COPD Evidence Tables

The evidence tables are presented in section order.

The methodological quality of each paper was rated using the Scottish Intercollegiate Guidelines Network (SIGN) system (Scottish Intercollegiate Guidelines Network. SIGN 50 Guideline Developers Handbook, 2001; ID 19457):

++	All or most of the SIGN methodology checklist criteria were fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
+	Some of the criteria were fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
-	Few or no criteria were fulfilled. The conclusions of the study are thought likely or very likely to alter.

Chronic Obstructive Pulmonary Disease: Management of adults with Chronic Obstructive Pulmonary Disease in Primary and Secondary Care

Managing Stable COPD
Theophylline and other methylxanthines
Phosphodiesterase type 4 inhibitors
Index

Author	Publication Date	ID
Ram FSF, Jones PW, Castro AA, De Brito JA, Atallah AN, Lacasse Y *et al*. Oral Theophylline for chronic obstructive pulmonary disease. (Cochrane Review). *The Cochrane Library.Oxford:Update Software* 2003;**Issue 3**. Date of most recent substantive amendment 2002.	2003	1713
Rossi, A., Kristufek, P., Levine, B. E., Thomson, M. H., Till, D., Kottakis, J., & Della Cioppa, G. 2002, "Comparison of the efficacy, tolerability, and safety of Formoterol dry powder and oral, slow-release Theophylline in the treatment of COPD", *Chest*, vol. 121, no. 4, pp. 1058-1069.	2002	966
Compton, C. H., Gubb, J., Nieman, R., Edelson, J., Amit, O., Bakst, A., Ayres, J. G., Creemers, J. P. H. M., Schultze-Werninghaus, G., Brambilla, C., & Barnes, N. C. 2001, "Cilomilast, a selective phosphodiesterase-4 inhibitor for treatment of patients with chronic obstructive pulmonary disease: a randomised, dose-ranging study", *Lancet*, vol. 358, no. 9278, pp. 265-270.	2001	1261

Author / Title / Reference / Yr	Ram FSF, Jones PW, Castro AA, De Brito JA, Atallah AN, Lacasse Y *et al*. Oral Theophylline for chronic obstructive pulmonary disease. (Cochrane Review). *The Cochrane Library.Oxford: Update Software* 2003;**Issue 3**. Date of most recent substantive amendment 2002.
N=	RCTs=20. Geographical Location=USA x 6, Canada x 3, UK x 2, Israel x 2, Ireland x 2, Japan x 2, Denmark x 1, France x 1, Germany x 1. Duration=Ranged from 7 to 90 days.
Research Design	Systematic Review of RCTs (cross over design)
Aim	To determine the effectiveness of oral Theophylline when compared to placebo in patients with stable COPD
Operational Definition	ATS 1995, BTS 1997, ERS 1995 criteria.
Population	Stable COPD (asthma excluded).
Intervention	Oral Theophylline (using dosing schedules to obtain plasma Theophylline levels in the therapeutic range 10 to 20 mg/ml Alexander 1980, Guyatt 1987, Muchraoui 1994, Marvin 1983, Schmidt 1979 – Short-action drug. All other studies – Long-action drug.
Comparison	Placebo
Outcome	Primary outcomes: Exercise capacity / Lung function measurements / Health status (QoL) Secondary outcomes: Arterial blood gas and oxygen saturation / Dyspnoea / Patient preference for treatment / Adverse events / Acute exacerbations / Mortality
Characteristics	Baseline mean FEV1 for patients in 20 studies ranged from 0.96 to 1.15 L. Mean age range 58 to 69 years. Four studies excluded use of bronchodilators Concomitant therapy varied from none to any other bronchodilator plus corticosteroid (oral and inhaled).
Results	FEV1 There was a statistically significant improvement in FEV1 in favour of the Theophylline group compared to the placebo group. WMD 100ml; 95%CI; 40 to 160ml. FVC There was a statistically significant improvement in FVC in favour of the Theophylline group compared to the placebo group. WMD 210ml; 95% CI; 100 to 320ml. VO2 max There was a statistically significant improvement in favour of the treatment group. WMD 195ml/min; 95%CI; 113 to 278ml/min. PaO2 There was a statistically significant improvement with treatment. WMD 3.18 mmHg; 95% CI; 1.23 to 5.13mmHg. PaCO2

	There was a statistically significant decrease with Theophylline compared to placebo. WMD –2.36 mmHg; 95% CI; -3.52 to –1.21mmHg Patient Preference Participants preferred Theophylline to placebo. RR 2.27; 95%CI 1.26 to 4.11 (see comments below*) Nausea The risk of experiencing nausea when on treatment with Theophylline was significantly increase (RR 7.67; 95%CI: 1.47 to 39.94) There were no statistically significant outcomes for: Distance walked, VAS for breathlessness, symptoms of wheeze and dyspnoea, exacerbations, dropouts. No data were available for health status or mortality. Conclusion Theophylline administered orally for at least 7 days to patients with moderate to severe stable COPD improves lung function, ventilatory capacity and arterial blood gas tensions. These benefits were apparent in patients receiving a variety of different concomitant therapies. The number of adverse effects (nauseas) was greater with Theophylline.
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1a
Papers included	Alexander 1980 N=53, Anderson 1982 N=21, Chrystyn 1988 N=38, Dullinger 1986 N=10, Fink 1994 N=22, Guyatt 1987 N=27, Iversen 1992 N=48, Kongragunta 1988 N=8, Machraoui 1994 N=25, Mahler 1985 N=12, Marvin 1983 N=15, Mulloy 1993 N=12, Murciano 1989 N=60, Newman 1994 N=12, Nishimura 1993 N=12, Nishimura 1995 N=32, Power 1992 N=37, Rivington 1988 N=12, Schmidt 1979 N=12, Thomas 1992 N=12.
NCC CC ID	1713

Author / Title / Reference / Yr	Rossi, A., Kristufek, P., Levine, B. E., Thomson, M. H., Till, D., Kottakis, J., & Della Cioppa, G. 2002, "Comparison of the efficacy, tolerability, and safety of Formoterol dry powder and oral, slow-release Theophylline in the treatment of COPD", *Chest*, vol. 121, no. 4, pp. 1058-1069. Ref ID: 966
N=	N=854 (N=622 completed the 12 month period). Geographical Location=81 centres worldwide. Site= Outpatients. Duration=12 months
Research Design	A randomised parallel group trial with double blind arms for Formoterol and placebo and an open arm for oral slow release Theophylline.
Aim	To compare the efficacy, tolerability, and safety of therapy with Formoterol and oral slow release Theophylline in patients with COPD.
Operational Definition	Diagnosis of COPD according to the ATS guidelines.

Population	Patients with COPD
Intervention	Twice daily-inhaled Formoterol dry powder (12 or 24 ug). Results excluded for this Evidence Table
Comparison	N=122 Placebo OR N=209 Theophylline (individualised doses), oral, slow release. Results for placebo and Theophylline included in this Evidence Table
Outcome	Pulmonary function, symptoms, quality of life, safety and tolerability
Characteristics	Mean age 63 years, range 34 to 88 years Gender – 83% male Mean duration of COPD 8 years (range 0 to 54 years). FEV1 mean – 1.37 L (range 0.5 to 3.9 L) Inclusion criteria: FEV1 was <70% predicted and >0.75 L, with an FEV1: FVC of <88% of that predicted in men and <89% of that predicted in women. Following reversibility testing with 200ug salbutamol at screening, patients were classified as irreversible / poorly reversible when their FEV1 increased <15% form the baseline value. For these pts a separate analysis of the primary variable was performed. The only concomitant medications that were allowed were inhaled corticosteroids
Results	FEV1 at 3/12 FEV1 at 12 months Total The comparison between Theophylline and placebo produced a statistically significant result in favour of the Theophylline group, estimated difference 0.116L, p<0.001. The comparison between Theophylline and placebo produced a statistically significant result in favour of the Theophylline group, estimated difference 0.130L, p<0.001. Irreversible / poorly reversible Estimated difference, L; 0.042; p=0.339 Estimated difference, L; 0.088; p=0.073 Reversible Estimated difference, L; 0.222 p<0.001 Estimated difference, L; 0.220

	p<0.001 FEV1 Theophylline was also significantly more effective than placebo at every time point and for each visit (all p<0.005) and the difference was clinically relevant at 5, 7, 8, 10, 11 and 12 hours. Morning premedication FEV1 values Theophylline significantly improved morning premedication FEV1 over placebo during the entire treatment period p<0.013. FVC over 12 hrs at 3 and 12 months Theophylline was significantly more effective than placebo (all p<0.007). Morning premedication PEF Theophylline as significantly more effective than placebo (p=0.007). Total diary symptom score There were no statistically significant differences between the treatment groups. Rescue medication There were no statistically significant differences between the Theophylline and placebo group for use of rescue medication. COPD exacerbations “Mild COPD exacerbation” - There was no significant difference between the Theophylline and placebo group. “Moderate COPD exacerbation” – Was lower while pts were receiving Theophylline (5%) than when they were receiving placebo (8%). P=0.019. “Severe COPD exacerbation” (COPD related hospitalisations) – Was higher in the placebo group (20) compared to the Theophylline group (6). P values not given. QoL Statistically significant improvements in the total SGRQ score at 12 months (compared to baseline) were seen for Theophylline compared to placebo p=0.013. Theophylline also produced a statistically significant reduction in the activity sub score vs placebo, p=0.003. Adverse Events and Safety There were higher numbers of GI adverse events in the Theophylline group compared to placebo. The number of pts reporting severe adverse events was N=59 in the placebo group and N=56 in the Theophylline group. 27 adverse events were reported by 17 pts (8%) receiving placebo and 136 were reported by 66 pts (32%) receiving Theophylline. In the Theophylline group (N=48, 23%), the total number of withdrawals due to adverse events (COPD related and not COPD related) was twofold higher than that in the placebo group (N=23 / 10%). Patients receiving Theophylline were twice as likely as patients receiving placebo to discontinue treatment due to adverse events or unsatisfactory therapeutic effect (Theophylline/placebo hazard ratio, 2.05; p=0.002). There were no deaths in the Theophylline or placebo groups.
SIGN Quality Rating	Given SIGN rating of “ – “ in light of “open-label” Theophylline arm and direction of results. SIGN rating only applicable to the Theophylline focus of this Evidence Table and not in application to this paper if it is reviewed for

	the Formoterol arms. (Studies included in the Cochrane Systematic Review for oral Theophylline (Ram 2002) were either double or single blind).
Hierarchy of Evidence Grading	1b
NCC CC ID	966

Author / Title / Reference / Yr	Compton, C. H., Gubb, J., Nieman, R., Edelson, J., Amit, O., Bakst, A., Ayres, J. G., Creemers, J. P. H. M., Schultze-Werninghaus, G., Brambilla, C., & Barnes, N. C. 2001, "Cilomilast, a selective phosphodiesterase-4 inhibitor for treatment of patients with chronic obstructive pulmonary disease: a randomised, dose-ranging study", *Lancet*, vol. 358, no. 9278, pp. 265-270. Ref ID: 1261
N=	N=424 Geographical Location=60 European centres. Duration=6 wk
Research Design	Randomised, double-blind, placebo-controlled, parallel-group study
Aim	To assess the safety, efficacy and dose response of cilomilast in the treatment of patients with COPD
Operational Definition	Clinical diagnosis of COPD consistent with ERS definition
Population	Stable COPD
Intervention	Cilomilast - twice daily N=109 - 5mg N=102 - 10mg N=107 - 15mg
Comparison	N=106 - Placebo
Outcome	**Primary outcome** Trough FEV1 before and after use of a bronchodilator **Secondary outcomes** PEF and FVC, and the first dose effect of active treatment on FEV1, FVC and PEF. QoL (SGRQ), $beta_2$-agonist use, adverse events
Characteristics	Mean age 63 yrs. Age range 40 to 80 years Patients had a ratio of prebronchodilator FEV1 to FVC of <70% and an FEV1 after use of an inhaled $beta_2$-agonist of 30 to 70% of the predicted value. Patients had fixed airflow obstruction, defined as <15% or less than a 200ml improvement in FEV1 measured 30 min after inhalation of 200ug salbutamol. With the exception of short acting $beta_2$-agonists and anticholinergics agents, all other COPD medications were discontinued before or at screening. Mean FEV1 of 46.8% of predicted, FEV1/FVC of 54.6% and post salbutamol reversibility of 5.4%

	Exclusions: Asthma Those with "poorly controlled COPD" (necessitating a hospital visit within 6wks before the study). Recent exacerbations of COPD Oral corticosteroid use within 4wks of study
Results	**FEV1** Cilomilast 15mg twice daily significantly improved FEV1 compared with placebo Mean 130ml vs 30ml; (95% CI; 90 to 240) at 6 weeks, p<0.0001 (maximum increase was 160ml) Post bronchodilator measurements of FEV1 also increased from baseline, with a maximum difference from placebo of 100ml (20 to 170ml) with cilomilast 15mg at 6 weeks. P<0.0096. **FVC** There was a statistically significant difference in favour of cilomilast 15mg compared to placebo at 6 weeks with a mean increase of 190ml (70 to 310); p=0.001 **PEF** Improvements in PEF were significantly greater in the cilomilast 15mg group than in placebo at all time points; at 6 weeks the mean increase was 34L/min (18 to 50; p<0.0001). **QoL** There were no statistically significant differences between the groups. **Beta$_2$-agonist use** In the high dose cilomilast group N=40 (38%) compared with N=21 (20%) in the placebo group had reduced their use of beta$_2$-agonists. **Adverse Events** There were no significant differences in the serious adverse events between the groups. However, the most common adverse reaction was nausea that arose in 11% of patients taking Cilomilast 15mg compared to 1% in the placebo group. Diarrhoea was reported by 9% of patients taking Cilomilast 15mg compared to 1% in the placebo group. **Conclusion** Authors highlight that "the improvements in pulmonary function and quality of life seen after 6 wks of treatment with cilomilast 15mg twice daily suggest that selective inhibitors of phosphodiesterase 4 might be effective as a maintenance treatment for COPD".
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1b
NCC CC ID	1261