Decisioni Cliniche e Prove di Efficacia

Riccione, 5-6 aprile 2002

Workshop Clinici Interattivi

Bronchite cronica, asma, BPCO. Pratica clinica ed eccesso di linee guida?

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Scenario Clinico (1)

- Il signor Valerio è un ex camionista di 72 anni, forte fumatore (30-40 sigarette/die), con pregressa diagnosi di BPCO, effettuata nel 1992 sulla base di dati clinico-anamnestici, radiologici e spirometrici (FEV1 = 70%).

- Il paziente, inoltre, ha una storia di iperconsumo alcolico con struttura e funzione epatica perfettamente conservate

- Da quando è stata posta diagnosi di BPCO, il paziente ha praticato terapia con aminofillina retard + salbutamolo spray al bisogno

Scenario Clinico (2)

- Sin dal 1993 il paziente va incontro a diversi episodi di riacutizzazione della BPCO, che vengono trattate con antibiotici (chinolonici e/o cefalosporine iniettive) e cortisonici sistemici.

- Alcuni di questi episodi hanno richiesto l'ospedalizzazione

- Al paziente non vengono prescritti mucolitici.

- In occasione di uno di tali ricoveri (1996) vengono aggiunti alla terapia cronica inalatoria un anticolinergico (ipratropio) ed una combinazione di beclometasone e salbutamolo

Scenario Clinico (3)

- Nel 1999, a causa del sopraggiungere di una insufficienza respiratoria ipossiemico-ipercapnica stabile (pO2 54, pCO2 50) con FEV1 < 50%, viene posta indicazione all'O2-terapia domiciliare

- Viene anche modificata la terapia farmacologica:
  - sostituisce lo spray combinato beclometasone-salbutamolo con l'uso sequenziale di formoterolo e fluticasone
  - sostituisce l'ipratropio con l'ossitropio
  - inizia terapia steroidea sistemica continuativa (prednisone 7,5 mg/die x os).

Scenario Clinico (4)

- Nell'agosto del 2000, a seguito di un trauma banale, il signor Valerio riportava la frattura non mielica di L1.

- Tutti i tentativi di sospendere la terapia steroidea sistemica comportavano un peggioramento soggettivo del quadro respiratorio

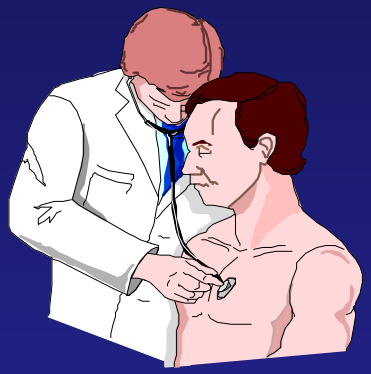
- Il paziente, comunque, continua a fumare

Scenario Clinico (5)

- Nel febbraio 2002 ricovero per insufficienza respiratoria acuta in terapia intensiva, dove viene sottoposto a ventilazione meccanica invasiva.

- Il paziente viene dimesso dopo circa 20 giorni di degenza in discrete condizioni generali

- Attualmente, il paziente continua a fumare (di nascosto)



CLINICAL QUESTIONS

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3A. Ritieni appropriata la scelta degli antibiotici (chinolonici e/o cefalosporine iniettive) per trattare gli episodi di riacutizzazione?

1. Sì
2. No

3B. In occasione di tali episodi avresti prescritto un mucolitico per via orale?

1. Sì
2. No

3C. Ritieni appropriato il timing di prescrizione dell'ossigenoterapia domiciliare

1. Sì
2. No

3D. Ritieni che il rapporto rischio/beneficio sull'uso long-term degli steroidi orali nella BPCO sia:

1. Verosimilmente favorevole
2. Verosimilmente sfavorevole

3E. In quale delle seguenti categorie collocheresti l'uso degli steroidi inalatori nella BPCO

1. Utile
2. Probabilmente utile
3. Da valutare caso per caso
4. Di efficacia sconosciuta
5. Probabilmente inutile
6. Inutile o dannoso

Hibble A, Kanka D, Pencheon D, Pooles F

Guidelines in general practice: the new Tower of Babel?

*BMJ 1998;317:**862 863***

Pile of 855 guidelines in general practices in the Cambridge and Huntingdon Health Authority

Hibble A, et al. BMJ,1998

Johnston BL, Conly BL

Guidelinitis. A new syndrome?

Can J Infect Dis 2000

Lacasse Y, Ferreira I, Brooks D, et al.

Critical appraisal of clinical practice guidelines targeting chronic obstructive pulmonary disease

Arch Intern Med 2001;161:69-74

OBIETTIVI

Esaminare le raccomandazioni cliniche e valutare criticamente le LG sulla BPCO

METODI

- Attraverso una **ricerca MEDLINE** (1/90 – 5-99) e **contatti** con esperti e società scientifiche venivano identificate 15 LG
- **Valutazione critica delle LG**
  - *rigore metodologico di elaborazione*
  - *contesto e contenuti*
  - *valutazione delle strategie di disseminazione-implementazione*
- **Confronto tra raccomandazioni**

Lacasse Y, et al. Arch Int Med 2001

RISULTATI

- Nessuna delle 15 LG si basava su una revisione sistematica della letteratura
- Le fonti di finanziamento erano chiaramente identificabili per 7/15 LG
- Le raccomandazioni erano difficili da interpretare (accordo tra i revisori: 0.41).
- Nessuna delle 15 LG era stata provata

Lacasse Y, et al. Arch Int Med 2001

Table 1. Content of Practice Guidelines Related to the Overall Management of COPD*

Component of Management	Practice Guideline Developers														
	CTS	ARG†	ERS	ATS	NOR	ANZ	GER	SPA	SWI	POL	FRE	BTS	SAF	CHI	FIN
Initial assessment	0	+	+	+	0	+	0	+	+	+	+	+	+	+	+
Therapeutic interventions															
Smoking cessation	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Vaccines															
Influenza	+	+	+	+	+	+	0	+	+	+	+	+	+	+	+
Pneumococcal	±	+	±	+	–	+	0	+	+	±	+	–	0	0	+
Haemophilus	±	0	0	0	–	±	0	0	±	0	0	0	0	0	0
Pharmacological management—bronchodilators															
β_2-Agonists	2	2	1/2	1	1	1	1	1/2	2	2	1/2	1	1/2	1/2	1/2
Ipratropium bromide	1	1	1/2	2	2	2	2	1/2	1	1	1/2	2	1/2	1/2	1/2
Theophylline	+	+	+	+	+	±	+	+	±	+	±	±	+	+	+
Corticosteroids (in selected patients)															
Oral	+	–	+	±	±	+	+	+	+	+	±	–	+	+	+
Inhaled	±	+	±	±	±	+	+	±	±	+	±	+	+	–	+
Mucolytics	±	±	–	–	–	+	±	±	+	±	±	–	–	0	±
Oxygen therapy															
Long-term therapy	+	+	+	+	0	+	+	+	+	+	+	+	+	+	+
Nocturnal therapy	–	+	+	+	0	±	+	+	+	+	±	+	–	0	+
Exercise	0	+	+	+	0	+	+	+	+	0	–	+	–	0	+

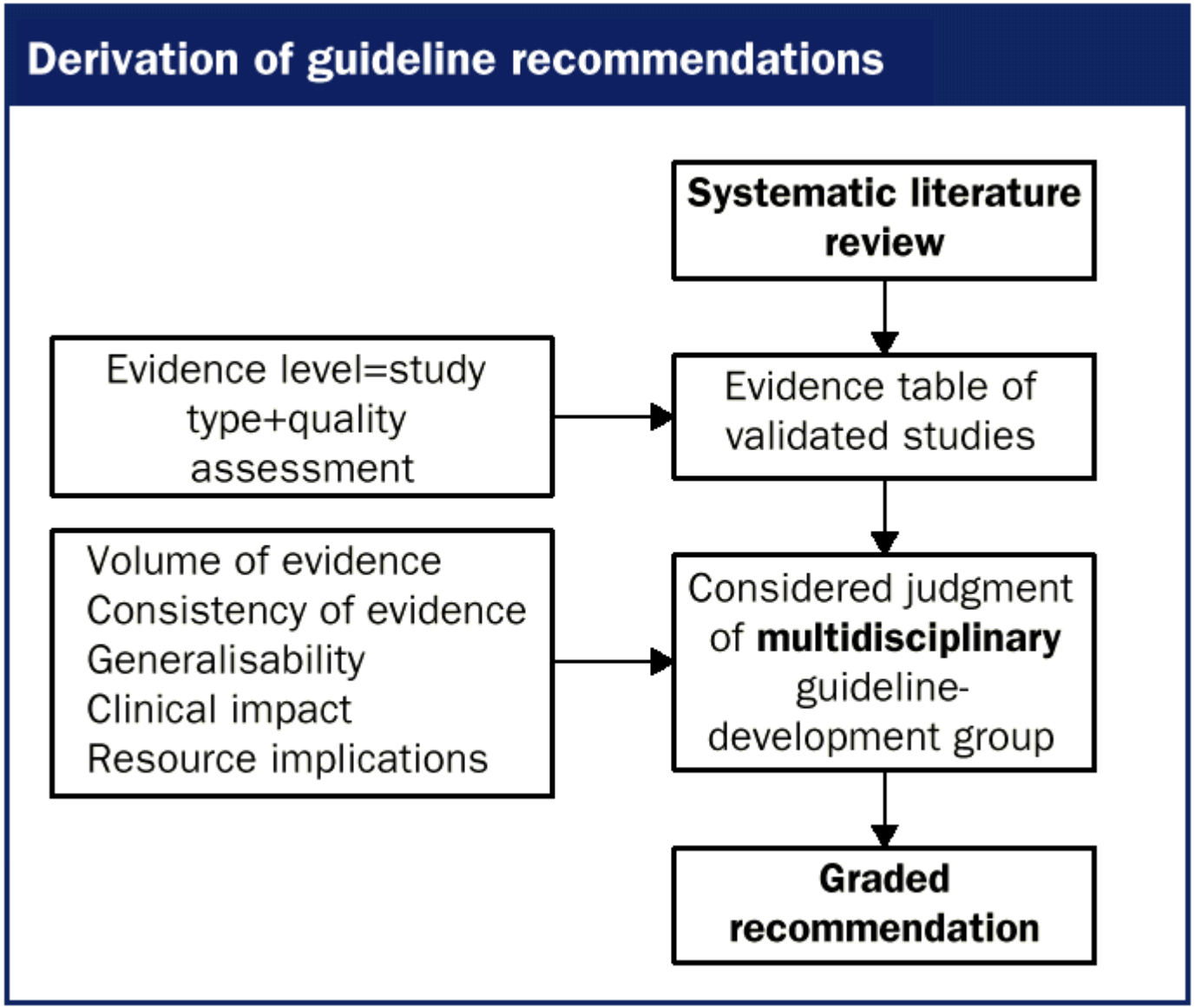
CONCLUSIONI

- La qualità metodologica delle LG sulla BPCO è modesta ed esiste una notevole discordanza tra le raccomandazioni delle diverse LG

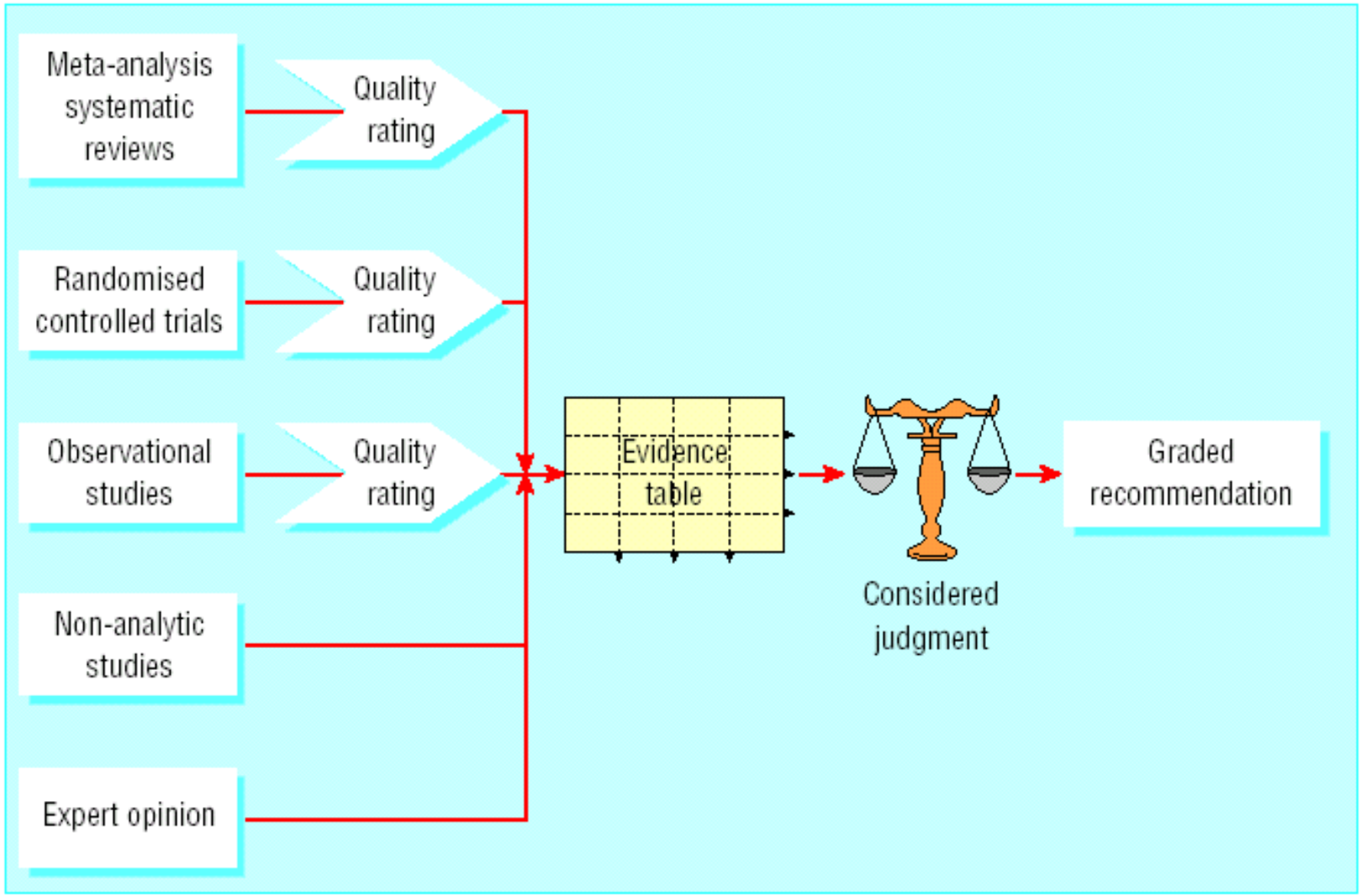
- E' necessario un evidence-report costantemente aggiornato, quale consistente base scientifica per chi deve assistere i pazienti con BPCO

Lacasse Y, et al. Arch Int Med 2001

Quale metodologia per la produzione delle linee guida nell'era dell'Evidence-based Medicine?



Miller J, et al. Lancet 2000



Overview of the process for developing and grading guideline recommendations

www.agreecollaboration.org

AGREE

Appraisal of Guidelines for Research & Evaluation

- Strumento per la valutazione di qualità delle LG
- Elaborata da un gruppo internazionale
- Finanziamento della Comunità Europea
- Disponibile in versione italiana

- 23 item in 6 dimensioni
  - obiettivi della LG
  - coinvolgimento delle parti in causa
  - rigore metodologico
  - chiarezza espositiva
  - applicabilità
  - indipendenza editoriale

GOLD

Global Initiative for Chronic Obstructive Lung Disease

World Health Organization
National Heart Lung and Blood Institute
April 2001

FUNDING SOURCE

ASTA Medica, AstraZeneca, Aventis, Bayer , Boehringer Ingelheim, Byk Gulden, Chiesi, GlaxoSmithKline, Merck, Sharp and Dohme, Mitsubishi-Tokyo, Nikken Chemicals, Novartis, Schering-Plough, Yamanouchi, Zambon.

Warlow C

Who pays the guideline writers?

BMJ 23 March 2002

Stoller JK

Acute Exacerbations of Chronic Obstructive Pulmonary Disease

N Engl J Med. March 28, 2002

American College of Chest Physicians
American College of Physicians
American Society of Internal Medicine

Evidence Base for Management of Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Ann Intern Med 2001;134.595-99

- Although suggestions for appropriate management can be made on the basis of available evidence, the supporting literature is scarce and further high-quality research is necessary.

- Such research will require an improved, generally acceptable, and transportable definition of acute exacerbation of COPD, as well as improved methods for observing and measuring outcomes

Antibiotics

- 11 RCTs have shown that antibiotic treatment is beneficial in selected patients with acute exacerbation of COPD.

- In particular, the studies showed that patients with more severe exacerbations (type 1) are more likely to experience benefit than those whose exacerbations are less severe.

- Typical administration periods ranged from 3 to 14 days, and tetracycline, amoxicillin, and trimethoprim–sulfamethoxazole were the most common antibiotics.

Antibiotics

- Although most of these RCTS were done before the emergence of multidrugresistant organisms, they show only a minimal benefit with antibiotic treatment in the more severe exacerbations.

- On the basis of these data and the emergence over time of more resistant organisms, particularly Streptococcus pneumoniae, it has become common practice to use more broad-spectrum antibiotics in acute exacerbations of COPD.

- To date, however, no RCTs have proved the superiority of the newer broad-spectrum antibiotics in such cases

Chronic Obstructive Pulmonary Disease

Clinical Evidence
Issue 6, March 2002

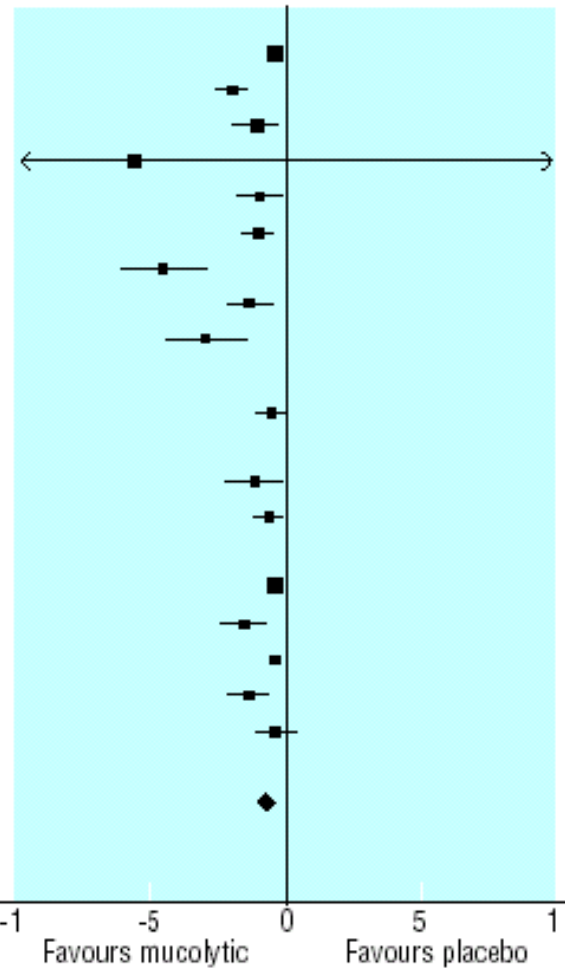
Poole PJ, Black PN.

Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease

In: The Cochrane Library, Issue 1, 2002
Oxford: Update Software

Study	No taking mucolytic	Mean (SD)	No taking placebo	Mean (SD)	Weighted mean difference (95% CI fixed)	Weight (%)	Weighted mean difference (95% CI fixed)
Allegra 1996	223	0.07 (0.11)	218	0.11 (0.14)		24.2	-0.04 (-0.06 to -0.02)
Babolini 1980	254	0.13 (0.18)	241	0.33 (0.27)		8.1	-0.20 (-0.24 to -0.16)
Boman 1983	98	0.20 (0.27)	105	0.32 (0.30)		2.2	-0.12 (-0.20 to -0.04)
Bontognali 1991	30	0.70 (3.76)	30	1.27 (4.58)		0.0	-0.57 (-2.69 to 1.55)
Borgia 1981	10	0.05 (0.08)	9	0.15 (0.17)		0.9	-0.10 (-0.22 to 0.02)
Castiglioni 1986	311	0.10 (0.21)	302	0.20 (0.29)		8.3	-0.10 (-0.14 to -0.06)
Cremonini 1986	21	0.25 (0.23)	20	0.71 (0.29)		0.5	-0.46 (-0.62 to -0.30)
Grassi 1976	35	0.14 (0.15)	34	0.27 (0.21)		1.8	-0.13 (-0.22 to -0.04)
Grassi 1994	42	0.16 (0.29)	41	0.45 (0.43)		0.5	-0.29 (-0.45 to -0.13)
Grillage 1985*	54	0.10 (0)	55	0.12 (0)		0	Not estimable
Hansen 1994	59	0.11 (0.15)	70	0.16 (0.19)		3.9	-0.05 (-0.11 to 0.01)
Jackson 1984*	61	0.11 (0)	60	0.13 (0.00)		0.0	Not estimable
McGavin 1985	72	0.42 (0.34)	76	0.52 (0.35)		1.1	-0.10 (-0.21 to 0.01)
Meister 1986	90	0.15 (0.15)	91	0.20 (0.19)		5.4	-0.05 (-0.10 to 0.00)
Meister 1999*	110	0.06 (0)	105	0.10 (0)		0	Not estimable
Nowak 1999	147	0.03 (0.06)	148	0.06 (0.12)		28.7	-0.03 (-0.05 to -0.01)
Olivieri 1987	110	0.18 (0.31)	104	0.33 (0.41)		1.4	-0.15 (-0.25 to -0.05)
Parr 1987	243	0.18 (0.21)	210	0.21 (0.21)		8.9	-0.03 (-0.07 to 0.01)
Pela 1999	83	0.17 (0.18)	80	0.29 (0.32)		2.1	-0.12 (-0.20 to -0.04)
Rasmussen 1988	44	0.13 (0.21)	47	0.14 (0.19)		2.0	-0.01 (-0.09 to 0.07)
Total (95%CI)	2097		2046			100.0	-0.07 (-0.08 to -0.05)

Test for overall effect z=11.15, P<0.0001



* Study could not be included in meta-analysis because no measure of spread of data was available.

Fig 1 Mean (SD) number of exacerbations per subject per month, weighted mean difference, and 95% confidence intervals

What is already know on this topic

Mucolytic drugs have properties that may be beneficial in chronic obstructive pulmonary disease

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These drugs are not prescribed in the United Kingdom and Australasia, although they are widely used in many other countries

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Drugs that reduce exacerbations may reduce the morbidity and healthcare costs associated with progressively severe disease

What this study adds

Regular use of mucolytic drugs for at least two months significantly reduces exacerbations and days of illness compared with placebo in patients with chronic bronchitis and chronic obstructive pulmonary disease

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Exacerbations that do occur may not be as severe, and the benefit may be greater in those with more severe disease

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Reductions are modest and treatment may not be cost effective

- There was significant heterogeneity between the RCTs

- Our systematic review shows that mucolytic drugs have a modest but significant effect on exacerbation rates in people with chronic bronchitis and chronic obstructive pulmonary disease.

- On the basis of the annualised exacerbation rate of 2.7 per patient per year in the control group, the number needed to treat for one subject to remain free of exacerbations for the study period would be 6.

Crockett AJ, Moss JR, Cranston JM, Alpers JH.

Domiciliary oxygen in chronic obstructive pulmonary disease

The Cochrane Library, Issue 1, 2002.
Oxford: Update Software

- We found limited evidence that domiciliary oxygen treatment improves survival in people with COPD and hypoxaemia.

- One RCT found that continuous treatment was more effective than nocturnal treatment.

- Domiciliary oxygen treatment seems to be more effective in people with severe hypoxaemia, than in people with moderate hypoxaemia or those who have arterial desaturation only at night.

Oral Corticosteroids

- One systematic review of short term RCTs has found that steroids versus placebo significantly improves lung function.

- We found no RCT of the effects of long term treatment on lung function.

- We found evidence of potentially serious adverse effects, including osteoporosis and induction of diabetes

Clinical Evidence. Issue 6, March 2002

McEvoy CE, Niewoehner DE.

Adverse effects of corticosteroid therapy for COPD: a critical review

Chest 1997;111:732–743.

Inhaled corticosteroids

Unlikely to be beneficial

- Short term RCTs found no evidence of benefit of inhaled corticosteroids.

- Large RCTs of at least 6 months have found that inhaled steroids increase FEV1 during the first 3–6 months of use, but found no subsequent effect on decline of lung function.

- Two studies also found a reduction in exacerbation frequency and an improvement in health status.

Clinical Evidence. Issue 6, March 2002