamber OR volumatic OR nebulizer OR aerochamber* OR fisonair OR extension OR spacing device OR inspirease OR accuhaler OR diskhaler OR turbobaler OR turbuhaler OR easibreathe OR easyhaler OR bricanyl OR clickhaler OR gentlehaler OR spiros OR cyclohaler OR autohaler OR rothaler OR dry powder OR MDI OR DPI OR CFC-free OR HFA*.

AND

b) salbutamol OR ventolin OR albuterol OR terbutaline OR isoprenaline OR orciprenaline OR metaproterenol OR isoproterenol OR reproterenol OR fenoterol OR pirbuterol OR reproterol OR rimiterol.

The reference lists of all included studies and review articles were checked in order to identify any further relevant citations not captured by electronic and manual hand searching. Authors of included RCTs were contacted for any other unpublished studies. If more data was required for the systematic review the authors of the trials were contacted for additional information or clarification.

Experts and leaders in respiratory medicine were also contacted in order to locate any ongoing studies.

In addition, UK pharmaceutical companies who manufacture inhaled asthma medication were contacted in order to obtain details of any further published or unpublished studies.

Data collection and analysis

SELECTION OF TRIALS

Studies were retrieved from the title, abstract, or descriptors. Two reviewers (FR, DB) independently reviewed the literature searches to identify potentially relevant trials for full review. Searches of bibliographies and texts were conducted to identify additional studies. From the full text, using pre-defined criteria, two reviewers (FR, DB) independently selected trials for inclusion. Inclusion criteria were: (1) Trials of a single beta-2 agonist bronchodilator delivered by a standard pMDI (with or without spacer) versus any other hand-held inhaler device in non-acute asthma, including HFA or CFC-free inhalers, (2) Randomised controlled trial [A, B or C: Cochrane categories], (3) Patients age greater than 2 years with asthma diagnosed by a clinician or according to internationally accepted criteria [BTS, ATS, ERS] & (4) Laboratory or community based study of any duration. All studies that did not meet the above criteria were excluded. Disagreements were resolved by consensus

or third party adjudication (JW). Selected studies subsequently excluded on methodological grounds were identified and the reason for exclusion recorded.

QUALITY ASSESSMENT

Methodological quality assessment was performed on all included studies using the following methods. Firstly using the Cochrane approach for the assessment of allocation concealment, all trials were scored according to the following grades:

Grade A: Adequate concealment
Grade B: Uncertain
Grade C: Clearly inadequate concealment
Grade D: Not used

In addition, the Jadad scale (Jadad 1996) (shown below) which evaluates the quality of randomisation, blinding, and description of withdrawals and dropouts was also used. The Jadad scale has three items: one point is allocated for randomisation, blinding, and description of withdrawals and drop-outs; an extra point can be added for methods of randomisation and blinding that are well described and adequate. Studies that used a clearly inadequate method of randomisation or blinding (such as alternating patients) lose the point allocated. The maximum score is five points and studies scoring below three points are usually regarded as being of low methodological quality.

Jadad scale:

- 1) Was the study described as randomised (1=yes; 0=no)?
- 2) Was the study described as double-blind (1=yes; 0=no)?
- 3) Was there a description of withdrawals and dropouts (1=yes; 0=no)?
- 4) Was the method of randomisation well described and appropriate (1=yes; 0=no)?
- 5) Was the method of double blinding well described and appropriate (1=yes; 0=no)?
- 6) Deduct 1 point if methods for randomisation or blinding were inappropriate

DATA EXTRACTION

Data abstraction of descriptive characteristics and study results was performed by one reviewer (FR) and was checked for accuracy by an independent person (SW). If data were not reported in an extractable form, one of the authors of the included study was contacted for additional information. If the authors could not be contacted or if the information was no longer available, this was reported. Where no original data were available from the authors, expansion of graphical representation of data from manuscripts was used to estimate the missing data. For studies where standard errors (SE) were reported, these were converted to standard deviations (SD) using square root of (n-1) x reported SE. Where studies reported the mean and the range, an estimation for SD was made by dividing the range by 4 [i.e. (HR-LR) / 4]. Where studies reported 90% or 95% confidence intervals the appropriate formula was used for estimating the SD's: CI = mean $\pm$ 2.58 x SE or CI = mean $\pm$ 1.96 x SE, and the equation solved for SE and converted to SD using the formula provided above.

All of the included studies reported continuous outcomes as mean values post bronchodilator except 10 studies (Bronsky 1999, Dockhorn 1995a, Dockhorn 1995b, Hawskworth 1999, Kemp 1997, Newhouse 1999, Nelson 1999, Nieminen 1994, Ramsdell 1999a,

Ramsdell 1999b, Seppala 1998b & Silvasti 1993) in which mean maximum values (post bronchodilator) were reported. A sensitivity analysis was conducted to test whether the results were different when these 10 studies were excluded. In all cases, the result was not different with or without the inclusion of these studies reporting maximum mean values.

For studies using cumulative dosing schedules (Bondesson 1998, Dirksen 1983, Ekstrom 1995, Haahtela 1998, Hetzel 1977, Johnsen 1988, Klerup 1996, Mellen 1999, Morice 1996, Persson 1988, Ramsdell 1998, Ruffin 1995 & Svedmyr 1982), the data that were generated after the administration of the last cumulative dose was used.

DATA ENTRY

Data from the studies was abstracted onto a Microsoft Excel worksheet from where it was entered into RevMan 4.1. To check the accuracy of entered data, the double-entry form in RevMan 4.1 was utilised and an independent person checked all the entries.

Throughout the review the term 'pMDI' refers to a CFC-containing pressurised metered dose inhaler.

STATISTICAL CONSIDERATIONS

Trials were combined for meta-analysis using RevMan 4.1. Both a fixed effect model (where only within study variation is taken to influence the uncertainty of the weighted mean results) and a random effect model (in which both within-study and between-study variations are included in the assessment of the uncertainty of the overall mean results) were used. Both models were used so that if there were significant heterogeneity within the results of the included studies, it would be seen in the wider confidence intervals of the random effect model as opposed to the fixed effect model.

Dichotomous outcomes such as exacerbation rate or adverse events were assessed using relative risks (RR) or odds ratio (OR) with 95% confidence intervals (95% CI's) and where possible the Number-Needed-to-Treat for Benefit (NNT) calculated. However most of the outcomes of interest in asthma are either continuous or categorical data such as the level of asthma symptoms, which are usually treated as if they were continuous data. Data from each of the continuous outcomes were analysed as weighted mean differences (WMD) with 95% CI's if the they are reported with the same scales (e.g. FEV1 L/min change from baseline). Continuous data were also analysed as standardised mean differences (SMD) if different scales were used (e.g. FEV1 L/min & FEV1 % predicted & FEV1 L/min changed from baseline & FEV1 L/min absolute value at end of study treatment).

Heterogeneity of effect sizes between studies being pooled was tested for each outcome measure. If heterogeneity were present ($p < 0.05$), subgroup analyses were planned to explore possible reasons for heterogeneity of study results. A priori defined subgroups were based on; asthma severity, type of beta-2 bronchodilator or use of a spacer device with the pMDI.

Publication or selection bias was tested by preparing funnel plots (Egger 1997). These were plots of standard error versus effect size, which was plotted for all the trials under any particular outcome. Funnel plot asymmetry may indicate statistical evidence of publication or selection bias.

DATA ANALYSIS

There were a large number of studies included in this review and the data analysis was grouped as follows:

(A) Studies in adults

(1) Crossover design studies:

Pressurised metered dose inhalers compared against each of the different hand-held inhaler devices (Turbuhaler, Diskhaler, CFC-free or HFA pMDI, Rotahaler, Spiros, Spinhaler, Easyhaler, Multiple dose dry powder inhaler, Clickhaler, Gentlehaler and Autohaler). Each of these comparisons was further separated into either; short-term (min-hours), long term (days-months) or cumulative dosing studies. Study outcomes were presented in three main ways; so data were further separated as mean absolute values, percentage change from baseline and absolute change from baseline.

Where trials examined early (15-45 min) as compared to late (hours) pulmonary function variables post-bronchodilator, these were reported separately as we considered the early and late effects for beta-2 bronchodilators to be clinically different. These early measurements of study variables were presented as a separate comparison (from the rest of the data) as shown in comparison 24 in the 'Table of Comparisons'.

There is disagreement on the approach to meta-analysis of crossover trials, so we had hoped to use only the first arm of the data in our analysis. These data were not reported in most studies and neither were any data on variance, which would have allowed us to conduct an inverse variance pooling in order to observe if outcomes were different. However, where studies or authors did provide the data (individual patient and not group means), we were able to test the effect of the RevMan software treating data from crossover studies as parallel data. In practice, the standard deviation was found to be very similar when the data were analysed in the two separate ways. The variability seems to be as high when comparing the same patient with himself or herself as opposed to when comparing the group means with each other. This indicates that analysing the data from crossover studies as if it were parallel data does not give different results. Therefore, the aggregate result (combined data from both arms of crossover studies) were used.

In cumulative dosing studies, we used the pulmonary function and other study measurements made after the final dose. We recognise that in most cases the total cumulative dose given in such studies would be much higher than that used in practice and may have reached the plateau of the dose-response curve. However, we hoped that pre-defined criteria would minimise any potential bias, as the reviewer was not able to choose the 'most relevant' dose from the many different doses used in these cumulative dosing studies.

(2) Parallel design studies:

Pressurised metered dose inhalers compared against all other hand-held inhaler devices including all DPI's and HFA devices. Each of these comparisons was further separated into either; short-term (min-hours), long term (days-months) or cumulative dosing studies.

(3) Challenge testing studies:

These studies used either methacholine, histamine or exercise challenge (usually causing a decrease in lung function after challenge) to test the bronchoprotective potential of administered beta-2 agonist bronchodilator from inhaler devices. The pMDI was compared against all other hand-held inhaler devices including all DPI's and HFA devices. Each of these comparisons was further separated into either; short-term (min-hours) or cumulative dosing studies.

(4) Different doses in devices compared:

We separated studies where different doses were used in the devices being compared (e.g. 100 mcg salbutamol from the pMDI versus 200 mcg from the Diskhaler). Pressurised metered dose inhalers compared against other hand-held inhaler devices including all DPI's and HFA devices. Each of these comparisons was further separated into either; short-term (min-hours), long term (days-months) or cumulative dosing studies.

(B) Studies in Children:

It was considered important to separate studies in children from adults. Pressurised metered dose inhalers were compared with each of the different hand-held inhaler devices including: Turbuhaler, Rotahaler and CFC-free or HFA pMDI. Each of these device comparisons was further separated into the different study designs (crossover, parallel or challenge-testing designs).

RESULTS

Description of studies

The number of studies were as follows: single-dose studies (n=45), long-term (n=16) and cumulative dosing studies (n=17); crossover design studies (n=62); parallel designs (n=10); different or double dosing schedules used in devices compared (n=6); challenge studies (n=9) and studies in children (n=13). Some studies could be listed in more than one category.

The oldest included study was published in 1977 and the newest in August 2000. There were equal numbers of included studies that were performed by pharmaceutical and non-pharmaceutical organisations. Studies that were included were conducted in many different parts of the world (New Zealand, Sweden, England, Germany, USA, Canada, UK, Belgium, Norway, Scotland, Hong Kong, Finland, Denmark, Australia and The Netherlands). There was a wide range of doses of beta-2 agonist used in the included studies. For salbutamol: single dose studies 100 mcg to cumulative dose studies up to 4200 mcg. Terbutaline: single doses of 0.25 mg up to cumulative doses of 4.0 mg. Fenoterol single doses of 200 mcg to 100 mcg. Salbutamol was used as the bronchodilator in 64 studies, terbutaline in 15 and fenoterol in five.

Most of the included studies recruited adult patients but 13 studies (3M UK 1996; Ahlstrom 1989; Bronsky 1995; Colice 1999; Croner 1980; Custovic 1995; Fuglsang 1989; Hirsch 1997; Hultquist 1989; Kemp 1989; Laberge 1994; Razzouk 1999; Svenonius 1994) involved children with asthma. Most of the studies included patients with mild-to-moderate asthma however, some of the trials did not describe asthma severity. In most crossover studies baseline FEV1 was not permitted to vary greater than 10-15% from pre-dose baseline values on study days and if variation was greater than 10-15% the visit was rescheduled.

A possible problem with RCTs is that patients are usually selected on the basis of being able to use a pMDI device as an inclusion criteria therefore, the study results would favour pMDI use. The majority (82/84) of RCTs included in this review did not mention previous patient familiarisation with either the pMDI or the DPIs as a requirement for study entry. The two studies that reported adequate pMDI device technique as an entry criteria were trials comparing the standard pMDI to HFA pMDI (Kleerup 1996, Bleecker 1998). Although proper inhaler device use was not a requirement for entry into the study most of the trials did report training all patients in the proper use of both pMDI and the DPIs prior to the start of the trial. However, we should assume that all patients recruited in the included RCTs were taught to use both the pMDI and the DPIs prior to commencing the study.

Risk of bias in included studies

Most of the studies included in this review were of good quality with all scoring a 'B' grade or better when using the Cochrane allocation concealment grading and >3 when using the Jadad (Jadad 1996) 5-point scoring system for study quality. Four of the included studies (Cohen 1999, Hawksworth 1999, Langley 1998a & Vidgren 1990) were reported as abstracts and were therefore devoid of substantial details for critical appraisal. The most frequently encountered problem was that many of the included studies were designed as tests of the superiority of one device over another in which the null hypothesis was of equal efficacy. Such studies require fewer patients than those designed to test equivalence (null hypothesis than one device is superior to the other). Thus most studies were underpowered. Failure to detect a difference does not necessarily imply equivalence.

Effects of interventions

SEARCH FOR STUDIES

The electronic search yielded 1,130 citations: 40 references were found in EMBASE, MEDLINE, CINAHL and online respiratory journal databases, 1,063 citations came from the Airways Group register. Additional 27 references were obtained from bibliographic searching of relevant articles. Of a total of 1,130 abstracts, 182 studies were identified independently by two reviewers as being potentially suitable for inclusion. After reading the full text of these 182 studies, the first author (FR) excluded 66 studies. Of the remaining 116 studies, 27 were excluded by at least two reviewers giving a total of 93 excluded studies (reasons for exclusion are provided in, Characteristics of Excluded Studies) and 89 included studies (with 9 studies being duplicate publications of studies already included). Five studies (Borgström 1996a, Dockhorn 1995a, Geoffroy 1999b, Langley 1998a, Ramsdell 1999a) reported more than one trial in their article or had additional independent study arms that met our inclusion criteria.

QUALITY OF INCLUDED STUDIES

All included studies were of good methodological quality (Cochrane B and Jadad score >3). They were all randomised with most of the studies being double-blinded and all used adequate allocation concealment. We wrote to 78 authors of the 84 included studies for further information and received 33 replies. The low response rate was not surprising as the oldest included trial was published in 1977. Any replies or data received from authors after publication of this review will be incorporated in future updates of the review.

Table 1

The results for each outcome measured are reported as overall effects of pMDI versus each hand-held inhaler device separately and then reported as pMDI vs. all hand-held inhaler devices combined using SMD where appropriate. For ease of reference, figures in square brackets indicate the comparison & outcome number for that particular outcome in RevMan under 'Tables: Comparisons and Data'. For example, [01:07] refers to comparison 01 and outcome 07. Number of studies beside each outcome indicates the number of studies that contributed towards the overall result for that particular outcome measure.

REVIEW COMPARISONS/OUTCOMES

The outcomes that were not significantly different ($p > 0.05$ in every case) have been tabulated and reported in Tables: [Table 1](#), [Table 2](#) and [Table 3](#) under 'Additional Tables' in RevMan. In summary, most of outcomes in this review were not significantly different when a standard pMDI was compared with any of the DPI's or HFA-pMDI device. Non-significant outcomes included: FEV1, FVC, PEFR, AUC-FEV1, blood pressure, symptoms, bronchial hyperreactivity, systemic bioavailability, inhaled steroid requirement, serum K⁺ and beta-2 usage. Most of the studies that used a 2:1 (or different) dosing schedule ([Chapman 1997](#), [Mathieu 1992](#), [Pover 1988](#), [Selroos 1994](#), [Thompson 1995](#) & [Tukiainen 1985](#)) did not show significantly different results and did not provide results that were different from studies that used a 1:1 dosing. Five studies used a spacer device with the pMDI ([Ahlstrom 1989](#), [Giannini 2000](#), [Golish 1998](#), [Laberge 1994](#) & [Selroos 1994](#)), when these were removed from the analyses, the results were not changed.

The following outcome measures were significantly different ($p < 0.05$) and did not show any heterogeneity ($p > 0.05$) when data from different trials were combined:

(A) STUDIES IN ADULT PATIENTS

(1) pMDI VS TURBUHALER:

(i) Heart rate-bpm

This outcome [Comparison 01:07] reported as absolute mean value at end of the study period in two cumulative dosing crossover studies in 86 patients ([Bondesson 1998](#), [Ekstrom 1995](#)), showed that the heart rate was lower with pMDI use, when compared to the Turbuhaler (WMD 4.34; 95%CI = 1.17,7.52). Heart rate reported as absolute change from baseline [Comparison 02:03] in another cumulative dosing crossover study in 18 patients ([Johnsen 1988](#)) was lower by 10 bpm with the pMDI (WMD 10.5; 95%CI = 4.49,16.51). When these three crossover studies were combined using an SMD [Comparison 04:03], the overall heart rate was significantly lower with pMDI use compared to the Turbuhaler (SMD 0.44; 95%CI = 0.05,0.84).

(ii) Preference for inhaler device

This outcome [Comparison 36:02] was reported by one long-term parallel study in 258 patients ([Osterman 1991](#)) and showed that patients preferred the Turbuhaler almost twice as often as the pMDI (RR 1.92; 95%CI = 1.29,2.85).

(2) pMDI VS ROTAHALER

(i) Heart rate-bpm

This outcome was reported as absolute change from baseline in one cumulative dosing crossover study in 14 patients ([Svedmyr 1982](#)) which showed that heart rate was lower by 5.5 bpm [Comparison 11:03] when using the Rotahaler (WMD -5.50; 95%CI -10.04,-0.96).

(ii) Preference for inhaler device

Two long-term crossover studies in 116 patients ([Hartley 1979](#), [Kiviranta 1985](#)) reported preference for inhaler device [Comparison 10:06] showing that patients preferred the pMDI two times more frequently when compared to the Rotahaler (RR 0.50; 95%CI 0.32,0.77). When data from these two long-term crossover studies were combined [Comparison 13:04] with that from a short-term study ([Boye 1983](#)) it still showed that patients preferred the pMDI almost two times more frequently than the Rotahaler (RR 0.53; 95%CI 0.36,0.78). The total combined number of patients was 156.

(3) pMDI VS MULTIDOSE POWDER INHALER

(i) Preference for inhaler device

This was reported [Comparison 19:03] by one short-term crossover study ([Seppala 1998b](#)) with 72 patients and showed that patients preferred the Multidose powder inhaler to the standard pMDI (RR 0.61; 95%CI 0.38,0.98).

(ii) Methacholine challenge (PD20-FEV1 mg Mch)

The effect of bronchodilators on methacholine challenge was reported by one short-term study in 52 patients ([Seppala 1998a](#)) using the Multidose powder inhaler device [Comparison 27:01]. The dose (mg) of methacholine required to reduce FEV1 by 20% from baseline (PD20-FEV1) was significantly lower when using the pMDI as opposed to the Multidose powder inhaler (WMD 1.12; 95%CI 0.82,1.42).

(4) pMDI VS SPINHALER

(i) Lung function (FEV1 & FVC)

Measurements of spirometry were reported as absolute change from baseline in one short-term crossover study using 40 patients ([Duncan 1977](#)). The FEV1 increased (WMD 0.80; 95%CI 0.00,0.16) with the pMDI as compared to the Spinhaler [Comparison 15:01] when reported as mean change from baseline over 300 minutes post bronchodilator. The FVC was also reported in the same study as absolute change from baseline. This also increased over 300 minutes (WMD 0.26; 95%CI 0.09,0.43) with pMDI as compared to the Spinhaler [Comparison 15:02].

(5) pMDI VS HFA-pMDI

(i) Short course oral corticosteroid required for the treatment of acute exacerbations

Three long-term parallel studies ([Ramsdell 1999a](#), [Ramsdell 1999b](#) & [Bronsky 1999](#)) compared pMDIs with HFA-pMDI's. The duration of the two Ramsdell studies were 12 months and that of Bronsky study was 12 weeks. Oral corticosteroid requirement use was reported as dichotomous data in 519 patients (156 in pMDI group & 363 in the HFA-pMDI group) [Comparison 39:04]. Use of HFA-pMDI containing salbutamol significantly reduced the number of patients who required additional treatment with short courses of oral steroids (RR 0.67; 95%CI 0.49,0.91). Use of inhaled corticosteroids, reported

in [Bronsky 1999](#) was similar in both study groups (54% for HFA-pMDI and 48% for the pMDI). The Ramsdell studies did not report the use of inhaled steroids during the study period. However, the risk difference from the three combined studies (RD 0.11; 95%CI 0.19,0.02) for the estimate of the number needed to treat (NNT) was 9 (95%CI 5.21,43.48) i.e. for every 9 patients treated with HFA-pMDI containing salbutamol one patient would avoid needing treatment with short course oral corticosteroids.

(B) STUDIES IN CHILDREN

(1) pMDI VS TURBUHALER

(i) Preference for inhaler device

One crossover study in 114 patients ([Hultquist 1989](#)) showed that children with asthma preferred the Turbuhaler greater than two more often than the pMDI [Comparison 45:04] (RR 2.15; 95%CI 1.25,3.72).

(ii) Adverse Events

Two studies ([Ahlstrom 1989](#), [Fuglsang 1989](#)) in 68 patients showed that there were less adverse events with the use of Turbuhaler compared to the pMDI (RR 0.12; 95%CI 0.02,0.61).

(2) pMDI VS ROTAHALER

(i) PEFR (daily)-L/min

One 4 week crossover study in 86 patients ([Croner 1980](#)) showed that daily PEFR was greater by 105 L/min when using the Rotahaler as opposed to the pMDI (WMD 105.40; 95%CI 59.99,150.81) [Comparison 50:02]. However, this study design used a 2:1 ratio for the dose of salbutamol, where the Rotahaler provided 200 mcg per puff and the pMDI provided 100 mcg per puff. Children were instructed to take 3-6 puffs from each device per day according to their need and the dose used was recorded on a diary card. It is possible that the increased PEFR seen with the Rotahaler could be a result of the higher dose.

(ii) Preference for inhaler device

One 12 week parallel study in 204 patients ([Kemp 1989](#)) showed that children preferred the pMDI almost twice more often than the Rotahaler (RR 1.69; 95%CI 1.14,2.51) [Comparison 55:04]. [Croner 1980](#) reported in their 4 week crossover study of 56 patients that more children preferred that pMDI than the Rotahaler (RR 2.67; 95%CI 1.22,5.81) [Comparison 50:07].

(iii) Acute Exacerbations

One 12 week parallel study in 204 patients ([Kemp 1989](#)) reported a significant reduction in the number of acute exacerbations that required medical intervention using the Rotahaler device compared to pMDI (RR 0.52; 95%CI 0.28,0.95) [Comparison 55:03].

No data were available for the following outcome measures in either the children or adult studies: quality of life, patient compliance, nocturnal awakening and days off work or school.

DISCUSSION

There have been a number of trials comparing the standard pMDI with other types of hand-held inhaler devices containing beta-2 agonists. These have been conducted with varying designs and with the data presented in many different forms. Their results are conflicting. To our knowledge, there are no previous systematic

reviews. The aim of this review was to determine if there were any differences in clinical effectiveness between the standard pMDI and any other available hand-held inhaler device. This was a large review of 84 included studies, which included 205 different outcome measures. The number of studies that could be combined in a meta-analysis was limited by inconsistencies in the measurement and reporting of these outcomes.

There were significant differences between the pMDI and the Turbuhaler, HFA-pMDI, Rotahaler, Spinhaler and MDPI for the following outcome measures: patient preference, heart rate and oral steroid requirement.

ADULTS

HFA (CFC-free)-pMDI - Short course oral corticosteroid requirement for the treatment of acute exacerbations

Use of HFA-pMDI containing salbutamol significantly reduced the number of patients requiring treatment with short courses of oral corticosteroids [Comparison 39:04]. However, in [Ramsdell 1999a](#) acute exacerbations were reported to be similar in the two study groups with 23% of patients having acute exacerbations in both treatment groups. In [Bronsky 1999](#) the number of patients experiencing acute exacerbations were not reported but they did report the percentage of patients requiring nebulised salbutamol during the study period (pMDI 19% vs. HFA-pMDI 4%). In addition, the Ramsdell 1999 study combined the results of two separate studies (Part A: a 12 week pilot study and Part B: a 12 month study). Upon completion of the pilot, RCT (Part A) subjects were entered into another study (Part B). Subjects who had received either HFA-pMDI or placebo in Part A were assigned to treatment with HFA-pMDI in Part B (this was done so that the patients would not be unblinded to the device being used). Patients who received CFC-pMDI in the pilot study A were randomised to either HFA-pMDI or CFC-pMDI in study B. Intervals between the two studies (Parts A and B) was a week. It can be argued that such allocation of patients may introduce bias. Exclusion of [Ramsdell 1999a](#) (Study Part A) from the comparison because of inappropriate patient allocation renders the overall result non-significant. Neither trial reported use of inhaled corticosteroids during the study period. The frequency and dose of salbutamol administration from the two inhaler devices were similar in both studies. Additional reliever medication was allowed as required, however, neither study provided this information. There were no significant differences in FEV1, AUC-FEV1, adverse effects or exacerbation rate between the study groups in these trials. Nevertheless, if the requirement for oral steroid can be decreased, it would help reduce some of unwanted side effects associated with oral steroid use. Comparative studies with CFC-pMDI have shown greater lung bioavailability ([Clark 1996](#)), higher dose delivery ([Chavan 1997](#)) and improved protection against increased asthma symptoms ([Klinger 1998](#)) with the use of HFA-pMDI containing salbutamol. In a recent 20 month study HFA-pMDI salbutamol use, was also shown to consistently lower the requirement for reliever medication compared to CFC-pMDI ([Boccuzzi 2000](#)). These and other explanations may relate to HFA-pMDIs greater effectiveness in reducing oral steroid requirement and treatment failure as seen in our review. The possibility of improvement in dosing characteristics with HFA-pMDI may translate into enhanced economic outcomes not only in decreasing the requirement for reliever medication and better symptom control but also in decreasing oral steroid requirement.

TURBUHALER - Heart Rate

Three crossover studies in adults (Bondesson 1998, Ekstrom 1995, Johnsen 1988) showed that heart rate were lower by 4-10 bpm with pMDI compared to Turbuhaler. This suggests that there is less systemic absorption of the inhaled dose from the pMDI. This finding is in agreement with previously published study (Borgström 1996b) which showed that percentage pulmonary deposition of inhaled drug is lower with the use of pMDI when compared to Turbuhaler (8.3% & 22.0%, respectively, after a nominal dose of 0.5 mg terbutaline). Due to the short half-life of beta-2 bronchodilators, unwanted effects of higher heart rate with the use of any DPI device would be short-lived and the clinical importance of such an increase in heart rate with the Turbuhaler device is not clear.

ROTAHALER - Preference

This is an old device that has been superseded by newer delivery systems in many markets. Three crossover studies in adults (one short-term; Boye 1983 & two long-term studies: Hartley 1979, Kiviranta 1985) showed that patients preference for the pMDI was two times greater than for the Rotahaler. Two long-term studies in children (one using different dose; Croner 1980 and the other a parallel design study; Kemp 1989) also showed that children preferred the pMDI compared to the Rotahaler. From the limited number of trials reporting this outcome, we are not able to make any firm conclusions on patient inhaler preference for any of the other inhaler devices. Also patient's preference is a potentially important outcome but its value is restricted since the grounds on which the patient's preferences are made are not known. It could be because of efficacy, ease of use, convenience or a combination of all three.

CHILDREN

Thirteen studies compared pMDI with other inhaler devices for inhaled beta-2 agonist drugs in children. The small number of children's studies allowed limited pooling of results so no overall conclusions could be drawn. From the limited data available, this review could find little or no evidence for additional clinical benefit of DPI devices over a standard pMDI for children with stable asthma.

TURBUHALER - Adverse Events

Two studies (Ahlstrom 1989, Fuglsang 1989) showed a decrease in adverse events when using the Turbuhaler. However, caution should be used in interpreting this result as these studies included different study designs. Ahlstrom 1989 was a 14 day study whereas Fuglsang 1989 was a cumulative dosing study lasting just over an hour and the adverse events reported in each study were coughing and tremor, respectively.

NON-SIGNIFICANT REVIEW FINDINGS

Meta-analysis of the data available from 84 randomised controlled trials included in this systematic review, found no statistically significant ($p > 0.05$) differences in patients (whether adults or children) who had stable asthma, when a standard pMDI was compared to any of the other ten hand-held inhaler devices (Turbuhaler, Diskhaler, HFA-pMDI, Rotahaler, Spiros, Easyhaler, MDPI, Clickhaler, Gentlehaler and Autohaler) for the following parameters: pulmonary lung function, asthma symptoms, use of additional relief medication, inhaled steroid requirement,

acute exacerbation, blood pressure, bronchial hyperreactivity or systemic bioavailability.

STUDIES WITH DIFFERENT DOSES IN INHALER DEVICES

Studies using 2:1 or greater dosing did not provide results that were different from 1:1 dosing studies, except in only one study with children (Croner 1980) where daily PEFR was significantly higher in the group using the Rotahaler device. Such 2:1 or greater dosing schedules used to show 'clinical superiority' of one inhaler device over another provide no clinical evidence in support of the prescribing recommendations commonly promoted by pharmaceutical companies of a 2:1 dosing between two different devices and approved by regulatory authorities. Pharmaceutical companies usually use in vitro lung deposition studies to support lower dosing schedules. To our knowledge there are no clinical trials in support of 2:1 or greater dosing schedule for beta-2 agonists. Furthermore, this review found that there are no differences in clinical effectiveness whether 1:1 or 2:1 dosing schedules are used.

STRENGTHS OF THE REVIEW

This review includes an extensive search for studies that was conducted without any language restriction. It also includes searches from respiratory journals that have been hand-searched and searches from individual online journals and clinical trial databases. Selection of studies for inclusion and data abstraction was conducted and checked independently by two reviewers.

WEAKNESSES OF THE REVIEW

The most frequently encountered problem with this review was that many of the included studies were designed as tests of the superiority of one device over another in which the null hypothesis was of equal efficacy. Such studies require fewer patients than those designed to test equivalence (null hypothesis than one device is superior to the other). Thus most studies were underpowered. Failure to detect a difference should not necessarily imply equivalence as trials designed to compare efficacy increase the chances of type II error.

Another problem with such trials is that patients are usually selected on the basis of being able to use a pMDI device as an inclusion criteria, therefore the results would favour pMDI use. The majority of the RCTs included in this review did not report previous patient familiarisation with either the pMDI or the DPIs as a requirement for study entry. Therefore the results of this review appear applicable to most patients with stable asthma. Although, adequate pMDI device technique was not a requirement for entry into the study, we should assume that all patients recruited in the RCTs included were taught to use both the pMDI and the DPIs prior to commencing the study.

Publication bias is a threat to the validity of most systematic reviews, it is unlikely to have had an important impact in this review since there was no evidence of funnel plot asymmetry in any of the comparisons.

A pitfall of crossover studies, such as those included in this review, is the presence of carry-over effects of the first treatment period into the second treatment period, leading to an underestimation of the real difference among treatments (Cleophas 1993). In the crossover studies included, treatment with short-acting beta2-

agonists did not seem to alter (the second arm) pre-bronchodilator respiratory function (FEV1), and if lung function did differ by greater than 10-15% from pre-dose baseline values than the patient was excluded from the study or the second arm visit rescheduled (e.g. Dirksen 1983, Ekstrom 1995, Löfdahl 1997, Hetzel 1977, Johnsen 1988). This suggests that carry-over effects are unlikely to have occurred in most of the included studies, despite their crossover design and since most studies did include a washout period (see table: "Characteristics of Included Studies").

Another possible pitfall is the software used (RevMan 4.1) for the meta-analysis as crossover studies are treated as if they were parallel studies. It is known (Cleophas 1996) that these two study designs (crossover and parallel) give identical results if the response to the two treatments in the same individual is completely unrelated, but parallel analysis may lead to decreased statistical power when compared to paired analysis, if the response to the two treatments is positively correlated (i.e. if patients improving during bronchodilator treatment from one device are also likely to improve during treatment with another device). This is the case in our review, since patients were responsive to both inhaler devices in all studies, as both comparative groups in all included crossover studies contained active treatment. Unfortunately, none of the studies reported the correlation between the responses to the inhaler devices used and majority of the studies did not provide any data on variance which would have allowed us to conduct inverse variance pooling in order to observe if results were different from the two analysis. Where studies or authors did provide the data (individual patient and not group means), we were able to test the effect of the RevMan software treating data from crossover studies as parallel data. Reassuringly the standard deviation was very similar when the data was analysed in the two separate ways. The variability seemed to be as high when comparing the same patient with himself or herself as opposed to when comparing the patient group means with each other. This indicates that analysing the data from crossover studies as if it was parallel data does not give different results. However, we cannot totally exclude that our analysis underestimated the statistical significance of the observed differences, as compared to a paired analysis. In this review studies using a parallel design were analysed separately from crossover designed studies.

Another possible weakness of this review has been the inaccessibility of data on outcomes known to have been measured (but unreported), and data not presented in a form that can be combined in the meta-analysis. This may be a confounding factor in the results and thus the conclusions. In particular, if pharmaceutical companies provided data from their large studies it could have appreciably added to this review. We believe that there is a need for journals editors (and the duty of all authors) to fully and explicitly report all results, methodology and details from studies so that trials can be duplicated in the exact manner in which they were conducted without readers having to infer what was probably done. Poor reporting of study data restricts not only duplication of studies but also makes the task of conducting a systematic review difficult. It is hoped that all authors publishing trials are aware of the CONSORT statement (Begg 1996).

SUMMARY & CONCLUSIONS

A range of different devices is available for the delivery of inhaled drugs in patients with chronic asthma. This, and the competing claims of the manufacturers, may make it difficult for prescribers to

choose the best device for different patients. The results discussed here are clearly average results drawn from groups of patients. Overall it appears that the standard pMDI remains a suitable delivery system for beta-2 agonists therapy for many patients. Furthermore, it is convenient and inexpensive. This conclusion must be qualified that specific groups of patients with special needs such as the very young, physically impaired and elderly were not well represented in these studies. We conclude that the pMDI should be the first delivery system tried in a patient and that it will prove to be suitable for many. If it is not suitable then other devices should be evaluated on an individual patient basis.

AUTHORS' CONCLUSIONS

Implications for practice

In stable asthma, short-acting beta-2 bronchodilators in standard CFC-pMDI's are as effective as dry powder inhalers, Autohalers and CFC-free or HFA-pMDI's. Selection of inhaler device for an individual patient should begin with a pMDI with more expensive devices being used only if the standard pMDI cannot be used reliably. This recommendation is restricted to older children and adults with asthma. There are no data to provide clear guidance on device selection for the very young, elderly or physically impaired. Professionals advising patients should be encouraged to use the cheapest drug delivery device that the patients can use while always considering patient preference, adverse events and compliance as important factors.

Implications for research

Due to the differences in study methodologies employed by the trials included in this review, there is need for further good quality randomised controlled trials in order to resolve some of the outstanding issues highlighted in this review. Studies should have sufficient statistical power to demonstrate "superior effect" rather than accept "equivalence". Studies should employ adequate washout periods if using a crossover design and data reported in absolute terms both at baseline and at study completion, and or report percentage and absolute differences from baseline for all outcomes measures in the study, not only significant differences.

Further randomised-controlled trials are needed in order to be able to make evidence-based recommendations on the use of the various inhaler devices available for the treatment of asthma. This is of particular importance due to the phasing out of CFC propellants in pMDI's.

There is a need for further studies using HFA-pMDI containing salbutamol used on an "as-required" basis in order to observe any effects on oral steroid requirement. Additional gaps highlighted in this review that need to be addressed in future trials using bronchodilators and comparing inhaler devices include: quality of life measures, patient compliance, days of work/school, patient preference, nocturnal awakening, asthma symptoms and adverse effects.

ACKNOWLEDGEMENTS

We would like to acknowledge the assistance provided by the following groups and individuals: Members of the Steering Group for the conduct of this review : Peter Barry (Leicester Royal Infirmary), Henry Chrystyn (University of Bradford), Chris Cates (Cochrane Airways Group), Linda Davies (University of York),

Graham Douglas (Aberdeen Royal Hospitals), Martin Muers (Leeds General Infirmary), & David Smith (University of York); Cochrane Airways Review Group (CAG) staff at St George's Hospital in London; Paul Jones for his input as the co-ordinating editor of the CAG; Sheree Wellington for double checking all the many data extraction forms and entry into RevMan. We would also like to thank the following authors and organisations for responding to our correspondence and supplying additional data for this review:

E Hood & R Spiers of 3M Health Care Ltd, UK; E Stahl, L-G Carlsson & L Borgstrom of AstraZeneca Lund, Sweden; K Laurikainen of Orion Pharma, Finland; M Hill of Dura Pharmaceuticals, USA; R Ruffin of The University of Adelaide, Australia; E Bleecker of University of Maryland, Baltimore, USA; O Selroos of Mjölby Hospital, Finland and H Tukiainen of Kuopio University Hospital, Finland. We acknowledge Felix Ram's previous involvement in this review as lead author.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

3M UK 1996

Methods	Design: open-labelled, randomised parallel, age stratified study - long term. Device: HFA-134a pMDI vs pMDI Drug: salbutamol Dose: 100ug per actuation (both devices) Duration: 4 weeks	
Participants	63 children, aged 4-11 (15 were 4-7 & 48 were 8-11 yrs) with at least a 6 month history of asthma and using an inhaled beta-agonist were enrolled. Criteria: FEV1 > 50% predicted and reversibility greater than 12% to bronchodilator.	
Interventions	Patients randomly assigned to receive either HFA-132a salbutamol or standard Ventolin pMDI. Two inhalations, qds for 4 weeks.	
Outcomes	Testing: Pulmonary function tests (PFTs) before and over a 6 hour period after two puffs of study medication at the end of the 4 week period. Study data also measured and provided for 1-2 weeks of study duration. Variables: all FEV1 values, PEFR (am & pm), asthma disability scores, beta-2 usage, sleep disturbances	
Notes	All study details provided by 3M Health Care, UK.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Ahlstrom 1989

Methods	Design: open-labelled, randomised crossover study - long term. Device: Turbuhaler vs pMDI + Nebuhaler Drug: terbutaline Dose: 0.5 mg tds (both devices) Duration: 14 days	
Participants	26 children initially but 5 withdrawn (2 due to poor compliance, 1 irregular budesonide use, 2 had exacerbations). Data presented for 21 children (7F), age range 2-5 yrs, mean age 3.9yrs, duration of asthma 1-4 yrs (mean 2.7 yrs). All other treatments kept constant during study except for the intervention.	

Ahlstrom 1989 (Continued)

Interventions	Patients randomly assigned to received either Bricanyl Turbuhaler (0.5 mg/dose; 1 inhalation tds) or Bricanyl pMDI + Nebuhaler spacer (0.25 mg/dose; 2 inhalations tds). Each treatment lasted for 14 days and than crossed over for another 14 days with other treatment arm.
Outcomes	Testing: PEFR measured 15 min after drug (bronchodilator) administration. Variables: Day and night symptom scores, day and night side effects and additional use of beta-2 medication. PEFR graphs presented but no SD's or SEM's available.
Notes	Potential bias: during the pMDI + Nebuhaler arm 2 inhalations tds was used as opposed to 1 inhalation tds for the Turbuhaler arm.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Andersen 1998

Methods	Methacholine challenge used. Design: double-blind, double-dummy, randomised crossover study - short term. Device: Turbuhaler vs pMDI Drug: terbutaline Dose: 1 mg (both devices). TH: 2x0.5 mg & pMDI: 4x0.25 mg Duration: 1 day x 2
Participants	16 adults (11 F), mean age 27 yrs (range 18-39) with asthma defined by ATS criteria and with FEV1 of 88% predicted. Patients who had a sufficient hyperresponsiveness to methacholine challenge were only recruited (PC30 < 9.6 mg/ml of methacholine).
Interventions	All patients were challenged with double dose of the last concentration of methacholine determined on screening day. If FEV1 decreased by 20% or more, patients were randomly assigned to receive either terbutaline via the Turbuhaler or pMDI (1mg). Spirometry was performed at 5, 15 7 30 mins after study treatment was administered.
Outcomes	Testing: Spirometry performed after methacholine challenge and study treatment. Variables: FEV1, FVC, PIF, FEF25%, FEF50%, FEF75%, PEF.
Notes	Potential bias: during the pMDI period 4 inhalations were used as opposed to 2 inhalations during the Turbuhaler period.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Baumgarten 2000

Methods	Design: randomised, single-blind parallel study. Device: HFA-134a pMDI Drug: salbutamol Dose: prn 100ug per puff (average recorded 4 puffs / day).
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Baumgarten 2000 (Continued)

Duration: 4 weeks

Participants	423 adults patients (51%F;49%M), mean age 47 & 48. 215 in HFA group and 208 in CFC-pMDI group. Percentage predicted FEV1 was between 50-100% and smoking history <20 pack years and documented history of asthma.
Interventions	All patients had a 2 week run-in period when their usual short-acting bronchodilator was replaced with salbutamol 100ug delivered by CFC-pMDI. At the end of this run-in period patients were randomised to receive prn salbutamol 100ug from the CFC-pMDI or HFA-pMDI for 4 weeks. This was followed by a 2 week run-out period with the same treatment as in the run-in period. Patients measured their PEFR and recorded it on a diary card plus their symptoms.
Outcomes	FEV1, adverse events, serum potassium, PEFR (am, pm), symptoms.
Notes	Statistical analysis was performed on all patients who had received at least one dose of study medication (intent-to-treat analysis).

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Bleecker 1998

Methods	Design: double-blind, double-dummy, randomised parallel study - long term. (3 way study also included a placebo HFA arm). Device: HFA-134a pMDI Drug: salbutamol Dose: 90 ug per actuation Duration: 12 weeks
Participants	379 adults (231 F), mean age 36(SD:12) with asthma defined by objective criteria (15% reversibility in FEV1 and between 40 to 80% predicted FEV1).
Interventions	Patients randomly assigned to received either HFA-132a salbutamol, standard Ventolin pMDI or placebo HFA. Two inhalations, qds for 12 weeks. Patients eligible for study entry after screening evaluation underwent a 7-day run-in period.
Outcomes	Testing: Pulmonary function tests (PFTs) before and over a 6 hour period after two puffs of study medication at the end of the 12 week period. Study data also measured and provided (as graphs) for weeks 0, 4 & 8 of study duration. Variables: FEV1, FEV1-AUC, inhaled steroid usage.
Notes	Parallel study therefore data entered separately from crossover studies. Study was published in 5 different journals in different forms.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Bondesson 1998

Methods	Design: open-labelled, randomised crossover study - cumulative dosing. Device: Turbuhaler Drug: salbutamol Dose: total 1600 ug in 12 min. (100, 100, 200, 400 & 800). Duration: 25 min after last dose.
Participants	12 adults (3 F), mean age 59 (range: 47-68). FEV1 %predicted 50%(range: 36-79). Mean reversibility 20% (range: 15-26). Seven patients were former smokers, 4 current and 1 never smoked.
Interventions	Patients randomly assigned to receive salbutamol from the TH or pMDI. Total dose delivered from each device was 1600 ug. Washout >= 24 hours.
Outcomes	Testing: Spirometry done 25 min after dose, all other measurements 15 min after dose. Variables: FEV1, tremor, serum potassium, adverse events and HR. Results after last cumulative dose entered into RevMan.
Notes	Author reply: randomisation / allocation by computer. Author did not provide requested spirometry data values.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Study investigators were not aware as to order to treatment group assignment (Cochrane Grade A)

Borgström 1996a

Methods	Design: randomised, double-blind, double-dummy, 4-way crossover study Device: Turbuhaler Drug: terbutaline Dose: Single doses of 0.25 mg per actuation Duration: 360 minutes
Participants	13 (9 male) patients with asthma with a mean FEV1 of 59% predicted (range 39%-72%). Mean FEV1 reversibility 15 minutes after inhalation of 1mg terbutaline via TH was 34% (range 20-59%). Mean age was 36 (range 18-50).
Interventions	Patients received on four different study days via Bricanyl pMDI or Bricanyl Turbuhaler 0.25 or 0.50 mg terbutaline as a single dose. Activated charcoal (30g) was given to all patients before and up to 2 hours after drug inhalation as an oral slurry to block gastrointestinal uptake of swallowed drug. Washout >= 24 hours.
Outcomes	Testing: Spirometry was done 15 min onwards after drug dose but only mean over the total 360 min study period was reported. Variables: FEV1, FVC, FEF25, FEF50, PEF, SGaw, AUC-FEV1., deposition,
Notes	Author reply: randomisation / allocation by computer.

Risk of bias

Bias	Authors' judgement	Support for judgement
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Borgström 1996a (Continued)

Allocation concealment?	Low risk	Study investigators were not aware as to order to treatment group assignment (Cochrane Grade A)
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Borgström 1996b

Methods	Same study as above but different arm. Design: randomised, double-blind, double-dummy, 4-way crossover study Device: Turbuhaler Drug: terbutaline Dose: Single doses of 0.50 mg (two puffs of 0.25 mg per actuation) Duration: 360 minutes
Participants	13 (9 male) patients with asthma with a mean FEV1 of 59% predicted (range 39%-72%). Mean FEV1 re- versibility 15 minutes after inhalation of 1mg terbutaline via TH was 34% (range 20-59%). Mean age was 36 (range 18-50).
Interventions	Patients received on four different study days via Bricanyl pMDI or Bricanyl Turbuhaler 0.25 or 0.50 mg terbutaline as a single dose. Activated charcoal (30 g) was given to all patients before and up to 2 hours after drug inhalation as an oral slurry to block gastrointestinal uptake of swallowed drug. Washout >= 24 hours.
Outcomes	Testing: Spirometry was done 15 min onwards after drug dose but only mean over the total 360 min study period was reported. Variables: FEV1, FVC, FEF25, FEF50, PEF, SGaw, AUC-FEV1 and deposition. Study only reported mean FEV1 in extractable form.
Notes	Author reply: randomisation / allocation by computer.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Study investigators were not aware as to order to treatment group assignment (Cochrane Grade A)

Boye 1983

Methods	Design: randomised crossover study Device: Rotahaler Drug: fenoterol Dose: 200 ug per actuation Duration: 1 to 5 hours
Participants	20 adults (8 females) with mean age 51 (range 20-69) with reversible airways disease. FEV1/PEF bron- chodilator reversibility of >15%
Interventions	Patients initially given 200 ug of fenoterol with spirometry over 1 hour later followed by PEF at home 5 hours later. Patients were also given 200 ug x 3 twice daily for four days with measurements of PEF at home. Washout not reported.
Outcomes	Testing: Spirometry was done before and 1, 5, 10, 30 & 60 minutes after a single 200ug dose but only PEF graph shown with no SEM or SD.

Boye 1983 (Continued)

Variables: PEFR, VC, FEV1 and preference for device which was the only extractable result that could be used.

Notes No reply to correspondence, from author to date.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Bronsky 1987

Methods Design: randomised, double-blind, double-dummy parallel study
Device: Rotahaler
Drug: salbutamol
Dose: 200 ug/puff from Rotahaler, but 180 ug/puff from pMDI
Duration: 6 hours

Participants 231 adults patients (RH:115; pMDI:116) with asthma were recruited. FEV1 $\leq$ 80% predicted. FEV1 bronchodilator reversibility was $>$ 15%, 15 minutes after 262 ug of isoproterenol.

Interventions Patients were either given salbutamol through the Rotahaler or pMDI and lung functions measured at 30 minutes and every hour for 6 hours.

Outcomes Testing: Spirometry done 30 minutes post-dose than every hour for 6 hours.
Variables: FEV1, FEF25-75, FVC. PEFR and treatment failure reported after 12 weeks of device use. Only mean over 6 hours reported for FEV1, FVC and FEF25-75 but none useful as no SD or SEM reported.

Notes Allocation of patients to treatment according to randomly generation codes.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Study investigators were not aware as to order to treatment group assignment (Cochrane Grade A)

Bronsky 1995

Methods Design: randomised double-blind double-dummy crossover study using, Latin-square treatment schedule. Exercise challenge used.
Device: Rotahaler vs pMDI alone
Drug: salbutamol
Dose: pMDI-180ug vs RH-200ug
Duration: 51 min

Participants 44 children, age range 4-11yrs, mean age 8yrs. FEV1 $\geq$ 70% predicted after bronchodilators have been held for 8 hours. FEV1 bronchodilator reversibility was $>$ 15%, 15 minutes after inhalation of a beta-adrenergic bronchodilator.

Bronsky 1995 (Continued)

Interventions	Pulmonary function test performed up to 51 min after taking the drug and running on a treadmill for 6 min at pre-determined target rates (85% of HRmax). Study also reported 15 min post dose FEV1 (i.e. pre-exercise).	
Outcomes	Pre and post exercise FEV1 after drug administration (i.e. before any exercise challenge).	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Bronsky 1999

Methods	Design: randomised, double-blinded, parallel study Device: HFA-134a pMDI Drug: salbutamol Dose: 2 puffs bd for 12 weeks (exact dose not reported for with device). Duration: 12 weeks	
Participants	51 adult patient with asthma, mean age 35 & 39 (range 18-65) years, 29 females, FEV1 of 40-80% predicted and >=15% increase in FEV1 30 minutes after 200ug of CFC-salbutamol from DPI.	
Interventions	All patients were initially optimised for 12 weeks on standard CFC-pMDI than 24 patients were assigned to HFA-pMDI for another 12 weeks while 27 remained on CFC-pMDI. Pulmonary function test reported as peak percentage change was carried out 2 hours post-dose and AUC until termination of effect. (i.e. FEV1 fell to 15% above baseline).	
Outcomes	FEV1, treatment failures, oral steroids use, AUC-FEV1, symptoms.	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Chapman 1997

Methods	Different doses used in devices. Design: randomised, double-blind, crossover study Device: Turbuhaler Drug: salbutamol Dose: 200ug in TH; 100ug in pMDI, both treatments given qid for 2 weeks each. Duration: 2 weeks	
Participants	37 adults (18 women), mean age 39 yrs, FEV1 72% predicted, and 15% or greater increase in FEV1 after 200ug salbutamol from pMDI.	

Chapman 1997 (Continued)

Interventions	Total study duration was 4 weeks; 1 week run-in followed by 2 weeks treatment and 1 week of washout in between.	
Outcomes	PEFR, FEV1 (measured 15 minutes post-dose), preference, beta-2 use and symptoms.	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Cohen 1999

Methods	Design: randomised double-blind parallel study Device: HFA-134a pMDI Drug: salbutamol Dose: 180ug per actuation Duration: 12 weeks	
Participants	Patients with asthma > 12 years of age. FEV1 of 50-80% predicted and increase in FEV1 of >=15% after salbutamol.	
Interventions	PRN use of 180ug salbutamol from either the HFA-134 pMDI or standard pMDI for 12 weeks	
Outcomes	Study measurements done at Day 1, weeks 6 and 12 were FEV1, AUC-FEV1, PEFr-morning & evening, symptoms, nocturnal awakenings and exacerbations.	
Notes	Study reported as abstract with no useful data for review. Written to author for further information.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Colice 1999

Methods	Design: randomised single-blind 4-period crossover study Device: HFA-134a pMDI Drug: salbutamol Dose: 2 puffs from each device (exact dose unknown) Duration: 90 minutes after exercise challenge	
Participants	16 patients (5F;11M) with stable asthma aged 6-11 yrs (mean 9.4) were recruited and 15 completed the study. Patients were required to have EIA (or EIB), defined as $>20\%$ but no $>50\%$ fall in FEV1 within 30 minutes following exercise. FEV1 had to be within 10% of pre-study value and % predicted FEV1 $> 70\%$ on study days. Screening % predicted FEV1 was 79.3 (SD 9.5)%.	
Interventions	After baseline spirometry, patients self-administered two puffs of one of the 4 treatments (Proventil HFA-3M Pharma, Ventolin, Proventil-Key Pharma or placebo) under supervision. Thirty minutes after drug administration exercise challenge on a treadmill (HR 160-190 bpm for 6 min) was performed. Dur-	

Colice 1999 (Continued)

ing the exercise patients inspired compressed air from a 170ml balloon reservoir through a two-way, non-rebreathing valve and face mask which cover the nose and mouth. Spirometry was performed 5, 10, 15, 30, 45, 60, 75 & 90 mins following exercise challenge.

Outcomes	Study measurements done 5 to 90 minutes after exercise challenge; spirometry, HR, BP, ECG Wash out was between 3-7 days. **There was a 1.9% increase from baseline in FEV1 with HFA pMDI, therefore recorded in comparison (29:01) as negative figure.
Notes	The sequence of treatment was randomised. The patients and study coordinator were not blinded to the treatments but the technician performing spirometry was blinded to the study treatments.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Croner 1980

Methods	Design: randomised, double-blind, crossover study Device: Rotahaler Drug: salbutamol Dose: 0.1 mg/puff in pMDI & 0.2 mg/puff in Rotahaler. 3-6 puffs of each/day prn. Duration: 4 weeks
Participants	43 children (11 girls) age range 3-16 years, mean 9.6.
Interventions	Children inhaled salbutamol 3-6 times a day as required from either a Rotahaler or pMDI for weeks. Daily pulmonary function measured with an air flow meter 10 minutes after drug dose.
Outcomes	PEFR, preference, symptoms, additional beta-2 use and inhaled steroid use.
Notes	Coding was used for treatment allocation and was not unblinded until the trial was completed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Study investigators were not aware as to order to treatment group assignment (Cochrane Grade A)

Custovic 1995

Methods	Design: randomised double-blind double-dummy crossover study. Device: HFA-pMDI Drug: salbutamol Dose: 200 ug (both devices) Duration: 30 min
Participants	25 children (9 girls), age range 6-14 yrs, mean age 10 yrs. FEV1 >50% predicted and PD20 of <3.91umol.

Custovic 1995 (Continued)

Interventions	Pulmonary function measured was performed 30 min post-dose, than histamine challenge performed and FEV1 measured until FEV1 decreased by 20% (PD20). Data used was before histamine challenge.
Outcomes	FEV1 and protection against histamine-induced bronchoconstriction as measured by PD20.
Notes	Allocation of treatment was predetermined according to a sequence of continuous patient randomisation numbers that were generated by computer.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Study investigators were not aware as to order to treatment group assignment (Cochrane Grade A)

Dirksen 1983

Methods	Design: randomised double-blind double-dummy crossover study. Device: Spinhaler Drug: fenoterol Dose: total dose 400 ug (both devices) Duration: 100 min (25 min x 4)
Participants	9 adults (8 women), age range 27-65, mean age 47 yrs. FEV1 % predicted mean was 54 (range 42-71). FEV1 reversibility of $\geq 15\%$, 15 min after 0.2 mg fenoterol from the pMDI.
Interventions	Study measurements were done 20 minutes after taking each cumulative dose in the following sequence 0.05 mg + 0.05 mg + 0.1 mg + 0.2 mg.
Outcomes	Pulse rate, tremor, FVC, FEV1, FEV1%, MVV, FEF, FMF, FMFT, side effects. Results after last cumulative dose entered into RevMan.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Dockhorn 1995a

Methods	Design: randomised double-blind double-dummy 6-way crossover study. Device: HFA-pMDI Drug: salbutamol Dose: 100ug (both devices) Duration: 480 minutes
Participants	26 non-smoking adult patients (6 women) with stable asthma, mean age 28 (range 18-50). FEV1 mean % predicted was 68.7%. FEV1 reversibility $\geq 20\%$ within 30 minutes after inhalation of 200ug of salbutamol from CFC-pMDI.

Dockhorn 1995a (Continued)

Interventions	Pulmonary function measurements done after single-dose of 100 ug salbutamol at 10 to 480 minutes post-dose.	
Outcomes	AUC, Time of onset, duration of effect, FEV1, adverse effects, rescue beta-2 use, BP, pulse rate.	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Dockhorn 1995b

Methods	Same study as above but different arm. Design: randomised double-blind double-dummy 6-way crossover study. Device: HFA-pMDI Drug: salbutamol Dose: 100ug (both devices) Duration: 480 minutes	
Participants	26 non-smoking adult patients (6 women) with stable asthma, mean age 28 (range 18-50). FEV1 mean % predicted was 68.7%. FEV1 reversibility >=20% within 30 minutes after inhalation of 200ug of salbutamol from CFC-pMDI.	
Interventions	Pulmonary function measurements done after single-dose of 200 ug salbutamol at 10 to 480 minutes post-dose.	
Outcomes	AUC, Time of onset, duration of effect, FEV1, adverse effects, rescue beta-2 use, BP, pulse rate.	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Dockhorn 1997

Methods	Design: randomised, single-blinded, 4-way crossover study. Device: HFA-134a pMDI Drug: salbutamol Dose: 2 puffs (both devices) exact dose not mentioned. Duration: 90 minutes	
Participants	20 (7 females) adults with stable asthma. Mean age 23.9 (range 14-43). FEV1 % predicted was 89.6%(SD 9.3). Patients had to have demonstrated exercise-induced asthma measured by decrease in FEV1 $>20\%$ but $<50\%$ after exercise.	

Dockhorn 1997 (Continued)

Interventions	Standardised exercise was performed thirty minutes after study drug administration and study measurements were performed from 5 to 90 minutes post exercise. Exercise was on a treadmill with speed and incline adjusted to reach 80-90% maximum heart rate (220-age in years), for 8 to 10 minutes. Washout was between 2 to 7 days.	
Outcomes	Spirometry, heart rate, ECG, blood pressure	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Duncan 1977

Methods	Design: randomised, double-blinded, double-dummy, crossover study Device: Spinhaler Drug: salbutamol Dose: 200ug Duration: 300 minutes	
Participants	20 adults patients (5 females) with stable asthma with FEV1 reversibility of >=20% after 0.5% salbutamol by IPPV. Mean age 59 (range 13-72) yrs.	
Interventions	Pulmonary function measured at 15, 30 min and at 30 min intervals until 300 minutes post-dose from inhaler device.	
Outcomes	FEV1, FVC, heart rate, side effects.	
Notes	Author reply: Latin square design used and computer generated coding used for allocation concealment. Pooled SEM was provided for FEV1, and FVC therefore it was converted to SD and used in RevMan.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Study investigators were not aware as to order to treatment group assignment (Cochrane Grade A)

Ekstrom 1995

Methods	Design: open, randomised, 2-way crossover study Device: Turbuhaler Drug: terbutaline Dose: total dose 4 mg Duration: 180 minutes (6 x 30 min)	
Participants	31 (13 women) adults with stable asthma, mean age 46 (range 18-69). FEV1 reversibility $\geq 15\%$ after 0.5 mg terbutaline from Turbuhaler. FEV1 % predicted was 65% (range 41-99). Two patients were current smokers, 15 former and 14 never smoked. Average duration of asthma was 16 years.	

Ekstrom 1995 (Continued)

Interventions	Cumulative doses every 30 minute in the following manner: 0.125, 0.125, 0.25, 0.5, 1.0 & 2.0 mg was given either by Turbuhaler or pMDI. Study measurements were done 25 minutes after each cumulative dose. Washout >20 hours
Outcomes	FEV1, FEF25-75%, FVC, PEFR, tremor, serum potassium, pulse rate, blood pressure. Results after last cumulative dose entered into RevMan.
Notes	Author reply: allocation concealment and randomisation by computer generated codes.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Study investigators were not aware as to order to treatment group assignment (Cochrane Grade A)

Fuglsang 1989

Methods	Design: single-blinded double-dummy crossover study, used computer generated schedule. Device: Turbuhaler Drug: terbutaline Dose: 2.0 mg (both devices) Duration: cumulative dosing study, giving a total dose of 2.0 mg within 80 min.
Participants	13 children (3 females), mean age 10.5, range 7-15 yrs. All children had stable asthma with $\geq 20\%$ reversibility in FEV1 after inhalation of 0.5 mg of terbutaline.
Interventions	Pulmonary function testing done 15 min post-dose. Initial dose in the two groups was different as it was impossible to produce a Turbuhaler that could deliver 0.125 mg terbutaline but it was considered important to have a response below .025 mg therefore 0.125 mg terbutaline was delivered from the pMDI only (total dose: pMDI=1.875 mg; TH=2 mg). Cumulative doses were administered every 20 minutes.
Outcomes	FEV1, FEF25-75%, PEFR or FVC, heart rate, tremor, symptoms, adverse effects,
Notes	Author reply: computer generated randomisation code was use for allocation of treatment.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Study investigators were not aware as to order to treatment group assignment (Cochrane Grade A)

Geoffroy 1999a

Methods	Same study as above but different arm. Design: randomised, double-blinded, double-dummy, 5-way crossover study Device: Spiros Drug: salbutamol Dose: 90ug Duration: 360 minutes
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Geoffroy 1999a (Continued)

Participants	60 adults enrolled (27 women), mean age 29.7 (SD 10.5), range 18-65. 44 patients completed the study. FEV1 reversibility to be $\geq 15\%$ 30 mins after inhalation of 90 ug salbutamol from pMDI. FEV1 was 59% predicted.
Interventions	Study measurements done from 10 to 360 minutes post-dose. Blood samples were also obtained and ECG performed at 30, 60 and 120 minutes. FEV1 on second study day had to be between 85-115% of study day 1. Washout >24 hrs <14 days.
Outcomes	FEV1, FVC, FEF25-75%, PEFR, blood pressure, heart rate, serum potassium, ECG,
Notes	Author reply: random allocation of patient to treatment sequence

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Study investigators were not aware as to order to treatment group assignment (Cochrane Grade A)

Geoffroy 1999b

Methods	Design: randomised, double-blinded, double-dummy, 5-way crossover study Device: Spiros Drug: salbutamol Dose: 180 ug Duration: 360 minutes
Participants	60 adults enrolled (27 women), mean age 29.7 (SD 10.5), range 18-65. 44 patients completed the study. FEV1 reversibility to be $\geq 15\%$ 30 mins after inhalation of 90 ug salbutamol from pMDI. FEV1 was 59% predicted.
Interventions	Study measurements done from 10 to 360 minutes post-dose. Blood samples were also obtained and ECG performed at 30, 60 and 120 minutes. FEV1 on second study day had to be between 85-115% of study day 1. Washout >24 hrs <14 days.
Outcomes	FEV1, FVC, FEF25-75%, PEFR, blood pressure, heart rate, serum potassium, ECG,
Notes	Author reply: random allocation of patient to treatment sequence

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Study investigators were not aware as to order to treatment group assignment (Cochrane Grade A)

Giannini 2000

Methods	Methacholine challenge used in study. Design: double-blind, double-dummy, randomised crossover study . Device: Autohaler vs pMDI + volumatic Drug: salbutamol
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Giannini 2000 (Continued)

Dose: 100 ug (both devices).
Duration: until PD20 reached

Participants	18 adults (8 women), mean age 40 (SD 18) yrs (range 19-72) with stable moderate asthma. Patients had to have a baseline fall in FEV1 of 20% after methacholine challenge.
Interventions	15 minutes after 100ug of salbutamol was administered methacholine challenge began until PD20 was reached. Challenge was done every 2 minutes from 0.04 to 0.32 mg of cumulative doses. Washout was 1 week.
Outcomes	FEV1, PD20
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Golish 1998

Methods	Different doses used in devices. Design: randomised, double-blind, double-dummy, 3-way crossover study . Device: Rotahaler vs pMDI + InspirEase spacer device Drug: salbutamol Dose: Rotahaler 400 ug vs pMDI 180 ug Duration: 360 minutes
Participants	20 adult patients (13 women) with stable asthma, mean age 40.9 (SD 14.2). FEV1 ≤80% predicted when inhaled beta-2 agonists with-held for 6 hrs and FEV1 >15% 15 minutes after inhalation of salbutamol via pMDI +spacer. FEV1 % predicted 50.7% (SD 15.9).
Interventions	Study measurements done from 15 to 360 minutes post-dose. Study also had third arm which was pMDI alone, we did not use this arm data. Washout was >24 hours.
Outcomes	FEV1, blood pressure, heart rate, symptoms.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Haahtela 1994

Methods	Design: open-labelled, randomised, 3-way crossover study Device: Easyhaler Drug: salbutamol Dose: total dose 720 ug
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Haahtela 1994 (Continued)

Duration: 2 hrs (30 min x 4)

Participants	20 adults patients (9 women), mean age 50, age range 23 to 66 yrs. FEV1 % predicted was 65%. All patients had FEV1 reversibility of $\geq 15\%$ after 200ug salbutamol. During study days FEV1 variation had to be less than 20% and on entry FEV1 % predicted had to be $< 85\%$.
Interventions	Four dose of salbutamol administered every 30 minutes: 90, 90, 180 & 360. Study measurements were done 20 minutes after each cumulative dose.
Outcomes	FEV1, FVC, PEFR, BP, HR, adverse events. Results after last cumulative dose entered into RevMan.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Harris 1981

Methods	Design: randomised, double-blind, double-dummy, crossover study Device: Rotahaler or Spinhaler Drug: fenoterol Dose: 200 ug Duration: 60 minutes
Participants	11 adults (5 women), age range 16-66, FEV1 reversibility of $\geq 20\%$ after standard sympathomimetic aerosol. On study days variation in lung function was less than 10%.
Interventions	On study days 200 ug fenoterol was administered either device in a double-blinded fashion. Study measurements were done 5, 15, 30 and 60 minutes post-dose. Patients studied on two occasions not more than one week apart.
Outcomes	FEV1, pulse rate.
Notes	Study included but no data used from the trial into the review as data is in non-extractable form. No reply from author to date.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Hartley 1977

Methods	Design: randomised, double-blind, double-dummy, crossover study Device: Rotahaler Drug: salbutamol Dose: 200 ug Duration: 240 minutes
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Hartley 1977 (Continued)

Participants	10 patients (6 women) with asthma, age range 21-52. Patients were admitted to hospital with severe attacks and studied in hospital (prior to discharge) when stable, over five days. FEV1 reversibility was $\geq 15\%$ following 200 ug salbutamol from pMDI.
Interventions	Each morning baseline PEFR, pulse and BP were measured until it was stable then patient was given 50, 100, 200 or 400 ug salbutamol from Rotahaler or 200 ug from the pMDI. Study measurements were made from 10 min post-dose to 240 minutes.
Outcomes	PEFR, pulse rate, BP.
Notes	Data was extracted from graph, but no SD was provided in graph for % increase in PEFR. Double Latin square design was used for treatment allocation and was double-blinded.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Study investigators were not aware as to order to treatment group assignment (Cochrane Grade A)

Hartley 1979

Methods	Design: double-blinded, crossover study. Not mentioned if randomised. Device: Rotahaler Drug: salbutamol Dose: 200 ug Duration: 3 months
Participants	38 adult patients completed the study (25 women), mean age 47, range 22-76, mean duration of asthma was 18.8 yrs. FEV1 reversibility was $\geq 15\%$ after salbutamol. Subjects who did not have a good pMDI technique were not entered into the study.
Interventions	200ug salbutamol was taken for 3 months each using both device in a double-blind fashion. Per puff pMDI delivered 100 ug and Rotahaler delivered 200 ug. Patients completed daily diary cards and made PEFR recordings.
Outcomes	Diary cards, PEFR, FEV1, preference, symptoms, additional beta-2 usage, rescue steroid use, wheeze.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Hawthornth 1999

Methods	Design: randomised double-blinded crossover study Device: HFA-134a pMDI Drug: salbutamol Dose: 200ug per actuation Duration: 60 minutes
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Hawthornth 1999 (Continued)

Participants	24 adult patients with a history of exercise induced asthma. Age range 19-45, mean 27. FEV1 $\geq$ 65% predicted and fall in FEV1 $\geq$ 20% post exercise.
Interventions	Single doses study drug administered 30 minutes prior to a 6 minute exercise test. Washout: $>$ 24 hours.
Outcomes	FEV1 measured 15 minutes pre-dosing, 5 minutes pre-exercise and at regular intervals for 60 minutes post 6 minutes exercise test. The maximum % fall in FEV1 post-exercise compared to the pre-exercise value reported.
Notes	Study was published as an abstract only.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Hetzel 1977

Methods	Design: open-labelled, randomised, crossover study Device: Rotahaler Drug: salbutamol Dose: total dose 1500 ug Duration: 60 minutes
Participants	17 patients, mean age 44, range 23-68, with stable asthma and good inhaler technique. FEV1 was $\geq$ 15%. 14 patients were studied in this cumulative dosing study. Baseline FEV1 could not vary by $>$ 15% on the two study days.
Interventions	Single dose of 100 ug salbutamol was given initially study measurements made from 2 to 15 min, than 200, 400 and 800 ug given followed by reading at 5 & 15 min after each cumulative dose.
Outcomes	FEV1, FVC, pulse rate. Acute exacerbations data was obtained from long-term (1 month) study, since there were 3 different studies in this trial. Results after last cumulative dose entered into RevMan.
Notes	Study mentions that the order of treatment was altered in consecutive patients, so a grade of 'C' is allocated to this study for concealment, after discussion with JWr. FEV1(SD) values obtained from graph.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	Alternate allocation

Hindle 1995

Methods	Design: open, randomised, crossover study Device: Diskhaler Drug: salbutamol Dose: total dose 400 ug Duration: 30 minutes
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Hindle 1995 (Continued)

Participants	10 patients 7 women, mean age 40.2(10.7), with stable asthma. FEV1 was 59.9%(22.3) predicted.
Interventions	Subjects inhaled 4x100ug salbutamol from pMDI and 1x400ug from Diskhaler. Each device was assessed on separate days with minimum of 7 day washout. Subjects withheld bronchodilators for >8 hrs prior to study days.
Outcomes	Spirometry (FEV1) was measured pre and 30 minutes post-dose.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Hirsch 1997

Methods	Design: randomised double-blind double-dummy parallel study, used drawing lots. Device: Turbuhaler vs pMDI alone Drug: terbutaline Dose: 0.5mg (both devices) Duration: 10 min
Participants	118 children, age range 8-15, mean age 11.3. FEV1 was <70% predicted.
Interventions	Pulmonary function testing done 10 min post dose.
Outcomes	Change from baseline FEV1, FVC and Vmax50%.
Notes	Author reply used drawing lots for allocation concealment and provided further details on the process of double-blinding.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Study investigators were not aware as to order to treatment group assignment (Cochrane Grade A)

Hultquist 1989

Methods	Design: randomised double-blind double-dummy crossover study. Device: Turbuhaler vs pMDI alone Drug: terbutaline Dose: 0.5 mg + prn (both devices) Duration: 2 weeks
Participants	57 children (14 girls), age range 6-18, mean age 11. All patients had bronchial reversibility of >15% and were well trained in using pMDI.
Interventions	Multi-center study involving 5 centers. One week run-in followed by 2 weeks treatment from each inhaler device. PEFR was measured 10 min post-dose.

Hultquist 1989 (Continued)

Outcomes PEFR (morning & evening), symptom scores and preference for device.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Jackson 1994

Methods Design: randomised, single-blinded, double-dummy, crossover study.
Device: Turbuhaler vs pMDI alone
Drug: terbutaline
Dose: 0.25 mg (both devices)
Duration: 45 minutes

Participants 10 adults (7 females), mean age 42 (range 19-66) yrs, with highly reactive airways were selected, defined as provocative concentration of methacholine producing a 20% fall in FEV1 $\leq$ 0.2 mg/ml and a diurnal variation of PEFR of $>15\%$.

Interventions Patients inhaled 0.25 mg terbutaline via each device and sGaw was measured at 10s intervals for 2 min than at intervals until 45 min. Washout of at least 2 days.

Outcomes sGaw, Raw, TGV, AUC

Notes Author reply: on randomisation methodology using blocks of six for the treatment sequence.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Johnsen 1988

Methods Design: open-labelled, randomised, crossover study
Device: Turbuhaler
Drug: terbutaline
Dose: total dose 4 mg (both devices)
Duration: 180 minutes (30 min x 6)

Participants 9 adults (4 females), mean age 30, range 20-46 yrs. All patients had stable asthma with duration from 2-34 yrs. Greater than 15% differences between baseline FEV1 values were not allowed. FEV1 reversibility of at least 20% after either 0.5 mg terbutaline or 0.2mg salbutamol.

Interventions Cumulative dose were given to patients every 30 minutes and study measurements done 5 and 20 minutes after each inhaled dose.
Mean washout period was 6 days (range 2-9 days).

Outcomes FEV1, FVC, HR, tremor, PIF, FIV1, FIVC, FIF. Results after last cumulative dose entered into RevMan.

Johnsen 1988 (Continued)

Notes FEV1, FVC, HR, tremor and all SD's obtained from graphs.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Kemp 1989

Methods	Design: 2 separate studies reported (a) randomised double-blind double-dummy crossover study using 2 doses: 100 & 200 ug on separate days & (b) a parallel run study using 200ug qid for 12 weeks. Used computer coded treatment. Device: Rotahaler vs pMDI alone Drug: salbutamol Dose: (a) 90-100 & 180-200 ug and study (b) 180-200 ug Duration: (a) 360 min & (b) 12 weeks.
Participants	(a) 30 children, mean age 9.4 yrs. ----- (b) 204 (164F) children, age range 4-11, mean age 8.2 yrs.
Interventions	Participants: (a) Lung function measured from 5 to 360 min post-dose. ----- Participants: (b) Lung function measured from 5 to 480 min post-dose.
Outcomes	Only data from 12 week (Study B) entered into RevMan. Study A: FEV1, HR and BP. Study B: FEV1, FEF25-75, FVC, PEFR, dropout rate or symptom scores. Number of acute exacerbations (requiring intervention).
Notes	SD for FEV1 estimated from range provided. Study used Latin-square design for allocation of treatment and it was double-blinded.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Study investigators were not aware as to order to treatment group assignment (Cochrane Grade A)

Kemp 1997

Methods	Design: randomised, partially-blinded, double-dummy, 3-way crossover study Device: Rotahaler Drug: salbutamol Dose: RH: 200 ug & pMDI: 180 ug Duration: 300 minutes
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Kemp 1997 (Continued)

Participants	12 (6 females) mild to moderate asthma patients, mean age 23.5 (SD 8.1), range 12-36 with FEV1% predicted 71.1% (SD 5.7). Baseline FEV1 could not vary more than 12% on any study day. FEV1 reversibility of >20% at 20 minutes after 2 puffs of Ventolin via pMDI.
Interventions	Each patient was given 2 inhalations of 90 ug/inhalation of salbutamol from pMDI and on another day 2 inhalation of 100 ug/inhalation from a Rotahaler. Study measurements were done 15 to 300 minutes post each single dose. Washout between 3 to 8 days.
Outcomes	FEV1max, FEV1, FVC, FEF25-75%, PEFR, Serum potassium, AUC, duration, onset, blood glucose, ECG, tremor, side effects
Notes	FEV1 (SD) abstracted from graph.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Kiviranta 1985

Methods	Design: randomised, double-blinded, double-dummy, crossover study. Device: Rotahaler Drug: fenoterol Dose: 0.2-0.4 mg 2 to 4 times daily. Duration: 4 weeks
Participants	20 adults (11 women), mean age 35, range 18-57, mean asthma duration 11 years (range 1-43). 9 patients were mild, moderate in 10 and one was severe. Mean PEFR was 430 L/min (SD 109) with >15% increase after bronchodilator.
Interventions	Run-in period lasted for a week than the patients were randomised to either receive fenoterol by RH or pMDI for another 2 weeks.
Outcomes	Diary of symptoms, PEFR 30 min post-dose,
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Kleerup 1996

Methods	Design: randomised, single-blinded, 2-way crossover study Device: HFA-134a pMDI Drug: salbutamol Dose: total dose 1440 ug (90 x 16) Duration: 150 minutes (30 min x 5)
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Kleerup 1996 (Continued)

Participants	24 adults (5 women), mean age 35.4 (SD 11.7), range 18-57 yrs with stable asthma for at least 12 months. Mean % predicted FEV1 was 68.2% (SD 10.9). Mean FEV1 reversibility after inhalation of 2 puffs of salbutamol from pMDI was 30.8% (SD 10.9). Baseline FEV1 was not allowed to vary greater than 15% between study days.
Interventions	Subjects received 1, 1, 2, 4 & 8 (18 total) inhalations from each device at 30 min intervals. Study measurements were made following each cumulative dose. Washout was between 24 hrs to 8 days.
Outcomes	HR, BP, serum potassium, spirometry. Results after last cumulative dose entered into RevMan.
Notes	Block randomisation in groups of 8 used for treatment allocation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Kou 1998

Methods	Design: randomised, double-blinded, double-dummy, crossover study Device: Diskhaler Drug: salbutamol Dose: 200 ug (both devices) Duration: 10-15 minutes post dose
Participants	12 Chinese patients (8 females), age range 2-60 yrs, with PEFR or FEV1 reversibility >15% after salbutamol challenge.
Interventions	Patients inhaled 200 ug of salbutamol from either a Diskhaler or pMDI. Study measurements were done 10-15 minutes post-dose from each device.
Outcomes	PEFR, side effects.
Notes	Treatment allocation according to balanced Latin-square and randomised protocol.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Laberge 1994

Methods	Design: randomised double-blind double-dummy crossover study. Device: Turbuhaler vs pMDI + Nebuhaler Drug: terbutaline Dose: total dose of 2.0 mg within 80 min than 20 minutes later followed by 5lmg of nebulised salbutamol.
Participants	10 children, age range 3-6lyrs, mean age 4.6lyrs. All patients had reversibility of >30% in airway resistance after inhalation of 2.5lmg nebulised salbutamol.

Laberge 1994 (Continued)

Interventions	Lung function measured 15 min after each dose of medication.
Outcomes	HR, BP, tremor and airways resistance. Raw (SD) obtained from graph.
Notes	Authors reply on allocation concealment, used random numbers table for allocation of treatment.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Study investigators were not aware as to order to treatment group assignment (Cochrane Grade A)

Langley 1998a

Methods	Design: randomised double-blind double-dummy crossover study Device: HFA 134a pMDI Drug: salbutamol Dose: single dosing study: 100ug Duration: 6 hours
Participants	63 adults patients, age range 13-63, mean age 36. FEV1 between 50-85% predicted and $\geq 15\%$ increase in FEV1 after 200 ug salbutamol.
Interventions	Single doses of 100 or 200 ug salbutamol administered through HFA-134a pMDI or standard pMDI. Washout: not reported.
Outcomes	FEV1 measured prior to dosing and at intervals until 6 hours post dosing. Mean over 6 hours reported for peak FEV1 and AUC-FEV1.
Notes	Study published only and an abstract in journal.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Langley 1998b

Methods	Design: randomised double-blind double-dummy crossover study Device: HFA 134a pMDI Drug: salbutamol Dose: single dosing study: 200 ug Duration: 6 hours
Participants	63 adults patients, age range 13-63, mean age 36. FEV1 between 50-85% predicted and $\geq 15\%$ increase in FEV1 after 200 ug salbutamol.
Interventions	Single doses of 100 or 200 ug salbutamol administered through HFA-134a pMDI or standard pMDI. Washout: not reported.

Langley 1998b (Continued)

Outcomes	FEV1 measured prior to dosing and at intervals until 6 hours post dosing. Mean over 6 hours reported for peak FEV1 and AUC-FEV1.	
Notes	Study published only and an abstract in journal.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Latimer 1982

Methods	Design: randomised, double-blind, double-dummy crossover study. Device: Rotahaler Drug: salbutamol Dose: 200 ug Duration: 4 hours	
Participants	10 adult patients (5 women) mean age 59.5, range 32 to 74. FEV1 reversibility >=20% 15 minutes after inhaling 200ug salbutamol from pMDI. Baseline FEV1 could not vary by >10% on between study days if it did visit was rescheduled.	
Interventions	Patients were given study medication from the inhaler devices and study measurements were done every 15 minutes for the first hour that every 30 min for 4 hours.	
Outcomes	FEV1, VC, AUC, pulse, blood pressure, tremor.	
Notes	Block design was used for randomisation and treatment allocation.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Löfdahl 1997

Methods	Two trials were included in study but only study 1 used in RevMan as it had the same doses in both devices. Design: randomised, double-blind, double-dummy crossover study. Device: Turbuhaler Drug: salbutamol Dose: 200 ug Duration: 6 hours	
Participants	12 adults patients (5 women), mean age 50, range 24-68. All patients had asthma duration of 10 yrs (range 3-24). Three current smokers, 6 former and 3 never smoked. Mean % predicted FEV1 was 71% (range 46-109), mean FEV1 reversibility was 24% (range 15-40) 15 minutes after inhalation of 200 ug of salbutamol from pMDI. Between study days baseline FEV1 was not allowed to vary by more than 15%, if it did the visit was rescheduled.	

Löfdahl 1997 (Continued)

Interventions	Patients were given salbutamol on separated days from the Turbuhaler at 50, 100 & 200 ug and the pMDI dose was 2x100 ug, therefore the 200 ug dose data was used. Study measurements were done before and 20 minutes to 6 hours post-dose.	
Outcomes	FEV1, FVC, adverse effects, tremor, serum potassium, ECG.	
Notes	Author reply: all requested data provided, allocation concealment was blind and used Latin-square for randomisation method.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Study investigators were not aware as to order to treatment group assignment (Cochrane Grade A)

Maesen 1986

Methods	Design: randomised, double-blind, double-dummy crossover study. Device: Aerohaler Drug: ipratropium bromide Dose: 40ug Duration: 360 minutes	
Participants	20 adult patients (6 women), mean age 46.7 (SD 16.7), age range 21 to 60 and all had an initial FEV1 of at least 1L to <=70% predicted. All patients had stable asthma and on study days baseline FEV1 could not vary by 15%. All patients showed FEV1 reversibility of >=15% after 40 ug ipratropium bromide 60 minutes after inhalation.	
Interventions	All patients received either study drug from the MDI or Aerohaler. Study measurements were performed 5 min before and 15, 30, 60, 120, 180, 300 and 360 post-dose and 15 minutes after additional fenoterol. At the end of each study day and 6 hours post-dose each patient received 400ug of fenoterol via the pMDI, this data was not included in RevMan.	
Outcomes	FEV1, FVC, PEF, FEF25, FEF50, FEF75, FEF25-75.	
Notes	Study included but no data used from the trial into the review as data is in non-extractable form. No reply from author to date. Also note that study used ipratropium bromide.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Mathieu 1992

Methods	Different doses in devices and study also used methacholine challenge. Design: open-labelled, randomised parallel, age stratified study Different doses and methacholine challenge used in study. Device: Diskhaler Drug: salbutamol Dose: pMDI: 200 ug & DH: 400 ug	
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Mathieu 1992 (Continued)

Duration: 30 minutes

Participants	12 adults (6 women) with stable asthma who met the ATS criteria for asthma were recruited. All had baseline FEV1 $\geq$ 80% predicted.
Interventions	Each subject inhaled methacholine aerosol, in progressively doubled concentrations until FEV1 decreased by 20% or more. Then each patient inhaled either 200 ug salbutamol from the pMDI or 400 ug from the Diskhaler. Washout at least 24 hours but $<$ 1 week.
Outcomes	FEV1, FVC, FRC, measured continuously for 30 minutes.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Mellen 1999

Methods	Design: randomised, double-blinded, double-dummy, crossover study Device: Turbuhaler Drug: salbutamol Dose: total dose 3,200 ug (both devices) Duration: 180 minutes (6 x 30 min)
Participants	24 adult patients (11 women), mean age 48 (range 21-68). Seven ex-smokers, 2 current smokers. FEV1 reversibility over baseline was $\geq$ 15% 15 minutes post-dose.
Interventions	Each patient received salbutamol in a cumulative fashion at 30 minutes intervals. The doses were 200, 200, 400, 800 and 1600ug. The nominal dose per actuation was 100ug from both devices. Study measurements were made 20-25 minutes post study each cumulative study dose. Washout was 2 to 10 days.
Outcomes	FEV1, serum potassium, AUC, HR, BP. Results after last cumulative dose entered into RevMan.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Morice 1996

Methods	Design: randomised, double-blinded, double-dummy, crossover study Device: DPI of undefined type Drug: salbutamol Dose: total dose 400 ug Duration: 240 minutes post dose
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Morice 1996 (Continued)

Participants	62 adult patients with >15% and ≥200 ml reversibility in FEV1.
Interventions	Two trials were done short-term 240 min post-dose and a long-term 4 week study. Only the short-term study provided enough data to be included into RevMan. Salbutamol was administered to each patients as 100, 100 & 200 ug than lung function measured until 240 minutes.
Outcomes	FEV1, FVC. Results after last cumulative dose entered into RevMan.
Notes	FEV1 (SD) obtained from published graphs.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Nelson 1999

Methods	Design: randomised, double-blind, double-dummy, parallel study. Device: Spiros Drug: salbutamol Dose: 2 puffs four times daily from each device (Spiros: 108 ug/puff & pMDI:90 ug/puff) Duration: 12 weeks
Participants	283 adult patients were enrolled, 240 completed the study. 97 Spiros group, 92 in pMDI group & 94 in placebo group. Females 60 in Spiros and 45 in pMDI. Mean age 34.2 & 34.6 (SD 13.4 & 15.4). Mean FEV1 %predicted was 64 (SD 11.4) & 64 (SD 10.3). mean FEV1 reversibility was 20.7 (SD 7.4) & 19.9 (SD 8.0).
Interventions	Two puffs four time daily from each inhaler device for 12 weeks. Schedule visits at weeks 4, 8 & 12 for assessment. End of week 12 study treatment administered and FEV1 measured for 360 minutes (no SD reported).
Outcomes	FEV1, PEFr, exacerbations, beta-2 use, symptoms, adverse effects, treatment failures.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Newhouse 1999

Methods	Design: randomised, double-blinded, double-dummy, 5-way crossover study Device: Clickhaler Drug: salbutamol Dose: 200 ug (both devices) Duration: 240 minutes post dose
Participants	16 adult patients (mean age 57.3 SD 18 yrs, 4 women) with stable asthma enrolled over 12 months, who had resting FEV1 of 40 to 80% predicted and a minimum of 15% increase in FEV1 after 200 ug salbuta-

Newhouse 1999 (Continued)

mol using a pMDI. Mean % predicted FEV1 was 60 (SD 9) and mean FEV1 increase after salbutamol was 25 (SD 9.33). Variation of FEV1 on study days was not allowed to be >15%.

Interventions	Salbutamol 200 ug was administered from either device and study measurements were done from 15 to 240 minutes post-dose.
Outcomes	FEV1, FVC, MEF, FEF25-75, respiratory rate, pulse rate, tremor, blood pressure
Notes	Data reported at various flow volumes but used comparable data for both devices when the flow rate was the same (30 L/min).

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Newman 1993

Methods	Design: randomised, crossover study Device: Gentlehaler Drug: salbutamol Dose: 100 ug radio-labelled (both devices) Duration: 60 minute
Participants	10 adult patients (3 women), age range 24-78, mean % predicted FEV1 52 (range 20-97). FEV1 reversibility was >15% after 200 ug of salbutamol from a pMDI. Baseline FEV1 could not vary by more than 15% on study days.
Interventions	Each patient inhaled 100 ug labelled salbutamol from each device and a gamma X-ray was taken, than 15, 30 and 60 minutes spirometry was done. Data for measurements at 15 minutes were used in Revman (as it was the first point of measure post-dose). Washout >48 hours.
Outcomes	FEV1, FVC, MMFR, lung deposition, PEFr.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Nieminen 1994

Methods	Design: randomised, double-blind, crossover study Device: Easyhaler Drug: salbutamol Dose: Easyhaler: 180 ug & pMDI: 200 ug Duration: 360 minutes
Participants	21 adult patients (11 women) with stable asthma, mean age 51 (range 20-73), mean asthma duration 16 years. Mean % predicted FEV1 was 64 (range 29-97). 5 patients had mild asthma, 9 moderate and 5

Nieminen 1994 (Continued)

severe. All patients showed >15% increase in baseline FEV1. Variation in FEV1 was not allowed to be greater than 15% on study days, if it was the visit was rescheduled.

Interventions	Each patient received salbutamol from either device. Two inhalations were received from the pMDI (total 200 ug) and one from the Easyhaler (180 ug). Study measurements were done from 15 to 360 minutes post-dose.
Outcomes	FEV1, FVC, BP, HR, PEFr, AUC,
Notes	Author reply: all requested data provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Study investigators were not aware as to order to treatment group assignment (Cochrane Grade A)

O'Callaghan 1997

Methods	Design: 2-way crossover design study Device: Clickhaler Drug: salbutamol Dose: 100 ug Duration: 2 hours
Participants	85 children, mean age 11.4 (SD 2.9) with mild-moderate asthma were recruited, all patients had reversibility of FEV1 of >15% to beta-2 agonist.
Interventions	Two trials were included in study but only used data from the short-term study as the 4 week study was open, and non-comparative.
Outcomes	FEV1, FVC, PEFr.
Notes	Study included but no data used from the trial into the review as data is in non-extractable form. No reply from author to date.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Osterman 1989

Methods	Design: open-labelled, randomised, crossover, study Device: Turbuhaler Drug: terbutaline Dose: 100ug per actuation Duration: 4 weeks
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Osterman 1989 (Continued)

Participants	23 adults with stable asthma with FEV1 reversibility of >15% after inhalation of terbutaline (or equivalent medication) were recruited but 19 (15 women) completed the study. Mean age 46 (range 20-66 yrs) and mean duration of asthma was 17 yrs (range 2-35). Basal FEV1 was >1L.
Interventions	Two treatment periods each lasting 2 weeks during which patients inhaled 0.5mg terbutaline four times daily from either device. Extra inhalation were permitted but patients were required to record this on the diary card. Patients recorded their PEFR at home 15 minutes post-dose.
Outcomes	PEFR, adverse effects, treatment failures, preference.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Osterman 1991

Methods	Design: open-labelled, randomised parallel study Device: Turbuhaler Drug: terbutaline Dose: 0.5 mg four times daily Duration: 6 weeks
Participants	258 patients recruited, 117 in Turbuhaler group and 81 in pMDI group. 160 in Turbuhaler group and 77 in pMDI group completed the study. Mean age 47-48 (range 17-77), mean duration of asthma 15-16 yrs (range 1-60), mean FEV1 reversibility 26-27% (range 15-79).
Interventions	Run-in period of 2 weeks followed by 6 weeks of treatment with either device. pMDI was 2 x 0.25 mg qid and Turbuhaler 1 x 0.50 mg qid. Extra inhalation were allowed but patients had to record usage in diary cards along with other study measurements.
Outcomes	Symptoms (4 point scale), PEFR, additional beta-2 usage, treatment failures,
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Parameswaran 1999

Methods	Study used methacholine challenge Design: randomised, double-blind, double-dummy, crossover study Device: HFA-pMDI Drug: salbutamol Dose: 100, 200 & 400 ug Duration: until PC20 reached
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Parameswaran 1999 (Continued)

Participants	18 adult (11 women) patients with baseline FEV1 % predicted of 92%, mean age 31 (range 19-53 yrs). FEV1 was not allowed to vary by more than 10% on study days.
Interventions	Baseline PC20 was determined after 200 ug salbutamol from the pMDI. On study days patients were given either 100, 200 or 400 ug salbutamol from either device and methacholine challenge started 10 min later until PC20 was reached. Five minutes after inhalation HR and BP were measured. Adverse effects to methacholine was measured using a 3 point Likert scale.
Outcomes	PC20, FEV1, BP, HR, respiratory rate.
Notes	Treatment allocation sequence was determined by 8 x 8 Latin square.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Study investigators were not aware as to order to treatment group assignment (Cochrane Grade A)

Persson 1988

Methods	Design: open-labelled, randomised, crossover study Device: Turbuhaler Drug: terbutaline Dose: total dose 4 mg Duration: 150 min (5 x 30 min)
Participants	13 adult patients (7 women), mean age 39 (range 20-59) with stable asthma and >20% increase in FEV1 and an absolute FEV1 >70% of predicted after inhalation of 0.50 mg terbutaline via pMDI. Baseline FEV1 was not allowed to vary by more than 15% between study days.
Interventions	Each patient received cumulative doses of terbutaline every 30 min (0.25, 0.25, 0.5, 1.0 & 2.0) from either device. Study measurements were done 20-25 min after each cumulative dose.
Outcomes	FEV1, tremor, AUC, FVC, PIFR, FIVC. Results after last cumulative dose entered into RevMan.
Notes	Author reply randomised in blocks of 4. FEV1 (SD) abstracted from graph.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Pover 1988

Methods	Different doses used in devices. Design: randomised, double-blind, double-dummy, crossover study Device: Diskhaler Drug: salbutamol Dose: DH: 400 ug & pMDI: 200 ug Duration: 240 minutes
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Pover 1988 (Continued)

Participants	42 adult patients (26 women), age range 16-75 yrs. All patients had FEV1 reversibility of >15% following 200 ug salbutamol. Patients whose baseline FEV1 was <0.5 L were excluded. Baseline FEV1 on study days could not vary by more than 10%.
Interventions	Each patient received either 400 ug salbutamol from the Diskhaler or 200 ug from the pMDI and FEV1 measurements were done from 5 to 240 min post-dose. The 30 min time point data was entered into RevMan.
Outcomes	FEV1, AUC
Notes	FEV1 (SD) abstracted from graph.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Ramsdell 1998

Methods	Design: randomised, single-blinded, 2-way crossover study Device: HFA-134a pMDI Drug: salbutamol Dose: total dose 1440 ug Duration: 120 minutes
Participants	22 adult patients, mean age 32.8 (SD 11.9), with at least 12 month history of asthma and FEV1 between 40-80% predicted and FEV1 reversibility of >15% 30 min after inhaling 2 inhalations of pirbuterol acetate via Maxair. FEV1 was required to be between 35%-85% predicted between each study days and not vary by >15% from baseline.
Interventions	Patients self-administered (under supervision) the study treatments at 30 minute intervals. After each cumulative dose study measurements were performed. Washout 48 hrs to 8 days.
Outcomes	FEV1, ECG, serum potassium, HR, blood pressure. Results after last cumulative dose entered into RevMan.
Notes	SD's, FEV1, HR, serum potassium and BP abstracted from graphs.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Ramsdell 1999a

Methods	Design: open-labelled, randomised, double-blind, double-dummy parallel study Device: HFA-134a pMDI Drug: salbutamol Dose: two puffs bd (strength or dose/puff not mentioned) Duration: 12 months
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Ramsdell 1999a (Continued)

Study A and B data provided separately from author regarding oral steroid requirement and treatment failure (therefore reported as two separate studies a & b and for all other outcomes data was referenced as Ramsdell 1999a if combined results were only obtained (where N-HFA=337, N-CFC=132).

Participants	469 adult stable asthma patients (337-HFA & 132-CFC), mean age 34 (SD 14), 100 women both groups, % predicted FEV1 69 (SD 18) in HFA group and 66 (SD 17) in CFC group. Severity: mild 30 in HFA & 26 in CFC, moderate 41 in HFA & 42 in CFC, severe 29 in HFA & 33 in CFC group. FEV1 reversibility was $\geq 15\%$ within 30 minutes of using a short-acting beta agonist.
Interventions	Patients inhaled two puffs twice a day for 12 months from either device and additional puffs were allowed if required. Clinic visit for study measurements were done at 0, 3, 6, 9 & 12 months. At each clinic visit patients self administered two puffs of the study drugs and study measurements were done up to 6 hours post-dose.
Outcomes	FEV1, adverse effects, treatment failure, exacerbations, oral steroid requirement (reported separately as Study A and B), AUC, duration, onset. Data from two studies were combined. Study A patients were recruited and continued from a previously conducted 12 week study and Study B which was a new 12 month study. All three studies (12 week, Study A & B) were randomised double-blind, double-dummy, and parallel in design.
Notes	Reply from 3M (UK) on steroid requirement for study A. Allocation of treatment was randomised and randomisation was done in blocks of 12, with two patients receiving HFA-pMDI for every one receiving CFC-pMDI. 11/05/01: Further replies from author regarding separate data on treatment failure and steroid requirement for study A.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Study investigators were not aware as to order to treatment group assignment (Cochrane Grade A)

Ramsdell 1999b

Methods	Design: open-labelled, randomised, double-blind, double-dummy parallel study Device: HFA-134a pMDI Drug: salbutamol Dose: two puffs bd (strength or dose/puff not mentioned) Duration: 12 months Study A and B data provided separately from author regarding oral steroid requirement and treatment failure (therefore reported as two separate studies a & b and for all other outcomes data was referenced as Ramsdell 1999a if combined results were only obtained (where N-HFA=337, N-CFC=132).
Participants	469 adult stable asthma patients (337-HFA & 132-CFC), mean age 34 (SD 14), 100 women both groups, % predicted FEV1 69 (SD 18) in HFA group and 66 (SD 17) in CFC group. Severity: mild 30 in HFA & 26 in CFC, moderate 41 in HFA & 42 in CFC, severe 29 in HFA & 33 in CFC group. FEV1 reversibility was $\geq 15\%$ within 30 minutes of using a short-acting beta agonist.
Interventions	Patients inhaled two puffs twice a day for 12 months from either device and additional puffs were allowed if required. Clinic visit for study measurements were done at 0, 3, 6, 9 & 12 months. At each clinic visit patients self administered two puffs of the study drugs and study measurements were done up to 6 hours post-dose.
Outcomes	FEV1, adverse effects, treatment failure, exacerbations, oral steroid requirement (reported separately as Study A and B), AUC, duration, onset. Data from two studies were combined. Study A patients were recruited and continued from a previously conducted 12 week study and Study B which was a new 12

Ramsdell 1999b (Continued)

month study. All three studies (12 week , Study A & B) were randomised double-blind, double-dummy, and parallel in design.

Notes	Reply from 3M (UK) on steroid requirement for study B. Allocation of treatment was randomised and randomisation was done in blocks of 12, with two patients receiving HFA-pMDI for every one receiving CFC-pMDI. 12/02/2001: Further replies from author regarding separate data on treatment failure for study B.
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Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Study investigators were not aware as to order to treatment group assignment (Cochrane Grade A)

Razzouk 1999

Methods	Design: randomised double-blind double-dummy 4-way crossover study. Device: Turbuhaler Drug: salbutamol Dose: 100 ug (both devices) Duration: 240 min
Participants	40 children, (9 F), age range 6-12, mean age 9. Mean duration of asthma 7 yrs (range 2-12), mean FEV1 % predicted 30 min after inhaling 200 ug salbutamol from a pMDI was 80% (range 61-109), mean FEV1 reversibility 20 (range 9-45)
Interventions	Study performed in 2 centers in France and 5 centers in Portugal. 37 patients received 50 ug via TH, 37 received 100 ug via TH, 38 received 100 ug via pMDI and 40 patients received placebo. Pulmonary function testing was performed from 15-240 min post-dose. Washout was >20 hours and <14 days.
Outcomes	FEV1, FEV1 max, adverse effects but not separated by group.
Notes	Author reply used sealed envelopes for allocation concealment.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Study investigators were not aware as to order to treatment group assignment (Cochrane Grade A)

Ruffin 1995

Methods	Design: randomised, single-blinded, 4-way crossover study. Device: HFA-134a pMDI Drug: salbutamol Dose: total dose 1920 ug (16 x 120 ug salbutamol sulphate) Duration: 150 minutes (5 x 30 min)
Participants	24 adults patients (16 women), mean age 40 (SD 12.4), mean % predicted FEV1 was 65 (SD 13.6), mean FEV1 reversibility 28.8 (SD 10.4) after 240 ug salbutamol.

Ruffin 1995 (Continued)

Interventions	All patients inhaled cumulative doses of salbutamol from each device as 1, 1, 2, 4 & 8 puffs every 30 minutes. Washout was 1 to 8 days.
Outcomes	FEV1, FVC, serum potassium, pulse rate, blood pressure. Results after last cumulative dose entered into RevMan.
Notes	Email and fax replies from author on allocation concealment, treatment generated before start of study and used codes for canisters.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Study investigators were not aware as to order to treatment group assignment (Cochrane Grade A)

Salat 2000

Methods	Design: randomised, double-blind parallel study. Device: HFA-134a pMDI Drug: salbutamol Dose: total dose 800ug/day (4 x 200 ug salbutamol) Duration: 12 weeks
Participants	547 adults patients (324F;223M), mean age 42-44, mean baseline FEV1 was 2.5 & 2.4 (SD 0.78). 277 in HFA group and 270 in CFC-pMDI group. Percentage predicted FEV1 was between 50-100% and reversibility in FEV1 of >15%, smoking history <20 pack years.
Interventions	All patients had a 4 week run-in period when their usual short-acting bronchodilator was replaced with salbutamol 200ug qid delivered by CFC-pMDI. At the end of this run-in period patients were randomised to receive qid salbutamol 200ug from the CFC-pMDI or HFA-pMDI for 12 weeks. This was followed by a 4 week run-out period with the same treatment as in the run-in period. Patients measured their PEFR and recorded it on a diary card plus their symptoms and use of rescue salbutamol.
Outcomes	FEV1, HR, adverse events, serum potassium, PEFR (am, pm), symptoms, rescue salbutamol usage, ECG. For FEV1 and PEFR used N from Table 2 as both outcomes were done at the same time during the trial. For serum potassium we estimated the SD from the 90%CI using: CI = mean +/- 2.58 x SE, and solving for SE than converting to SD using: SD = SE x square root of n-1.
Notes	Statistical analysis was performed on all patients who had received at least one dose of study medication (intent-to-treat analysis).

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Salorinne 1983

Methods	Design: randomised, double-blind, double-dummy crossover study Device: Rotahaler Drug: fenoterol Dose: 0.2 mg
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Salorinne 1983 (Continued)

Duration: 360 minutes

Participants	10 adults patients (3 women) with moderate to severe asthma, mean age 49 (range 19-70), mean FEV1 % predicted 51 (range 32-78), FEV1 reversibility was >15% after 0.4mg rimiterol.
Interventions	Patients inhaled single doses of 0.2 mg fenoterol from either device and study measurements were done from 10 to 360 minutes post-dose. Washout at least 24 hours.
Outcomes	FEV1, PEFR, FVC, MEF50, AUC.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Selroos 1994

Methods	Different dose used in devices. Design: randomised, double-blinded, double-dummy crossover (re: author reply) study Device: Turbuhaler vs pMDI + 750 ml Nebuhaler spacer Drug: terbutaline Dose: TH: 1 mg vs pMDI: 1mg Duration: 15 minutes post-dose
Participants	15 adult patients (10 women) were selected who showed <10% improvement in FEV1 after 0.4 mg salbutamol or 1mg terbutaline. Mean age 45.9 (SD 13.7).
Interventions	Patients received terbutaline from either device on separate days and study measurements were done 15 minutes post-dose.
Outcomes	FEV1.
Notes	Author reply: randomisation was done in block of 4 and the study was of crossover design.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Seppala 1998b

Methods	Design: randomised, double-blind, double-dummy crossover study Device: MDPI vs pMDI + 270 ml spacer Drug: salbutamol Dose: 100 ug (both devices) Duration: 360 minutes
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Seppala 1998b (Continued)

Different type of device to that used by Geoffroy et al. 1999 as this is a more rounder device, see picture in published paper. The device used by Geoffroy et al study was shaped like the diskhaler.

Participants	41 non-smoking adult patients (17 women) with stable asthma, mean age 43.6 (SD 14.9, range 20-69), mean FEV1 % predicted 58.1 (SD 9.9, range 35-70) and mean FEV1 reversibility was 39.2 (SD 18.9) 20 minutes after 200 ug of salbutamol from a pMDI.
Interventions	Patients inhaled study drugs from either device and study measurements were done from 10 to 360 min post-dose. Washout was >24 hours.
Outcomes	FEV1, Raw, blood pressure, HR, AUC, adverse effects, preference.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Seppala1998a

Methods	Study used methacholine challenge. Design: randomised, double-blind, double-dummy crossover study Device: MDPI vs pMDI + volumatic spacer Drug: salbutamol Dose: 100 ug Duration: until PD20-FEV1 was reached
Participants	26 adult patients (20 women), mean age 43.3 (SD 13.9, range 19-64) and FEV1 % predicted was 79.9% (SD 11.2, range 60-100). Baseline FEV1 on each study day had to be between 60 to 90% predicted.
Interventions	Patients were given 100ug salbutamol from either device and 30 minutes later methacholine challenge was started in cumulative doses every 5 minutes (18, 36, 71, 110, 180, 360, 530, 890, 1600 & 2300ug) and FEV1 was measured every 3-4 minutes after each dose. Methacholine challenge continued until FEV1 decreased by 20% compared to baseline (PD20-FEV1). Washout was >24 hours but < 2 weeks.
Outcomes	FEV1, blood pressure, HR, ECG, adverse effects, PD20-FEV1.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Silvasti 1993

Methods	Design: randomised, double-blind, double-dummy, crossover study Device: Easyhaler Drug: salbutamol
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Silvasti 1993 (Continued)

Dose: 180 ug (both devices)
Duration: 360 minutes

Participants	23 adult patients (8 women), mean age 49.3 (SD 13.1), mean duration of asthma 12 yrs (SD 14.6), severity: mild 4, moderate 9, severe 2 & very severe 3. All patients showed $\geq 15\%$ in FEV1 after inhalation of 200ug of salbutamol. Variation of $< 15\%$ on study days in FEV1 was required, if variation was greater visit was rescheduled.
Interventions	A single dose of 180ug salbutamol was delivered to all patients from either device on separate days and study measurements were done until 360 min post-dose. 30 minute data points entered into RevMan. Washout between study days was one week.
Outcomes	PEFR, FVC, FEV1, AUC-Raw, Tmax, FEV1max, adverse effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Svedmyr 1982

Methods	Design: open-labelled, randomised, crossover study Device: Rotahaler Drug: salbutamol Dose: total dose 4.2 mg Duration: 150 minutes (5 x 30 min)
Participants	7 adult patients (2 women) with asthma, mean age 51.29 (SD 11.94), mean duration of asthma 11.14 yrs (SD 10.16). All patients showed FEV1 reversibility to 1.25 mg terbutaline of between 20-50%.
Interventions	Starting dose for both the devices was not the same as the pMDI had a initial dose of 100 ug and none for the Rotahaler until pMDI 200 than Rotahaler 200 etc, until 4.2 mg.
Outcomes	FEV1, FVC, HR. Results after last cumulative dose entered into RevMan.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Svenonius 1994

Methods	Exercise challenge used in study. Design: randomised double-blind double-dummy crossover study. Device: Turbuhaler Drug: terbutaline Dose: 1mg (both devices)
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Svenonius 1994 (Continued)

Duration: 15 min post-dose

Participants	12 children (2F), mean age 13.8 (range 9-17) and mean duration of asthma was 12 yrs (range 8-15). Patients were selected if FEV1 decreased by $\geq 15\%$ after a 6 min exercise test. This fall in FEV1 could not vary by more than 5% on study days.
Interventions	Lung function measured before exercise on treadmill than given the drug and measured again up from 4 to 15 min post-dose to observe reversibility of EIA. Terbutaline dose per puffs was 0.5 mg for Turbuhaler and 0.25 for pMDI. 15 min data point was used in RevMan.
Outcomes	FEV1 and VTG.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Taggart 1995

Methods	Design: double-blind, double-dummy, crossover study (not mentioned if randomised but implied in paper). Device: HFA-pMDI + volumatic spacer vs pMDI + volumatic spacer Drug: salbutamol Dose: 200 ug (100 x 2 from both devices) Duration: 30 min post-dose
Participants	24 non-smoking adult patients (14 women), mean age 37. Baseline FEV1 was allowed to vary by more than 15%.
Interventions	Patients were given two puffs of from either device using a volumatic spacer lung function measurements were done 30 minutes later and histamine challenge was started. Only used data at 30 min post-dose (pre histamine challenge) in RevMan. Washout < 24 hours < 7 days.
Outcomes	FEV1, FVC.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Tammivaara 1997

Methods	Design: open-labelled, randomised parallel study Device: MDPI Drug: salbutamol Dose: 200ug twice daily
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Tammivaara 1997 (Continued)

Duration: 12 weeks

Participants	115 adults patients (70 women), who showed an improvement in FEV1 or PEFr of >15% after inhalation of 200ug salbutamol. 2 patients were excluded therefore analysis was based on 113 patients (MDPI=77 & pMDI=36, mean age 49 (SD 13) & 49 (SD 14), mean duration of asthma 8.4 (SD 8.6) & 9.4 (SD 9.9) and % predicted FEV1 82.5 (SD 18.2) & 74.4 (SD 20.8).
Interventions	There was a run-in period of 2 weeks followed by 12 weeks of treatment period. Two puffs twice daily was delivered from each device for 12 weeks (both devices were 100 ug/puff). Additional relieve medication was allowed with a second inhaler of the same tube in each group. Study measurements were noted daily by patients. 30 min post-dose data was entered into RevMan but 15 min post-dose for PEFr.
Outcomes	PEFr, FVC, FEV1, treatment failures, preference, additional beta-2 use, adverse effects, symptoms
Notes	Author reply: treatment allocation was randomly done and computer generated codes.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Study investigators were not aware as to order to treatment group assignment (Cochrane Grade A)

Thompson 1995

Methods	Different dose was used in the devices. Design: randomised, single-blind, double-dummy, 4-way crossover study Device: HFA-134a pMDI Drug: salbutamol Dose: HFA: 8 puffs vs pMDI: 16 puffs (strength/dose not specified) Duration: 150 minutes (5 x 30 min)
Participants	24 adult patients, aged 18-65 yrs with at least 12 month history of asthma. All patients had FEV1 reversibility of >15%.
Interventions	During study days patients received consecutive doses of 1, 1, 2, 4, & 8 inhalations of salbutamol from either device at 30 minutes intervals. Washout was between 1 to 8 days between study days.
Outcomes	FEV1, FEF25-75.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Tukiainen 1985

Methods	Different doses used in devices. Design: randomised, double-blind, double-dummy crossover study Device: Rotahaler Drug: salbutamol
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Tukiainen 1985 (Continued)

Dose: RH: 400 ug vs pMDI: 200 ug
Duration: 120 minutes

Participants	22 adult hospital-in patients with stabilised asthma, mean age 63, 19 women. All patients were admitted to hospital for worsening asthma and when stabilised were included in the study.
Interventions	On consecutive mornings the patients inhaled two puffs from the pMDI (100 ug/puff) followed 2 minutes later by one capsule from the Rotahaler (400 ug/capsule). Study measurements were done before and 5, 15, 30, 60 and 120 minutes post-dose. The 30 minute time point data was entered into RevMan. All drugs were inhaled at the same time each morning.
Outcomes	PEFR, blood pressure, heart rate.
Notes	PEFR and SD was extracted from the graph.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Vidgren 1995a

Methods	Design: randomised, double-blind, double-dummy, crossover study Device: Easyhaler Drug: salbutamol Dose: 100 ug (both devices) Duration: 240 minutes post-dose
Participants	40 adult patients, 15 women, with >15% improvement in FEV1 or PEFR after inhaling 0.2 mg salbutamol. Mean duration of asthma 9 yrs (range 1-33), mean baseline FEV1 58.8% predicted. Variation between study days in baseline FEV1 could not be >15%, if variation was greater than 15% visit was rescheduled.
Interventions	All patients received single doses of salbutamol at the same time on test days from either device and study measurements were done from 15 to 240 minutes post-dose.
Outcomes	Blood pressure, heart rate, FEV1, PEFR, AUC, FVC, preference, adverse effects.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Villiger 1990

Methods	Design: open-labelled, randomised, crossover study Device: Turbuhaler Drug: salbutamol Dose: 500 ug (both devices)
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Villiger 1990 (Continued)

Duration: 360 min

Participants	10 adult patients with stable asthma entered the study.
Interventions	All patients either received 1 puff (500 ug) from the Turbuhaler or 2 puffs (500 ug) from the pMDI. Study measurements were done from 15 to 360 minutes post-dose.
Outcomes	Side effects, FEV, VC.
Notes	Abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Waterhouse 1992

Methods	Design: randomised, double-blind, double-dummy, 2-way crossover study Device: Autohaler Drug: salbutamol Dose: 200ug (both devices) Duration: 240 min
Participants	25 adult hospital outpatients with stable asthma entered the study. All patients had FEV1 <75% predicted and an increase of >15% 50 minutes after 200ug salbutamol. Women were 6 in pMDI and 5 in Autohaler group, mean age was 60.5 (SD 9.6) & 51.3 (SD 13.3), FEV1 % predicted 40 (17) & 43 (15).
Interventions	Single dose of 200ug were administered from either device and study measurements done from 5 to 240 minutes post-dose.
Outcomes	FEV1, FVC, PEFR.
Notes	FEV1, FVC, PEFR and SD's extracted from graphs.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Zainudin 1990

Methods	Design: randomised, double-blind, double-dummy, 2-way crossover study Device: Rotahaler Drug: salbutamol Dose: 400 ug (both devices) Duration: 60 min
Participants	9 adult patients (6 women) aged 20-68, asthma duration 10-60 yrs, FEV1 improved by >15% after 200ug salbutamol via pMDI, mean baseline FEV1 was 55%.

Zainudin 1990 *(Continued)*

Interventions	All patients inhaled technetium labelled salbutamol, from either pMDI, Rotahaler or nebuliser and study measurements were done 60 minutes post-dose. Washout was >3 days.	
Outcomes	PEFR, FEV1, FVC, lung deposition using gamma camera.	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Agertoft 1994	Study used budesonide not a bronchodilator.
Avital 1995	Salbutamol vs placebo using pMDI with Babyhaler and facemask measured against methacholine-induced bronchoconstriction.
Battistini 1997	Comparison of autohaler vs MDI with either aerochamber, Babyhaler or volumatic spacer.
Becker 1985	Comparison of pMDI vs pMDI with a tube spacer
Biddiscombe 1993	Not a RCT. An in vivo study to test the in vitro 'Andersen MKII cascade impactor' method.
Bloomfield 1979	Comparison was with and without a tube spacer using pMDI.
Bollert 1997	Study did not use a beta-2 agonist but used ipratropium bromide.
Booth 1999	UK, National Research Register database but listed investigator has no knowledge of study and therefore not study details could be obtained.
Borgström 1993	Study used healthy volunteers.
Burgess 1993	Study on spacer comparisons. pMDI + 700 ml volumatic vs pMDI + 1500 ml plastic bottle.
Campbell 1995	Study in acute patients en route to hospital via ambulance.
Cavagni 1993	Comparison of MDI vs MDI with a jet disposable spacer
Chambers 1980	Study excluded as device (Italseber) is not a commonly known device. I was unable to obtain further details from the contact author and sponsor company.
Chhabra 1987	Bioavailability/bioequivalence comparison between two generic pMDIs.
Chipps 1992	MDI canister fitted with a gentle-haler (actuator) vs MDI with aerochamber spacer.
Cissik 1986	Study did not compare the same drug(s) with the same system of delivery.
Clark 1996	Study used healthy volunteers.

Study	Reason for exclusion
Cordero 1987	Spacer comparison using terbutaline MDI with or without an extension tube.
Crimi 1989	Comparison of MDI vs MDI with InspiRase spacer device. Study also used clenbuterol.
Cunningham 1994	Study of spacer effectiveness. pMDI vs pMDI with spacer.
Dawson 1985	Study compared a DPI against another (Rotahaler vs inhalator).
Deenstra 1988	Study comparison was a DPI vs DPI, no pMDI involved.
Donateo 1996	Comparison of MDI vs MDI with jet spacer.
Donnell 1995	Study carried out a comparison between propellants not between devices. HFA-placebo vs CFC-placebo vs HFA-salbutamol.
Dubus 1997	Comparison of five spacers with pMDI (aerochamber vs aeroscopic vs Babyhaler with a face mask vs Nebuhaler vs volumatic).
Fuglsang 1988	Spacer comparisons, pMDI versus pMDI with spacer versus pMDI with Nebuhaler versus placebo.
Fuller 1986	Spacer comparisons, pMDI versus pMDI with aerochamber versus pMDI with spacer.
Gioulekas 1996	No pMDI used, study compared turbuhaler versus Rotahaler.
Glaxo Wellcome SALB3	Poor quality response from company as to providing data, therefore study had to be excluded as no data could be obtained after repeated requests. .
Gomm 1980	Study of spacer effectiveness. pMDI vs pMDI with tube spacer.
Green 1991	Comparison was with and without a volumatic spacer using pMDI.
Gunawardena 1997	Study compared large volume spacer (volumatic) versus small volume spacer (Spacehaler) using pMDI.
Haahtela 1998	Comparison of two dry powder inhalers (DPI). Easyhaler vs Diskhaler.
Harrison 1996	Study did not use any bronchodilator drugs. It was a study of pMDIs containing CFC vs HFA-134a without any drugs inside canister.
Harvey 1992	Patient allocation not randomised and patients not clearly diagnosed as having asthma.
Haworth 1996	Not an RCT, but a retrospective analysis of written and computerised patient information.
Herer 1993	Study presented data as percentage of predicted value, the only study that presented data in a such a manner. Study was also only a published abstract and missing other relevant data.
Hidinger 1981	Study of spacer effectiveness. pMDI vs pMDI with tube spacer.
Hidinger 1984a	pMDI versus pMDI with collapsible spacer (750ml).
Hidinger 1984b	Study of spacer effectiveness. pMDI vs pMDI with 750ml spacer.
Hindle 1997	Study used healthy volunteers instead of patients with asthma.

Study	Reason for exclusion
Huchon 2000	Study used combination of two drugs in both devices (fenoterol hydrobromide 50ug and ipratropium bromide 20ug).
Jenkins 1995	Not a clinical trial but a review of trials.
Kaiser 1994	Not a RCT but an observational study also used pirbuterol acetate as the bronchodilator.
Kerac 1998	Comparison of MDI vs MDI with volumatic spacer vs MDI with bottle spacer.
Kishida 1993	MDI with or without spacer or extension tube.
Kraemer 1985	MDI with a 750ml volumatic spacer or 80ml spacer and vs nebuliser.
Kunkel 2000	Study used combination of two drugs (fenoterol and ipratropium bromide).
Lahdensuo 1986	Only partially randomised. The pMDI not randomised, all patients got pMDI on Day 1. DPI vs DPI (placebo) arm randomised.
Langaker 1982	pMDI versus pMDI with a tube extension.
Laurikainen 1997	DPI (Easyhaler) vs another DPI, no pMDI involved in the study.
Lee 1987	Three way spacer comparison. pMDI with InspiRase vs pMDI with aerochamber vs pMDI with aerosol bag.
Liljas 1997	Combined used of salbutamol and budesonide using MDI versus turbuhaler.
Lindsay 1994	Two different drugs compared. Terbutaline in Turbuhaler vs salbutamol in pMDI.
Lipworth 1997	Study employed healthy volunteers, not patients with asthma.
Lipworth 1999	Study employed healthy volunteers, not patients with asthma.
Mahadewsingh 1996	No pMDI used in study comparisons. Study used turbuhaler versus Diskhaler versus Rotahaler.
Malmstrom 1999	Easyhaler compared against a pMDI in children but the study was open and not randomised.
Morice 2000	Not a randomised controlled trial, design more suitable to cohort (both retrospective and prospective) study.
Mortensen 1991	Study on mucociliary clearance and all patients inhaled nebulised albumin labelled with technetium-99m and isotonic saline.
Muittari 1979	Not randomised, all patients got pMDI than they all got DPI.
Nelson 1994	Comparison of spacers (Optihaler and aerochamber) vs pMDI with spacer.
Newman 1998	Healthy volunteers used in study not patients with asthma.
Nimmo 1993	Study used 2 different drugs (albuterol & terbutaline) in 2 DPI's (Turbuhaler & Diskhaler) than retrospectively compared with patients previous use of MDI's.
O'Reilly 1986	Comparison of pMDI with or without a conical spacer.
Oliver 1982	Study of spacer effectiveness. pMDI vs pMDI with tube spacer.

Study	Reason for exclusion
Pauwels 1984	pMDI versus pMDI with a tube extension.
Pauwels 1996	Study used two different steroids and beta agonist with both the turbuhaler and pMDI Turbuhaler (budesonide & terbutaline) vs pMDI (short-acting beta-2 and beclomethasone dipropionate).
Pedersen 1983	Comparison of spacer versus no spacer using pMDI.
Pedersen 1985	Different drugs used in the two devices: Rotahaler (salbutamol) vs pMDI + tube spacer (terbutaline).
Rachelefsky 1986	Study of spacer effectiveness. pMDI vs pMDI with tube spacer.
Rivilin 1984	Study of spacer effectiveness. pMDI vs pMDI with 750 ml spacer and also vs nebuliser.
Rogers 1995	Not an RCT, but consensus statement from a workshop of the British Association for Lung Research.
Rymza 1998	Study compared the MAGhaler with patients usual device (and not specifically a pMDI).
Schecker 1993	Pirbuterol acetate (Maxair) used as the bronchodilator in Autohaler vs MDI, not one of drugs used in our search criteria.
Selroos 1996	Not an RCT, but a review of the comparative clinical studies where two or more delivery devices have been used.
Serra 1996	Different bronchodilators and dosage used in the two groups compared: salbutamol (Group A) vs terbutaline (Group B).
Sly 1988	Study of spacer effectiveness with the use of placebo. pMDI (salbutamol) with aerochamber vs pMDI (placebo) with aerochamber.
Stenius-Aarniala1993	Study of spacer effectiveness. Salbuvent vs volumatic vs Rondo spacer (new spacer).
Terzano 1996	In vitro study, which uses a device that, simulates human inspiratory patterns. Comparison between pMDI and Autohaler.
Vazquez-Aceves 1995	Comparison of pMDI with an aerochamber and another spacer device.
Vervloet 1994	Two different drugs used Maxair autohaler (pirbuterol) vs Ventodisks (salbutamol sulfate).
Vidgren 1990	Study used healthy volunteers and involved a dry powder inhaler (Chiesi) versus the Rotahaler.
Vidgren 1994	Deposition study comparing (99mTc-labelled salbutamol) Easyhaler vs pMDI, unblinded and not randomised.
Vidgren 1995b	Not a randomised controlled trial but a review on Easyhaler device.
Vilsvik 1991	Study used different drugs and doses with the inhaler devices. Turbuhaler (terbutaline 0.5 mg) vs MDI (salbutamol 0.2 mg).
Waterhouse 1993	Study used healthy volunteers instead of patients with asthma.
Waterhouse 1995	Study used healthy volunteers instead of patients with asthma.
Wong 1993	Not an RCT but a narrative review on clinical equivalence of generic inhaler devices.
Wong 1995	MDI vs MDI with 750ml spacer vs MDI with 1.5L bottle.

Study	Reason for exclusion
Wong 1998	Study was designed to observe the effect against methacholine bronchoconstriction.
Xuan 1989	Study of spacer effectiveness. pMDI vs pMDI with 750 ml spacer.

DATA AND ANALYSES

Comparison 1. Adults - Crossover design: Turbuhaler vs pMDI (mean absolute value)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 (L)	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Short term studies (min-hours)	3	76	Mean Difference (IV, Fixed, 95% CI)	0.19 [-0.30, 0.69]
1.2 Cumulative dosing studies	1	62	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.35, 0.45]
2 FVC (L)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Short term studies (min-hours)	1	24	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.84, 1.24]
2.2 Cumulative dosing studies	1	62	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.52, 0.58]
3 PEFR - Daily (L/min)	1	62	Mean Difference (IV, Fixed, 95% CI)	4.30 [-65.05, 73.65]
3.1 Cumulative dosing trials	1	62	Mean Difference (IV, Fixed, 95% CI)	4.30 [-65.05, 73.65]
4 PEFR (morning)	1	38	Mean Difference (IV, Fixed, 95% CI)	13.0 [-42.64, 68.64]
4.1 Long term Studies (days-months)	1	38	Mean Difference (IV, Fixed, 95% CI)	13.0 [-42.64, 68.64]
5 PEFR (evening)	1	38	Mean Difference (IV, Fixed, 95% CI)	-49.0 [-104.01, 6.01]
5.1 Long term Studies (days-months)	1	38	Mean Difference (IV, Fixed, 95% CI)	-49.0 [-104.01, 6.01]
6 AUC-FEV1 (L x min)	1	40	Mean Difference (IV, Fixed, 95% CI)	9.0 [-66.69, 84.69]
6.1 Cumulative dosing trials	1	40	Mean Difference (IV, Fixed, 95% CI)	9.0 [-66.69, 84.69]
7 Heart Rate (bpm)	2	86	Mean Difference (IV, Fixed, 95% CI)	3.51 [-0.38, 7.40]
7.1 Cumulative dosing studies	2	86	Mean Difference (IV, Fixed, 95% CI)	3.51 [-0.38, 7.40]
8 Systolic Pressure (mmHg)	1	62	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-6.32, 5.72]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Cumulative dosing trials	1	62	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-6.32, 5.72]
9 Diastolic Pressure (mmHg)	1	62	Mean Difference (IV, Fixed, 95% CI)	0.20 [-4.08, 4.48]
9.1 Cumulative dosing trials	1	62	Mean Difference (IV, Fixed, 95% CI)	0.20 [-4.08, 4.48]
10 Serum K ⁺ (mmol/L)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
10.1 Short term studies (min-hours)	1	23	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.22, 0.14]
10.2 Cumulative dosing studies	1	45	Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.42, 0.04]
11 Adverse Events	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 Short term studies (min-hours)	1	24	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 67.06]
11.2 Long term studies (days-months)	1	38	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 14.85]
11.3 Cumulative dosing studies	1	24	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.45, 8.94]
12 Treatment Failures/Dropouts	1	38	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 69.31]
12.1 Long term studies (days-months)	1	38	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 69.31]
13 Preference for inhaler	1	38	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.51 [0.13, 1.90]
13.1 Long term studies (days-months)	1	38	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.51 [0.13, 1.90]

Analysis 1.1. Comparison 1 Adults - Crossover design: Turbuhaler vs pMDI (mean absolute value), Outcome 1 FEV₁ (L).

Analysis 1.2. Comparison 1 Adults - Crossover design: Turbuhaler vs pMDI (mean absolute value), Outcome 2 FVC (L).

Analysis 1.3. Comparison 1 Adults - Crossover design: Turbuhaler vs pMDI (mean absolute value), Outcome 3 PEFR - Daily (L/min).

Analysis 1.4. Comparison 1 Adults - Crossover design: Turbuhaler vs pMDI (mean absolute value), Outcome 4 PEFR (morning).

Analysis 1.5. Comparison 1 Adults - Crossover design: Turbuhaler vs pMDI (mean absolute value), Outcome 5 PEFR (evening).

Analysis 1.6. Comparison 1 Adults - Crossover design: Turbuhaler vs pMDI (mean absolute value), Outcome 6 AUC-FEV1 (L x min).

Analysis 1.7. Comparison 1 Adults - Crossover design: Turbuhaler vs pMDI (mean absolute value), Outcome 7 Heart Rate (bpm).

Analysis 1.8. Comparison 1 Adults - Crossover design: Turbuhaler vs pMDI (mean absolute value), Outcome 8 Systolic Pressure (mmHg).

Analysis 1.9. Comparison 1 Adults - Crossover design: Turbuhaler vs pMDI (mean absolute value), Outcome 9 Diastolic Pressure (mmHg).

Analysis 1.10. Comparison 1 Adults - Crossover design: Turbuhaler vs pMDI (mean absolute value), Outcome 10 Serum K⁺ (mmol/L).

Analysis 1.11. Comparison 1 Adults - Crossover design: Turbuhaler vs pMDI (mean absolute value), Outcome 11 Adverse Events.

Analysis 1.12. Comparison 1 Adults - Crossover design: Turbuhaler vs pMDI (mean absolute value), Outcome 12 Treatment Failures/Dropouts.

Analysis 1.13. Comparison 1 Adults - Crossover design: Turbuhaler vs pMDI (mean absolute value), Outcome 13 Preference for inhaler.

Comparison 2. Adults - Crossover design: Turbuhaler vs pMDI (absolute change from baseline)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 (L)	2	44	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.17, 0.25]
1.1 Cumulative dosing studies	2	44	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.17, 0.25]
2 FVC (L)	2	44	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.14, 0.23]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Cumulative dosing studies	2	44	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.14, 0.23]
3 Heart Rate (bpm)	1	18	Mean Difference (IV, Fixed, 95% CI)	10.5 [1.98, 19.02]
3.1 Cumulative dosing studies	1	18	Mean Difference (IV, Fixed, 95% CI)	10.5 [1.98, 19.02]

Analysis 2.1. Comparison 2 Adults - Crossover design: Turbuhaler vs pMDI (absolute change from baseline), Outcome 1 FEV1 (L).

Analysis 2.2. Comparison 2 Adults - Crossover design: Turbuhaler vs pMDI (absolute change from baseline), Outcome 2 FVC (L).

Analysis 2.3. Comparison 2 Adults - Crossover design: Turbuhaler vs pMDI (absolute change from baseline), Outcome 3 Heart Rate (bpm).

Comparison 3. Adults - Crossover design: Turbuhaler vs pMDI (% change from baseline)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1	1	20	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.1 Short term studies (min-hours)	1	20	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 3.1. Comparison 3 Adults - Crossover design: Turbuhaler vs pMDI (% change from baseline), Outcome 1 FEV1.

Comparison 4. Adults - Crossover design: Turbuhaler vs pMDI (combined using SMD)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1	7		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Short term studies (min-hours)	4	96	Std. Mean Difference (IV, Fixed, 95% CI)	0.17 [-0.28, 0.62]
1.2 Cumulative dosing studies	3	106	Std. Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.46, 0.30]
2 FVC	4		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Short term studies (min-hours)	1	24	Std. Mean Difference (IV, Fixed, 95% CI)	0.15 [-0.65, 0.95]
2.2 Cumulative dosing studies	3	106	Std. Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.34, 0.42]
3 Heart Rate	3		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Cumulative dosing studies	3	104	Std. Mean Difference (IV, Fixed, 95% CI)	0.47 [0.07, 0.86]

Analysis 4.1. Comparison 4 Adults - Crossover design: Turbuhaler vs pMDI (combined using SMD), Outcome 1 FEV1.

Analysis 4.2. Comparison 4 Adults - Crossover design: Turbuhaler vs pMDI (combined using SMD), Outcome 2 FVC.

Analysis 4.3. Comparison 4 Adults - Crossover design: Turbuhaler vs pMDI (combined using SMD), Outcome 3 Heart Rate.

Comparison 5. Adults - Crossover design: Diskhaler vs pMDI (mean absolute value)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 (L)	1	18	Mean Difference (IV, Fixed, 95% CI)	-0.5 [-1.23, 0.23]
1.1 Short term studies (min-hours)	1	18	Mean Difference (IV, Fixed, 95% CI)	-0.5 [-1.23, 0.23]
2 PEFR - Daily (L/min)	1	24	Mean Difference (IV, Fixed, 95% CI)	27.0 [-36.34, 90.34]
2.1 Short term studies (min-hours)	1	24	Mean Difference (IV, Fixed, 95% CI)	27.0 [-36.34, 90.34]
3 Adverse Events	1	24	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.36, 24.92]
3.1 Short term studies (min-hours)	1	24	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.36, 24.92]

Analysis 5.1. Comparison 5 Adults - Crossover design: Diskhaler vs pMDI (mean absolute value), Outcome 1 FEV1 (L).

Analysis 5.2. Comparison 5 Adults - Crossover design: Diskhaler vs pMDI (mean absolute value), Outcome 2 PEFR - Daily (L/min).

Analysis 5.3. Comparison 5 Adults - Crossover design: Diskhaler vs pMDI (mean absolute value), Outcome 3 Adverse Events.

Comparison 6. Adults - Crossover design: HFA-pMDI vs pMDI (mean absolute value)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 (L)	1	48	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.39, 0.49]
1.1 Short term studies (min-hours)	1	48	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.39, 0.49]
2 FVC (L)	1	48	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.57, 0.53]
2.1 Short term studies (min-hours)	1	48	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.57, 0.53]

Analysis 6.1. Comparison 6 Adults - Crossover design: HFA-pMDI vs pMDI (mean absolute value), Outcome 1 FEV1 (L).

Analysis 6.2. Comparison 6 Adults - Crossover design: HFA-pMDI vs pMDI (mean absolute value), Outcome 2 FVC (L).

Comparison 7. Adults - Crossover design: HFA-pMDI vs pMDI (absolute change from baseline)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 (L)	2	92	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.04, 0.12]
1.1 Cumulative dosing studies	2	92	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.04, 0.12]
2 FVC (L)	1	48	Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.23, 0.39]
2.1 Cumulative dosing studies	1	48	Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.23, 0.39]
3 Heart Rate (bpm)	2	86	Mean Difference (IV, Fixed, 95% CI)	1.88 [-0.87, 4.63]
3.1 Cumulative dosing studies	2	86	Mean Difference (IV, Fixed, 95% CI)	1.88 [-0.87, 4.63]
4 Systolic Pressure (mmHg)	2	86	Mean Difference (IV, Fixed, 95% CI)	-2.38 [-5.40, 0.63]
4.1 Cumulative dosing trials	2	86	Mean Difference (IV, Fixed, 95% CI)	-2.38 [-5.40, 0.63]
5 Diastolic Pressure (mmHg)	1	48	Mean Difference (IV, Fixed, 95% CI)	2.2 [-3.40, 7.80]
5.1 Cumulative dosing trials	1	48	Mean Difference (IV, Fixed, 95% CI)	2.2 [-3.40, 7.80]
6 Serum K+ (mmol/L)	2	86	Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.18, 0.05]
6.1 Cumulative dosing studies	2	86	Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.18, 0.05]
7 Adverse Events	1	42	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.53, 1.89]
7.1 Cumulative dosing studies	1	42	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.53, 1.89]
8 AUC-FEV1 (L x min)	2	252	Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.47, 0.11]
8.1 Short term studies (min-hours)	2	252	Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.47, 0.11]

Analysis 7.1. Comparison 7 Adults - Crossover design: HFA-pMDI vs pMDI (absolute change from baseline), Outcome 1 FEV1 (L).

Study or subgroup	HFA-pMDI Group		pMDI Group		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
7.1.1 Cumulative dosing studies							
Kleerup 1996	24	1.1 (0.6)	24	1 (0.6)		6.37%	0.08[-0.24,0.4]
					Favours pMDI		Favours HFA-pMDI

Analysis 7.2. Comparison 7 Adults - Crossover design: HFA-pMDI vs pMDI (absolute change from baseline), Outcome 2 FVC (L).

Analysis 7.3. Comparison 7 Adults - Crossover design: HFA-pMDI vs pMDI (absolute change from baseline), Outcome 3 Heart Rate (bpm).

Analysis 7.4. Comparison 7 Adults - Crossover design: HFA-pMDI vs pMDI (absolute change from baseline), Outcome 4 Systolic Pressure (mmHg).

Analysis 7.5. Comparison 7 Adults - Crossover design: HFA-pMDI vs pMDI (absolute change from baseline), Outcome 5 Diastolic Pressure (mmHg).

Analysis 7.6. Comparison 7 Adults - Crossover design: HFA-pMDI vs pMDI (absolute change from baseline), Outcome 6 Serum K⁺ (mmol/L).

Analysis 7.7. Comparison 7 Adults - Crossover design: HFA-pMDI vs pMDI (absolute change from baseline), Outcome 7 Adverse Events. **Analysis 7.8. Comparison 7 Adults - Crossover design: HFA-pMDI vs pMDI (absolute change from baseline), Outcome 8 AUC-FEV1 (L x min).** **Comparison 8. Adults - Crossover design: HFA-pMDI vs pMDI (% change from baseline)**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Short term studies (min-hours)	2	100	Mean Difference (IV, Fixed, 95% CI)	-1.39 [-9.61, 6.83]
1.2 Cumulative dosing studies	1	72	Mean Difference (IV, Fixed, 95% CI)	-2.70 [-11.46, 6.06]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 FVC	1	71	Mean Difference (IV, Fixed, 95% CI)	-0.5 [-6.87, 5.87]
2.1 Cumulative dosing studies	1	71	Mean Difference (IV, Fixed, 95% CI)	-0.5 [-6.87, 5.87]
3 AUC-FEV1	2	100	Mean Difference (IV, Fixed, 95% CI)	-13.79 [-58.29, 30.70]
3.1 Short term studies (min-hours)	2	100	Mean Difference (IV, Fixed, 95% CI)	-13.79 [-58.29, 30.70]
4 Adverse Events	2	100	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.31, 1.93]
4.1 Short term studies (min-hours)	2	100	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.31, 1.93]

Analysis 8.1. Comparison 8 Adults - Crossover design: HFA-pMDI vs pMDI (% change from baseline), Outcome 1 FEV1.

Analysis 8.2. Comparison 8 Adults - Crossover design: HFA-pMDI vs pMDI (% change from baseline), Outcome 2 FVC.

Study or subgroup	HFA-pMDI Group		pMDI Group		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI				
	N	Mean(SD)	N	Mean(SD)							
Heterogeneity: Not applicable											
Test for overall effect: Z=0.15(P=0.88)											
					-100	-50	0	50	100		
					Favours pMDI					Favours HFA-pMDI	

Analysis 8.3. Comparison 8 Adults - Crossover design: HFA-pMDI vs pMDI (% change from baseline), Outcome 3 AUC-FEV1.

Study or subgroup	HFA-pMDI Group		pMDI Group		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
8.3.1 Short term studies (min-hours)							
Dockhorn 1995a	25	74.4 (89.9)	25	98.1 (114.9)		60.54%	-23.7[-80.89,33.49]
Dockhorn 1995b	25	117 (136.5)	25	115.6 (118.4)		39.46%	1.4[-69.43,72.23]
Subtotal ***	50		50			100%	-13.79[-58.29,30.7]
Heterogeneity: Tau ² =0; Chi ² =0.29, df=1(P=0.59); I ² =0%							
Test for overall effect: Z=0.61(P=0.54)							
Total ***	50		50			100%	-13.79[-58.29,30.7]
Heterogeneity: Tau ² =0; Chi ² =0.29, df=1(P=0.59); I ² =0%							
Test for overall effect: Z=0.61(P=0.54)							
					Favours pMDI -100 -50 0 50 100 Favours HFA-pMDI		

Analysis 8.4. Comparison 8 Adults - Crossover design: HFA-pMDI vs pMDI (% change from baseline), Outcome 4 Adverse Events.

Study or subgroup	HFA-pMDI Group	pMDI Group	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
8.4.1 Short term studies (min-hours)					
Dockhorn 1995a	4/25	4/25		44.44%	1[0.28,3.56]
Dockhorn 1995b	3/25	5/25		55.56%	0.6[0.16,2.25]
Subtotal (95% CI)	50	50		100%	0.78[0.31,1.93]
Total events: 7 (HFA-pMDI Group), 9 (pMDI Group)					
Heterogeneity: Tau ² =0; Chi ² =0.3, df=1(P=0.58); I ² =0%					
Test for overall effect: Z=0.54(P=0.59)					
Total (95% CI)	50	50		100%	0.78[0.31,1.93]
Total events: 7 (HFA-pMDI Group), 9 (pMDI Group)					
Heterogeneity: Tau ² =0; Chi ² =0.3, df=1(P=0.58); I ² =0%					
Test for overall effect: Z=0.54(P=0.59)					
			Lower with HFA-pMDI 0.1 0.2 0.5 1 2 5 10 Lower with pMDI		

Comparison 9. Adults - Crossover design: HFA-pMDI vs pMDI (combined using SMD)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1	6		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Short term studies (min-hours)	3	148	Std. Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.26, 0.38]
1.2 Cumulative dosing studies	3	164	Std. Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.28, 0.35]
2 AUC-FEV1	4		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Short term studies (min-hours)	4	352	Std. Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.29, 0.13]

Analysis 9.1. Comparison 9 Adults - Crossover design: HFA-pMDI vs pMDI (combined using SMD), Outcome 1 FEV1. **Analysis 9.2. Comparison 9 Adults - Crossover design: HFA-pMDI vs pMDI (combined using SMD), Outcome 2 AUC-FEV1.**

Comparison 10. Adults - Crossover design: Rotahaler vs pMDI (mean absolute value)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 (L)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Short term studies (min-hours)	1	20	Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.69, 0.31]
1.2 Cumulative dosing studies	1	106	Mean Difference (IV, Fixed, 95% CI)	0.08 [-13.63, 13.79]
2 PEFR (morning)	1	40	Mean Difference (IV, Fixed, 95% CI)	2.0 [-60.63, 64.63]
2.1 Long term Studies (days-months)	1	40	Mean Difference (IV, Fixed, 95% CI)	2.0 [-60.63, 64.63]
3 PEFR (evening)	1	40	Mean Difference (IV, Fixed, 95% CI)	1.0 [-63.16, 65.16]
3.1 Long term Studies (days-months)	1	40	Mean Difference (IV, Fixed, 95% CI)	1.0 [-63.16, 65.16]
4 AUC-FEV1 (L x min)	1	20	Mean Difference (IV, Fixed, 95% CI)	-12.30 [-85.36, 60.76]
4.1 Short term studies (min-hours)	1	20	Mean Difference (IV, Fixed, 95% CI)	-12.30 [-85.36, 60.76]
5 Heart Rate (bpm)	1	18	Mean Difference (IV, Fixed, 95% CI)	-2.0 [-8.66, 4.66]
5.1 Cumulative dosing studies	1	18	Mean Difference (IV, Fixed, 95% CI)	-2.0 [-8.66, 4.66]
6 Preference for inhaler	2	116	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.32, 0.77]
6.1 Long term studies (days-months)	2	116	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.32, 0.77]
7 Adverse Events	1	40	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.34, 26.45]
7.1 Long term studies (days-months)	1	40	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.34, 26.45]

Analysis 10.1. Comparison 10 Adults - Crossover design: Rotahaler vs pMDI (mean absolute value), Outcome 1 FEV1 (L).

Analysis 10.2. Comparison 10 Adults - Crossover design: Rotahaler vs pMDI (mean absolute value), Outcome 2 PEFR (morning).

Analysis 10.3. Comparison 10 Adults - Crossover design: Rotahaler vs pMDI (mean absolute value), Outcome 3 PEFR (evening).

Analysis 10.4. Comparison 10 Adults - Crossover design: Rotahaler vs pMDI (mean absolute value), Outcome 4 AUC-FEV1 (L x min).

Analysis 10.5. Comparison 10 Adults - Crossover design: Rotahaler vs pMDI (mean absolute value), Outcome 5 Heart Rate (bpm).

Analysis 10.6. Comparison 10 Adults - Crossover design: Rotahaler vs pMDI (mean absolute value), Outcome 6 Preference for inhaler.

Analysis 10.7. Comparison 10 Adults - Crossover design: Rotahaler vs pMDI (mean absolute value), Outcome 7 Adverse Events.

Comparison 11. Adults - Crossover design: Rotahaler vs pMDI (absolute change from baseline)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 (L)	2	32	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.09, 0.12]
1.1 Cumulative dosing studies	2	32	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.09, 0.12]
2 FVC (L)	1	14	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.22, 0.42]
2.1 Cumulative dosing trials	1	14	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.22, 0.42]
3 Heart Rate (bpm)	1	14	Mean Difference (IV, Fixed, 95% CI)	-5.5 [-10.04, -0.96]
3.1 Cumulative dosing studies	1	14	Mean Difference (IV, Fixed, 95% CI)	-5.5 [-10.04, -0.96]

Analysis 11.1. Comparison 11 Adults - Crossover design: Rotahaler vs pMDI (absolute change from baseline), Outcome 1 FEV1 (L).

Analysis 11.2. Comparison 11 Adults - Crossover design: Rotahaler vs pMDI (absolute change from baseline), Outcome 2 FVC (L).

Analysis 11.3. Comparison 11 Adults - Crossover design: Rotahaler vs pMDI (absolute change from baseline), Outcome 3 Heart Rate (bpm).

Comparison 12. Adults - Crossover design: Rotahaler vs pMDI (% change from baseline)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Short term studies (min-hours)	3	62	Mean Difference (IV, Fixed, 95% CI)	-3.03 [-9.65, 3.58]
1.2 Cumulative dosing studies	1	28	Mean Difference (IV, Fixed, 95% CI)	-3.75 [-32.57, 25.07]
2 FVC	2	38	Mean Difference (IV, Fixed, 95% CI)	1.66 [-5.52, 8.84]
2.1 Short term studies (min-hours)	2	38	Mean Difference (IV, Fixed, 95% CI)	1.66 [-5.52, 8.84]
3 PEFR - Daily	3	78	Mean Difference (IV, Fixed, 95% CI)	-7.70 [-25.08, 9.68]
3.1 Short term studies (min-hours)	3	78	Mean Difference (IV, Fixed, 95% CI)	-7.70 [-25.08, 9.68]
4 AUC-FEV1	1	24	Mean Difference (IV, Fixed, 95% CI)	-3.10 [-10.67, 4.47]
4.1 Short term studies (min-hours)	1	24	Mean Difference (IV, Fixed, 95% CI)	-3.10 [-10.67, 4.47]
5 Acute Exacerbations	1	28	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.26, 95.61]
5.1 Cumulative dosing studies	1	28	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.26, 95.61]
6 Preference for inhaler	1	40	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.54 [0.15, 1.90]
6.1 Short term studies (min-hours)	1	40	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.54 [0.15, 1.90]
7 Adverse Events	1	24	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.1 Short term studies (min-hours)	1	24	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 12.1. Comparison 12 Adults - Crossover design: Rotahaler vs pMDI (% change from baseline), Outcome 1 FEV1.

Analysis 12.2. Comparison 12 Adults - Crossover design: Rotahaler vs pMDI (% change from baseline), Outcome 2 FVC.

Analysis 12.3. Comparison 12 Adults - Crossover design: Rotahaler vs pMDI (% change from baseline), Outcome 3 PEFR - Daily.

Analysis 12.4. Comparison 12 Adults - Crossover design: Rotahaler vs pMDI (% change from baseline), Outcome 4 AUC-FEV1.

Analysis 12.5. Comparison 12 Adults - Crossover design: Rotahaler vs pMDI (% change from baseline), Outcome 5 Acute Exacerbations.

Analysis 12.6. Comparison 12 Adults - Crossover design: Rotahaler vs pMDI (% change from baseline), Outcome 6 Preference for inhaler.

Analysis 12.7. Comparison 12 Adults - Crossover design: Rotahaler vs pMDI (% change from baseline), Outcome 7 Adverse Events.

Comparison 13. Adults - Crossover design: Rotahaler vs pMDI (combined using SMD)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1	8		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Short term studies (min-hours)	4	82	Std. Mean Difference (IV, Fixed, 95% CI)	-0.16 [-0.60, 0.28]
1.2 Cumulative dosing studies	4	166	Std. Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.30, 0.30]
2 FVC	3		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Short term studies (min-hours)	2	38	Std. Mean Difference (IV, Fixed, 95% CI)	-0.09 [-0.73, 0.55]
2.2 Cumulative dosing trials	1	14	Std. Mean Difference (IV, Fixed, 95% CI)	0.30 [-0.75, 1.36]
3 AUC-FEV1	2		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Short term studies (min-hours)	2	44	Std. Mean Difference (IV, Fixed, 95% CI)	-0.24 [-0.83, 0.36]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Preference for inhaler	3	156	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.36, 0.78]
4.1 Short term studies (min - hours)	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.29, 1.52]
4.2 Long term studies (days - months)	2	116	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.32, 0.77]

Analysis 13.1. Comparison 13 Adults - Crossover design: Rotahaler vs pMDI (combined using SMD), Outcome 1 FEV1.

Analysis 13.2. Comparison 13 Adults - Crossover design: Rotahaler vs pMDI (combined using SMD), Outcome 2 FVC.

Analysis 13.3. Comparison 13 Adults - Crossover design: Rotahaler vs pMDI (combined using SMD), Outcome 3 AUC-FEV1.

Analysis 13.4. Comparison 13 Adults - Crossover design: Rotahaler vs pMDI (combined using SMD), Outcome 4 Preference for inhaler.

Comparison 14. Adults - Crossover design: Spiros vs pMDI (mean absolute value)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 (L)	2	176	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.21, 0.22]
1.1 Short term studies (min-hours)	2	176	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.21, 0.22]
2 FVC (L)	2	176	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.30, 0.29]
2.1 Short term studies (min-hours)	2	176	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.30, 0.29]
3 PEFR - Daily (L/min)	2	176	Mean Difference (IV, Fixed, 95% CI)	4.06 [-26.95, 35.08]
3.1 Short term studies (min-hours)	2	176	Mean Difference (IV, Fixed, 95% CI)	4.06 [-26.95, 35.08]
4 AUC-FEV1 (L x min)	2	176	Mean Difference (IV, Fixed, 95% CI)	8.22 [-23.82, 40.26]
4.1 Short term studies (min-hours)	2	176	Mean Difference (IV, Fixed, 95% CI)	8.22 [-23.82, 40.26]
5 Heart Rate (bpm)	2	198	Mean Difference (IV, Fixed, 95% CI)	1.13 [-1.11, 3.36]
5.1 Short term studies (min-hours)	2	198	Mean Difference (IV, Fixed, 95% CI)	1.13 [-1.11, 3.36]
6 Systolic Pressure (mmHg)	2	176	Mean Difference (IV, Fixed, 95% CI)	0.11 [-2.57, 2.80]
6.1 Short term studies (min-hours)	2	176	Mean Difference (IV, Fixed, 95% CI)	0.11 [-2.57, 2.80]
7 Diastolic Pressure (mmHg)	2	176	Mean Difference (IV, Fixed, 95% CI)	0.17 [-1.91, 2.24]
7.1 Short term studies (min-hours)	2	176	Mean Difference (IV, Fixed, 95% CI)	0.17 [-1.91, 2.24]
8 Serum K+ (mmol/L)	2	176	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.06, 0.08]
8.1 Short term studies (min-hours)	2	176	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.06, 0.08]

Analysis 14.1. Comparison 14 Adults - Crossover design: Spiros vs pMDI (mean absolute value), Outcome 1 FEV1 (L).

Study or subgroup	Spiros Group		pMDI Group		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
14.1.1 Short term studies (min-hours)							
Geoffroy 1999a	44	2.8 (0.7)	44	2.8 (0.8)		49.34%	0[-0.31,0.31]
Geoffroy 1999b	44	2.9 (0.8)	44	2.9 (0.7)		50.66%	0.01[-0.3,0.32]
Subtotal ***	88		88			100%	0.01[-0.21,0.22]
					-1 -0.5 0 0.5 1		
					Favours pMDI Favours Spiros

Analysis 14.2. Comparison 14 Adults - Crossover design: Spiros vs pMDI (mean absolute value), Outcome 2 FVC (L).

Analysis 14.3. Comparison 14 Adults - Crossover design: Spiros vs pMDI (mean absolute value), Outcome 3 PEFr - Daily (L/min).

Analysis 14.4. Comparison 14 Adults - Crossover design: Spiros vs pMDI (mean absolute value), Outcome 4 AUC-FEV1 (L x min).

Analysis 14.5. Comparison 14 Adults - Crossover design: Spiros vs pMDI (mean absolute value), Outcome 5 Heart Rate (bpm).

Analysis 14.6. Comparison 14 Adults - Crossover design: Spiros vs pMDI (mean absolute value), Outcome 6 Systolic Pressure (mmHg).

Study or subgroup	Spiros Group		pMDI Group		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Test for overall effect: Z=0.08(P=0.94)							
<div><div></div><div>Favours Spiros-10-50510Favours pMDI</div></div>							

Analysis 14.7. Comparison 14 Adults - Crossover design: Spiros vs pMDI (mean absolute value), Outcome 7 Diastolic Pressure (mmHg).

Study or subgroup	Spiros Group		pMDI Group		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
14.7.1 Short term studies (min-hours)							
Geoffroy 1999a	44	76.9 (7)	44	75.7 (7)		49.93%	1.18[-1.76,4.12]
Geoffroy 1999b	44	76 (7.1)	44	76.9 (6.9)		50.07%	-0.84[-3.77,2.09]
Subtotal ***	88		88			100%	0.17[-1.91,2.24]
Heterogeneity: Tau ² =0; Chi ² =0.91, df=1(P=0.34); I ² =0%							
Test for overall effect: Z=0.16(P=0.87)							
Total ***	88		88			100%	0.17[-1.91,2.24]
Heterogeneity: Tau ² =0; Chi ² =0.91, df=1(P=0.34); I ² =0%							
Test for overall effect: Z=0.16(P=0.87)							
<div style="display: flex; justify-content: space-between;">Favours Spiros-10-50510Favours pMDI</div>							

Analysis 14.8. Comparison 14 Adults - Crossover design: Spiros vs pMDI (mean absolute value), Outcome 8 Serum K+ (mmol/L).

Study or subgroup	Spiros Group		pMDI Group		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
14.8.1 Short term studies (min-hours)							
Geoffroy 1999a	44	4.3 (0.2)	44	4.3 (0.3)		52.04%	0.04[-0.06,0.14]
Geoffroy 1999b	44	4.3 (0.3)	44	4.3 (0.2)		47.96%	-0.02[-0.12,0.08]
Subtotal ***	88		88			100%	0.01[-0.06,0.08]
Heterogeneity: Tau²=0; Chi²=0.66, df=1(P=0.42); I²=0%							
Test for overall effect: Z=0.3(P=0.76)							
Total ***	88		88			100%	0.01[-0.06,0.08]
Heterogeneity: Tau²=0; Chi²=0.66, df=1(P=0.42); I²=0%							
Test for overall effect: Z=0.3(P=0.76)							
<div style="display: flex; justify-content: space-between;">Favours Spiros-0.5-0.2500.250.5Favours pMDI</div>							

Comparison 15. Adults - Crossover design: Spinhaler vs pMDI (absolute change from baseline)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 (L)	1	40	Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.16, 0.00]
1.1 Short term studies (min-hours)	1	40	Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.16, 0.00]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 FVC (L)	1	40	Mean Difference (IV, Fixed, 95% CI)	-0.26 [-0.43, -0.09]
2.1 Short term studies (min-hours)	1	40	Mean Difference (IV, Fixed, 95% CI)	-0.26 [-0.43, -0.09]

Analysis 15.1. Comparison 15 Adults - Crossover design: Spinhaler vs pMDI (absolute change from baseline), Outcome 1 FEV1 (L).

Analysis 15.2. Comparison 15 Adults - Crossover design: Spinhaler vs pMDI (absolute change from baseline), Outcome 2 FVC (L).

Comparison 16. Adults - Crossover design: Easyhaler vs pMDI (mean absolute value)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 (L)	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Short term studies (min-hours)	2	114	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.35, 0.41]
1.2 Cumulative dosing studies	1	30	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.80, 0.68]
2 FVC (L)	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Short term studies (min-hours)	3	152	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.36, 0.38]
2.2 Cumulative dosing trials	1	106	Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.56, 0.40]
3 PEFR - Daily (L/min)	3	152	Mean Difference (IV, Fixed, 95% CI)	-5.91 [-48.72, 36.90]
3.1 Short term studies (min-hours)	3	152	Mean Difference (IV, Fixed, 95% CI)	-5.91 [-48.72, 36.90]
4 PEFR - Morning (L/min)	1	30	Mean Difference (IV, Fixed, 95% CI)	-9.0 [-169.04, 151.04]
4.1 Cumulative dosing trials	1	30	Mean Difference (IV, Fixed, 95% CI)	-9.0 [-169.04, 151.04]
5 AUC-FEV1 (L x min)	2	114	Mean Difference (IV, Fixed, 95% CI)	4.11 [-98.96, 107.18]
5.1 Short term studies (min-hours)	2	114	Mean Difference (IV, Fixed, 95% CI)	4.11 [-98.96, 107.18]
6 Heart Rate (bpm)	1	42	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-7.68, 5.68]
6.1 Short term studies (min-hours)	1	42	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-7.68, 5.68]
7 Systolic Pressure (mmHg)	1	42	Mean Difference (IV, Fixed, 95% CI)	2.0 [-8.30, 12.30]
7.1 Short term studies (min-hours)	1	42	Mean Difference (IV, Fixed, 95% CI)	2.0 [-8.30, 12.30]
8 Diastolic Pressure (mmHg)	1	65	Mean Difference (IV, Fixed, 95% CI)	1.0 [-3.33, 5.33]
8.1 Short term studies (min-hours)	1	65	Mean Difference (IV, Fixed, 95% CI)	1.0 [-3.33, 5.33]
9 Adverse Events	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Short term studies (min-hours)	2	80	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.37, 4.27]
9.2 Cumulative dosing studies	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.21, 1.20]

Analysis 16.1. Comparison 16 Adults - Crossover design: Easyhaler vs pMDI (mean absolute value), Outcome 1 FEV1 (L).

Analysis 16.2. Comparison 16 Adults - Crossover design: Easyhaler vs pMDI (mean absolute value), Outcome 2 FVC (L).

Analysis 16.3. Comparison 16 Adults - Crossover design: Easyhaler vs pMDI (mean absolute value), Outcome 3 PEFr - Daily (L/min).

Analysis 16.4. Comparison 16 Adults - Crossover design: Easyhaler vs pMDI (mean absolute value), Outcome 4 PEFR - Morning (L/min).

Analysis 16.5. Comparison 16 Adults - Crossover design: Easyhaler vs pMDI (mean absolute value), Outcome 5 AUC-FEV1 (L x min).

Analysis 16.6. Comparison 16 Adults - Crossover design: Easyhaler vs pMDI (mean absolute value), Outcome 6 Heart Rate (bpm).

Analysis 16.7. Comparison 16 Adults - Crossover design: Easyhaler vs pMDI (mean absolute value), Outcome 7 Systolic Pressure (mmHg).

Analysis 16.8. Comparison 16 Adults - Crossover design: Easyhaler vs pMDI (mean absolute value), Outcome 8 Diastolic Pressure (mmHg).

Analysis 16.9. Comparison 16 Adults - Crossover design: Easyhaler vs pMDI (mean absolute value), Outcome 9 Adverse Events. **Comparison 17. Adults - Crossover design: Easyhaler vs pMDI (% change from baseline)**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 (L)	1	38	Mean Difference (IV, Fixed, 95% CI)	-3.60 [-10.81, 3.61]
1.1 Short term studies (min-hours)	1	38	Mean Difference (IV, Fixed, 95% CI)	-3.60 [-10.81, 3.61]

Analysis 17.1. Comparison 17 Adults - Crossover design: Easyhaler vs pMDI (% change from baseline), Outcome 1 FEV1 (L).

Comparison 18. Adults - Crossover design: Easyhaler vs pMDI (combined using SMD)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 (L)	3	152	Std. Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.37, 0.26]
1.1 Short term studies (min-hours)	3	152	Std. Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.37, 0.26]

Analysis 18.1. Comparison 18 Adults - Crossover design: Easyhaler vs pMDI (combined using SMD), Outcome 1 FEV1 (L).

Comparison 19. Adults - Crossover design: Multi Dose Powder Inhaler vs pMDI (mean absolute value)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 (L)	1	72	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.35, 0.37]
1.1 Short term studies (min-hours)	1	72	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.35, 0.37]
2 AUC-FEV1 (L x min)	1	72	Mean Difference (IV, Fixed, 95% CI)	4.0 [-124.66, 132.66]
2.1 Short term studies (min-hours)	1	72	Mean Difference (IV, Fixed, 95% CI)	4.0 [-124.66, 132.66]
3 Preference for inhaler	1	72	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.38, 0.98]
3.1 Short term studies (min-hours)	1	72	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.38, 0.98]
4 Adverse Events	1	72	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.05, 5.27]
4.1 Short term studies (min-hours)	1	72	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.05, 5.27]

Analysis 19.1. Comparison 19 Adults - Crossover design: Multi Dose Powder Inhaler vs pMDI (mean absolute value), Outcome 1 FEV1 (L).

Analysis 19.2. Comparison 19 Adults - Crossover design: Multi Dose Powder Inhaler vs pMDI (mean absolute value), Outcome 2 AUC-FEV1 (L x min).

Analysis 19.3. Comparison 19 Adults - Crossover design: Multi Dose Powder Inhaler vs pMDI (mean absolute value), Outcome 3 Preference for inhaler.

Analysis 19.4. Comparison 19 Adults - Crossover design: Multi Dose Powder Inhaler vs pMDI (mean absolute value), Outcome 4 Adverse Events.

Comparison 20. Adults - Crossover design: Clickhaler vs pMDI (absolute change from baseline)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 (L)	1	32	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.14, 0.12]
1.1 Short term studies (min-hours)	1	32	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.14, 0.12]
2 Adverse Events	1	32	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 68.57]
2.1 Short term studies (min-hours)	1	32	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 68.57]

Analysis 20.1. Comparison 20 Adults - Crossover design: Clickhaler vs pMDI (absolute change from baseline), Outcome 1 FEV1 (L).

Analysis 20.2. Comparison 20 Adults - Crossover design: Clickhaler vs pMDI (absolute change from baseline), Outcome 2 Adverse Events.

Comparison 21. Adults - Crossover design: Gentlehaler vs pMDI (% change from baseline)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1	1	20	Mean Difference (IV, Fixed, 95% CI)	4.20 [-19.03, 27.43]
1.1 Short term studies (min-hours)	1	20	Mean Difference (IV, Fixed, 95% CI)	4.20 [-19.03, 27.43]
2 FVC	1	20	Mean Difference (IV, Fixed, 95% CI)	6.70 [-13.98, 27.38]
2.1 Short term studies (min-hours)	1	20	Mean Difference (IV, Fixed, 95% CI)	6.70 [-13.98, 27.38]
3 PEFR - Daily	1	20	Mean Difference (IV, Fixed, 95% CI)	1.5 [-26.11, 29.11]
3.1 Short term studies (min-hours)	1	20	Mean Difference (IV, Fixed, 95% CI)	1.5 [-26.11, 29.11]

Analysis 21.1. Comparison 21 Adults - Crossover design: Gentlehaler vs pMDI (% change from baseline), Outcome 1 FEV1.

Analysis 21.2. Comparison 21 Adults - Crossover design: Gentlehaler vs pMDI (% change from baseline), Outcome 2 FVC.

Analysis 21.3. Comparison 21 Adults - Crossover design: Gentlehaler vs pMDI (% change from baseline), Outcome 3 PEFr - Daily.

Comparison 22. Adults - Crossover design: Autohaler vs pMDI (absolute change from baseline)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 (L)	1	50	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.16, 0.12]
1.1 Short term studies (min-hours)	1	50	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.16, 0.12]
2 FVC (L)	1	50	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.20, 0.22]
2.1 Short term studies (min-hours)	1	50	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.20, 0.22]
3 PEFR - Daily (L/min)	1	50	Mean Difference (IV, Fixed, 95% CI)	0.0 [-20.51, 20.51]
3.1 Short term studies (min-hours)	1	50	Mean Difference (IV, Fixed, 95% CI)	0.0 [-20.51, 20.51]

Analysis 22.1. Comparison 22 Adults - Crossover design: Autohaler vs pMDI (absolute change from baseline), Outcome 1 FEV1 (L).

Analysis 22.2. Comparison 22 Adults - Crossover design: Autohaler vs pMDI (absolute change from baseline), Outcome 2 FVC (L).

Analysis 22.3. Comparison 22 Adults - Crossover design: Autohaler vs pMDI (absolute change from baseline), Outcome 3 PEFR - Daily (L/min).

Comparison 23. Adults - Crossover design: All other inhaler devices vs pMDI (combined using SMD)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1	32		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Short term studies (min-hours)	22	886	Std. Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.16, 0.10]
1.2 Cumulative dosing studies	10	422	Std. Mean Difference (IV, Fixed, 95% CI)	-0.00 [-0.19, 0.19]
2 FVC	18		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Short term studies (min-hours)	12	548	Std. Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.21, 0.12]
2.2 Cumulative dosing studies	6	298	Std. Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.25, 0.21]
3 PEFR - Daily	12		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Short term studies (min-hours)	11	500	Std. Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.18, 0.19]
3.2 Cumulative dosing trials	1	62	Std. Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.47, 0.53]
4 PEFR (morning)	3		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Long term Studies (days-months)	2	78	Std. Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.36, 0.52]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2 Cumulative dosing trials	1	30	Std. Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.75, 0.68]
5 PEFR (evening)	2		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Long term Studies (days-months)	2	78	Std. Mean Difference (IV, Fixed, 95% CI)	-0.26 [-0.71, 0.19]
6 AUC-FEV1	9		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 Short term studies (min-hours)	8	444	Std. Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.18, 0.19]
6.2 Cumulative dosing trials	1	40	Std. Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.55, 0.69]
7 Heart Rate	10		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 Short term studies (min-hours)	3	240	Std. Mean Difference (IV, Fixed, 95% CI)	0.13 [-0.12, 0.39]
7.2 Cumulative dosing studies	7	222	Std. Mean Difference (IV, Fixed, 95% CI)	0.18 [-0.08, 0.45]
8 Preference for inhaler	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
8.1 Short term studies (min-hours)	2	112	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.54 [0.73, 3.23]
8.2 Long term studies (days-months)	3	150	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.33 [0.17, 0.62]
9 Adverse Events	12		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Short term studies (min-hours)	7	256	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.64, 3.51]
9.2 Long term studies (days-months)	2	78	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.39, 10.30]
9.3 Cumulative dosing studies	3	106	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.53, 1.40]
10 Serum K+	6		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
10.1 Short term studies (min-hours)	3	199	Std. Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.26, 0.30]
10.2 Cumulative dosing studies	3	131	Std. Mean Difference (IV, Fixed, 95% CI)	-0.29 [-0.64, 0.06]

Analysis 23.1. Comparison 23 Adults - Crossover design: All other inhaler devices vs pMDI (combined using SMD), Outcome 1 FEV1.

Analysis 23.2. Comparison 23 Adults - Crossover design: All other inhaler devices vs pMDI (combined using SMD), Outcome 2 FVC. **Analysis 23.3. Comparison 23 Adults - Crossover design: All other inhaler devices vs pMDI (combined using SMD), Outcome 3 PEFR - Daily.**

Analysis 23.4. Comparison 23 Adults - Crossover design: All other inhaler devices vs pMDI (combined using SMD), Outcome 4 PEFR (morning).

Analysis 23.5. Comparison 23 Adults - Crossover design: All other inhaler devices vs pMDI (combined using SMD), Outcome 5 PEFR (evening).

Analysis 23.6. Comparison 23 Adults - Crossover design: All other inhaler devices vs pMDI (combined using SMD), Outcome 6 AUC-FEV1.

Analysis 23.7. Comparison 23 Adults - Crossover design: All other inhaler devices vs pMDI (combined using SMD), Outcome 7 Heart Rate.

Study or subgroup	DPI Group		pMDI Group		Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Test for overall effect: Z=1.35(P=0.18)							
Test for subgroup differences: Chi²=0.07, df=1 (P=0.79), I²=0%							
Lower with DPI -1 -0.5 0 0.5 1 Lower with pMDI							

Analysis 23.8. Comparison 23 Adults - Crossover design: All other inhaler devices vs pMDI (combined using SMD), Outcome 8 Preference for inhaler.

Analysis 23.9. Comparison 23 Adults - Crossover design: All other inhaler devices vs pMDI (combined using SMD), Outcome 9 Adverse Events.

Analysis 23.10. Comparison 23 Adults - Crossover design: All other inhaler devices vs pMDI (combined using SMD), Outcome 10 Serum K+.

Comparison 24. Adults - Crossover design: All other inhalers vs pMDI (for outcomes measured 15-45 mins post-dose, using SMD)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1	15	506	Std. Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.25, 0.10]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Short term studies (min-hours)	8	256	Std. Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.37, 0.12]
1.2 Cumulative dosing studies	7	250	Std. Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.28, 0.23]
2 FVC	12	624	Std. Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.16, 0.16]
2.1 Short term studies (min-hours)	7	352	Std. Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.17, 0.25]
2.2 Cumulative dosing studies	5	272	Std. Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.29, 0.19]
3 AUC-FEV1	1	40	Std. Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.55, 0.69]
3.1 Cumulative dosing trials	1	40	Std. Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.55, 0.69]
4 Heart Rate	8	396	Std. Mean Difference (IV, Fixed, 95% CI)	0.18 [-0.02, 0.38]
4.1 Short term studies (min-hours)	3	240	Std. Mean Difference (IV, Fixed, 95% CI)	0.13 [-0.12, 0.39]
4.2 Cumulative dosing studies	5	156	Std. Mean Difference (IV, Fixed, 95% CI)	0.24 [-0.08, 0.56]
5 PEFR - Daily	7	350	Std. Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.17, 0.25]
5.1 Short term studies (min-hours)	6	288	Std. Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.19, 0.27]
5.2 Cumulative dosing trials	1	62	Std. Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.47, 0.53]
6 PEFR - Morning	3	108	Std. Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.33, 0.42]
6.1 Long term Studies (days-months)	2	78	Std. Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.36, 0.52]
6.2 Cumulative dosing trials	1	30	Std. Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.75, 0.68]
7 PEFR - Evening	2	78	Std. Mean Difference (IV, Fixed, 95% CI)	-0.26 [-0.71, 0.19]
7.1 Long term Studies (days-months)	2	78	Std. Mean Difference (IV, Fixed, 95% CI)	-0.26 [-0.71, 0.19]

Analysis 24.1. Comparison 24 Adults - Crossover design: All other inhalers vs pMDI (for outcomes measured 15-45 mins post-dose, using SMD), Outcome 1 FEV1. **Analysis 24.2. Comparison 24 Adults - Crossover design: All other inhalers vs pMDI (for outcomes measured 15-45 mins post-dose, using SMD), Outcome 2 FVC.**

Analysis 24.3. Comparison 24 Adults - Crossover design: All other inhalers vs pMDI (for outcomes measured 15-45 mins post-dose, using SMD), Outcome 3 AUC-FEV1.

Analysis 24.4. Comparison 24 Adults - Crossover design: All other inhalers vs pMDI (for outcomes measured 15-45 mins post-dose, using SMD), Outcome 4 Heart Rate.

Analysis 24.5. Comparison 24 Adults - Crossover design: All other inhalers vs pMDI (for outcomes measured 15-45 mins post-dose, using SMD), Outcome 5 PEFR - Daily.

Analysis 24.6. Comparison 24 Adults - Crossover design: All other inhalers vs pMDI (for outcomes measured 15-45 mins post-dose, using SMD), Outcome 6 PEFR - Morning. **Analysis 24.7. Comparison 24 Adults - Crossover design: All other inhalers vs pMDI (for outcomes measured 15-45 mins post-dose, using SMD), Outcome 7 PEFR - Evening.** **Comparison 25. Adults - Crossover design - Challenge testing: Turbuhaler vs pMDI (mean absolute values)**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 (L) - Adults: Increase post Mch challenge and bronchodilator	1	32	Std. Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.82, 0.57]
1.1 Short term studies (min-hours)	1	32	Std. Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.82, 0.57]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 FEV1 (L) - Children: Increase post exercise challenge and bronchodilator	1	22	Mean Difference (IV, Fixed, 95% CI)	0.11 [-0.71, 0.93]
2.1 Short term studies (min-hours)	1	22	Mean Difference (IV, Fixed, 95% CI)	0.11 [-0.71, 0.93]

Analysis 25.1. Comparison 25 Adults - Crossover design - Challenge testing: Turbuhaler vs pMDI (mean absolute values), Outcome 1 FEV1 (L) - Adults: Increase post Mch challenge and bronchodilator.

Analysis 25.2. Comparison 25 Adults - Crossover design - Challenge testing: Turbuhaler vs pMDI (mean absolute values), Outcome 2 FEV1 (L) - Children: Increase post exercise challenge and bronchodilator.

Comparison 26. Adults - Crossover design - Challenge testing: Diskhaler vs pMDI (mean absolute values)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 (L)	1	24	Std. Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.78, 0.82]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Short term studies (min-hours)	1	24	Std. Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.78, 0.82]
2 FVC (L)	1	24	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.68, 0.56]
2.1 Short term studies (min-hours)	1	24	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.68, 0.56]

Analysis 26.1. Comparison 26 Adults - Crossover design - Challenge testing: Diskhaler vs pMDI (mean absolute values), Outcome 1 FEV1 (L).

Analysis 26.2. Comparison 26 Adults - Crossover design - Challenge testing: Diskhaler vs pMDI (mean absolute values), Outcome 2 FVC (L).

Comparison 27. Adults - Crossover design - Challenge testing: Multi Dose Powder Inhaler vs pMDI (mean absolute values)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Methacholine Challenge (mg Mch) (PD20-FEV1)	1	52	Mean Difference (IV, Fixed, 95% CI)	1.12 [0.82, 1.42]
1.1 Short term studies (min-hours)	1	52	Mean Difference (IV, Fixed, 95% CI)	1.12 [0.82, 1.42]

Analysis 27.1. Comparison 27 Adults - Crossover design - Challenge testing: Multi Dose Powder Inhaler vs pMDI (mean absolute values), Outcome 1 Methacholine Challenge (mg Mch) (PD20-FEV1).

Study or subgroup	MDPI Group		pMDI Group		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
27.1.1 Short term studies (min-hours)							
Seppala1998a	26	1.7 (0.5)	26	0.6 (0.6)		100%	1.12[0.82,1.42]
Subtotal ***	26		26			100%	1.12[0.82,1.42]
Heterogeneity: Not applicable							
Test for overall effect: Z=7.41(P<0.0001)							
Total ***	26		26			100%	1.12[0.82,1.42]
Heterogeneity: Not applicable							
Test for overall effect: Z=7.41(P<0.0001)							
					-4 -2 0 2 4	Favours pMDI Favours MDPI	

Comparison 28. Adults - Crossover design - Challenge testing: Autohaler vs pMDI (mean absolute values)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Methacholine Challenge (mg Mch) (PD20-FEV1)	1	36	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-1.61, 0.41]
1.1 Short term studies (min-hours)	1	36	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-1.61, 0.41]

Analysis 28.1. Comparison 28 Adults - Crossover design - Challenge testing: Autohaler vs pMDI (mean absolute values), Outcome 1 Methacholine Challenge (mg Mch) (PD20-FEV1).

Study or subgroup	Autohaler Group		pMDI Group		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
28.1.1 Short term studies (min-hours)							
Giannini 2000	18	2.4 (1.7)	18	3 (1.4)		100%	-0.6[-1.61,0.41]
Subtotal ***	18		18			100%	-0.6[-1.61,0.41]
Heterogeneity: Not applicable							
					-4 -2 0 2 4	Favours pMDI Favours Autohaler

Comparison 29. Adults - Crossover design - Challenge testing: HFA vs pMDI (% fall in outcome)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 - adults	1	47	Mean Difference (IV, Fixed, 95% CI)	0.5 [-4.11, 5.11]
1.1 Short term studies (min-hours)	1	47	Mean Difference (IV, Fixed, 95% CI)	0.5 [-4.11, 5.11]
2 FEV1 - children	1	30	Mean Difference (IV, Fixed, 95% CI)	-2.20 [-12.31, 7.91]
2.1 Short term studies (min-hours)	1	30	Mean Difference (IV, Fixed, 95% CI)	-2.20 [-12.31, 7.91]

Analysis 29.1. Comparison 29 Adults - Crossover design - Challenge testing: HFA vs pMDI (% fall in outcome), Outcome 1 FEV1 - adults.

Analysis 29.2. Comparison 29 Adults - Crossover design - Challenge testing: HFA vs pMDI (% fall in outcome), Outcome 2 FEV1 - children.

Comparison 30. Adults - Crossover design - Different doses in inhalers: Turbuhaler vs pMDI (mean absolute value)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 (L)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Short term studies (min-hours)	1	30	Mean Difference (IV, Fixed, 95% CI)	0.29 [-0.02, 0.60]
1.2 Long term studies (days-months)	1	74	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.29, 0.35]
2 PEFR - Morning (L/min)	1	74	Mean Difference (IV, Fixed, 95% CI)	-7.0 [-53.94, 39.94]
2.1 Long term studies (days-months)	1	74	Mean Difference (IV, Fixed, 95% CI)	-7.0 [-53.94, 39.94]
3 PEFR - Evening (L/min)	1	74	Mean Difference (IV, Fixed, 95% CI)	-7.0 [-51.20, 37.20]
3.1 Long term studies (days-months)	1	74	Mean Difference (IV, Fixed, 95% CI)	-7.0 [-51.20, 37.20]
4 Preference	1	74	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.45 [0.17, 1.14]
4.1 Long term studies (days-months)	1	74	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.45 [0.17, 1.14]

Analysis 30.1. Comparison 30 Adults - Crossover design - Different doses in inhalers: Turbuhaler vs pMDI (mean absolute value), Outcome 1 FEV1 (L).

Analysis 30.2. Comparison 30 Adults - Crossover design - Different doses in inhalers: Turbuhaler vs pMDI (mean absolute value), Outcome 2 PEFR - Morning (L/min).

Analysis 30.3. Comparison 30 Adults - Crossover design - Different doses in inhalers: Turbuhaler vs pMDI (mean absolute value), Outcome 3 PEFR - Evening (L/min).

Analysis 30.4. Comparison 30 Adults - Crossover design - Different doses in inhalers: Turbuhaler vs pMDI (mean absolute value), Outcome 4 Preference.

Comparison 31. Adults - Crossover design - Different doses in inhalers: Diskhaler vs pMDI (mean absolute value)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 (L)	1	84	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.16, 0.12]
1.1 Short term studies (min-hours)	1	84	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.16, 0.12]

Analysis 31.1. Comparison 31 Adults - Crossover design - Different doses in inhalers: Diskhaler vs pMDI (mean absolute value), Outcome 1 FEV1 (L).

Comparison 32. Adults - Crossover design - Different doses in inhalers: HFA vs pMDI (absolute change from baseline)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 (L)	1	48	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.19, 0.13]
1.1 Cumulative dosing studies	1	48	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.19, 0.13]

Analysis 32.1. Comparison 32 Adults - Crossover design - Different doses in inhalers: HFA vs pMDI (absolute change from baseline), Outcome 1 FEV1 (L).

Comparison 33. Adults - Crossover design - Different doses in inhalers: Rotahaler vs pMDI (absolute change from baseline)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 PEFR - Daily (L/min)	1	44	Mean Difference (IV, Fixed, 95% CI)	12.5 [-6.80, 31.80]
1.1 Short term studies (min-hours)	1	44	Mean Difference (IV, Fixed, 95% CI)	12.5 [-6.80, 31.80]

Analysis 33.1. Comparison 33 Adults - Crossover design - Different doses in inhalers: Rotahaler vs pMDI (absolute change from baseline), Outcome 1 PEFR - Daily (L/min).

Comparison 34. Adults - Crossover design - Different doses in inhalers: Rotahaler vs pMDI (% change from baseline)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1	1	40	Mean Difference (IV, Fixed, 95% CI)	13.80 [-1.95, 29.55]
1.1 Short term studies (min-hours)	1	40	Mean Difference (IV, Fixed, 95% CI)	13.80 [-1.95, 29.55]
2 Symptom Scores - Daily (higher score worse)	1	40	Std. Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.60, 0.64]
2.1 Short term studies (min-hours)	1	40	Std. Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.60, 0.64]

Analysis 34.1. Comparison 34 Adults - Crossover design - Different doses in inhalers: Rotahaler vs pMDI (% change from baseline), Outcome 1 FEV1.

Analysis 34.2. Comparison 34 Adults - Crossover design - Different doses in inhalers: Rotahaler vs pMDI (% change from baseline), Outcome 2 Symptom Scores - Daily (higher score worse).

Comparison 35. Adults - Crossover design - Different doses in inhalers: All other inhaler devices vs pMDI (combined using SMD)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1	5		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Short term studies (min-hours)	3	154	Std. Mean Difference (IV, Fixed, 95% CI)	0.22 [-0.10, 0.54]
1.2 Long term studies (days-months)	1	74	Std. Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.41, 0.50]
1.3 Cumulative dosing studies	1	48	Std. Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.67, 0.46]

Analysis 35.1. Comparison 35 Adults - Crossover design - Different doses in inhalers: All other inhaler devices vs pMDI (combined using SMD, Outcome 1 FEV1.

Comparison 36. Adults - Parallel design: Turbuhaler vs pMDI (mean absolute value)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment Failures/Dropouts	1	258	Risk Ratio (M-H, Fixed, 95% CI)	1.94 [0.68, 5.60]
1.1 Long term studies (days-months)	1	258	Risk Ratio (M-H, Fixed, 95% CI)	1.94 [0.68, 5.60]
2 Preference for inhaler	1	258	Risk Ratio (M-H, Fixed, 95% CI)	1.92 [1.29, 2.85]
2.1 Long term studies (days-months)	1	258	Risk Ratio (M-H, Fixed, 95% CI)	1.92 [1.29, 2.85]

Analysis 36.1. Comparison 36 Adults - Parallel design: Turbuhaler vs pMDI (mean absolute value), Outcome 1 Treatment Failures/Dropouts.

Analysis 36.2. Comparison 36 Adults - Parallel design: Turbuhaler vs pMDI (mean absolute value), Outcome 2 Preference for inhaler.

Comparison 37. Adults - Parallel design: HFA-pMDI vs pMDI (mean absolute values)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 (L)	1	534	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.12, 0.16]
1.1 Long term studies (days-months)	1	534	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.12, 0.16]
2 PEFR - Daily (L/min)	1	534	Mean Difference (IV, Fixed, 95% CI)	-8.0 [-26.83, 10.83]
2.1 Long term studies (days-months)	1	534	Mean Difference (IV, Fixed, 95% CI)	-8.0 [-26.83, 10.83]
3 PEFR (morning)	1	321	Mean Difference (IV, Fixed, 95% CI)	-4.0 [-24.36, 16.36]
3.1 Long term Studies (days-months)	1	321	Mean Difference (IV, Fixed, 95% CI)	-4.0 [-24.36, 16.36]
4 Beta-2 usage (doses per week)	1	321	Mean Difference (IV, Fixed, 95% CI)	0.91 [-1.03, 2.85]
4.1 Long term studies (days-months)	1	321	Mean Difference (IV, Fixed, 95% CI)	0.91 [-1.03, 2.85]
5 Serum K+ (mmol/L)	1	490	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-1.36, 1.30]
5.1 Long term studies (days - months)	1	490	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-1.36, 1.30]
6 Treatment Failures/Dropouts	2	926	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.72, 1.67]
6.1 Long term studies (days-months)	2	926	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.72, 1.67]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 Acute Exacerbations	1	379	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.65, 1.84]
7.1 Long term studies (days-months)	1	379	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.65, 1.84]
8 Adverse Events	2	926	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.89, 1.08]
8.1 Long term studies (days-months)	2	926	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.89, 1.08]
9 Inhaled steroid requirement	1	379	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.91 [0.61, 1.36]
9.1 Long term studies (days-months)	1	379	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.91 [0.61, 1.36]

Analysis 37.1. Comparison 37 Adults - Parallel design: HFA-pMDI vs pMDI (mean absolute values), Outcome 1 FEV1 (L).

Analysis 37.2. Comparison 37 Adults - Parallel design: HFA-pMDI vs pMDI (mean absolute values), Outcome 2 PEFR - Daily (L/min).

Analysis 37.3. Comparison 37 Adults - Parallel design: HFA-pMDI vs pMDI (mean absolute values), Outcome 3 PEFR (morning).

Analysis 37.4. Comparison 37 Adults - Parallel design: HFA-pMDI vs pMDI (mean absolute values), Outcome 4 Beta-2 usage (doses per week).

Analysis 37.5. Comparison 37 Adults - Parallel design: HFA-pMDI vs pMDI (mean absolute values), Outcome 5 Serum K+ (mmol/L).

Analysis 37.6. Comparison 37 Adults - Parallel design: HFA-pMDI vs pMDI (mean absolute values), Outcome 6 Treatment Failures/Dropouts. **Analysis 37.7. Comparison 37 Adults - Parallel design: HFA-pMDI vs pMDI (mean absolute values), Outcome 7 Acute Exacerbations.** **Analysis 37.8. Comparison 37 Adults - Parallel design: HFA-pMDI vs pMDI (mean absolute values), Outcome 8 Adverse Events.**

Analysis 37.9. Comparison 37 Adults - Parallel design: HFA-pMDI vs pMDI (mean absolute values), Outcome 9 Inhaled steroid requirement.

Comparison 38. Adults - Parallel design: HFA-pMDI vs pMDI (absolute change from baseline)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Heart Rate (bpm)	1	534	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.1 Long term studies (days-months)	1	534	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Adverse Events	1	423	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [0.97, 1.99]
2.1 Long term studies (days-months)	1	423	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [0.97, 1.99]
3 Acute Exacerbations	1	423	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.33, 1.87]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Long term studies (days-months)	1	423	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.33, 1.87]

Analysis 38.1. Comparison 38 Adults - Parallel design: HFA-pMDI vs pMDI (absolute change from baseline), Outcome 1 Heart Rate (bpm).

Study or subgroup	HFA-pMDI Group		pMDI Group		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
38.1.1 Long term studies (days-months)							
Salat 2000	269	2 (0)	265	1 (0)			Not estimable
Subtotal ***	269		265				Not estimable
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	269		265				Not estimable
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							

Lower with HFA-pMDI -10 -5 0 5 10 Lower with pMDI

Analysis 38.2. Comparison 38 Adults - Parallel design: HFA-pMDI vs pMDI (absolute change from baseline), Outcome 2 Adverse Events.

Study or subgroup	HFA-pMDI Group	pMDI Group	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
38.2.1 Long term studies (days-months)					
Baumgarten 2000	56/215	39/208		100%	1.39[0.97,1.99]
Subtotal (95% CI)	215	208		100%	1.39[0.97,1.99]
Total events: 56 (HFA-pMDI Group), 39 (pMDI Group)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.78(P=0.07)					
Total (95% CI)	215	208		100%	1.39[0.97,1.99]
Total events: 56 (HFA-pMDI Group), 39 (pMDI Group)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.78(P=0.07)					

Less with HFA-pMDI

0.10.20.512510

Less with pMDI

Analysis 38.3. Comparison 38 Adults - Parallel design: HFA-pMDI vs pMDI (absolute change from baseline), Outcome 3 Acute Exacerbations.

Comparison 39. Adults - Parallel design: pMDI vs HFA-pMDI (% change from baseline)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1	3	898	Mean Difference (IV, Fixed, 95% CI)	-1.68 [-4.90, 1.55]
1.1 Long term studies (days-months)	3	898	Mean Difference (IV, Fixed, 95% CI)	-1.68 [-4.90, 1.55]
2 AUC-FEV1	3	898	Mean Difference (IV, Fixed, 95% CI)	-6.29 [-22.11, 9.52]
2.1 Long term studies (days-months)	3	898	Mean Difference (IV, Fixed, 95% CI)	-6.29 [-22.11, 9.52]
3 Treatment Failures/Dropouts	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Long term studies (days-months)	3	519	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.61, 1.24]
4 Oral corticosteroid requirement for treatment of acute exacerbations	3	519	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.49, 0.91]
4.1 Long term studies (days-months)	3	519	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.49, 0.91]
5 Acute Exacerbations	1	469	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.69, 1.46]
5.1 Long term studies (days-months)	1	469	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.69, 1.46]
6 Adverse Events	2	519	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.96, 1.14]
6.1 Long term studies (days-months)	2	519	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.96, 1.14]

Analysis 39.1. Comparison 39 Adults - Parallel design: pMDI vs HFA-pMDI (% change from baseline), Outcome 1 FEV1.

Analysis 39.2. Comparison 39 Adults - Parallel design: pMDI vs HFA-pMDI (% change from baseline), Outcome 2 AUC-FEV1.

Analysis 39.3. Comparison 39 Adults - Parallel design: pMDI vs HFA-pMDI (% change from baseline), Outcome 3 Treatment Failures/Dropouts.

Analysis 39.4. Comparison 39 Adults - Parallel design: pMDI vs HFA-pMDI (% change from baseline), Outcome 4 Oral corticosteroid requirement for treatment of acute exacerbations.

Analysis 39.5. Comparison 39 Adults - Parallel design: pMDI vs HFA-pMDI (% change from baseline), Outcome 5 Acute Exacerbations.

Analysis 39.6. Comparison 39 Adults - Parallel design: pMDI vs HFA-pMDI (% change from baseline), Outcome 6 Adverse Events.

Comparison 40. Adults - Parallel design: HFA-pMDI vs pMDI (combined using SMD)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1	4	1432	Std. Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.14, 0.07]
1.1 Long term studies (days-months)	4	1432	Std. Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.14, 0.07]
2 Treatment Failures/Dropouts	4	1285	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.72, 1.29]
2.1 Long term studies (days-months)	4	1285	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.72, 1.29]
3 Acute Exacerbations	3	1271	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.75, 1.33]
3.1 Long term studies (days-months)	3	1271	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.75, 1.33]
4 Adverse Events	5	1868	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.97, 1.11]
4.1 Long term studies (days-months)	5	1868	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.97, 1.11]

Analysis 40.1. Comparison 40 Adults - Parallel design: HFA-pMDI vs pMDI (combined using SMD), Outcome 1 FEV1.

Analysis 40.2. Comparison 40 Adults - Parallel design: HFA-pMDI vs pMDI (combined using SMD), Outcome 2 Treatment Failures/Dropouts.

Analysis 40.3. Comparison 40 Adults - Parallel design: HFA-pMDI vs pMDI (combined using SMD), Outcome 3 Acute Exacerbations.

Analysis 40.4. Comparison 40 Adults - Parallel design: HFA-pMDI vs pMDI (combined using SMD), Outcome 4 Adverse Events.

Comparison 41. Adults - Parallel design: Rotahaler vs pMDI (absolute change from baseline)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment Failures/Dropouts	1	231	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.72, 1.98]
1.1 Long term studies (days-months)	1	231	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.72, 1.98]
2 Acute Exacerbations	1	231	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.51, 2.39]
2.1 Long term studies (days-months)	1	231	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.51, 2.39]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Adverse Events	1	231	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.41, 1.20]
3.1 Long term studies (days-months)	1	231	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.41, 1.20]

Analysis 41.1. Comparison 41 Adults - Parallel design: Rotahaler vs pMDI (absolute change from baseline), Outcome 1 Treatment Failures/Dropouts.

Analysis 41.2. Comparison 41 Adults - Parallel design: Rotahaler vs pMDI (absolute change from baseline), Outcome 2 Acute Exacerbations.

Analysis 41.3. Comparison 41 Adults - Parallel design: Rotahaler vs pMDI (absolute change from baseline), Outcome 3 Adverse Events.

Comparison 42. Adults - Parallel design: Spiros vs pMDI (mean absolute value)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 AUC-FEV1 (L x min)	1	160	Mean Difference (IV, Fixed, 95% CI)	-0.56 [-30.54, 29.42]
1.1 Long term studies (days-months)	1	160	Mean Difference (IV, Fixed, 95% CI)	-0.56 [-30.54, 29.42]
2 Treatment Failures/Dropouts	1	189	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.63, 2.67]
2.1 Long term studies (days-months)	1	189	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.63, 2.67]
3 Acute Exacerbations	1	189	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [0.41, 4.88]
3.1 Long term studies (days-months)	1	189	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [0.41, 4.88]
4 Adverse Events	1	189	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.86, 1.33]
4.1 Long term studies (days-months)	1	189	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.86, 1.33]

Analysis 42.1. Comparison 42 Adults - Parallel design: Spiros vs pMDI (mean absolute value), Outcome 1 AUC-FEV1 (L x min).

Analysis 42.2. Comparison 42 Adults - Parallel design: Spiros vs pMDI (mean absolute value), Outcome 2 Treatment Failures/Dropouts.

Analysis 42.3. Comparison 42 Adults - Parallel design: Spiros vs pMDI (mean absolute value), Outcome 3 Acute Exacerbations.

Analysis 42.4. Comparison 42 Adults - Parallel design: Spiros vs pMDI (mean absolute value), Outcome 4 Adverse Events.

Comparison 43. Adults - Parallel design: Multi Dose Powder Inhaler vs pMDI (mean absolute value)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 (L)	1	106	Mean Difference (IV, Fixed, 95% CI)	0.22 [-0.14, 0.58]
1.1 Long term studies (days-months)	1	106	Mean Difference (IV, Fixed, 95% CI)	0.22 [-0.14, 0.58]
2 FVC (L)	1	106	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.27, 0.47]
2.1 Long term studies (days-months)	1	106	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.27, 0.47]
3 PEFR - Daily (L/min)	1	106	Mean Difference (IV, Fixed, 95% CI)	17.0 [-25.24, 59.24]
3.1 Long term studies (days-months)	1	106	Mean Difference (IV, Fixed, 95% CI)	17.0 [-25.24, 59.24]
4 Beta-2 usage (doses per week)	1	106	Mean Difference (IV, Fixed, 95% CI)	-6.10 [-12.75, 0.55]
4.1 Long term studies (days-months)	1	106	Mean Difference (IV, Fixed, 95% CI)	-6.10 [-12.75, 0.55]
5 Symptom Scores - Day time (higher score worse)	1	106	Std. Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.37, 0.44]
5.1 Long term studies (days-months)	1	106	Std. Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.37, 0.44]
6 Symptom Scores - Night time (higher score worse)	1	106	Std. Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.51, 0.30]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Long term studies (days-months)	1	106	Std. Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.51, 0.30]
7 Treatment Failures/Dropouts	1	113	Risk Ratio (M-H, Fixed, 95% CI)	2.81 [0.35, 22.45]
7.1 Long term studies (days-months)	1	113	Risk Ratio (M-H, Fixed, 95% CI)	2.81 [0.35, 22.45]
8 Adverse Events	1	106	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.44, 1.35]
8.1 Long term studies (days-months)	1	106	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.44, 1.35]

Analysis 43.1. Comparison 43 Adults - Parallel design: Multi Dose Powder Inhaler vs pMDI (mean absolute value), Outcome 1 FEV1 (L).

Analysis 43.2. Comparison 43 Adults - Parallel design: Multi Dose Powder Inhaler vs pMDI (mean absolute value), Outcome 2 FVC (L).

Analysis 43.3. Comparison 43 Adults - Parallel design: Multi Dose Powder Inhaler vs pMDI (mean absolute value), Outcome 3 PEFR - Daily (L/min).

Analysis 43.4. Comparison 43 Adults - Parallel design: Multi Dose Powder Inhaler vs pMDI (mean absolute value), Outcome 4 Beta-2 usage (doses per week).

Analysis 43.5. Comparison 43 Adults - Parallel design: Multi Dose Powder Inhaler vs pMDI (mean absolute value), Outcome 5 Symptom Scores - Day time (higher score worse).

Analysis 43.6. Comparison 43 Adults - Parallel design: Multi Dose Powder Inhaler vs pMDI (mean absolute value), Outcome 6 Symptom Scores - Night time (higher score worse).

Analysis 43.7. Comparison 43 Adults - Parallel design: Multi Dose Powder Inhaler vs pMDI (mean absolute value), Outcome 7 Treatment Failures/Dropouts.

Analysis 43.8. Comparison 43 Adults - Parallel design: Multi Dose Powder Inhaler vs pMDI (mean absolute value), Outcome 8 Adverse Events.

Comparison 44. Adults - Parallel design: All other inhaler devices vs pMDI (combined using SMD)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment Failures/Dropouts	8	2076	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.88, 1.39]
1.1 Long term studies (days-months)	8	2076	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.88, 1.39]
2 FEV1 (L)	5	1538	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.09, 0.17]
2.1 Long term studies (days-months)	5	1538	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.09, 0.17]
3 PEFR - Daily (L/min)	2	640	Mean Difference (IV, Fixed, 95% CI)	-3.86 [-21.05, 13.34]
3.1 Long term studies (days-months)	2	640	Mean Difference (IV, Fixed, 95% CI)	-3.86 [-21.05, 13.34]
4 Beta-2 usage (doses per week)	2	427	Mean Difference (IV, Fixed, 95% CI)	0.36 [-1.51, 2.22]
4.1 Long term studies (days-months)	2	427	Mean Difference (IV, Fixed, 95% CI)	0.36 [-1.51, 2.22]
5 Acute Exacerbations	5	1691	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.79, 1.34]
5.1 Long term studies (days-months)	5	1691	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.79, 1.34]
6 Adverse Events	8	2394	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.95, 1.09]
6.1 Long term studies (days-months)	8	2394	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.95, 1.09]
7 AUC-FEV1	4	1058	Mean Difference (IV, Fixed, 95% CI)	-5.05 [-19.04, 8.94]
7.1 Long term studies (days-months)	4	1058	Mean Difference (IV, Fixed, 95% CI)	-5.05 [-19.04, 8.94]

Analysis 44.1. Comparison 44 Adults - Parallel design: All other inhaler devices vs pMDI (combined using SMD), Outcome 1 Treatment Failures/Dropouts.

Analysis 44.2. Comparison 44 Adults - Parallel design: All other inhaler devices vs pMDI (combined using SMD), Outcome 2 FEV1 (L).

Analysis 44.3. Comparison 44 Adults - Parallel design: All other inhaler devices vs pMDI (combined using SMD), Outcome 3 PEFR - Daily (L/min).

Analysis 44.4. Comparison 44 Adults - Parallel design: All other inhaler devices vs pMDI (combined using SMD), Outcome 4 Beta-2 usage (doses per week).

Analysis 44.5. Comparison 44 Adults - Parallel design: All other inhaler devices vs pMDI (combined using SMD), Outcome 5 Acute Exacerbations.

Analysis 44.6. Comparison 44 Adults - Parallel design: All other inhaler devices vs pMDI (combined using SMD), Outcome 6 Adverse Events. **Analysis 44.7. Comparison 44 Adults - Parallel design: All other inhaler devices vs pMDI (combined using SMD), Outcome 7 AUC-FEV1.**

Comparison 45. Children - Crossover design: Turbuhaler vs pMDI (mean absolute value)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 (L)	1	74	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.21, 0.17]
1.1 Short term studies (min-hours)	1	74	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.21, 0.17]
2 PEFR (morning) L/min	1	106	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.1 Long term Studies (days-months)	1	106	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 PEFR (evening) L/min	1	106	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.1 Long term Studies (days-months)	1	106	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Preference for inhaler	1	114	Risk Ratio (M-H, Fixed, 95% CI)	2.15 [1.25, 3.72]
4.1 Long term studies (days-months)	1	114	Risk Ratio (M-H, Fixed, 95% CI)	2.15 [1.25, 3.72]

Analysis 45.1. Comparison 45 Children - Crossover design: Turbuhaler vs pMDI (mean absolute value), Outcome 1 FEV1 (L).

Analysis 45.2. Comparison 45 Children - Crossover design: Turbuhaler vs pMDI (mean absolute value), Outcome 2 PEFR (morning) L/min.

Study or subgroup	Turbuhaler Group		pMDI Group		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
45.2.1 Long term Studies (days-months)							
Hultquist 1989	53	357 (0)	53	357 (0)			Not estimable
Subtotal ***	53		53				Not estimable
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	53		53				Not estimable
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Favours pMDI -1000 -500 0 500 1000 Favours Turbuhaler							

Analysis 45.3. Comparison 45 Children - Crossover design: Turbuhaler vs pMDI (mean absolute value), Outcome 3 PEFR (evening) L/min.

Study or subgroup	Turbuhaler Group		pMDI Group		Mean Difference	Weight	Mean Difference				
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI				
45.3.1 Long term Studies (days-months)											
Hultquist 1989	53	362 (0)	53	362 (0)			Not estimable				
Subtotal ***	53		53				Not estimable				
Heterogeneity: Not applicable											
Test for overall effect: Not applicable											
Total ***	53		53				Not estimable				
Heterogeneity: Not applicable											
Test for overall effect: Not applicable											
					Favours pMDI	-1000	-500	0	500	1000	Favours Turbuhaler

Analysis 45.4. Comparison 45 Children - Crossover design: Turbuhaler vs pMDI (mean absolute value), Outcome 4 Preference for inhaler.

Study or subgroup	Turbuhaler Group	pMDI Group	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
45.4.1 Long term studies (days-months)					
Hultquist 1989	28/57	13/57		100%	2.15[1.25,3.72]
Subtotal (95% CI)	57	57		100%	2.15[1.25,3.72]
Total events: 28 (Turbuhaler Group), 13 (pMDI Group)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.76(P=0.01)					
Total (95% CI)	57	57		100%	2.15[1.25,3.72]
Total events: 28 (Turbuhaler Group), 13 (pMDI Group)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.76(P=0.01)					
<div><div></div><div>Prefer pMDI</div><div>0.01</div><div>0.1</div><div>1</div><div>10</div><div>100</div><div>Prefer Turbuhaler</div></div>					

Comparison 46. Children - Crossover design: Turbuhaler vs pMDI (absolute change from baseline)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptom Scores - Day time (higher score worse)	1	42	Std. Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.55, 0.66]
1.1 Long term studies (days-months)	1	42	Std. Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.55, 0.66]
2 Symptom Scores - Night time (higher score worse)	1	42	Std. Mean Difference (IV, Fixed, 95% CI)	0.11 [-0.50, 0.71]
2.1 Long term studies (days-months)	1	42	Std. Mean Difference (IV, Fixed, 95% CI)	0.11 [-0.50, 0.71]
3 Adverse Events	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 2.05]
3.1 Long term studies (days-months)	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 2.05]

Analysis 46.1. Comparison 46 Children - Crossover design: Turbuhaler vs pMDI (absolute change from baseline), Outcome 1 Symptom Scores - Day time (higher score worse).

Analysis 46.2. Comparison 46 Children - Crossover design: Turbuhaler vs pMDI (absolute change from baseline), Outcome 2 Symptom Scores - Night time (higher score worse).

Analysis 46.3. Comparison 46 Children - Crossover design: Turbuhaler vs pMDI (absolute change from baseline), Outcome 3 Adverse Events.

Comparison 47. Children - Crossover design: Turbuhaler vs pMDI (% change from baseline)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1	1	26	Mean Difference (IV, Fixed, 95% CI)	2.0 [-16.74, 20.74]
1.1 Cumulative dosing studies	1	26	Mean Difference (IV, Fixed, 95% CI)	2.0 [-16.74, 20.74]
2 Adverse Events	1	26	Risk Ratio (M-H, Fixed, 95% CI)	0.07 [0.00, 1.06]
2.1 Cumulative dosing studies	1	26	Risk Ratio (M-H, Fixed, 95% CI)	0.07 [0.00, 1.06]

**Analysis 47.1. Comparison 47 Children - Crossover design:
Turbuhaler vs pMDI (% change from baseline), Outcome 1 FEV1.** **Analysis 47.2. Comparison 47 Children - Crossover design: Turbuhaler
vs pMDI (% change from baseline), Outcome 2 Adverse Events.** **Comparison 48. Children - Crossover design: Turbuhaler vs pMDI (combined using SMD)**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1	2		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Short term studies (min-hours)	1	74	Std. Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.50, 0.41]
1.2 Cumulative dosing studies	1	26	Std. Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.69, 0.85]
2 Adverse Events	2	68	Risk Ratio (M-H, Fixed, 95% CI)	0.12 [0.02, 0.61]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Long term studies (days-months)	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.03, 1.57]
2.2 Cumulative dosing studies	1	26	Risk Ratio (M-H, Fixed, 95% CI)	0.07 [0.00, 1.06]

Analysis 48.1. Comparison 48 Children - Crossover design: Turbuhaler vs pMDI (combined using SMD), Outcome 1 FEV1.

Analysis 48.2. Comparison 48 Children - Crossover design: Turbuhaler vs pMDI (combined using SMD), Outcome 2 Adverse Events.

Comparison 49. Children - Crossover design: HFA-pMDI vs pMDI (mean absolute value)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 (L)	1	50	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.42, 0.38]
1.1 Short term studies (min-hours)	1	50	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.42, 0.38]

Analysis 49.1. Comparison 49 Children - Crossover design: HFA-pMDI vs pMDI (mean absolute value), Outcome 1 FEV1 (L).

Comparison 50. Children - Crossover design: pMDI vs Rotahaler (mean absolute value)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 (L)	1	92	Std. Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.43, 0.38]
1.1 Short term studies (min-hours)	1	92	Std. Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.43, 0.38]
2 PEFR - Daily (L/min)	1	86	Mean Difference (IV, Fixed, 95% CI)	-105.40 [-150.80, -58.00]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Long term studies & different dose used (days-months)	1	86	Mean Difference (IV, Fixed, 95% CI)	-105.40 [-150.80, -58.00]
3 Beta-2 usage	1	86	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.11 [0.45, 2.75]
3.1 Long term studies & different dose used (days-months)	1	86	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.11 [0.45, 2.75]
4 Symptom Scores - Day time (higher score worse)	1	86	Std. Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.40, 0.45]
4.1 Long term studies & different dose used (days-months)	1	86	Std. Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.40, 0.45]
5 Symptom Scores - Night time (higher score worse)	1	86	Std. Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.39, 0.45]
5.1 Long term studies & different dose used (days-months)	1	86	Std. Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.39, 0.45]
6 Inhaled steroid requirement	1	86	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.0 [0.34, 2.94]
6.1 Long term studies & different dose used (days-months)	1	86	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.0 [0.34, 2.94]
7 Preference	1	56	Risk Ratio (M-H, Fixed, 95% CI)	2.67 [1.22, 5.81]
7.1 Long term studies & different dose used (days-months)	1	56	Risk Ratio (M-H, Fixed, 95% CI)	2.67 [1.22, 5.81]

Analysis 50.1. Comparison 50 Children - Crossover design: pMDI vs Rotahaler (mean absolute value), Outcome 1 FEV1 (L).

Analysis 50.2. Comparison 50 Children - Crossover design: pMDI vs Rotahaler (mean absolute value), Outcome 2 PEFR - Daily (L/min).

Analysis 50.3. Comparison 50 Children - Crossover design: pMDI vs Rotahaler (mean absolute value), Outcome 3 Beta-2 usage.

Analysis 50.4. Comparison 50 Children - Crossover design: pMDI vs Rotahaler (mean absolute value), Outcome 4 Symptom Scores - Day time (higher score worse).

Analysis 50.5. Comparison 50 Children - Crossover design: pMDI vs Rotahaler (mean absolute value), Outcome 5 Symptom Scores - Night time (higher score worse).

Analysis 50.6. Comparison 50 Children - Crossover design: pMDI vs Rotahaler (mean absolute value), Outcome 6 Inhaled steroid requirement.

Analysis 50.7. Comparison 50 Children - Crossover design: pMDI vs Rotahaler (mean absolute value), Outcome 7 Preference.

Comparison 51. Children - Crossover design: pMDI vs All other inhaler devices (combined using SMD)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1	4		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Short term studies (min-hours)	3	216	Std. Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.25, 0.28]
1.2 Cumulative dosing studies	1	26	Std. Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.85, 0.69]

Analysis 51.1. Comparison 51 Children - Crossover design: pMDI vs All other inhaler devices (combined using SMD), Outcome 1 FEV1.

Comparison 52. Children - Parallel design: pMDI vs Turbuhaler (mean absolute value)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 (L)	1	118	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.08, 0.48]
1.1 Short term studies (min-hours)	1	118	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.08, 0.48]
2 FVC (L)	1	118	Mean Difference (IV, Fixed, 95% CI)	0.22 [-0.12, 0.56]
2.1 Short term studies (min-hours)	1	118	Mean Difference (IV, Fixed, 95% CI)	0.22 [-0.12, 0.56]

Analysis 52.1. Comparison 52 Children - Parallel design: pMDI vs Turbuhaler (mean absolute value), Outcome 1 FEV1 (L).

Study or subgroup	pMDI Group		Turbuhaler Group		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
52.1.1 Short term studies (min-hours)							
Hirsch 1997	59	2.3 (0.8)	59	2.1 (0.8)		100%	0.2[-0.08,0.48]
Subtotal ***	59		59			100%	0.2[-0.08,0.48]
Heterogeneity: Not applicable							
Test for overall effect: Z=1.39(P=0.16)							
Total ***	59		59			100%	0.2[-0.08,0.48]
Heterogeneity: Not applicable							
Test for overall effect: Z=1.39(P=0.16)							

Favours Turbuhaler -1 -0.5 0 0.5 1 Favours pMDI

Analysis 52.2. Comparison 52 Children - Parallel design: pMDI vs Turbuhaler (mean absolute value), Outcome 2 FVC (L).

Study or subgroup	pMDI Group		Turbuhaler Group		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
52.2.1 Short term studies (min-hours)							
Hirsch 1997	59	2.8 (0.9)	59	2.5 (1)		100%	0.22[-0.12,0.56]
Subtotal ***	59		59			100%	0.22[-0.12,0.56]
Heterogeneity: Not applicable							
Test for overall effect: Z=1.25(P=0.21)							
Total ***	59		59			100%	0.22[-0.12,0.56]
Heterogeneity: Not applicable							
Test for overall effect: Z=1.25(P=0.21)							
					-1-0.5000.51		
					Favours Turbuhaler	Favours pMDI	

Favours Turbuhaler -1 -0.5 0 0.5 1 Favours pMDI

Comparison 53. Children - Parallel design: pMDI vs HFA-pMDI (mean absolute value)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 PEFR - morning (L/min)	1	62	Mean Difference (IV, Fixed, 95% CI)	6.70 [-23.82, 37.22]
1.1 Long term studies (days-months)	1	62	Mean Difference (IV, Fixed, 95% CI)	6.70 [-23.82, 37.22]
2 PEFR - evening (L/min)	1	62	Mean Difference (IV, Fixed, 95% CI)	14.40 [-21.47, 50.27]
2.1 Long term studies (days-months)	1	62	Mean Difference (IV, Fixed, 95% CI)	14.40 [-21.47, 50.27]
3 Beta-2 usage (daily mean)	1	62	Mean Difference (IV, Fixed, 95% CI)	0.40 [-0.19, 0.99]
3.1 Long term studies (days-months)	1	62	Mean Difference (IV, Fixed, 95% CI)	0.40 [-0.19, 0.99]

Analysis 53.1. Comparison 53 Children - Parallel design: pMDI vs HFA-pMDI (mean absolute value), Outcome 1 PEFR - morning (L/min).

Analysis 53.2. Comparison 53 Children - Parallel design: pMDI vs HFA-pMDI (mean absolute value), Outcome 2 PEFR - evening (L/min).

Analysis 53.3. Comparison 53 Children - Parallel design: pMDI vs HFA-pMDI (mean absolute value), Outcome 3 Beta-2 usage (daily mean).

Comparison 54. Children - Parallel design: pMDI vs HFA-pMDI (absolute change from baseline)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 AUC-FEV1 (L x min)	1	63	Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.50, 0.28]
1.1 Long term studies (days-months)	1	63	Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.50, 0.28]

Analysis 54.1. Comparison 54 Children - Parallel design: pMDI vs HFA-pMDI (absolute change from baseline), Outcome 1 AUC-FEV1 (L x min).

Comparison 55. Children - Parallel design: pMDI vs Rotahaler (% change from baseline)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1	1	184	Mean Difference (IV, Fixed, 95% CI)	0.0 [-1.68, 1.68]
1.1 Long term studies (days-months)	1	184	Mean Difference (IV, Fixed, 95% CI)	0.0 [-1.68, 1.68]
2 Treatment Failures	1	204	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.25, 1.48]
2.1 Long term studies (days-months)	1	204	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.25, 1.48]
3 Acute Exacerbations	1	204	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.28, 0.95]
3.1 Long term studies (days-months)	1	204	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.28, 0.95]
4 Preference	1	204	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [1.14, 2.51]
4.1 Long term studies (days-months)	1	204	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [1.14, 2.51]

Analysis 55.1. Comparison 55 Children - Parallel design: pMDI vs Rotahaler (% change from baseline), Outcome 1 FEV1.

Analysis 55.2. Comparison 55 Children - Parallel design: pMDI vs Rotahaler (% change from baseline), Outcome 2 Treatment Failures.

Analysis 55.3. Comparison 55 Children - Parallel design: pMDI vs Rotahaler (% change from baseline), Outcome 3 Acute Exacerbations.

Analysis 55.4. Comparison 55 Children - Parallel design: pMDI vs Rotahaler (% change from baseline), Outcome 4 Preference.

ADDITIONAL TABLES

Table 1. Non-significant outcomes from studies in adults

Crossover studies	Outcomes	Parallel studies	Outcomes	Challenge studies	Outcomes	Different doses	Outcomes
Turbuhaler	FEV1, FVC, PEFR, AUC-FEV1, blood pressure, adverse events, treatment failure	DPI or HFA-pMDI	FEV1, FVC, PEFR, AUC-FEV1, beta-2 use, symptoms scores, exacerbations, adverse effects, preference, inhaled steroid requirement	DPI or HFA-pMDI	FEV1, FVC	DPI or HFA-pMDI	FEV1, FVC, PEFR, preference, symptoms
Diskhaler	PEFR, adverse events						
HFA-pMDI	FEV1, FVC, exacerbations, adverse events, treatment failures, AUC-FEV1, pulse rate, blood pressure, serum K ⁺ , inhaled steroid requirement						
Rotahaler	FEV1, FVC, PEFR, AUC-FEV1, adverse events, exacerbations						
Spiros	FEV1, FVC, AUC-FEV1, adverse effects, exacerbations						
Easyhaler	FEV1, FVC, PEFR, AUC-FEV1, pulse rate, blood pressure, adverse events						
Multi dose powder	FEV1, FVC, PEFR, AUC-FEV1, adverse events						
Clickhaler	FEV1, adverse events						
Gentlehaler	FEV1, FVC, PEFR						
Autohaler	FEV1, FVC, PEFR						
All Combined	FEV1, FVC, PEFR, AUC-FEV1, adverse events, treatment failure						

Table 1. Non-significant outcomes from studies in adults *(Continued)*

Combined (15-30min)	FEV1, FVC, AUC-FEV1, PEFR, pulse rate
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Table 2. Non-significant outcomes from studies in children

Crossover & Parallel	Outcome
Turbuhaler	FEV1, FVC, PEFR, symptoms
Rotahaler	FEV1, beta-2 use, symptoms, treatment failures, inhaled steroid usage
HFA-pMDI	FEV1, PEFR, beta-2 use, AUC-FEV1
All Combined	FEV1

Table 3. Non-significant outcomes, grouped by trial design (No of trials).

Crossover	Non-sig Outcomes	Parallel	Non-sig Outcomes	Challenge	Non-sig Outcomes	Different Doses	Non-sig Outcomes
Turbuhaler	FEV1 (6: Hetzel 1997, Mellen 1999, Ruffin 1998, Mathieu 1992, Zainudin 1990, Langley 1998), FVC (4: Hetzel 1997, Mellen 1999, Ruffin 1998, Mathieu 1992), pulse rate (3: Elstrom 1995, Hetzel 1997, Mellen 1999, Parameswaran 1999), treatment failure (1: Parameswaran 1999), serum potassium (2: Hetzel 1997, Mathieu 1992)	DPI or HFA - pMDI	FEV1 (6: Bronsky 1987, Cohen 1999, Selroos 1994, Tinkelman 1998, Hawksworth 1999, Silvasti 1993), FVC (2: Cohen 1999, Tinkelman 1998), PEFr (3: Selroos 1994, Tinkelman 1998), AUC - FEV1 (4: Bronsky 1987, Hawksworth 1999, Ramsdell 1999, Silvasti 1993), B2 use (2: Tinkelman 1998, Vidgren 1995), symptoms scores (1: Tinkelman 1998), exacerbations (4: Boye 1983, Vidgren 1995, Ramsdell 1999, Silvasti 1993), adverse effects (6: Boye 1983, Selroos, 1994, Vidgren 1995, Ramsdell 1999, Silvasti 1993), preference (1: Pover 1988), inhaled steroid requirement (1: Bronsky 1987), pulse rate (1: Selroos 1994)	DPI or HFA - pMDI	FEV1 (4: Bleeker 1998, O'Callaghan 1989, Custovic 1989, Newhouse 1999), FVC (1: O'Callaghan 1997), PD20 - FEV1 (2: Harris 1981, Borgstrom 1996),	DPI or HFA - pMDI	FEV1 (5: Dockhorn 1997, Hartley 1979, Salorinne 1983, Taggart 1995, Tinkelman 1998) PEFR (1: Villiger 1990), preference (1: Dockhorn 1997), symptoms (1: Hartley 1977)
Diskhaler	PEFR (1: Lofdahl 1997) adverse events (1: Lofdahl 1997)						
HFA-pMDI	FEV1 (5: Morice 1988, Svedmyr 1982, Egger 1997, Thompson 1995, Kemp 1997) FVC (3:						

Table 3. Non-significant outcomes, grouped by trial design (No of trials). *(Continued)*

	Morice 1988, Egger 1997, Thompson 1995) adverse events (2: Svedmyr 1982, Kemp 1997), AUC - FEV1 (2: Kemp 1997, Selroos 1996), pulse rate (2: Morice 1996, Svedmyr 1982), blood pressure (2: Morice 1996, Svedmyr 1982), serum potassium (2: Morice 1996, Svedmyr)
Rotahaler	FEV1 (8: Haatela 1994, Kleerup 1996, Ramsdell 1998, Svenonius 1994, Maesen 1986, Seppala 1994 1998, coner 1980, Nelson 1999), FVC (3: Svenonius 1994, Maesen 1986, Colice 1980) PEFR (4: Chapman 1997, Kiviranta 1985, Latimer 1982, Colice 1999), AUC - FEV1(2:Maesen 1986, Nelson 1999) adverse events (2: Chapman 1997, Nelson 1999) exacerbations (1: Kleerup 1996)
Spiros	FEV1(1: Cleophas 1993), FVC (1: Cleophas 1993), AUC - FEV1 (1: Cleophas 1993), PEFR (1: Cleophas 1993), pulse rate (1: Cleophas 1993), blood pressure (1: Cleophas 1993), serum potassium (1: Cleophas 1993)
Spinhaler	FEV1 (1: Golish 1998), FVC (1: Golish 1998)
Easyhaler	FEV1 (4: Johnsen 1988, Waterhouse 1992, Nelson 1999, Geoffroy 1999), FVC (4: Johnsen 1988, Waterhouse 1992, Nelson 1999, Geoffroy 1999), PEFR (3: Waterhouse 1992, Nelson 1999, Geoffroy 1999), AUC - FEV1 (2: Waterhouse 1992, Nelson 1999), pulse rate (1: Nelson 1999), blood pressure (1: Nelson 1999), adverse events (1: Borgstrom 1996)
Multi dose powder	FEV1 (1: Borgstrom 1996) , AUC - FEV, (1: Borgstrom 1996), adverse events (1: Borgstrom 1996), preference (1: Borgstrom 1996)
Clickhaler	FEV1 (1: Nieminem 1994), adverse events (1: Nieminem 1994)

Table 3. Non-significant outcomes, grouped by trial design (No of trials). *(Continued)*

Gentlehaler	FEV1 (1:Osterman 1989), FVC (1: Osterman 1989), PEFR (1: Osterman 1989)
Autohaler	FEV1 (1:Bronsky 1995), FVC (1: Bronsky 1995), PEFR (1: Bronsky 1995)

WHAT'S NEW

Date	Event	Description
18 August 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 3, 2000

Review first published: Issue 1, 2002

Date	Event	Description
29 November 2001	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Felix Ram (previous author) carried out all of the work involved in this review with help from the following people. David Brocklebank was involved in the duplicate screening of abstracts and full text papers for inclusion. John Wright was the third reviewer whose opinions was sort if disagreements persisted for study inclusion he also commented on draft versions. John White was involved in the early developmental stages of the review and also commented on the draft versions of the review. Paul Jones edited and revised many versions of the review before approval for the Cochrane library.

DECLARATIONS OF INTEREST

There are no known conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- NHS R&D Health Technology Assessment Programme, UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

*Nebulizers and Vaporizers; Adrenergic beta-Agonists [*administration & dosage]; Asthma [*drug therapy]; Bronchodilator Agents [*administration & dosage]; Pressure; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans