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

Management of exacerbations of COPD
Theophylline and other methylxanthines
Index

Author	Publication Date	ID
Barr RG, Rowe BH, Camargo CA Jr. Methylxanthines for exacerbations of chronic obstructive pulmonary disease (Cochrane Review). In: *The Cochrane Library*, Issue 2, 2003. Oxford: Update Software. CD002168	2002	859

Reference Exclusion List
Original literature search N=121 hits

Reference	Reason for exclusion
Rice, K. L., Leatherman, J. W., Duane, P. G., Snyder, L. S., Harmon, K. R., Abel, J., & Niewoehner, D. E. 1987, "Aminophylline for acute exacerbations of chronic obstructive pulmonary disease. A controlled trial", *Annals of Internal Medicine*, vol. 107, pp. 305-309. Ref ID: 1110	Included in Cochrane
Seidenfeld, J. J., Jones, W. N., Moss, R. E., & Tremper, J. 1984, "Intravenous aminophylline in the treatment of acute bronchospastic exacerbations of chronic obstructive pulmonary disease", *ANN EMERG.MED*, vol. 13, pp. 248-252. Ref ID: 1111	Included in Cochrane
Dolcetti, A., Osella, D., De Filippis, G., Carnuccio, C., & Grossi, E. 1988, "Comparison of intravenously administered doxofylline and placebo for the treatment of severe acute airways obstruction", *Journal of International Medical Research*, vol. 16, pp. 264-269. Ref ID: 1107	Included in Cochrane
Wrenn, K., Slovis, C. M., Murphy, F., & Greenberg, R. S. 1991, "Aminophylline therapy for acute bronchospastic disease in the emergency room", *Annals of Internal Medicine*, vol. 115, no. 4, pp. 241-247. Ref ID: 1289	Included in Cochrane
Tandon, M. K. & Kailis, S. G. 1991, "Bronchodilator treatment for partially reversible chronic obstructive airways disease", *Thorax*, vol. 46, no. 4, pp. 248-251. Ref ID: 496	Stable COPD

Barbera, J. A., Reyes, A., Roca, J., Montserrat, J. M., Wagner, P. D., & Rodriguez, R. R. 1992, "Effect of intravenously administered aminophylline on ventilation/perfusion inequality during recovery from exacerbations of chronic obstructive pulmonary disease", *American Review of Respiratory Disease*, vol. 145, pp. 1328-1333. Ref ID: 1106	N=9 / Recovery from exacerbation of COPD
Murata, G. H., Gorby, M. S., Chick, T. W., & Halperin, A. K. 1990, "Aminophylline in the outpatient management of decompensated chronic obstructive pulmonary disease", *Chest*, vol. 98, no. 6, pp. 1346-1350. Ref ID: 93	Outpatient management
ZuWallack, R. L., Mahler, D. A., Reilly, D., Church, N., Emmett, A., Rickard, K., & Knobil, K. 2001, "Salmeterol plus theophylline combination therapy in the treatment of COPD", *Chest*, vol. 119, no. 6, pp. 1661-1670. Ref ID: 1118	Stable COPD
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	Stable COPD
Murciano, D., Auclair, M. H., Pariente, R., & Aubier, M. 1989, "A randomised controlled trial of theophylline in patients with severe chronic obstructive pulmonary disease", *New England Journal of Medicine*, vol. 320, no. 23, pp. 1521-1525. Ref ID: 201	Stable COPD
All papers cross referenced to: McCrory, D. C., Brown, C., Gray, R. N., Goslin, R. E., MacIntyre, N. R., Kolimaga, J. T., Oddone, E. Z., & Matchar, D. 2001, *Management of acute exacerbations of chronic obstructive pulmonary disease.*, Agency for Healthcare Research and Quality., Rockville, MD, USA, 256. Ref ID: 1145	

Author / Title / Reference / Yr	Barr RG, Rowe BH, Camargo CA, Jr. Methylxanthines for exacerbations of chronic obstructive pulmonary disease. (Cochrane Review). *The Cochrane Library.Oxford: Update Software* 2003;**Issue 3**.
N=	N=4 RCTs. Total sample size N=172.
Design	Systematic Review with meta-analysis
Aim	To determine the benefit of methyl-xanthines compared to standard care for COPD exacerbations.
Operational Definition	Dolcetti - 15% or more improvement in FEV1 with salbutamol and prior diagnosis of COPD. Exacerbation not defined. Although all patients were described as having an exacerbation a cross over design was used. Rice - Prior spirometry of FEV1 <2SD below predicted and FEV1/FVC <60% and prior diagnosis of COPD. Exacerbation not defined. Seidenfield - ATS definition of chronic bronchitis. Wrenn - Not defined. Inclusion criteria state "asthma exacerbation or wheeze". No prior PFT data, likely to be some misclassification with asthma.
Population	Acute exacerbation COPD
Intervention	Methyl-xanthines (oral or intravenous)
Comparison	Placebo (with or without standard care)
Outcomes	FEV1 at 2hrs, PEFR at 2 hrs, hospitalisation or relapse at 48hrs after discharge, symptom scores and adverse events.
Characteristics	• Dolcetti – Mean age 58, gender 80% male. Experimental group 200mg doxofylline / 50ml saline over 15min. Control=placebo. • Rice – Mean age 65, gender 96% male. Experimental group IV aminophylline 0-6mg/kg load, 0.5mg/kg maintenance infusion for level of 72-94 umol/l (different in abstract 72-82). Control=placebo. • Seidenfield – Mean age 52, gender 100% male. Experimental group IV aminophylline 2.8-5.6 mg/kg over 1 hr. Control="D5W". • Wrenn – Mean age 62, gender 64% male. Experimental group IV aminophylline 5.6 mg/kg over 20 min, then 0.9mg/kg constant infusion. Control=placebo.
SIGN Quality Rating	++
Hierarchy of Evidence Grading	1a

Results	**Pulmonary Function (3 trials)** Mean change in FEV1 at 2 hrs was non significant in methyl-xanthine and placebo groups (FEV1 WMD: -8ml; 95% CI: -85 to 69ml). One trial (Dolcetti 1988) which failed to include standard treatment demonstrated a significant treatment effect, however this was a cross over trial with a sample size of N=10. **Hospitalisation rate (One trial N=39)** Non significant reduction with methyl-xanthines (OR: 0.3; 95% CI:0.1 to 1.8). **Symptoms scores (2 trials)** There was significant heterogeneity (p=0.02) between the two trials that were aggregated. (Wrenn 1991 and Dolcetti 1988). The difference between the symptom scores in patients receiving methyl-xanthines compared to placebo not statistically significant (OR 5.6; 95%CI: 0.2 to 1.38). **Adverse Effects (3 trials)** The odds of nausea or vomiting were significantly higher for patients receiving a methyl-xanthine (OR: 4.8; 95% CI: 1.01 to 23) than those receiving placebo. Other effects were not recorded often enough to allow combination.
ID	859
Included references	Dolcetti 1988 (N=10), Rice 1982 (N=30), Seidenfield 1984 (N=52), Wrenn 1991 (N=39)